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HTA Core Model® Online

Disclaimer
This information collection is a core HTA, i.e. an extensive analysis of one or more health technologies using all nine domains of the HTA Core Model. The core HTA is intended to be used as an information base for local (e.g. national or regional) HTAs.

Collection name
Fecal Immunochemical Test (FIT) versus guaiac-based fecal occult blood test (FOBT) for colorectal cancer screening
Scope

Fecal Immunochemical Test (FIT) for colorectal cancer screening compared to CRC screening with Guaiac –based fecal occult blood test (gFOBT) in the screening of Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). in healthy and/or asymptomatic adults and elderly Any adult over 50 years old, both men and women, with average risk of CRC.

(See detailed scope below)

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Fecal Immunochemical Test (FIT) versus guaiac-based fecal occult blood test (FOBT) for colorectal cancer screening

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Collection summary

Background

Colorectal cancers (CRCs) arise mostly from previously begin adenomas and have effective treatment if diagnosed early in their evolution. It is for these reasons that they are amenable to screening. Screening can be done via three approaches: imaging, endoscopy and stool-based identification. Two of the techniques used in stool-

based based identification are the object of this core HTA, collectively knows as Fecal occult blood tests (FOBT): (guaiac, so-called gFOBT and immunochemical testing, so called FIT, also known as Immunochemical Faecal Occult Blood Test (iFOBTs).

CRC is the 3rd most common cancer worldwide, and the second most frequent in developed countries with an estimated 1,234,000 cases worldwide in 2008. There are large variations between regions. Incidence rates are higher in Australia/New Zealand (39.0 per 100,000), Western Europe (33.1 per 100,000) and Southern Europe (31.1 per 100,000) and lower in Western Africa (4.9 per 100,000), South-Central Asia (4.5 per 100,000) and Middle Africa (3.7 per 100,000) {6}. In 2008 an estimated 8% of total cancer-related deaths was caused by CRC. Incidence and mortality from CRC are higher in men that in women.

Currently screening practices vary considerably across Europe (see assessment element CUR 14),

Several different types and brands of FOB tests are available, with different performance characteristics.

gFOBT is the longest established of the two basic techniques, guaiac and immune based. There are several potential advantages and disavantages of gFOBT use. The advantages are mainly due to the cheapness, acceptability and long standing nature of the procedure. The disadvantages of gFOBT are its lack of automation, laboriousness and lack of specificity for human Haemoglobin, requiring a period of dietary preparation before testing.

FITs are a newer class of Faecal Occult Blood tests compared to gFOBTs and reputedly have improved test characteristics compared to gFOBT. iFOBTs have been used for population CRC screening in Japan since 1992. In the US, the first iFOBT (OC-Sensor) was approved by the FDA (Food and Drug Administration) since 2001. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both, *prevention* (by the removal of adenomas before they had a chance to become malignant, so CRC incidence is reduced) and *earlier diagnosis* of CRC (at early, curable stage).

A wide range of qualitative and quantitative FITs is presently available, with varying levels of sensitivity and specificity. They all use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces.

The aim of this core HTA was to compare the diagnostic and clinical performance of FITs with gFOBT for detection of CRC.

Results

Safety of the technology (SAF)

As FIT and gFOBT are non-invasive tests no direct harms are likely. Indirect harms can be caused by a wrong or delayed diagnosis or by harms related to subsequent colonoscopy (such as local trauma). The psychological impact of screening (including consequences of any false-positive and false-negative test results) and patient discomfort related to the procedures are the potential harms to be assessed as the overall number of adverse events depends on sensitivity and specificity of the screening tests. False-positive results may cause anxiety and distress, overdiagnosis and overtreatment. The false-negative test results may delay the detection of illness and the start of treatment. Organisational factors affecting harms include false-positive test results from gFOBT with a lax dietary preparation and FIT samples should be kept in refrigerated. Personnel experience and dexterity is also a factor.

Harms colonoscopy are estimated at 5% of procedures whereas 68% of people who received a false positive experienced stress and 46% of those who received an invitation to screening were worried and 15% very worried.

Effectiveness of the technology (EFF)

Our searches were unable to identify a direct comparison of the two techniques with meaningful cancer-specific outcomes such as CRC mortality within screening programmes.

However on the basis of several single studies and systematic review FIT have higher detection rates than gFOBT for adenomas, at the expense of a drop in specificity. We concluded that Overall, FIT performance is superior to the standard gFOBT for the detection of CRC and advanced adenomas in a population based screening setting.

Costs, economic evaluation of the technology (ECO)

FIT lacks evidence of its effect on mortality when used in a screening programme, but both tests are more cost-effective than no screening. Cost-effectiveness models tend to suggest FIT has more favourable ICERs than gFOBT but its higher sensitivity means that there is a need for higher capacity in undertaking diagnostic colonoscopies with an increased up-front resource use and cost associated with the increased number of colonoscopies.

Ethical aspects of the technology (ETH)

The tests are very similar, making ethical problems around choice less important. Overall there appears to be dominance of FIT over gFOBT and both dominate no screening. However in the absence of a direct clinical comparison the evidence base is unstable as shown by the different ICERs in ECO5. A full assessment should be carried out in context to define the costs and opportunity costs as well as the benefits of choice between the two types of test.

Organisational aspects of the technology (ORG)

CRC screening is carried out with significant variation across the EU in terms of organization and type of screening test. There partial or complete screening programmes in 19 of the 27 EU countries. Organised screening is considered better than opportunistic screening. In 2007, gFOBT was used as the only screening method in twelve countries: Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and United Kingdom. In six countries, two types of tests were used: FIT and FS in Italy, and gFOBT and colonoscopy in Austria, Cyprus, Germany, Greece, and Slovak Republic. FIT is being used in 6 European countries: Russia, Lithuania, Italy, Scotland, Spain and Slovenia.

National screening programmes use risk-based criteria to define who should receive screening invitations. The target population for a CRC screening programme includes all people eligible to attend screening on the basis of age and geographical area of residence. Altough there are variations, people who are between 50 and 75 are invited to be screened.

Screening programmes with FIT carry an investment penalty including equipment for screening, premises, office material for posting invitations and re-invitations, IT equipment and other office devices such as printers, and human resources including administrative and health personnel, investment in education of personnel and their training. Every country needs to assess their costs independently using cost-effectiveness analyses or other economic evaluation method. Investments that are needed for implementation of FIT are therefore country specific.

Social aspects of the technology (SOC)

We found good evidence that FIT has better compliance than gFOBT in screening. The reasons for this finding are unclear and under researched but may include socio-cultural factors and the need for dietary prepration for gFOBT.

Legal aspects of the technology (LEG)

Legals implications of detecting colorectal cancer include the necessity to provide Sufficient information and informed consent, the right of access to (best) health care once a presumptive diagnosis is made, freedom in taking part, protection of personal data, equal right of access according to need and in the case of regional inequalities, access abroad and the right to charge contributions to the cost of the programme.

Closing Remarks

The Core Model is not intended to provide a cookbook solution to all problems but to suggest a way in which information can be assembled and structured, and to facilitate its local adaptation. The information is assembled around the nine domains, each with several result cards in which questions and possible answers are reported.

The reasons for having a standardised but flexible content and layout are rooted in the way HTA is conducted in the EU and in the philosophy of the first EUnetHTA Joint Action (JA1) production experiment.

HTA is a complex multidisciplinary activity addressing a very complex reality – that of healthcare. Uniformly standardised evidence-based methods of conducting assessments for each domain do not exist (Corio M, Paone S, Ferroni E, Meier H, Jefferson TO, Cerbo M. Agenas – Systematic review of the methodological instruments used in Health Technology Assessment. Rome, July 2011.)). There are sometimes variations across and within Member States in how things are done and which aspects of the evaluation are privileged. This is especially so for the “softer” domains such as the ethical and social domains.

Collection methodology

Objective

To produce a Core Health Technology Assessment (HTA) comparing the performance of fecal occult blood tests (FOBT - guaiac, so-called gFOBT and immunochemical testing, so called FIT, also known as Immunochemical Faecal Occult Blood Test - iFOBT) for colorectal cancers (CRCs) based on the EUnetHTA Core Model.

Methods

The work was based on the HTA Core Model on screening technologies, which was developed during the EUnetHTA Joint Action 1 (JA1).

The first phase was the selection of the technology to be assessed using the Core Model; this phase was carried out through a three-step process that is described in our MSP.

Then there was the check of Partners’ availability to assume responsibility, as an institution, to take the lead in one of the nine evaluation domains. At the same time, the nine domain teams were built-up in accordance with partners’ preferences and some general guidelines (i.e.: “*each WP4/B Associated partner AP should be involved in at least one domain, indicating its interest for at least one domain*”)

Finally the specific work plan was shared, according with the general WP4 3-year work plan and objectives. This specific work plan included the phases scheduled in the “HTA Core Model Handbook” (Production of Core HTAs and structured HTA information).

An editorial team was set up for discussion and major decisions on basic principles and solutions related to the content of core HTA. The editorial team was chaired by Tom Jefferson (Agenas) and composed of all the primary investigators of the domains.

To allow collaboration between partners a draft protocol for Core Model use was agreed by the researchers involved. The research questions for each of the nine domains of the Core Model were formulated and the corresponding relevant assessment elements (AEs) were selected.

The research strategy was carried out by Agenas with input from the other partners.

Evidence from published and manufacturer sources was identified, retrieved, assessed, and included according to pre-specified criteria, and summarised to answer each AE. Work was carried with domain assessments being made by a single agency and by different investigators from different agencies, in a mixed organisational model.

Introduction to collection

This brief document provides background information on the preparation and development of the Core HTA on CRC detection. The core HTA document was produced during the course of the second EUnetHTA Joint Action (JA2) 2012-2015.

The idea behind EUnetHTA’s Core Model is to provide a framework for structuring relevant HTA information while at the same time facilitating local use and adaptation of the information or guiding its production.

The Model is based on nine dimensions or “domains” of evaluation:

1. Health Problem and Current Use of the Technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)
4. Effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects (LEG)

The Core HTA was sent to the Stakeholder Advisory Group (SAG) for feedback before the final Public Consultation and the comments received where included where applicable.

Scope

Technology

Fecal Immunochemical Test (FIT) for colorectal cancer screening

Description

FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).

Intended use of the technology

Screening

CRC screening with faecal inmunochemical test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC).

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC).

Target condition

Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC).

Target condition description

CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease.

Target population

Target population sex: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people.

Target population description

Adults, average risk of CRC, aged 50 years or over.

The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis).

Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population

Comparison

CRC screening with Guaiac –based fecal occult blood test (gFOBT)

Description

CRC screening with Guaiac–based fecal occult blood test (gFOBT)

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet.

Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC)

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers

- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a "new" detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Health Problem and Current Use of the Technology

Authors: Mirjana Huic, Eleftheria Karampli, Silvia Florescu, Cipriana Mihaescu-Pintia

Summary

Aim To give broad overview on the health problem of colorectal carcinoma (CRC), the screening population and the current use of different CRC screening methods in Europe, as well as FIT use, an alternative name for Immunochemical faecal occult bleeding test (iFOBT), a class of occult blood tests which represents one out of few different screening options CRC.

Methods The Project scope is applied in this Domain. Results cards are covered by evidence gathered from basic literature search, hand searched literature, manufacturers web sites, company brochures and information for use, and survey (questionnaire) results. No quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources. The assessment elements questions are answered by cooperation of Domain investigators.

Results Colorectal cancer (CRC) is the 3rd most common cancer worldwide, and the second most frequent in developed countries. Most colon cancers arise from non-malignant adenomas in form of adenomatous polyps. Due such natural course, CRC is particularly suitable for screening. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both *prevention* (by the removal of adenomas before they become malignant) and *earlier diagnosis* of CRC (at early, curable stage). In developed countries, approximately, 40.50% of the population develop one or more adenomas in a lifetime, but the majority of these adenomas will never develop into CRC. Only 5.6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is unobserved, but is estimated to take at least 10 years. Focusing on Europe, in 2008, CRC accounted for 12.4% of deaths caused by malignancy in European countries (11.5% and 13.5% of total cancer deaths in men and women respectively). In Europe, an increasing trend in average incidence of CRC has been observed in recent years, and in the future, the number of new cases and deaths related to CRC are expected to increase. In specific, the International Agency on Research for Cancer (IARC) estimates the number of new CRC cases in Europe (in all ages) to rise to 502,000 in 2020, whereas the annual deaths from CRC in Europe are expected to rise to 248,000.

Target population for CRC screening includes asymptomatic people at average risk, of both genders, age 50-74. There are various methods available for colorectal cancer screening. They can be broadly divided into endoscopic and radiologic methods (for example colonoscopy) and stool-based tests (guaiac-based or immunochemical Faecal occult blood tests - FOBTs, Faecal DNA testing). Routine screening of stool for occult blood may facilitate early detection. Guaiac-based Faecal Occult Blood (gFOBT) tests are those mostly studied in RCTs as screening test for CRC and are an established screening strategy for CRC. Several large randomized studies have demonstrated a reduction in cancer-related mortality. FIT (Faecal Immunochemical test) is an alternative name for Immunochemical Faecal Occult Blood Test (iFOBT), a class of occult blood tests which represents one out of few different screening options for colorectal cancer (CRC). A number of countries have organised CRC screening programmes utilising different strategies. FOB testing is a widely implemented strategy, however there are differences in the type of tests used (gFOBT or iFOBT). From the information provided via the EUnetHTA member survey, use of immunochemical testing (FIT) was reported in 5 out of 11 responded (i. e. Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia) European countries. In specific, FIT is used in the Regions of Veneto and Lazio in Italy, Lithuania, Russia, Slovenia and Spain. In Austria, FIT is used only in one province (Burgenland). According to data (May 2008) from the International Cancer Screening Network, CRC screening programmes utilising immunochemical techniques had been implemented in Hungary (2 pilots) and Italy. In Italy, the majority of programmes use FIT, a limited number offer flexible sigmoidoscopy (FS) once in a lifetime and FIT for non-responders to FS.

Participation rates in various CRC screening programmes (pilot programmes, established programmes) in Europe and abroad broadly varies from 14.4%-63.8%. Various technologies are available for the diagnosis of adenomas and CRC. Colonoscopy is the gold standard and allows biopsy for histology.

Several different types and brands of FOB tests are available, with different performance characteristics. Potential advantages of gFOBT, as main comparator in this Core HTA, are: the collection card and reagent are cheap, the card based collection system is easy to pack using automated machinery and easy to send by post, easy to print patients details on the cards, the samples are considered to be stable on the cards for up to 21 days, the system has been validated in numerous RCTs, has been implemented in a number of bowel cancer screening programmes and work successfully. Disadvantages of gFOBT are: testing is not automated, test is labour intensive and involves subjective visual reading, the participants is required to prove samples from three separate bowel motions, it is not specific for human Hb, it is not possible to adjust the cut-off Hb concentration of the test.

According the EU Guideline 2010, "iFOBT have improved test characteristics than gFOBT, and they are currently the test of choice for population CRC screening. In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme (Level of evidence II, Grade of recommendation A). Adoption of test device and the selection of a cut-off concentration should follow a local pilot study to ensure that chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable (Level of evidence VI, Grade of recommendation A). Maximum period between collection and analysis is significantly shorter than for gFOBT (14-21 days), and screening programmes should adopt the conditions and period of storage described in manufacturer's Instructions for use and should be appropriate for local conditions which might expose samples to high temperatures for long period of time (Level of evidence III, Grade of recommendation A). Despite the fact that dietary constituents present potential interference in gFOBT, dietary restriction has not been demonstrated to significantly increase screening specificity and risks reducing participation rate. The potential for dietary interference is significantly less for iFOBT. Some drugs which could cause GI bleeding like aspirin, NSAIDs and anticoagulants present potential interference in gFOBT and iFOBT, drug restriction is not recommended for population screening programmes using either gFOBT or iFOBT."

The most clinically and cost-effective CRC screening method still should be determine in additional comparative effectiveness research. When making decision between different FOB tests (gFOBT or FIT) should be used for CRC screening, their analytical performance should be keep in mind as well as compliance and general acceptance of the test by the public.

Introduction

Colorectal cancer (CRC) is the 3rd most common cancer worldwide, and the second most frequent in developed countries. In the US, CRC accounts for 10% of cancer-related deaths; focusing on Europe, in 2008, CRC accounted for 12.4% of deaths caused by malignancy in European countries (11.5% and 13.5% of total cancer deaths in men and women respectively); incidence increases above age 50, the average age at diagnosis is 60-65 years. Different factors could increase or decrease risk for colorectal cancer. Factor which increased risk for CRC are: environmental factors (prevalence is increased in developed countries, urban areas); advantaged socioeconomic groups; hypercholesterolemia; coronary artery diseases; low-fiber, high-animal-fat diets; obesity; smoking; acromegaly; sugar consumption; family history (risk is increased in first-degree relatives of patients, families with increased prevalence of cancer, patients with breast or gynecologic cancer, familial polyposis syndromes);>10-year history of ulcerative colitis or Crohn's colitis;>15-year history of uretherosygmoidostomy. Risk is decreased with long term dietary calcium supplementation, vegetable, garlic, exercise, daily aspirin ingestion (after 5 years daily aspirin there is a 35% reduction in all GI cancers) and other NSAIDs.

Most colon cancers arise from non-malignant adenomas in form of adenomatous polyps. Due such naturale course, CRC is particularly suitable for screening.

The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both *prevention* (by the removal of adenomas before they become malignant) and *earlier diagnosis* of CRC (at early, curable stage). Different screening tests for CRC are available, classified according to three categories:

Stool-based techniques: Fecal occult blood test (FOBT) (either guaiac, so called gFOBT and immunochemical, so called FIT); Fecal DNA testing. **Endoscopic techniques**: Optical colonoscopy; Flexible sigmoidoscopy (FS). **Imaging techniques**: Virtual colonoscopy techniques using: a) Computed tomographic colonography (CT colonography), b) Magnetic resonance colonography (MR colonography); Wireless capsule endoscopy; Double-contrast barium enema. The aim of this Domain is to give broad overview on the health problem of colorectal carcinoma, the screening population and the current use of different CRC screening methods in Europe, as well as FIT, an alternative name for Immunochemical faecal occult bleeding test (iFOBT), a class of occult blood tests introduced in US market in 2001, which represents one out of few different screening options for colorectal cancer (CRC).

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the

adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease.

Target population

Target population sex: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people.

Target population description

Adults, average risk of CRC, aged 50 years or over.

The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis).

Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population

Comparison

CRC screening with Guaiac –based fecal occult blood test (gFOBT)

Description

CRC screening with Guaiac–based fecal occult blood test (gFOBT)

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet.

Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC)

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)

- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
A0001	Target Condition	Which disease/health problem/potential health problem will the technology be used for?	yes	Which disease/health problem/potential health problem will FIT be used for?
A0002	Target Condition	What, if any, is the precise definition/ characterization of the target disease? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?	yes	What, if any, is the precise definition/ characterization of adenomas and/or colorectal carcinoma (CRC)? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?
A0003	Target Condition	Which are the known risk factors for acquiring the condition?	yes	Which are the known risk factors for acquiring adenomas and/or CRC?
A0004	Target Condition	What is the natural course of the condition?	yes	What is the natural course of CRC?
A0005	Target Condition	What are the symptoms at different stages of the disease?	yes	What are the symptoms at different stages of adenomas and/or CRC?
A0006	Target Condition	What is the burden of the condition?	yes	What is the burden of CRC?
A0009	Target Condition	What aspects of the burden of disease are targeted by the technology?	yes	What aspects of the burden of CRC are targeted by CRC screening with FIT?
A0007	Target Population	What is the target population of the technology?	yes	What is the target population for colorectal carcinoma screening with FIT?
A0023	Target Population	How many people belong to the target population?	yes	How many people belong to the target population in Europe?
A0011	Utilisation	How much is the technology being used?	yes	Which countries use FIT for CRC screening? Which percentage of target population is accually screened in countries with CRC screening program with FIT?
A0012	Utilisation	What kind of variations in use are there across countries/regions/settings?	yes	What kind of variations in use of CRC screening methods are there across countries/regions/settings?
A0013	Current Management of the Condition	How is the disease/health condition currently diagnosed or screened?	yes	How are adenomas/CRC currently diagnosed? How are adenomas/CRC currently screened?
A0014	Current Management of the Condition	How should the condition be diagnosed or screened according to published algorithms/guidelines?	yes	How should adenomas/CRC be diagnosed or screened according to published algorithms/guidelines?
A0015	Current Management of the Condition	How is the condition currently managed?	yes	How are adenomas/CRC currently managed?
A0016	Current Management of the Condition	How should the condition be managed according to published algorithms/guidelines?	yes	How should adenomas/CRC be managed according to published algorithms/guidelines?
A0017	Current Management of the Condition	What are the differences in the management for different stages of disease?	yes	What are the differences in the management for different stages of CRC?
A0018	Current Management of the Condition	What are the other evidence-based alternatives to the current technology?	yes	What are the other evidence-based alternatives to CRC screening with FIT? What are the technical characteristics and analytical validity of guaiac-based fecal occult blood test (FOBT), as main CRC screening comparator in this assessment?
A0019	Life-Cycle	In which phase is the development of the technology?	yes	In which phase is the development of FIT?
A0020	Regulatory Status	Which market authorization status has the technology in other countries, or international authorities?	yes	Which market authorization status (CE mark) has FIT in other countries, or international authorities?
A0021	Regulatory Status	What is the reimbursement status of the technology across countries?	yes	What is the reimbursement status of CRC screening with FIT across countries?

Methodology description

Domain frame

The Project scope is applied in this domain.

Information sources

- Basic systematic search. Common (basic) literature search strategy was used, run for the whole project and described in COL Appendix 1;

- Hand search;

- Additional search for published literature in PubMed and internet search of grey literature using Google search engine;

- Review of the reference lists and bibliographies of studies identified through the basic systematic search;

- International Organisations' websites (OECD, WHO, NICE etc.);

- Manufacturers web sites;

- Company brochures and Information for use;

- Survey: two questionnaires were administered, to EUnetHTA Partners and Manufacturers (more information in COL Appendix 2), with aim to get further information about primary CRC screening methods and tests in different EU countries; please see in COL Appendix 2.

Quality assessment tools or criteria

No quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources.

Analysis and synthesis

Descriptive analysis was performed on different information sources. The assessment elements questions are answered by cooperation of Domain investigators.

Results cards are covered by evidence gathered from basic search (COL Appendix 1), hand searched literature, manufacturers web sites, company brochures and information for use, and survey (questionnaire) results.

Result cards

Target Condition

Result card for CUR1: "Which disease/health problem/potential health problem will FIT be used for?"

View full card

CUR1: Which disease/health problem/potential health problem will FIT be used for?

Result

FIT (Faecal Immunochemical test) is an alternative name for Immunochemical Faecal Occult Blood Test (iFOBT), a class of occult blood tests introduced in the US market in 2001, which represents one out of few different **screening options for colorectal cancer (CRC)**. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both *prevention* (by the removal of adenomas before they become malignant) and *earlier diagnosis* of CRC (at early, curable stage) {1-3,5,69}.

Importance: Critical

Transferability: Completely

Result card for CUR2: "What, if any, is the precise definition/ characterization of adenomas and/or colorectal carcinoma (CRC)? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?"

View full card

CUR2: What, if any, is the precise definition/ characterization of adenomas and/or colorectal carcinoma (CRC)? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?

Result

CRC is usually polypoid mass with ulceration, spreads by direct infiltration through bowel wall, and involves lymphatic and blood vessels with subsequent spread, commonly to the liver and lung. Rectosigmoid tumors may spread to lungs early because of systemic paravertebral venous drainage of this area. Histology is nearly always adenocarcinoma; 75% located distal to the splenic flexure. May be polypoid, sessile, fungating, or constricting {1-3}.

Degree of invasiveness at surgery (Dukes classification) is single best predictor of prognosis (Table 1). Other predictors of poor prognosis are preoperative serum CEA >5 mg/ml (>5 µg/l), poorly differentiated histology, bowel perforation, venous invasion, adherence to adjacent organs, aneuploidy, specific deletion in chromosome 5, 17, 18, and mutation of ras proto-oncogene. 15% have defects in DNA repair {1-3}.

Table 1. Staging and survival of colorectal cancers {1}

TNM classification			Modified Dukes classification	5-year survival (%)
Stage I (N0, M0)	Tumours invade submucosa Tumours invade muscularis propria	T1 T2	A	90
Stage II A (N0,M0) Stage II B	Tumours invade into subserosa Tumours invade directly into other organs	T3 T4	B	70 65

Stage II (M0)	T1,T2+1-3 regional lymph nodes involved T3, T4+1-3 regional lymph nodes involved	N1	C	60
IIIB	Any T+4 or more regional lymph nodes	N1		35
IIIC		N2		25
Stage IV	Any T, any N+distant metastases	M1	D	7

ICD-10: the ICD-10 (2010 version) codes for CRC are C18-21. Specifically,

C18 Malignant neoplasm of colon;

C19 Malignant neoplasm of rectosigmoid junction;

C20 Malignant neoplasm of rectum;

C21 Malignant neoplasm of anus and anal canal.

The above codes are those adopted by the World Health Organization International Agency for Research in Cancer (IARC) (http://globocan.iarc.fr/), which includes code C21 anal cancer. Codes included may differ, depending on guidelines that apply.

EU Guideline 2010 {2}

“Due to the improved diagnostic reproducibility of the revised Vienna classification, use of this classification in a format modified for lesions detected in screening is recommended to ensure consistent international communication and comparison of histopathology of biopsies and resection specimens **(IV – B).** Only two grades of colorectal neoplasia (low grade and high grade) should be used, to minimise intraobserver and interobserver error **(V - B).** The terms

intra-mucosal adenocarcinoma or in-situ carcinoma should not be used **(VI - B).**

The WHO definition of colorectal adenocarcinoma should be used: “an invasion of neoplastic cells through the muscularis mucosae into the submucosa” **(VI - A).**

Adenocarcinomas should be reported according to the TNM classification. The version of TNM

to be used should be decided nationally and should be stated e.g. pT1 pN0 pMX (Version 5) or

pT4 pN2 pM1 (Version 7). These can be further abbreviated to pT1N0MX **(v5)** or to pT4N2M1

(v7) (VI - B).

The WHO classification of adenomas into tubular, tubulo-villous and villous should be used

(VI - A).

Due to the increased risk of colorectal cancer associated with flat and/or depressed lesions they should be reported as non-polypoid lesions **(III)**, and further classified by the Paris classification

(V - B).

Sub-staging of T1 cancers should be performed to determine the risk of residual disease. Consideration should be given to the appropriate method, which may vary depending on the morphology of the lesion (Kikuchi/Haggitt or measurement). For non-polypoid lesions the Kikuchi stage and for pedunculated lesions Haggitt are currently recommended **(VI - C)**. High-risk features for residual disease such as lack of margin clearance (≤1 mm), poor differentiation and lymphatic and vascular invasion should be reported **(V - B)**. The multidisciplinary team should be consulted on whether or not surgical resection of pT1 adenocarcinoma is recommended; if surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high-risk features **(VI - A).”**

Adaptation of the revised Vienna classification[1] for colorectal cancer screening {2} **1. NO NEOPLASIA:[2]** Vienna Category 1 (Negative for neoplasia) **2. MUCOSAL LOW GRADE NEOPLASIA**: Vienna Category 3 (Mucosal low-grade neoplasia, Low-grade adenoma, Low-grade dysplasia); Other common terminology mild and moderate dysplasia; WHO: low-grade intra-epithelial neoplasia **3. MUCOSAL HIGH GRADE NEOPLASIA**: Vienna: Category 4.1–4.4 (Mucosal high grade neoplasia, High-grade adenoma/dysplasia, Non-invasive carcinoma (carcinoma in situ), Suspicious for invasive carcinoma, Intramucosal carcinoma); Other common terminology severe dysplasia; high-grade intraepithelial neoplasia; WHO: high-grade intraepithelial neoplasia TNM: pTis **4. CARCINOMA** invading the submucosa or beyond: 4a. Carcinoma confined to submucosa Vienna: Category 5 (Submucosal invasion by carcinoma); TNM: pT1 4b. Carcinoma beyond submucosa TNM: pT2-T4 [1] For revised Vienna classification see Dixon (2002), for WHO classification see WHO (2000), for TNM see (TNM

classification of malignant tumours, 5th edition 1997; TNM Classification of malignant tumours, 6th edition 2002; TNM Classification of Malignant Tumours, 7th edition 2009). [2] Category 2 of the Vienna Classification (indefinite) is not recommended for screening.

Importance: Critical

Transferability: Completely

Result card for CUR4: "Which are the known risk factors for acquiring adenomas and/or CRC?"

View full card

CUR4: Which are the known risk factors for acquiring adenomas and/or CRC?

Result

Different factors could **increase or decrease risk** for colorectal cancer (CRC) {1,3,4}.

Factor which **increased risk** for CRC are: environmental factors (prevalence is increased in developed countries, urban areas); advantaged socioeconomic groups; hypercholesterolemia; coronary artery diseases; low-fiber, high-animal-fat diets; obesity; smoking; acromegaly; sugar consumption; family history (risk is increased in first-degree relatives of patients, families with increased prevalence of cancer, patients with breast or gynaecologic cancer, familial polyposis syndromes);>10-year history of ulcerative colitis or Crohns colitis;>15-year history of uretherosygmoidostomy.

Risk is **decreased** with long term dietary calcium supplementation, vegetable, garlic, exercise, daily aspirin ingestion (after 5 years daily aspirin there is a 35% reduction in all GI cancers) and other NSAIDs.

Importance: Important

Transferability: Partially

Result card for CUR6: "What is the natural course of CRC?"

View full card

CUR6: What is the natural course of CRC?

Result

Most colon cancers arise from non-malignant adenomas in form of adenomatous polyps. Genetic steps from polyp to dysplasia to carcinoma in situ is defined (the adenoma-carcinoma sequence) (point mutation in K-ras proto-oncogene, hypomethylation of DNA leading to enhanced gene expression, allelic loss of tumour suppressor APC gene, allelic loss at DCC gene (deleted in colon cancer) on chromosome 18, and loss and mutation of p53 on chromosome 17 {1-3}.

Due such natural course, CRC is particularly suitable for screening. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. Adenomas are most often polypoid, but can also be sessile or flat. An adenoma grows in size and can develop high-grade neoplasia. At a certain point in time, the adenoma can invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms yet (preclinical). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed {1-3}.

In developed countries, approximately, 40.50% of the population develop one or more adenomas in a lifetime, but the majority of these adenomas will never develop into CRC. Only 5.6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is unobserved, but is estimated to take at least 10 years. This long latent phase provides an excellent window of opportunity for early detection of the disease. When detected in the adenoma-phase, removal of the adenoma can prevent the incidence of CRC. But even when detected as an early-stage cancer, prognosis is considerably better than for late-stage cancer {1-3}.

An adenoma is benign, dysplastic tumour of columnar cells or glandular tissue. They have tubular, tubulovillous or villous morphology. The likelihood of an adenoma being present increase with age. At the age of 60-70, 5% of asymptomatic subject will have a polyp of >1 cm, or cancer with no symptoms, and up to 50% will have at least one small<1cm adenoma {1-3}.

Removal of adenoma at colonoscopy and subsequent surveillance reduces the risk of development of colon cancer by approximately 80%. The remaining 20% are either newly formed, missed, or difficult to detect, e.g. flat adenoma.

About 5% of CRC have well defined single gen basis. Onset of cancer is earlier than in sporadic cases, at age 40-50 or younger {1-3}.

Importance: Critical

Transferability: Completely

Result card for CUR8: "What are the symptoms at different stages of adenomas and/or CRC?"

View full card

CUR8: What are the symptoms at different stages of adenomas and/or CRC?

Result

Symptoms of adenomas

Polyps in the rectum and sigmoid often present with rectal bleeding. More proximal lesion rarely produce symptoms and most are diagnosed on barium enema, CT colonography or on colonoscopy performed for screening. Large villous adenomas can present with profuse diarrhoea with mucus and hypocalcaemia {1-3}.

Colon cancer symptoms

Colon cancer of left-side presents most commonly with rectal bleeding, altered bowel habits (constipation, intermittent diarrhoea, tenesmus, narrowing), abdominal or back pain. Cecal and ascending colon cancers more frequently present with symptoms of anaemia (50% of right-sided lesions), occult blood in stool or weight loss. Possible complication varied from perforation, fistula, volvulus, inguinal hernia {1-3}.

Anal cancer accounts for 1-2% of large-bowel cancer. Women are more commonly affected than men. Presents with bleeding, pain, and perianal mass {1-3}.

Importance: Critical

Transferability: Completely

Result card for CUR9: "What is the burden of CRC?"

View full card

CUR9: What is the burden of CRC?

Result

Incidence, prevalence, survival

Colorectal cancer (CRC) is the 3rd most common cancer worldwide, and the second most frequent in developed countries {5}. In 2008, there were 1,234,000 estimated cases of CRC worldwide, the majority of which (60%) occurred in the most developed countries {6}. The disease is more common in westernized countries than Asia or Africa. The estimated age-standardized incidence rate [world age standardization (ASR-W)] of CRC in 2008 was 17.2 per 100,000 inhabitants; however, there are large variations between regions. Incidence rates are higher in Australia/New Zealand (39.0 per 100,000), Western Europe (33.1 per 100,000) and Southern Europe (31.1 per 100,000) and lower in Western Africa (4.9 per 100,000), South-Central Asia (4.5 per 100,000) and Middle Africa (3.7 per 100,000) {6}. The number of deaths due to CRC worldwide in 2008 was estimated at 608,000, equivalent to 8% of total cancer-related deaths. CRC was the third cause of cancer-related death in women (after breast and lung cancer) and the fourth (after lung, liver and stomach cancer) in men {6}. Estimated CRC age-standardized mortality rates (world age standardization) in both sexes were highest in Central and Eastern Europe (15.1 per 100,000) and lowest in Middle Africa (3.1 per 100,000) {6}. As the case in incidence, mortality from CRC is higher in men that in women.

Focusing on Europe, in 2008, CRC accounted for 12.4% of deaths caused by malignancy in European countries (11.5% and 13.5% of total cancer deaths in men and women respectively) {6}. It represented the second cause of cancer death for the total population, lung cancer being the first. The number of deaths attributed to CRC in Europe in 2008 was 212,219. According to estimates on cancer incidence in Europe {6}, in 2008 CRC was the most frequent malignancy in both sexes, comprising 13.5% of all newly-diagnosed carcinomas in the European population (men 13.5%, women 13.5%). Breast cancer and lung cancer were the 2nd and 3rd most frequent malignancies respectively (13.2% and 12.1% of all malignancies in both sexes). Overall, 432,414 people were estimated to have been newly diagnosed in 2008 with CRC in Europe. A more detailed analysis of individual diagnoses from 96 individual cancer registries in Europe for the period 1998-2002 identified malignant disease of the colon as the most frequent, accounting for 57% of all cases (> 35 cases/100,000 inhabitants), followed by malignant diseases of the rectum and rectosigmoid {5}.

Variations are observed in CRC incidence and mortality rates among European countries {6}. Age-standardized incidence rates estimates (European age standard) range from 106 per 100,000 in Hungary to 13.6 per 100,000 in Albania for men and from 55.6 per 100,000 in Switzerland to 21.3 per 100,000 in Greece for women. Estimated age-standardized mortality rates (ASR-W) were higher in Hungary, the Czech Republic and Slovakia and lowest in Iceland, Albania and Cyprus. The mortality rate for Europe was 13.3 per 100,000 population {6}. Part of the differences in CRC incidence and mortality can be explained by differences in lifestyle, screening practices and treatment patterns between countries {2}. However, a detailed comparison of data for European countries is made difficult because of the absence of unified data, as not all countries maintain population and cancer registers {5}. European funded projects such as EUROCARE have aimed at collecting standardised information.

In addition to CRC incidence and mortality, population-based survival is an important indicator for evaluating management of CRC {7}. Survival rates are strongly associated with stage of CRC at diagnosis (see related Table in CUR2). Data on cancer survival for European countries are available through various national and/or regional cancer registries and through the EUROCARE (European cancer registry-based study of cancer patients' survival and care) study. 5-year relative CRC survival rates in 2004-2009 for European countries for which data were available varied from 38.6% in Latvia to 66.1% in Iceland as is depicted in Table 1. There are significant differences in relative survival rates between European countries. CRC survival disparities have also been observed within countries between geographical regions and ethnic or racial groups {7-9}.

Table 1: Colorectal cancer five-year relative survival rate, 2004-2009 (or nearest period)

Age-sex standardised rate per 100 patients

	2004-2009		
	Value		95% CI deviation
Belgium	64.7		1.8
Austria	63.1		1.9
Finland	61.8	2003-08	1.1
Netherlands	61.0		1.2
Sweden	60.7		1.0
Germany	60.4	2003-08	0.8
Portugal	57.4		0.0
Slovenia	55.8		3.2
Denmark	55.5		2.1
United Kingdom	53.3		0.6
Ireland	52.9		1.6
Czech Republic	49.6	2003-08	0.7
Latvia	38.6		4.2
Norway	63.1		1.7
Iceland	66.1	2003-08	9.5
Source: OECD Health Data 2012			

An important source of information regarding CRC survival rates in Europe are the findings of the EUROCARE study, which began in 1989 and is the most extensive population study monitoring relative survival rate (RSR) {5}. Its aim is to measure and explain international differences in cancer survival in Europe, by using standard definitions, quality control and standard analytic techniques and taking into consideration the demographic variables and background mortality in the participating countries {10}. The indicator that is predominantly used is the 5-year relative CRC survival rate, defined as "the ratio of the recorded survival to the expected survival in the general population of the same age and sex" {7}. The most recent publications include data up to the EUROCARE-4 round, which collected information from 83 cancer registries in 23 European countries on adults diagnosed with cancer in 1995–99 and followed up to December 2003. According to the study results {7}, mean European age-adjusted 5-year relative survival of both sexes for colorectal cancer was 53.8% [95% CI 53.3-54.1]. CRC 5-year survival was >57% in the Nordic countries (except Denmark) and some countries of central and southern Europe, but 51% in the UK. Relative survival rates in eastern European countries were lower (<45%). Survival, however, presents a continuous increase over the period of 1991–2002 in all countries, with the largest improvements observed in eastern European countries, thus, decreasing the gap between the various European areas {11}.

Trends in incidence, mortality and survival

In Europe, an increasing trend in average incidence of CRC has been observed in recent years (2001-2005) {5}. However, these trends have not been uniform. Analysis of cancer registries' data in 21 European countries from the mid-1990s to approximately 2005 {12} showed a modest increase on average in CRC incidence among males, whereas in women CRC incidence rates remained stable and even decreased in some countries. Internationally, CRC incidence rates have been stabilizing or declining in historically high-risk areas (United States, New Zealand, Canada), but rapidly increasing in several historically low-risk countries, including Japan, Korea, China, and Eastern European countries {13}.

Observed increases in cancer incidence might relate to increasing risk factors or improvements in the diagnosis and recording of cancer cases and early detection through population screening {12}. For example, the increase in incidence rates in several Asian and Eastern European countries as well as in Spain has been attributed largely to changes in risk factors (changes in dietary and physical activity patterns, smoking) that are most likely related to their westernization {12, 13}. In Japan both increased screening and the transition to a more westernized lifestyle with changes in dietary intake have been reported as the main explanatory factors for the increases in CRC incidence {14}. On the contrary, in the US the decrease in CRC incidence observed in the most recent time period is mainly attributed to detection and removal of precancerous lesions through screening {13}.

Regarding tends in CRC mortality, according to Eurostat data {15}, average mortality rates from CRC in 25 EU member-states fell from 22.2 per 100,000 population in 2000 to 20.5 per 100,000 in 2010. Inequalities, however, exist between European countries also in CRC mortality trends. Mortality rates decreased since the mid-1990s for men and women almost in all countries, the exceptions been Croatia, Poland, Lithuania (men), Slovenia (men) and Spain (men) {12}. The least favourable trends in those countries (in which CRC mortality was lowest in the past) probably reflect a convergence of lifestyle and dietary habits towards those in other European countries {16}. Tends in mortality rates reflect the effect of cancer care, screening and diagnosis as well as changes in incidence {17} .

Regarding CRC survival, data from the EUROCARE rounds have revealed improvements in average survival in the long-term {18}, {11}, {19}. Disparities in survival rates observed in earlier rounds seemed to narrow {7}. An analysis of data from 25 cancer registries in 16 European countries covering years of diagnosis from 1984 to 2002 {20}, concluded that for time periods from 1988–1990 to 2000–2002, CRC survival substantially increased over time in all European regions under

study[1] and for both sexes. Increase in survival was observed also for all age groups (15–59, 60–74 and 75+ years), with the exception of Eastern European countries were 5-year relative survival in those over 75 years fell. However, the increase in survival was less pronounced for older patients (75+ age group) than for younger ones (aged 15–59 and 60–74) in all other European regions except Central Europe. Data from six countries in which registries included information on site and stage of diagnosis suggest that survival benefits were also larger for patients in earlier than in more advanced cancer stages and for rectum than for colon cancer. However, the substantial variation of CRC survival between European countries that was observed in earlier EUROCARE studies (highest levels of 5-year relative survival in Central and Northern Europe, followed by South European countries and UK and England, and lowest levels in Eastern Europe), were found to have persisted.

Differences in survival and trends over time depend on several reasons including increased access to more effective treatment, better management of co-morbidity, treatment being more effective due to earlier diagnosis, and lead-time bias or over diagnosis {21}, {10}. During the last two decades both early detection and treatment of CRC have improved {15), {22}. Accuracy and utilization of diagnostic technologies have increased as well as awareness among patients and primary care physicians {20}. Technological advances in the treatment and perioperative care of CRC (for example adjuvant chemotherapy, new surgical techniques, preoperative radiotherapy) that became available have also contributed to improvements in CRC survival {22, 23}.

In the framework of EUROCARE, high resolution studies were undertaken in an effort towards interpreting the impact of the aforementioned factors. The rationale adopted is that, if survival differences persist after adjustment for stage at diagnosis, there is evidence to suggest that differences in treatment significantly affect survival {21}. These studies brought forward the impact on CRC survival of (between and within countries) variations in disease stage at diagnosis as well as variations in availability and use of effective diagnostic technologies and treatments {24-26} as referenced in {10}).

In the future, the number of new cases and deaths related to CRC are expected to increase. In specific, the International Agency on Research for Cancer (IARC) estimates the number of new CRC cases in Europe (in all ages) to rise to 502,000 in 2020, whereas the annual deaths from CRC in Europe are expected to rise to 248,000 {6}.

Burden of disease and Quality of life

According to WHO estimations {27}, in 2004, cancers were responsible for 151,461,000 Disability Adjusted Life Years (DALYs) in the European Region (11.3% of total DALYs). Trachea/bronchus/lung cancers, CRC and breast cancer were the main contributors, accounting for 19.1%, 11.1% and 10.2% of total DALYs due to cancer. Analysing the two components of DALYs, premature mortality was the main component for all cancer sites. DALYs in the European Region are projected to decrease to 116,729,000 in 2030, mainly due to the shift in age at death to older ages. The burden of disease due to CRC is estimated to follow this trend and decrease to 1,862,000 DALYs, corresponding to 11.7% of the total cancer burden.

Taking into consideration that both cancer and its treatment affect the physical and psychosocial condition of patients, policy-makers have been increasingly interested in evaluating the impact of cancer on patients' and survivors' quality of life (QoL) {28}. Until recently, there has been little research on the effects of long-term (≥5 years) survival from colon cancer on survivors' health status {29, 30}. Available evidence relates mainly to studies on patients during the treatment phase or the first years after diagnosis {31, 11}. Cross-sectional studies have shown that during the early years of diagnosis and treatment, CRC patients have poorer outcomes in terms of QoL, productivity losses and self-rated health than similar individuals with no history of cancer. They also report higher levels of psychological disability and problems with activities of daily living than controls {32,33,28, 34}.

In long-term (≥5 years) CRC survivors considered as cured (without recurrence or metastasis), overall QoL is similar to that of the general population; nevertheless, specific physical and psychosocial problems such as fatigue, dyspnea, insomnia, bowel problems and deficits in emotional and social functioning persist over time and are also reported by survivors even 10 years after diagnosis {35,29, 36,37,38}.

In a prospective population-based cohort study from Germany {30}, long-term development of QoL depended on age at diagnosis. Younger survivors were found to report continuously substantial deficits in role, cognitive, emotional, and social functioning as well as presence of long-lasting symptoms in comparison to controls throughout the study period. In older survivors QoL was comparable to that of the general population during the first (1 to 3) years after diagnosis, however, QoL dimensions related to functioning, symptoms and problems worsened significantly between 3 and 10 years after diagnosis which suggests that detriments in older survivors become apparent in the long run. Global QoL scores of survivors were comparable to population norms regardless of duration of follow-up and despite the presence of limitations.

[1] Northern Europe: Sweden, Norway, Finland, Iceland; Southern Europe: Italy, Slovenia; Central Europe: Austria, France, Germany, the Netherlands, Switzerland; Eastern Europe: Poland, Slovakia; UK: Scotland, England, Wales.

Comment

As was noted, not all countries maintain population and cancer registers, therefore detailed comparisons are difficult. Data on incidence and mortality were extracted from the database of the GLOBOCAN project (International Agency for Research on Cancer), which provides contemporary estimates of these measures {6}. The most recent estimates are for 2008. Incidence data also derive from population-based cancer registries. More information on the GLOBOCAN data and sources are available on the project's website. Regarding CRC survival, results of the EUROCARE project were preferred as it is a projects that aims to describe and interpret differences in cancer patient survival in Europe. However, there are limitations to the project, already acknowledged by the researchers {21}. The reader should keep in mind that not all European countries are involved in the EUROCARE project. Furthermore, for several countries cancer registration covers only a fraction of the total national population. The first round (EUROCARE-1) included 30 cancer registry populations diagnosed from 12 European countries. During the rounds that followed more regional and national registries participated. The current, fifth round (EUROCARE-5) includes data from 116 Cancer Registries in 30 European countries and for patients diagnosed during 2000-2007 {39}. Strengths, limitations and the value of findings are discussed in detail by the researchers {21, 40}.

Importance: Critical

Transferability: Partially

Result card for CUR11: "What aspects of the burden of CRC are targeted by CRC screening with FIT?"

View full card

CUR11: What aspects of the burden of CRC are targeted by CRC screening with FIT?

Result

CRC screening in general aims to reduce morbidity and mortality from CRC through both, *prevention* (by the removal of adenomas before they become malignant) and *earlier diagnosis* of CRC (at early, curable stage). CRC is particularly suitable for screening due to natural course of disease (adenoma-carcinoma sequence). When detected in the adenoma-phase, removal of the adenoma prevents the incidence of CRC; when detected as an early-stage cancer, prognosis is considerably better than for late-stage cancer. An increase in incidence in the target age range may be observed immediately after the introduction of a CRC screening programme, however, incidence rates should return to background level at re-screening apart from the advancement of the age of diagnosis by screening {43}. For the individual, CRC screening in general can prevent the negative impact of CRC morbidity on quality-of-life {44}. As cancer treatment also represents a significant economic cost for the health system, CRC screening also results in cost-savings ({45} cited by {5}).

There are various methods available for colorectal cancer screening (see Result card CUR22). They can be broadly divided into endoscopic and radiologic methods (for example colonoscopy) and stool-based tests (guaiac-based or immunochemical Faecal occult blood tests - FOBTs, Faecal DNA testing) {42}. Routine screening of stool for occult blood may facilitate early detection.

Guaiac-based Faecal Occult Blood (gFOBT) tests are those mostly studied in RCTs as screening test for CRC and are an established screening strategy for CRC. Several large randomized studies have demonstrated a reduction in cancer-related mortality. In three systematic reviews of RCTs using gFOBT for CRC screening, a reduction of 14 - 16 % in CRC mortality was found {46, 47, 48} as referenced in {49}. In a matched-cohort study in Scotland, a reduction of 10% in CRC mortality was found {50}. The disadvantage of screening with gFOBT is relatively low sensitivity (many negative colonoscopies). gFOBT sensitivity is only around 50% for carcinoma; specificity for tumour or polyp around 25-40%. In FOBT screen-positive patients in the UK National Bowel Cancer Screening Programme (NHS BCSP) about 10% have cancer, 40% have adenomas and the colon is normal in 50%. False positive results of gFBOT tests are related to ingestion of red meat, iron, aspirin, upper GI bleeding. False negatives can be produced by vitamin C ingestion, intermittent bleeding. The dietary requirements for people preparing for screening with gFBOT may limit patient acceptance {51}.

As it the case with gFOBTs, a range of immunochemical tests are available with varying sensitivity and specificity (5). It has been argued that, since efficacy of gFOBT has already been demonstrated, decisions on screening with FITs can be based on the performance characteristics of the tests (sensitivity, specificity, positive predictive values) {44}. Performance characteristics are addressed in subsequent domains FITs can also be used as a "reflex" test, after primary screening with gFOBT. Available data on this screening strategy, from either research studies or screening programmes is limited {44} .

Importance: Critical

Transferability: Completely

Target Population

Result card for CUR10: "What is the target population for colorectal carcinoma screening with FIT?"

View full card

CUR10: What is the target population for colorectal carcinoma screening with FIT?

Result

Target population for CRC screening includes asymptomatic people at average risk, of both genders, age 50-74. Similar age range is currently recommended by the Council of the EU for CRC screening (50-74 years), taking into account that over 100 million men and women in EU are in this age group. Persons in whom age is the only risk factor for CRC are considered to be at average risk {41}. Factors that place individuals at higher risk include a family history of CRC or adenoma, personal history of CRC or adenoma, and inflammatory bowel disease. There is evidence endorsing the provision of CRC screening to average-risk individuals, beginning at age 50, to detect cancers at a favourable stage before they have advanced to a potentially lethal disease state. Individuals in higher risk are not included in the target population in the present report. Recommendations may slightly differ for specific population groups, for example, in the US; the Institute for Clinical Systems Improvement (ICSI) recommends routine colorectal cancer screening for all average-risk patients 45 years of age and older for African Americans or American Indians {42}. In some cases, upper age limits are recommended. The U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF), recommends routine colorectal cancer screening continuing until age 75 years {42} .

In the absence of additional evidence, the age range for a screening programme with iFOBT can be based on the limited evidence for the optimal age range in gFOBT trials {2}. According to the EU Guidelines {2}, the best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (Level of the evidence IV). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (Level of the evidence VI - B).

Importance: Critical

Transferability: Partially

Result card for CUR26: "How many people belong to the target population in Europe?"

View full card

CUR26: How many people belong to the target population in Europe?

Result

The data about number of target population for colorectal cancer screening in Europe are retrieved from already published literature data and EUnetHTA JA2 Surveys conducted in 2013.

In EUnetHTA Partners Survey, data from only 9 countries was available, including data for two Italy regions. Only 1 Manufacturer responded on EUnetHTA JA2 Manufacturers survey.

According to the 2008 Report on the Implementation of the Council Recommendation on Cancer Screening (58), in 2008 the target group included approximately 136 million individuals suitable for CRC screening (aged 50 to 74 years). Of this number, 43% individuals came from 12 countries where CRC population screening was performed or being prepared on either national or regional levels; 34% came from 5 countries where national population screening has been implemented (Finland, France, Italy, Poland, and United Kingdom). In 7 EU countries, national non-population based screening was carried out, which covered 27% of the target population.

The target population in the countries for which information was provided through the EUnetHTA JA2 Survey (2013) is :

Croatia ≈ 1,320,000	**Italy (Lazio region)** 1,649,561 (2012)	**Italy (Veneto Region)** 1,210,000 (2012)	**Slovenia** ≈ 540.000	**France** 16-17 million
Romania 4,926,951 for the 2013 plan	**Spain** 10,851,924 (2013)	**Lithuania** 904,872	**Luxembourg** at least 185,000	**Russia** About 1/3 of the population 45+

Importance: Critical

Transferability: Not

Utilisation

Result card for CUR12: "Which countries use FIT for CRC screening?" and CUR13: "Which percentage of target population is accually screened in countries with CRC screening program with FIT?"

View full card

CUR12: Which countries use FIT for CRC screening?

Method

- Data for Greece were added by one of the domain Investigators (EK).

Result

A number of countries have organised CRC screening programmes (see CUR14), utilising different strategies. FOB testing is a widely implemented strategy, however there are differences in the type of tests used (gFOBT or iFOBT). From the information provided via the EUnetHTA members' survey, use of immunochemical testing (FIT) was reported in 5 out of 11 (i. e. Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia) European countries. In specific, FIT is used in the Regions of Veneto and Lazio in Italy, Lithuania, Russia, Slovenia and Spain. In Austria, FIT is used only in one province (Burgenland).

According to data (May 2008) from the International Cancer Screening Network {52}, CRC screening programmes utilising immunochemical techniques had been implemented in Hungary (2 pilots) and Italy. In Italy, the majority of programmes use FIT, a limited number offer flexible sigmoidoscopy (FS) once in a lifetime and FIT for non-responders to FS {53}.

Outside of Europe, FIT is the preferred method for CRC screening in Japan {54} and Australia {51}. In Canada, 3 out of 7 provinces (B. Columbia, Saskatchewan and Nova Scotia) implementing CRC screening programs with FOBTs as the entry method were utilising a FIT test {55}.

Importance: Important

Transferability: Partially

CUR13: Which percentage of target population is accually screened in countries with CRC screening program with FIT?

Result

Please see also ORG Domain.

Uptake or participation rate is defined in the European guidelines on CRC screening as *"the number of people who have been screened, within a defined time frame following an invitation, as a proportion of all people who are invited to attend for screening"* {43}. Participation rate is an early performance indicator as it is important for the overall effectiveness and cost-effectiveness of the CRC screening programme. European Guidelines {43} consider a minimum uptake of at least 45% as acceptable, however, it is recommended to aim for a participation rate of at least 65%.

Participation rates in FIT-based screening

Participation rates in various CRC screening programmes (pilot programmes, established programmes) in Europe and abroad are presented in the following Table 1.

Table 1: Participation rates in CRC screening with FIT

Country/Region	Participation rate	Source
Established population - based CRC screening programmes		
Burgenland, Austria	35%	EUnetHTA Members Survey
Japan	17% (2002)	(54)
Tuscany, Italy	41% (1st round) (2001)	(44)
Lazio Region, Italy	30% (2011)	EUnetHTA Members Survey
Veneto Region, Italy	63.8% (2012)	EUnetHTA Members Survey
Lithuania	16.4%	EUnetHTA Members Survey
Russia	n.a. (programme established in 2013)	EUnetHTA Members Survey
Slovenia	1st screening round: 49.8%	EUnetHTA Members Survey
Spain	Catalonia 2000-2008: 14.4% adherence to screening recommendations, 18.4% were occasionally adherent	EUnetHTA Members Survey
Pilot CRC screening programmes		
Australia	45.5% (2002-2004)	(56)
Netherlands	60% (1st round; 2006-2007)	(44)

Participation rates in gFOBT-based screening

In a review by the Irish Health Information and Quality Authority {44}, uptake (the proportion of individuals who complete a screening test in a particular screening round) of CRC screening using the gFOBT in the 1st round of pilot screening programmes ranged from 47% in the Netherlands to 55% in Scotland. Uptake increased to 53% and 55% in the 2nd and 3rd round respectively in the pilot from Scotland. Similar rates were reported in a 3-round pilot in France.

Data from the survey conducted in the framework of the present report provided additional information on participation rates in national population-based CRC screening programmes in France (for the period 2010-2011 participation rate was approximately 32%) and Croatia (19.9%).

Importance: Critical

Transferability: Partially

Result card for CUR14: "What kind of variations in use of CRC screening methods are there across countries/regions/settings?"

View full card

CUR14: What kind of variations in use of CRC screening methods are there across countries/regions/settings?

Result

Population-based screening requires the identification and personal invitation of each person in the eligible target population (by an office or special agency). There are a number of established CRC screening programmes worldwide. Other countries are implementing pilots or considering the introduction of screening programmes {52, 57}. Several variations exist among the various programmes. Dimensions in which the programmes may differ include for example: population targeted (age groups targeted most often include persons aged ≥50 years), screening interval, monitoring mechanisms, methods of contacting eligible population, location of testing etc. The primary method used for screening also varies between countries. The following Table provides an overview of the screening strategies employed in European countries. It is based on data from First Report on the implementation of the European Council Recommendation on cancer screening {58}. Data were updated in the cases where more recent information was found.

Table 1: Overview of CRC screening practices in European countries

Country	CRC screening programme	Target population (eligible age in years)	Screening strategy	Screening interval (years or times in LT)	Source
Austria	Natw, opp	50+	colonoscopy	10	EUnetHTA Survey 2013
			FOBT (gFOBT)	1 or 2	EUnetHTA Survey 2013
	Pop-b (province of Burgenland)	50+	FOBT (FIT)	1	EUnetHTA Survey 2013
Belgium	Natw, pop-b	n.a.	FOBT/CS	n.a.	(59) (status in 2011)
Bulgaria	Natw, opp	31+	FOBT	1	(58) (status in 2007)
Cyprus	Natw, pop-b	n.a.	colonoscopy	n.a.	(59) (status in 2011)
		n.a.	FOBT (gFOBT)	n.a.	
Croatia	Natw, pop-b	50-74	FOBT (gFOBT)	2	EUnetHTA Survey 2013
Czech Republic	Natw, opp	50-54	FOBT	1	(57) (status in 2009)
		55+	FOBT (gFOBT)	2	
		55+	colonoscopy	10	
Denmark	Natw, pop-b	n.a.	FOBT/CS	n.a.	(59) (status in 2011)
Estonia	Pop-b, planned	n.a.	FOBT	n.a.	(60)
Finland	Natw, pop-b	60-69	FOBT	2	(58) (status in 2007)
France	Natw, pop-b	50-74 with no symptoms of CRC and moderate risk of CRC.	FOBT (gFOBT*)	2	EUnetHTA Survey 2013
Germany	opp	50-55	FOBT (gFOBT)	1	(57) (status in 2009)
		55+	FOBT (gFOBT)	2	
		50+	colonoscopy	10	
Greece	opp	50-70	FOBT	2	Ministerial Decision (Government Gazette B 3054/2012)
		50+	Colonoscopy	10	
Hungary	Pop-b, natw pilot	50-70	FOBT	2	(58) (status in 2007)
Ireland	Pop-b	n.a.	FOBT	n.a.	(59) (status in 2011)
Italy	Regional variations	50-69 (70-75)	FOBT only 1 out of 21 programmes proposes flexible sigmoidoscopy (FS) once in a lifetime to subjects 60+ and FIT for non-responders to FS	2	(58) (status in 2007)
Italy (Lazio Region)	Pop-b	50-74	FOBT (FIT)	2	EUnetHTA Survey 2013
Italy (Veneto Region)	Pop-b	50-69	FOBT (FIT)	2	EUnetHTA Survey 2013
Latvia	Natw, opp	50+	FOBT	1	(58) (status in 2007)
Lithuania	Natw, pop-b	50-75	FOBT (FIT)	2	EUnetHTA Survey 2013
Luxembourg	Opp natw pop-b planned	50+	FOBT	2	EUnetHTA Survey 2013
		50+	colonoscopy	10	

Malta	Pop-b	n.a.	FOBT	n.a.	(59) (status in 2011)
Netherlands	No prog				(58) (status in 2007)
Poland	Natw, pop-b	50-65	colonoscopy	10	(58) (status in 2007)
Portugal	Pop-b, natw planned	50-70	FOBT	2	(58) (status in 2007)
Romania	Pop-b, natw planned	50-47	FOBT	2	EUnetHTA Survey 2013
Russia	Pop-b	Certain age groups 45+ The programme is planned to cover the total population over 45 y. o. in 2016.	FOBT (FIT)		EUnetHTA Survey 2013
Scotland	Pop-b	50-74	FOBT (gFOBT) FIT as a reflex test	2	EUnetHTA Survey 2013
Slovak Republic	Opp, natw	50+	FOBT		(58) (status in 2007)
	Opp, natw planned	50+	colonoscopy	10	
Slovenia	Natw, pop-b	50-69	FOBT (FIT)	2	EUnetHTA Survey 2013
Spain	Pop-b: Catalonia, Valencia, Murcia, Canary Islands, La Rioja and Basque Country opp: rest of Spain	50-69	FOBT (FIT)	2	EUnetHTA Survey 2013
Sweden	Pop-b, regional planned	60-69	FOBT	2	(58) (status in 2007)
England	Pop-b, natw	50-75	FOBT	2	(57) (status in 2009)

* France: Although gFOBT is still considered as the reference test, a switch to FIT is recommended and encouraged by national authorities. The Cancer plan 2009-2013, sets the goal odf "Gradually roll out use of the immunological test for colorectal cancer screening to the whole of the country". 7 regions tried using FIT for the national screening programme: Alsace, Aquitaine, Lorraine, Midi-Pyrénées, Pays de la Loire, Picardie, Rhône-Alpes.

Abbreviations: pop-b (population-based), opp (opportunistic), no prog (no programme), natw (nationwide), pilot (piloting), plan (planning)

In CUR14-Appendix 1, epidemiological data on CRC are presented for groups of countries according to CRC screening practices.

Comment

The text in this Assessment Element describes CRC screening programmes targeting individuals at average risk for CRC (which is the scope of the current report). Screening programmes for high-risk individuals are not discussed.

Importance: Important

Transferability: Partially

Current Management of the Condition

Result card for CUR15: "How are adenomas/CRC currently diagnosed?" and CUR16: "How are adenomas/CRC currently screened?"

View full card

CUR15: How are adenomas/CRC currently diagnosed?

Result

Various technologies are available for the diagnosis of adenomas and CRC {1-3}.

Colonoscopy is the gold standard and allows biopsy for histology. Biopsy is mandatory, usually at endoscopy. Double-contrast barium enema can visualize the large bowel; now it is superseded by CT colonography. Endoanal ultrasound and pelvic MRI are used for staging rectal cancer. Chest, abdominal and pelvic MRI scanning

are utilised to evaluate tumour size, local spread and liver and lung metastases. PET scanning is performed for detecting occult metastases and for evaluation of suspicious lesions found on CT or MR. MR is also useful for evaluating suspicious lesion found on CT or US, especially in the liver. CEA is useful for follow-up, rising level suggest recurrence {1-3}.

FOBTs are used for mass population screening and are of value in hospital or general practice. Early diagnosis by screening asymptomatic persons with FOBT, >50% of all colon cancers are within reach of a 60-cm flexible sigmoidoscope; air-contrast barium enema will diagnose around 85% of colon cancer not within reach of sigmoidoscope; colonoscopy is most sensitive and specific, permits tumour biopsy and removal of synchronous polypus, but is more expensive. Radiographic or virtual colonoscopy has not been shown to be better diagnostic method than colonoscopy {1-3}.

Annual digital rectal exam and FOBT are recommended for patients over age 40, screening by flexible sigmoidoscopy every 3 years after age 50; careful evaluation of all patients with positive occult blood test (flexible sigmoidoscopy and air-contrast barium enema or colonoscopy alone) reveals polyps in 20-40% and carcinoma in around 5%.

Importance: Important

Transferability: Partially

CUR16: How are adenomas/CRC currently screened?

Result

Several screening tests for CRC are available, classified according to three categories {61}:

Stool-based techniques: Faecal occult blood test (FOBT) (either guaiac, so called gFOBT and immunochemical, so called FIT); Faecal DNA testing. **Endoscopic techniques**: Optical colonoscopy, Flexible sigmoidoscopy (FS). **Imaging techniques**: Virtual colonoscopy techniques using: a) Computed tomographic colonography (CT colonography), b) Magnetic resonance colonography (MR colonography); Wireless capsule endoscopy (PillCam Colon); Double-contrast barium enema (DCBE). **Faecal DNA tests** represent a new group of fecal tests designed to detect molecular abnormalities in cancer or precancerous lesion that are shed into the stool. Two faecal DNA tests were commercially available: **PreGen Plus**, from 2003 to 2008, and **ColoSure** (single marker faecal DNA assay for methylated vimentin), intended for individuals who are not eligible for more invasive CRC screening. New test showed evolution in the composition of the test, as well in pre-analytical factors and analytic factors in comparison with older faecal DNA tests. Authors of the 2012 AHRQ HTA Report concluded that faecal DNA tests have insufficient evidence about its diagnostic accuracy to screen for colorectal cancer in asymptomatic, average-risk patients; insufficient evidence for the harms, analytic validity, and acceptability of testing in comparison to other screening modalities. Existing evidence has little or no applicability to currently available faecal DNA testing {62}.

Importance: Important

Transferability: Partially

Result card for CUR17: "How should adenomas/CRC be diagnosed or screened according to published algorithms/guidelines?"

View full card

CUR17: How should adenomas/CRC be diagnosed or screened according to published algorithms/guidelines?

Result

Results {1-3}

EU Guideline 2010 {2}

According the EU Guideline 2010, "iFOBT have improved test characteristics than gFOBT, and they are currently the test of choice for population CRC screening. In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme (Level of evidence II, Grade of recommendation A).

Adoption of test device and the selection of a cut-off concentration should follow a local pilot study to ensure that chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable (Level of evidence VI, Grade of recommendation A).

Maximum period between collection and analysis is significantly shorter than for gFOBT (14-21 days), and screening programmes should adopt the conditions and period of storage described in manufacturer’s Instructions for use and should be appropriate for local conditions which might expose samples to high temperatures for long period of time (Level of evidence III, Grade of recommendation A).

Despite the fact that dietary constituents present potential interference in gFOBT, dietary restriction has not been demonstrated to significantly increase screening specificity and risks reducing participation rate. The potential for dietary interference is significantly less for iFOBT. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported, dietary restriction is not indicated for programmes using either gFOBT or iFOBT (Level of evidence II, Strength of recommendation D).

Some drugs which could cause GI bleeding like aspirin, NSAIDs and anticoagulants present potential interference in gFOBT and iFOBT, drug restriction is not recommended for population screening programmes using either gFOBT or iFOBT (Level of evidence III, Strength of recommendation D).

Since many factors influence the uptake and reliability of sample collection, a local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable (Level of evidence VI, Grade of recommendation A).

The number of laboratory sites (analytical centres) should be minimised with automated analytical systems utilised whenever possible and agreed common testing procedures adopted by each centre, since the analysis need to be reproducible across screening population. The samples should be analysed without delay to avoid further sample denaturation and avoid an increase in false negative results. Inter-laboratory analytical imprecision can be observed through established external quality assurance schemes. Common analytical platforms, analytical and quality standards and shared staff training will improve consistency. (Level of evidence VI, Grade of recommendation B).

All laboratories providing population screening should be led by a qualified clinical chemist trained and experienced in the techniques used for analysis and with clinical quality assurance procedures (Level of evidence VI, Grade of recommendation B).

All laboratories providing screening service should be associated with a laboratory accredited to ISO 15189:2007 Medical laboratories-Particular requirements for quality and competence. Also they should perform Internal Quality Control procedures and participate in appropriate External Quality Assessment Scheme (Level of evidence VI, Grade of recommendation B).

Distribution of FOBT kits by mail, using local postal service is an effective way of reaching the designated population (Level of evidence II, Grade of recommendation B).

Automated check protocols should be implemented to ensure correct identification of the screen population and complete and accurate recording of individual screening participation and test results. Protocols should be implemented to ensure standardised and reliable classification of the test results (Level of evidence VI, Grade of recommendation A).

Quality assurance of iFOBT

Manufacturer’s Instructions for Use must be followed. Daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit should be performed. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures. Performance data (both internal quality control and external quality assessment data) should be shared and reviewed by a Quality Assurance team working across the programme. (Level of evidence VI, Grade of recommendation B).

All laboratory performance outcomes like uptake, undelivered mail, time from collection to analysis, analytical performance, positivity rates, lots and spoilt kits and technical failure rate, technical performance variability and bias should be each subject to rigorous monitoring (Level of evidence VI, Grade of recommendation A).

The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (Level of evidence III, Grade of recommendation A)."

Box 1. Some published Guidelines on adenomas/CRC screening and diagnosis

EU Guideline 2010 {2}	
Screening	iFOBT have improved test characteristics than gFOBT, and they are currently the test of choice for population CRC screening. In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme (Level of evidence II, Grade of recommendation A).
Diagnosis	Colonoscopy as recommended test for follow-up investigation for individuals who have tested positive with other CRC screening tools (FOBT, Flexible sigmoidoscopy (FS), and also in experimental studies assessing potential screening tools, e.g. DNA faecal markers and CT colonography).
NICE Guideline 2011 {63}	
Screening	NA
Diagnosis	Colonoscopy for patients without major comorbidity, to confirm a diagnosis of colorectal cancer; a biopsy to obtain histological proof of diagnosis (unless it is contraindicated); Flexible sigmoidoscopy then barium enema for patients with major Comorbidity; Computed tomographic (CT) colonography as an alternative to colonoscopy or flexible sigmoidoscopy then barium enema, if the local radiology service can demonstrate competency in this technique (if a lesion suspicious of cancer is detected on CT colonography, a colonoscopy with biopsy should be offered to confirm the diagnosis (unless it is contraindicated)
SIGN Guideline 2011 {64}	
Screening	Screening colonoscopy for all patients with ulcerative colitis or Crohn's colitis of 10 years duration;

	Surveillance colonoscopies should be performed yearly, 3-yearly or 5-yearly according to risk-stratification; Patients who have undergone colonoscopic polypectomy for adenomas should be offered follow-up colonoscopy based on risk stratification; Patients with one or two adenomas <1 cm in size without high-grade dysplasia are at low risk and only require follow-up colonoscopy at five years if other factors indicate the need for further surveillance (if no polyps are found, further surveillance is not required); The presence of either 3-4 small adenomas (<1 cm), or one adenoma >1 cm in size confers an intermediate risk, and surveillance colonoscopy should be undertaken at three years (if surveillance colonoscopy is subsequently normal on two consecutive occasions, it may cease); Patients with ≥5 small adenomas or ≥3 adenomas with at least one polyp ≥1 cm in size are at high risk, and should undergo colonoscopy at one year.
Diagnosis	Colonoscopy is recommended as a very sensitive method of diagnosing colorectal cancer, enabling biopsy and polypectomy.
	CT colonography can be used as a sensitive and safe alternative to colonoscopy.
Canadian Guideline 2011 {65}	
Screening	For opportunistic colorectal cancer screening: annual or biennial FIT, flexible sigmoidoscopy every 10 years and colonoscopy every 10 years. Faecal DNA testing, computed tomography (CT) colonography, and double-contrast barium enema are not recommended for either programmatic or opportunistic colorectal cancer screening.
USA Guidelines {66-68}	
Screening	The US Preventive Services Task Force (66) and American College of Gastroenterology (67) recommendations similar the Canadian; the US Multi-Society Task Force (68) differs from Canadian by including faecal DNA testing and CT colonography; flexible sigmoidoscopy is recommended at an interval of every five years

In the majority of jurisdictions in the EUnetHTA survey in 2013, local and/or regional guidelines or recommendations on CRC screening were reported (Box 2).

Box 2. EUnetHTA survey (2013) about adenomas/CRC screening/diagnosis in different MSs

Austria No national guideline. A voluntary quality assurance program for screening colonoscopy is in place (partners: Main Association of Social Security Institution and Austrian Society for Gastroenterology and Hepatology OeGGH). **Russia** Russian Gastroenterology Association Guidelines. **Luxembourg** European guidelines for quality assurance in colorectal cancer screening and diagnosis. **Lithuania** National guidelines. **Italy (Lazio and Veneto Region)** National and regional recommendations on the basis of European guidelines. **Scotland** Guidance is provided by the UK National Screening Committee. **Spain** Grupo de trabajo de la guía de práctica clínica de prevención del cáncer colorrectal. Actualización 2009. Guía de práctica clínica. Barcelona: Asociación Española de Gastroenterología, Sociedad Española de Medicina de Familia y Comunitaria, y Centro Cochrane Iberoamericano; 2009. Programa de Elaboración de Guías de Práctica Clínica en Enfermedades Digestivas, desde la Atención Primaria a la Especializada: 4 **France** Guidance for good practice by HAS (updated in June 2013). The document contains epidemiological data, general description of the screening programmes, algorithms for different groups at risk. **Croatia** National Programme for CRC Screening. **Slovenia** 2003 guidelines (currently being updated).

Importance: Important

Transferability: Partially

Result card for CUR18: "How are adenomas/CRC currently managed?"

View full card

CUR18: How are adenomas/CRC currently managed?

Result

Results {1-3}

Treatment

Adenoma

Removal of adenoma at colonoscopy and subsequent surveillance reduces the risk of development of colon cancer by approximately 80%. The remaining 20% are either newly formed, missed, or difficult to detect, e.g. flat adenoma.

CRC

Treatment of CRC should be taken by multidisciplinary teams working in special units.

Long-term survival relates to the stage of the primary tumour and the presence of metastatic disease. Long-term survival is only likely when the cancer is completely removed by surgery with adequate clearance margins and regional lymph node clearance.

Local disease

Surgical resection of colonic segment containing tumor (preoperative evaluation to assess prognosis and surgical approach includes full colonoscopy, chest RTG, biochemical liver tests, plasma CEA level, and possible abdominal CT). Resection of isolated hepatic metastases possible in selected cases.

Rectal carcinoma

Adjuvant radiotherapy to pelvis (with or without concomitant 5FU chemotherapy) decreases local recurrence rate of rectal carcinoma, radiation may improve resectability and local control in patients with rectal cancer. Total mesorectal excition is more effective than conventional anteroposterior resection in rectal cancer.

Adjuvant chemotherapy (5FU/leucovorin plus oxaliplatin, or FOLFOX plus bevacizumab, or 5FU/leucovorin plus irinotecan, or FOLFIRI) decreases recurrence rate and improves survival in stage C (III); survival benefit is not clear in stage B (II) tumours; periodic determination of serum CEA level useful to follow up therapy and assess recurrence.

Follow up after curative resection: yearly liver tests, complete blood count, follow-up radiologic or routine screen interim; if polyps detected, repeat 1 year after resection.

Advanced tumours (locally unresectable or metastatic)

Systemic chemotherapy (5FU/leucovorin plus oxaliplatin plus bevacizumab), irinotecan usually in second treatment; antibodies to the EGF receptor (cetuximab, panitumumab for those with wild type KRAS and BRAF genes) appear to enhance the effect of chemotherapy to 68% and the median survival from 14 to 24 months; intraarterial chemotherapy (floxuridine (FUDR) and/or radiation therapy may palliate symptoms from hepatic metastases.

With appropriate selection of patients with a good performance status and in whom MRI and PET-CT scans do not demonstrate extrahepatic disease local treatment can prolong good quality survival (with surgical resection to gamma knife irradiation, radiofrequency, or cryoablation, or hepatic artery embolization. Small lesion can be ablated; larger lesions are best managed by partial hepatectomy or a combination approach: embolization is followed by hepatic regeneration before final resection. Long-term survival without recurrence is reported up to 20% of patients at 5-years with a single <4 cm lesion.

Advanced CRC is successfully palliated with little toxicity by 5FU and folinic acid regiments or oral capecitabine in approximately 30% of patient with a median of 12-14 months. The addition of irinotecan or oxaliplatin increases the proportion that benefit to 55% and extended median survival to 18 months but with increased toxicity.

Anal cancer

Radiation therapy plus chemotherapy (5FU and mitomycin) leads to complete response in 80% when the primary lesion is <3 cm. For patients with large lesions or whose disease recurs after chemoradiotherapy, abdominoperineal resection with permanent colostomy is reserved.

Based on responses from the survey in EUnetHTA members in 8 countries for which information was available (Russia, Luxembourg, Lazio and Veneto Region in Italy, Spain, Romania, France, Croatia, Slovenia), management involves the treatment approaches described in the European guidelines for quality assurance in colorectal cancer screening and diagnosis. In 4 cases direct reference to European and/or international guidelines was made.

Importance: Important

Transferability: Partially

Result card for CUR20: "How should adenomas/CRC be managed according to published algorithms/guidelines?"

View full card

CUR20: How should adenomas/CRC be managed according to published algorithms/guidelines?

Result

Answers could be found also in previous Results card, CUR18.

Standard treatment options for Stage 1 and II colon cancer include wide surgical resection and anastomosis. The potential value of adjuvant chemotherapy for patients with Stage II colon cancer remains controversial. Standard treatment options for Stage III colon cancer include surgery and adjuvant chemotherapy. Chemotherapy is also used for Stage IV and recurrent colon cancer treatment. Different drugs are available that are used alone and in combination with other drugs in different chemotherapy regiments. The best way to combine and sequence these agents is still not established. Management according to some guidelines {2,63,64}

is summarised in the following Table 1. Due the fact that the best way to combine and sequence these agents is still not established, guidelines described below are slightly different according regiments used in 1st- or 2nd -line treatment.

Table 1. Management of adenomas/CRC according the guidelines

NICE Guideline, 2011 {**63**}	
	Stage I colorectal cancer
	Surgical resection, with further treatment to patients whose tumour had involved resection margins (less than 1 mm)
	The colorectal multidisciplinary team (MDT) should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer, taking into account pathological characteristics of the lesion, imaging results and previous treatments.
	Follow-up after curative resection
	Regular surveillance with: a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years and regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).
	Advanced and metastatic colorectal cancer
	FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
	FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
	XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment
SIGN Guideline, 2011 {**64**}	
	Laparoscopic and open surgery can be offered for resection of colorectal cancer.
	All patients with Stage III colorectal cancer should be considered for adjuvant chemotherapy
	Combination treatment with 5-FU/leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/leucovorin/irinotecan is the preferred options in patients with good performance status and adequate organ function.
	Consider raltitrexed for patients with metastatic colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable.
	Second line chemotherapy should be considered for patients with metastatic colorectal cancer with good performance status and adequate organ function.
	Irinotecan should be used as second line therapy following first line oxaliplatin (or vice versa).
	Cetuximab should be considered in combination with 5-FU/leucovorin/ oxaliplatin or 5-FU/leucovorin/irinotecan chemotherapy for patients with unresectable liver metastases if patients fulfil the SMC criteria.
	Rectal cancer
	Patients considered to have a moderate risk of local recurrence with total mesorectal excision surgery alone, and in whom the CRM is not threatened or breached on MRI, could be considered for preoperative radiotherapy (25 Gy in five fractions over one week) and immediate TME surgery.
	Patients who require down staging of the tumour because of encroachment on the mesorectal fascia should receive combination chemotherapy and radiotherapy, (BED >30 Gy) followed by surgery at an interval to allow cytoreduction.
EU Guideline, 2010 {2}	
	General requirements for treatment of colorectal cancer and pre-malignant lesions Colorectal neoplasia should be managed by a multi-disciplinary team **(VI - A).** The interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised and in 95% of cases should be no more than 31 days **(VI - B).** Colonoscopy should always be done with therapeutic intent i.e. the endoscopist carrying out screening or follow-up colonoscopy should have the necessary expertise to remove all but the most demanding superficial lesions **(VI - A).** **Management of pre-malignant colorectal lesions**

Pre-malignant lesions detected at screening endoscopy should be removed **(III - A).**

Lesions that have been removed should be retrieved for histological examination (**VI - A).**

Colorectal lesions should only be removed by endoscopists with adequate training in techniques of polypectomy **(V - A).**

Large sessile lesions of the rectum should be considered for transanal surgical removal **(II - B).**

For large sessile rectal lesions, transanal endoscopic microsurgery (TEM) is the recommended method of local excision **(II - B).**

Consideration should be given to tertiary referral for patients with large sessile colorectal lesions **(V - B).**

Patients with large pre-malignant lesions not suitable for endoscopic resection should be referred for surgical resection **(VI - A).**

Appropriate precautions should be taken prior to endoscopic excision of colorectal lesions in patients on anticoagulants **(V - C).**

In patients with bare coronary stents, polypectomy should be delayed for at least one month from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**

In patients with drug-eluting coronary stents, polypectomy should be delayed for 12 months from placement of the stents, when it is safe to discontinue clopidogrel temporarily **(V - B).**

In patients with drug-eluting coronary stents, when early polypectomy is deemed essential, it can be delayed for only 6 months from placement of the stents, when it is probably safe to discontinue clopidogrel temporarily **(VI - C).**

Aspirin therapy can **(IV – C)** - and in patients with stents should - be continued prior to and during polypectomy **(VI – B).**

Management of pT1 colorectal cancer

If there is clinical suspicion of a pT1 cancer, a site of excision should be marked with submucosal India ink **(VI - C).**

Where a pT1 cancer is considered high-risk for residual disease consideration should be given to completion colectomy along with radical lymphadenectomy, both for rectal cancer **(II - A)** and colon cancer **(VI - A)**. If surgical resection is recommended, consideration should be given to obtaining an opinion from a second histopathologist as variation exists in evaluating high risk features **(VI - B).**

After excision of a pT1 cancer, a standardised follow-up regime should be instituted **(VI - A).** The surveillance policy employed for high-risk adenomas is appropriate for follow-up after removal of a low-risk pT1 cancer **(III - B).**

Management of colon cancer

If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or for any other reason for failure to complete colonoscopy, the rest of the colon should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 3 to 6 months of colectomy **(VI - B).**

Patients with a proven screen-detected cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(V - B).** Routine chest CT is not recommended **(III - D).**

Patients with screen-detected colon cancer that has not been adequately resected endoscopically should have surgical resection by an adequately trained surgeon **(III - A).**

Where appropriate, laparoscopic colorectal surgery should be considered **(I - A).**

Management of rectal cancer

If a complete colonoscopy has not been performed either because the primary lesion precluded total colonoscopy, or any other reason for failure to complete colonoscopy, the rest of the colorectum should be visualised radiologically before surgery if at all possible. This should be performed ideally by CT colography, or if this is not available, by high-quality double-contrast barium enema. If for any reason the colon is not visualised prior to surgery, complete colonoscopy should be carried out within 6 months to 1 year of excision of the rectal cancer **(VI - B).**

Patients with a proven screen-detected rectal cancer should undergo pre-operative staging by means of CT scanning of the abdomen and pelvis **(VI - B)**. Routine chest CT is not recommended **(III - D).**

Patients with a proven screen-detected rectal cancer should ideally undergo pre-operative local staging by means of MRI scanning of the pelvis in order to facilitate planning of pre-operative radiotherapy **(III - B)**, although high-quality multi-slice CT scanning may provide adequate information **(VI - C).**

All patients undergoing radical surgery for rectal cancer should have mesorectal excision **(II - A)** by an adequately trained specialist surgeon **(VI - A).**

Patients undergoing surgery for rectal cancer may be considered for laparoscopic surgery **(I - B).**

All patients undergoing surgery for rectal cancer (and certainly those predicted on imaging to have T3/4 cancers and/or lymph node metastases) should be considered for pre-operative adjuvant radiotherapy with or without chemotherapy **(I - A).**

	Local excision alone should only be performed for T1 sm1 rectal cancers, and if the patient is fit for radical surgery **(III - B).** In the patient in whom there is doubt about fitness for radical surgery, local excision of more advanced rectal cancer should be considered **(III - B).** In patients in whom local excision for rectal cancer is planned, consideration should be given to pre-operative CRT **(III - C).** If a local excision is carried out, and the pT stage is T1 sm3 or worse, then radical excision should be performed if the patient is fit for radical surgery **(II- B).**

Importance: Important

Transferability: Partially

Result card for CUR21: "What are the differences in the management for different stages of CRC?"

View full card

CUR21: What are the differences in the management for different stages of CRC?

Result

Please see Results card, CUR18.

Importance: Important

Transferability: Partially

Result card for CUR22: "What are the other evidence-based alternatives to CRC screening with FIT?" and CUR27: "What are the technical characteristics and analytical validity of guaiac-based fecal occult blood test (FOBT), as main CRC screening comparator in this assessment?"

View full card

CUR22: What are the other evidence-based alternatives to CRC screening with FIT?

Result

Several screening tests for CRC are available, classified according to three categories {61}:

Stool-based techniques: Fecal occult blood test (FOBT) (either guaiac, so called gFOBT and immunochemical, so called FIT); Fecal DNA testing. **Endoscopic techniques**: Optical colonoscopy; Flexible sigmoidoscopy (FS). **Imaging techniques**: Virtual colonoscopy techniques using: a) Computed tomographic colonography (CT colonography), b) Magnetic resonance colonography (MR colonography); Wireless capsule endoscopy (PillCam Colon); Double-contrast barium enema (DCBE). **gFOBT** (Please see Result card CUR27 in this Domain for details) FOBT is an alternative name for the Guaiac-based faecal occult blood test (gFOBT), a class of faecal occult blood test which detects non-visible blood in the faeces associated with colorectal cancer (CRC) and adenomas. It detects the peroxidase reaction of haemoglobin, which causes the detection paper impregnated with guaiac resin to turn blue. Dietetic provisions are necessary to exclude false-positive results. A recent study showed limited sensitivity of this test for both, advanced adenomas (11%) and carcinomas (13%) ({69} cited in {5}). With the use of gFOBT, a decrease in mortality for CRC by 15 to 33% has been proved ({70}cited in {5}). **Stool DNA testing** (Please see also Result cards CUR23 in this Domain and TEC3 in the Domain Technical description and characteristics of the technology) Faecal DNA tests represent new group of faecal tests designed to detect molecular abnormalities in cancer or precancerous lesion that are shed into the stool. Two faecal DNA tests were commercially available: PreGen Plus, from 2003 to 2008, and ColoSure (single marker faecal DNA assay for methylated vimentin) intended for individuals who are not eligible for more invasive CRC screening. New test showed evolution in the composition of the test, as well in pre-analytical factors and analytic factors in comparison with older faecal DNA tests. Recent systematic review on evidence on faecal DNA testing to screen for CRC in adults at average risk for CRC {71} concluded that faecal DNA tests have insufficient evidence about its diagnostic accuracy to screen for colorectal cancer in asymptomatic, average-risk patients; insufficient evidence for the harms, analytic validity, and acceptability of testing in comparison to other screening modalities also. Existing evidence has little or no applicability to currently available faecal DNA testing. **Sigmoidoscopy** According to the EU Guidelines {2}: **"**There is reasonable evidence from one large RCT that flexible sigmoidoscopy (FS) screening reduces CRC incidence and mortality if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs (II). The available evidence suggests that the optimal interval for FS screening should not be less than 10 years and may even be extended to 20 years (IV - C). There is limited evidence suggesting that the best age range for FS screening should be between 55 and 64 years (III – C). After age 74, average-risk FS screening should be discontinued, given the increasing co-morbidity in this age range (V - D). The impact on CRC incidence and mortality of combining sigmoidoscopy screening with annual or biennial FOBT has not yet been evaluated in trials. There is currently no evidence for extra benefit from adding a once-only FOBT to sigmoidoscopy screening **(II)**. " Recent meta-analysis {72} of randomized controlled trials demonstrates that FS-based screening significantly reduces the incidence and mortality of CRC in average-risk patients. By intention to treat analysis, FS-based screening was associated with an 18% relative risk reduction in the incidence of CRC (0.82, 95% CI 0.73–0.91, p,0.001, number needed to screen [NNS] to prevent one case of CRC = 361), a 33% reduction in the incidence of left sided CRC (RR 0.67, 95% CI 0.59–0.76, p,0.001, NNS = 332), and a 28% reduction in the mortality of CRC (relative risk [RR] 0.72, 95% CI 0.65–0.80, p,0.001, NNS = 850). **Colonoscopy** The EU Guideline {2} states: "Limited evidence exists on the efficacy of colonoscopy screening in reducing CRC incidence and mortality **(III)**. However, recent studies suggest that colonoscopy screening might not be as effective in the right colon as in other segments of the colorectum **(IV).** Limited available evidence suggests that the optimal interval for colonoscopy screening should not be less than 10 years and may even extend up to 20 years **(III - C).** Indirect evidence suggests that the prevalence of neoplastic lesions in the population below 50 years of age is too low to justify colonoscopic screening, while in the elderly population (75 years and above) lack of benefit could be a major issue. The optimal age for a single colonoscopy appears to be around 55 years **(IV - C).** Average risk colonoscopy screening should not be performed before age 50 and should be discontinued after age 74 **(V - D)."** Recent interim report of RCT {73} involving asymptomatic adults 50 to 69 years of age comparing the one-time colonoscopy in 26,703 subjects with FIT every 2 years in 26,599 subjects and primary outcome - the rate of death from colorectal cancer at 10

years, showed that subjects in the FIT group were more likely to participate in screening than were those in the colonoscopy group (34.2% vs. 24.6%, P<0.001). On the baseline screening examination, the numbers of subjects in whom colorectal cancer was detected were similar in the two study groups, but more adenomas were identified in the colonoscopy group. Advanced adenomas were detected in 514 subjects (1.9%) in the colonoscopy group and 231 subjects (0.9%) in the FIT group (odds ratio, 2.30; 95% CI, 1.97 to 2.69; P<0.001), and non-advanced adenomas were detected in 1109 subjects (4.2%) in the colonoscopy group and 119 subjects (0.4%) in the FIT group (odds ratio, 9.80; 95% CI, 8.10 to 11.85; P<0.001). **CT colonography (CTC)** Computed tomographic colonography (CTC) is a potential technique for CRC screening. With CTC, two- and three-dimensional digital images are constructed to investigate the presence of lesions in the colon and rectum. Studies on the impact of CTC screening on CRC incidence or mortality have not yet been conducted. **Capsule endoscopy** Colon capsule endoscopy is a new technique to visualize the colon. Compared with full colonoscopy, the accuracy of colon capsule is considerably lower and an even more extensive bowel cleansing is needed. Capsule endoscopy has not yet been evaluated in an average risk screening population. With capsule endoscopy, a camera with the size and shape of a pill is swallowed to visualise the gastrointestinal tract. No studies have reported on CRC incidence and mortality reduction from capsule endoscopy. **New screening technologies under evaluation** {2} There currently is no evidence on the effect of new screening tests under evaluation on CRC incidence and mortality **(VI)**. New screening technologies such as CT colonography, stool DNA testing and capsule endoscopy should therefore not be used for screening the average-risk population **(VI - D).**

Importance: Important

Transferability: Partially

CUR27: What are the technical characteristics and analytical validity of guaiac-based fecal occult blood test (FOBT), as main CRC screening comparator in this assessment?

Result

Results {2,74,75,76}

FOBT is an alternative name for the Guaiac-based faecal occult blood test (gFOBT), a class of faecal occult blood test which detects non-visible blood in the faeces associated with CRC and adenomas. They represent one out of few different screening options for CRC. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both, *prevention* (by the removal of adenomas before they had a chance to become malignant) and *earlier diagnosis* of CRC (at early, curable stage).

The gFOBT has been shown to be clinically and economically effective when used for CRC screening and is at present the most frequently used method in screening programs. It detects the peroxidase reaction of haemoglobin, which causes the detection paper impregnated with guaiac resin to turn blue. Dietetic provisions are necessary to exclude false-positive results. A recent study showed limited sensitivity of this test for both, advanced adenomas (11%) and carcinomas (13%) ({69} cited in {5}). With the use of gFOBT, a decrease in mortality for CRC by 15 to 33% has been proved ({70} cited in {5}).

Potential advantages and disadvantages of gFOBT are presented in Table 1.

Table 1. Potential advantages and disadvantages of gFOBT {74}

Advantages of gFOBT	Disadvantages of gFOBT
The collection card and reagent are cheap	Testing is not automated, is labour intensive and involves subjective visual reading
The card based collection system is easy to pack using automated machinery and easy to send by post	The participants is required to prove samples from three separate bowel motions
Easy to print patients details on the cards	Not specific for human Hb
The samples are considered to be stable on the cards for up to 21 days	Not as sensitive as iFOBT to human Hb
The system has been validated in numerous RCTs, has been implemented in a number of bowel cancer screening programmes and work successfully	Not possible to adjust the cut-off Hb concentration of the test

Several different types and brands of tests are available (Table 2). Still it is not possible to adjust the analytical sensitivity of gFOBT, with the exception of the simple adjunct of hydrating the specimen prior the testing with Hemoccult SENSA: hydration increases test sensitivity and decrease specificity and positive predictive value.

Table 2. Different types, brands and some characteristics of Guaiac-based faecal occult bleeding test (gFOBT)

Product names of Guaiac-based fecal occult bleeding test (gFOBT)	Manufacturer/Supplier	Analytical Sensitivity
Coloscreen	Helena Laboratories, Texas,USA	0.9 mg Hb/g
Hema-screen	Immunostics Inc. New Jersey,07712, USA	0.6 mg Hb/g
Hemoccult	Beckman Coulter Inc. Fullerton,CA 92835, USA	30% positivity at 0.3 mg Hb/g

Hemoccult SENSA	Beckman Coulter Inc. Fullerton,CA 92835, USA	75% positivity at 0.3 mg Hb/g
MonoHaem	Chemicon Europe Ltd	1.05 mg Hb/g
Hema-Check	Siemens PLC	6 mg Hb/g
HemaWipe	Medtek Diagnostics LLC/BioGnosis Ltd	2 mg Hb/g

EU Guideline 2010 {2}

“Evidence for efficacy in CRC screening

There is good evidence that gFOBT screening reduces CRC mortality by 14%. 16% in people of appropriate age invited to attend screening. The observed, modest reduction in CRC mortality has not been shown to impact overall mortality (Level of the evidence I).

Evidence for the interval

Both annual and biennial screening with gFOBT has been shown to be effective methods for significantly reducing CRC mortality (Level of the evidence I). The results of the Minnesota trial imply that the benefit from annual screening appears to be greater than for biennial screening (Level of the evidence II). No clear recommendation regarding the best time interval for offering screening by gFOBT can be drawn. To ensure effectiveness, the screening interval in a national screening programme should not exceed two years (Level of the evidence II - B).

Evidence for the age range

The best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (Level of the evidence IV). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (Level of the evidence VI - B).“

According a report for the Ontario Ministry of Health and Long-Term Care (41) persons in whom age is the only risk factor for CRC are considered to be at average risk. Factors that place individuals at higher risk include a family history of CRC or adenoma, personal history of CRC or adenoma, and inflammatory bowel disease. There is evidence endorsing the provision of CRC screening to average-risk individuals, beginning at age 50, to detect cancers at a favourable stage before they have advanced to a potentially lethal disease state.

Evidence on risks vs. Benefit {2}

gFOBT screening is a safe screening method with no direct adverse health effects. However, it is associated with false-positive test results, leading to anxiety and unnecessary follow-up colonoscopies. No colonoscopy-related deaths were reported in any of the RCTs, or in the UK pilot programme. In a well-organised, high-quality screening programme using unrehydrated gFOBT, the risks of adverse effects are limited (Level of the evidence I).

gFOB tests have proven characteristics that make them suitable for population CRC screening. Despite the known disadvantages of gFOBT they could be more practicable and affordable than iFOBT in some settings which depend on local labour costs, the mechanism of kit distribution and collection and the reduced sample stability of iFOBT (Level of evidence I, Grade of recommendation B).

Quality assurance of gFOBT {75}

Countries with CRC screening programmes that adopt a traditional gFOBT need to apply additional laboratory quality procedures to minimise variability and error associated with visual tests reading including manual results input. These procedures include use of appropriate temperature for artificial lighting and neutral-coloured walls un the reading laboratory; use of a national laboratory training programme to prosper consistency of interpretation; a blinded internal QC check each day for each analyst prior to commencing testing; adoption of a monitoring programme to identify operator related analytical performance; double entry of test results. (Level of evidence VI, Grade of recommendation B).

Despite the fact that dietary constituents present potential interference in gFOBT, dietary restriction has not been demonstrated to significantly increase screening specificity and risks reducing participation rate. The potential for dietary interference is significantly less for iFOBT. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported, dietary restriction is not indicated for programmes using either gFOBT or iFOBT (Level of evidence II, Strength of recommendation D).

Some drugs which could cause GI bleeding like aspirin, NSAIDs and anticoagulants present potential interference in gFOBT and iFOBT, drug restriction is not recommended for population screening programmes using either gFOBT or iFOBT (Level of evidence III, Strength of recommendation D).

Since many factors influence the uptake and reliability of sample collection, a local pilot study should be undertaken to ensure that the chosen device and associated distribution, sampling and labelling procedures are acceptable (Level of evidence VI, Grade of recommendation A).

All laboratories providing population screening should be led by a qualified clinical chemist trained and experienced in the techniques used for analysis and with clinical quality assurance procedures (Level of evidence VI, Grade of recommendation B).

All laboratories providing screening service should be associated with a laboratory accredited to ISO 15189:2007 Medical laboratories-Particular requirements for quality and competence. Also they should perform Internal Quality Control procedures and participate in appropriate External Quality Assessment Scheme (Level of evidence VI, Grade of recommendation B).

Distribution of FOBT kits by mail, using local postal service is an effective way of reaching the designated population (Level of evidence II, Grade of recommendation B).

Automated check protocols should be implemented to ensure correct identification of the screen population and complete and accurate recording of individual screening participation and test results. Protocols should be implemented to ensure standardised and reliable classification of the test results (Level of evidence VI, Grade of recommendation A).

All laboratory performance outcomes like uptake, undelivered mail, time from collection to analysis, analytical performance, positivity rates, lots and spoilt kits and technical failure rate, technical performance variability and bias should be each subject to rigorous monitoring (Level of evidence VI, Grade of recommendation A).

The proportion of unacceptable tests received for measurement is influenced by the ease of use of the test kit and the quality of the instructions for use. This proportion should not exceed 3% of all kits received; less than 1% is desirable (Level of evidence III, Grade of recommendation A).

Importance: Important

Transferability: Partially

Life-Cycle

Result card for CUR23: "In which phase is the development of FIT?"

View full card

CUR23: In which phase is the development of FIT?

Result

Same as Result card TEC3 in the Domain Technical description and characteristics of the technology.

FITs (Faecal immunochemical tests), also known as Immunochemical faecal occult blood test (iFOBTs), are a newer class of Faecal Occult Blood tests (the first FOBTs developed and marketed were gFOBTs). According the EU Guideline 2010 (2), iFOBT have improved test characteristics than gFOBT. iFOBTs have been used for population CRC screening in Japan since 1992. In the US, iFOBTs have been approved by FDA (Food and Drug Administration) since 2001 (OC-Sensor).

Today, a wide range of qualitative and quantitative tests is available worldwide. Overtime, manufacturers have developed new sampling methods (brush-sampling vs stick-sampling FIT) with the aim of increasing simplicity of use and acceptability of test by participants {77}.

New generation DNA tests for CRC screening will combine genetic markers with an immunochemical assay for haemoglobin {62}. A multi-marker fecal DNA test plus FIT, Cologuard has been developed by Exact Sciences Corp. They announced results of preliminary analysis of recently completed DeeP-C pivotal clinical trial in April 2013 {78} registered in ClinicalTrial.gov (NCT01397747) {79}. No study results posted on ClinicalTrials.gov yet. This study compared the performance of the Cologuard test to colonoscopy and fecal immunochemical testing or FIT (according the ClinicalTrial.gov, Primary outcome was Sensitivity and Specificity of the Exact CRC screening test with comparison to colonoscopy, both with respect to cancer; Secondary outcome was to compare the performance of the Exact CRC screening test to a commercially available FIT, both with respect to cancer and advanced adenoma). Exact Sciences planned to submit data from the DeeP-C study to the U.S. Food and Drug Administration as part of its pre-market approval (PMA) submission, and will submit the study's complete data set for publication in a peer-reviewed journal, presentation at a major medical meeting or both.

Importance: Important

Transferability: Completely

Regulatory Status

Result card for CUR24: "Which market authorization status (CE mark) has FIT in other countries, or international authorities?"

View full card

CUR24: Which market authorization status (CE mark) has FIT in other countries, or international authorities?

Result

Data about market authorization status (CE mark) on FIT are provided by EUnetHTA Partners and Manufactures, and are presented below according answers from EUnetHTA Partners survey and EUnetHTA Manufacturers survey.

Data from EUnetHTA Partners Survey

Eight EUnetHTA Partner organisations provided information on market authorisation status of FIT (and/or FOBT) products and some of them provided information on their use in CRC screening programmes.

Croatia Product(s): Hemcare and Immocare-C, Care diagnostic Productions-und Vetriebsgssellschaft m.b.H, Austria Status: CE mark as in vitro diagnostic for occult blood testing in stool Use in CRC screening: not used in CRC screening programme (g-FOBT Hemognost test, BioGnost d.o.o., Zagreb is used in CRC screening) ***Italy (Veneto Region)*** Product(s): OC SENSOR, EIKEN distributed by MEDICAL SYSTEM. Status: regular CE mark Use in CRC screening: Yes ***Russia*** Product(s): FOB Gold Status: Russian registration certificate issued by Roszdravnadzor Use in CRC screening: Yes ***Luxembourg*** FIT is currently not on the market ***Lithuania*** Product(s): multiple registered FITs Status: Market authorization status here under Directive 98/79/EC of the European Parliament and the Council of European Union Use in CRC screening: information on the test specifically is used in CRC programme was not available ***Spain*** Product(s): not specified Status: Approved Use in CRC screening: Yes ***Slovenia*** Product(s): EIKEN, Japan Status: CE certificate Use in CRC screening: Yes ***France*** Product(s): not specified Status: CE mark Use in CRC screening: used in CRC screening programmes in 7 regions

Data from Manufactures survey

Only one manufacturer provided information on their FITs (Sentinel Diagnostics). The following products have CE mark: FOB Gold® NG, FOB Gold® Tube Screen, SENTiFIT®- FOB Gold® latex, SENTiFIT®mini - FOB Gold® latex, SENTiFIT® pierceTube.

The FOB Gold® is distributed in all EU countries and in non-EU countries such as Turkey, Russia, and Czech Republic.

Importance: Critical

Transferability: Completely

Result card for CUR25: "What is the reimbursement status of CRC screening with FIT across countries?"

View full card

CUR25: What is the reimbursement status of CRC screening with FIT across countries?

Result

Data about reimbursement status of CRC screening with FIT are provided by EUnetHTA Partners and Manufactures, and are presented below according answers from EUnetHTA Partners survey and EUnetHTA Manufacturers survey.

Data from EUnetHTA Partners Survey

Eleven EUnetHTA Partners provided data on FIT reimbursement for their respective countries; FIT is fully reimbursed in all cases where FIT is used as part of a CRC screening programme (5 countries, please see also Result card CUR12).

In specific, FIT is used in the Regions of Veneto and Lazio in Italy, Lithuania, Russia, Slovenia and Spain. FIT is also reimbursed in the Austrian province of Burgenland in the framework of the CRC FIT-based screening programme (no details for reimbursement are available).

Data from Manufactures Survey

Full reimbursement of the FIT test in the case of organised CRC screening activities by the National Public Health System was also reported by one Manufacturer that responded to the EUnetHTA survey (Sentinel Diagnostics, manufacturer of FOB Gold®).

Importance: Important

Transferability: Completely

Discussion

Few limitations were observed during assessment of domain questions. Detailed comparisons were difficult due the fact that not all countries maintain population and cancer registers. Data on incidence and mortality were extracted from the database of the GLOBOCAN project (International Agency for Research on Cancer), which provides contemporary estimates of these measures {6}. The most recent estimates are for 2008. Incidence data also derive from population-based cancer registries. More information on the GLOBOCAN data and sources are available on the project's website. Regarding CRC survival, results of the EUROCARE project were preferred as it is a project that aims to describe and interpret differences in cancer patient survival in Europe. However, there are limitations to the project, already

acknowledged by the researchers {21}. The reader should keep in mind that not all European countries are involved in the EUROCARE project. Furthermore, for several countries cancer registration covers only a fraction of the total national population. The first round (EUROCARE-1) included 30 cancer registry populations diagnosed from 12 European countries. During the rounds that followed more regional and national registries participated. The current, fifth round (EUROCARE-5) includes data from 116 Cancer Registries in 30 European countries and for patients diagnosed during 2000-2007 {39}. Strengths, limitations and the value of findings are discussed in detail by the researchers {21,40}.

Differences among MSs on screening methods, adherence rates, marketing authorization and reimbursement status of the tests were not fully established since in the Survey applied to MSs Partner only 11 countries were answered, and in Survey applied to Manufacturers only one responded.

The most clinically and cost-effective CRC screening method still should be determine in additional comparative effectiveness research. Analytical performance of different FOB tests (gFOBT or FIT) should be keep in mind when make decision on which FOB test should be used for CRC screening as well as compliance and general acceptance of the test by the public.

References

1. Gallagher C, Lister T, Smith M. Malignant disease. In: Kumar P, Clark M, editors. Clinical Medicine 8th ed. Edinburgh: Elsevier; 2012. p. 431-83.

2. Segnan N, Patnick J, von Karsa L, editors. European guidelines for quality assurance in colorectal cancer screening and diagnosis - First Edition. 1st ed. Luxembourg: Publications Office of the European Union; 2010.

3. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Colorectal cancer. Harrison's manual of medicine. 18th ed. New York: McGraw-Hill; 2013. p. 453-57.

4. Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Obesity. Harrison's manual of medicine. 18th ed. New York: McGraw-Hill; 2013. p. 1134-7.

5. Zavoral M, Suchanek S, Zavada F, Dusek L, Muzik J, Seifert B, et al. Colorectal cancer screening in Europe. World journal of gastroenterology : WJG. 2009 Dec 21;15(47):5907-15. PubMed PMID: 20014454. Pubmed Central PMCID: PMC2795177. Epub 2009/12/17. eng.

6. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010 [cited 2013 May 15]. Available from: http://globocan.iarc.fr.

7. Berrino F, De Angelis R, Sant M, Rosso S, Lasota MB, Coebergh JW, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–99: results of the EUROCARE-4 study. The Lancet Oncology. 2007 9//;8(9):773-83.

8. Grande E, Inghelmann R, Francisci S, Verdecchia A, Micheli A, Baili P, et al. Regional estimates of colorectal cancer burden in Italy. Tumori. 2007 Jul-Aug;93(4):352-9. PubMed PMID: 17899865. Epub 2007/09/29. eng.

9. American Cancer Society. Colorectal Cancer Facts & Figures 2011-2013. Atlanta: American Cancer Society, 2011.

10. Coleman MP, Gatta G, Verdecchia A, Estève J, Sant M, Storm H, et al. EUROCARE-3 summary: cancer survival in Europe at the end of the 20th century. Annals of Oncology. 2003 December 1, 2003;14(suppl 5):v128-v49.

11. Verdecchia A, Francisci S, Brenner H, Gatta G, Micheli A, Mangone L, et al. Recent cancer survival in Europe: a 2000?02 period analysis of EUROCARE-4 data. The Lancet Oncology. 2007;8(9):784-96.

12. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JWW. Recent trends of cancer in Europe: A combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. European journal of cancer (Oxford, England : 1990). 2008;44(10):1345-89.

13. Jemal A, Center MM, DeSantis C, Ward EM. Global Patterns of Cancer Incidence and Mortality Rates and Trends. Cancer Epidemiology Biomarkers & Prevention. 2010 August 1, 2010;19(8):1893-907.

14. Center MM, Jemal A, Ward E. International Trends in Colorectal Cancer Incidence Rates. Cancer Epidemiology Biomarkers & Prevention. 2009 June 1, 2009;18(6):1688-94.

15. OECD. Health at a Glance: Europe 2012. Paris: OECD Publishing; 2012. Available from: http://ec.europa.eu/health/reports/docs/health_glance_2012_en.pdf.

16. La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, et al. Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. Annals of Oncology. 2010 June 1, 2010;21(6):1323-60.

17. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. Journal of internal medicine. 2006 Aug;260(2):103-17. PubMed PMID: 16882274. Epub 2006/08/03. eng.

18. Sant M, Capocaccia R, Coleman MP, Berrino F, Gatta G, Micheli A, et al. Cancer survival increases in Europe, but international differences remain wide. European journal of cancer (Oxford, England : 1990). 2001;37(13):1659-67.

19. Verdecchia A, Guzzinati S, Francisci S, De Angelis R, Bray F, Allemani C, et al. Survival trends in European cancer patients diagnosed from 1988 to 1999. European journal of cancer (Oxford, England : 1990). 2009;45(6):1042-66.

20. Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. International journal of cancer Journal international du cancer. 2012 Oct 1;131(7):1649-58. PubMed PMID: 21607946. Epub 2011/05/25. eng.

21. Berrino F. The EUROCARE Study: strengths, limitations and perspectives of population-based, comparative survival studies. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2003;14 Suppl 5:v9-13. PubMed PMID: 14684497. Epub 2003/12/20. eng.

22. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. Gut. 2002 Jul;51(1):60-4. PubMed PMID: 12077093. Pubmed Central PMCID: PMC1773269. Epub 2002/06/22. eng.

23. Ostenfeld EB, Erichsen R, Iversen LH, Gandrup P, Norgaard M, Jacobsen J. Survival of patients with colon and rectal cancer in central and northern Denmark, 1998-2009. Clinical epidemiology. 2011;3 Suppl 1:27-34. PubMed PMID: 21814467. Pubmed Central PMCID: PMC3144775. Epub 2011/08/05. eng.

24. Gatta G, Capocaccia R, Sant M, Bell CM, Coebergh JW, Damhuis RA, et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. Gut. 2000 Oct;47(4):533-8. PubMed PMID: 10986214. Pubmed Central PMCID: PMC1728079. Epub 2000/09/15. eng.

25. Engeland A, Haldorsen T, Dickman PW, Hakulinen T, Möller TR, Storm HH, et al. Relative survival of cancer patients--a comparison between Denmark and the other Nordic countries. Acta oncologica (Stockholm, Sweden). 1998 /;37(1):49-59.

26. Monnet E, Faivre J, Raymond L, Garau I. Influence of stage at diagnosis on survival differences for rectal cancer in three European populations. British journal of cancer. 1999 Oct;81(3):463-8. PubMed PMID: 10507771. Pubmed Central PMCID: PMC2362908. Epub 1999/10/03. eng.

27. WHO. The global burden of disease: 2004 update. Geneva: World Health Organization 2008.

28. Glaser AW, Fraser LK, Corner J, Feltbower R, Morris EJ, Hartwell G, et al. Patient-reported outcomes of cancer survivors in England 1-5 years after diagnosis: a cross-sectional survey. BMJ open. 2013;3(4). PubMed PMID: 23578682. Pubmed Central PMCID: PMC3641492. Epub 2013/04/13. eng.

29. Caravati-Jouvenceaux A, Launoy G, Klein D, Henry-Amar M, Abeilard E, Danzon A, et al. Health-Related Quality of Life Among Long-Term Survivors of Colorectal Cancer: A Population-Based Study. The Oncologist. 2011 November 1, 2011;16(11):1626-36.

30. Jansen L, Herrmann A, Stegmaier C, Singer S, Brenner H, Arndt V. Health-Related Quality of Life During the 10 Years After Diagnosis of Colorectal Cancer: A Population-Based Study. Journal of Clinical Oncology. 2011 August 20, 2011;29(24):3263-9.

31. Yost K, Hahn E, Zaslavsky A, Ayanian J, West D. Predictors of health-related quality of life in patients with colorectal cancer. Health Qual Life Outcomes. 2008 2008/08/25;6(1):1-10. English.

32. Eakin EG, Youlden DR, Baade PD, Lawler SP, Reeves MM, Heyworth JS, et al. Health Status of Long-term Cancer Survivors: Results from an Australian Population-Based Sample. Cancer Epidemiology Biomarkers & Prevention. 2006 October 1, 2006;15(10):1969-76.

33. Yabroff KR, Lawrence WF, Clauser S, Davis WW, Brown ML. Burden of Illness in Cancer Survivors: Findings From a Population-Based National Sample. Journal of the National Cancer Institute. 2004 September 1, 2004;96(17):1322-30.

34. Schneider EC, Malin JL, Kahn KL, Ko CY, Adams J, Epstein AM. Surviving colorectal cancer. Cancer. 2007;110(9):2075-82.

35. Jansen L, Koch L, Brenner H, Arndt V. Quality of life among long-term (>5years) colorectal cancer survivors – Systematic review. European journal of cancer 2010;46(16):2879-88.

36. Domati F, Rossi G, Benatti P, Roncucci L, Cirilli C, Ponz de Leon M. Long-term survey of patients with curable colorectal cancer with specific reference to the quality of life. Intern Emerg Med. 2011 2011/12/01;6(6):529-35. English.

37. Trentham-Dietz A, Remington PL, Moinpour CM, Hampton JM, Sapp AL, Newcomb PA. Health-Related Quality of Life in Female Long-Term Colorectal Cancer Survivors. The Oncologist. 2003 August 1, 2003;8(4):342-9.

38. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, et al. Quality of life in survivors of colorectal carcinoma. Cancer. 2000;88(6):1294-303.

39. EUROCARE. EUROCARE [Internet]. Istituto Superiore di Sanità - Settore I - Informatica; 2013 [cited 2013 July 27th]. Available from: http://www.eurocare.it/

40. Berrino F, Verdecchia A, Lutz JM, Lombardo C, Micheli A, Capocaccia R. Comparative cancer survival information in Europe. European journal of cancer (Oxford, England : 1990). 2009 Apr;45(6):901-8. PubMed PMID: 19217771. Epub 2009/02/17. eng.

41. Medical Advisory Secretariat. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, 2009 Contract No.: 10.

42. Qaseem A, Denberg TD, Hopkins JRH, Humphrey LL, Levine J, Sweet DE, et al. Screening for Colorectal Cancer: A Guidance Statement From the American College of Physicians. Annals of Internal Medicine. 2012;156(5):378-86.

43. Moss S, Ancelle-Park R, Brenner H. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Evaluation and interpretation of screening outcomes. Endoscopy. 2012 Sep;44 Suppl 3:SE49-64. PubMed PMID: 23012122. Epub 2012/10/04. eng.

44. Health Information and Quality Authority. Health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland. Dublin: Health Information and Quality Authority, 2009.

45. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, Habbema JD, Kuipers EJ. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. J Natl Cancer Inst. 2009 Oct 21;101(20):1412-22. PubMed PMID: 19779203. Pubmed Central PMCID: PMC2765263. Epub 2009/09/26. eng.

46. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews. 2007 (1):CD001216. PubMed PMID: 17253456. Epub 2007/01/27. eng.

47. Heresbach D, Manfredi S, D'Halluin P N, Bretagne JF, Branger B. Review in depth and meta-analysis of controlled trials on colorectal cancer screening by faecal occult blood test. European journal of gastroenterology & hepatology. 2006 Apr;18(4):427-33. PubMed PMID: 16538116. Epub 2006/03/16. eng.

48. Kerr J, Day P, Broadstock M, Weir R, Bidwell S. Systematic review of the effectiveness of population screening for colorectal cancer. The New Zealand medical journal. 2007;120(1258):U2629. PubMed PMID: 17653247. Epub 2007/07/27. eng.

49. Lansdorp-Vogelaar I, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Introduction. Endoscopy. 2012 Sep;44 Suppl 3:SE15-30. PubMed PMID: 23012118. Epub 2012/10/04. eng.

50. Libby G, Brewster DH, McClements PL, Carey FA, Black RJ, Birrell J, et al. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study. British journal of cancer. 2012 Jul 10;107(2):255-9. PubMed PMID: 22735907. Pubmed Central PMCID: PMC3394992. Epub 2012/06/28. eng.

51. Allison JE. Colon Cancer Screening Guidelines 2005: the fecal occult blood test option has become a better FIT. Gastroenterology. 2005;129(2):745-8. eng.

52. International Cancer Screening Network. Inventory of Colorectal Cancer Screening Activities in ICSN Countries, May 2008 [Internet]. 2008 [updated 2009 Feb 09 cited 2013 Aug 09]. Available from: http://appliedresearch.cancer.gov/icsn/colorectal/screening.html.

53. Zorzi M, Fedato C, Grazzini G, Sassoli de' Bianchi P, Naldoni C, Pendenza M, et al. [Screening for colorectal cancer in Italy, 2010 survey]. Epidemiol Prev. 2012 2012 Nov-Dec;36(6 Suppl 1):55-77. ita.

54. Saito H. Colorectal cancer screening using immunochemical faecal occult blood testing in Japan. Journal of Medical Screening. 2006 December 1, 2006;13(suppl 1):6-7.

55. Bryant HE, Fekete SV, Major DH. Pan-Canadian initiatives in colorectal cancer screening: adopting knowledge translation tools to accelerate uptake and impact. Current oncology (Toronto, Ont). 2011 Jun;18(3):111-8. PubMed PMID: 21655157. Pubmed Central PMCID: PMC3108864. Epub 2011/06/10. eng.

56. Australian Government. National Bowel Cancer Screening Program. About the Bowel Cancer Screening Pilot [Internet]. Australian Government, Department of Health and Aeging; 2013 [updated 2013 Jan 31; cited 2013 Aug 9]. Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/pilot.

57. Swan H, Siddiqui AA, Myers RE. International Colorectal Cancer Screening Programs: Population Contact Strategies, Testing Methods and Screening Rates. Practical Gastroenterology. 2012;XXXVI(8):8.

58. von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M, et al. Cancer Screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening. First Report. Luxembourg: WHO International Agency for Research on Cancer, 2008.

59. Von Karsa L. Colorectal Cancer Screening in Europe. European Guidelines Workshop: National Centre for Screening Monitoring and Italian Colorectal Cancer Screening Group.

60. United European Gastroenterology. Real progress in colorectal cancer screening in Europe as Estonia develops ‘road map’ for population-based programme [Internet]. 2012 [cited 2013 Aug 9]. Available from: http://www.ueg.eu/news-press/releases/ueg-press-release/article/real-progress-in-colorectal-cancer-screening-in-europe-as-estonia-develops-road-map-for-popula/.

61. Medical Advisory Secretariat. Screening Methods for Early Detection of Colorectal Cancers and Polyps. Summary of Evidence-Based Analyses. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, 2009 Contract No.: 6.

62. Lin JS, Webber EM, Beil TL, Goddard KA, Whitlock EP. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults 2012 2012 Feb. Report No.

63. NICE. Colorectal cancer: the diagnosis and management of colorectal cancer. London: National Institute for Health and Care Excellence, 2011.

64. SIGN. Diagnosis and management of colorectal cancer. Edinburgh: Scottish Intercollegiate Guidelines Network, 2011 Contract No.: 126.

65. Telford JJ. Canadian guidelines for colorectal cancer screening. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2011;25(9):479-81. eng.

66. U.S. Preventive Services Task Force. Screening for Colorectal Cancer. Recommendation Statement. Internet. March 2009.

67. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. The American journal of gastroenterology. 2009 Mar;104(3):739-50. PubMed PMID: 19240699. Epub 2009/02/26. eng.

68. Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA: a cancer journal for clinicians. 2008;58(3):130-60. eng.

69. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population. New England Journal of Medicine. 2004;351(26):2704-14. PubMed PMID: 15616205.

70. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing Mortality from Colorectal Cancer by Screening for Fecal Occult Blood. New England Journal of Medicine. 1993;328(19):1365-71. PubMed PMID: 8474513.

71. Lin J, Webber E, Beil T, Goddard K, EP W. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults. Rockville, MD: Agency for Healthcare Research and Quality, 2012 Contract No.: AHRQ Publication 12-EHC022-EF.

72. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of Flexible Sigmoidoscopy-Based Screening on Incidence and Mortality of Colorectal Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS Med. 2012;9(12):e1001352.

73. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. The New England journal of medicine.

74. NHS Centre for Evidence-based Purchasing. Evaluation report: Immunohistocemical faecal occult blood tests. NHS Purchasing and Supply Agency, 2009 CEP09042.

75. von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, Lansdorp-Vogelaar I, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy. 2013;45(1):51-9. PubMed PMID: 23212726. Epub 2012/12/06. eng.

76. Whyte S, Chilcott J, Cooper K, Essat M, Stevens J, Wong R, et al. Re-appraisal of the options for colorectal cancer screening. Report for the NHS Bowel Cancer Screening Programme. Sheffield: University of Sheffield, School of Health and related Research, 2011.

77. Young G. Fecal Immunochemical Tests (FIT) vs. Office-Based Guaiac Fecal Occult Blood Test (FOBT). Practical Gastroenterology. 2004;XXVIII(6).

78. Corp. ES. Top-Line Data Show Exact Sciences' Cologuard Test Demonstrates 92 Percent Sensitivity in the Detection of Colorectal Cancer [Internet]. 2013 [updated 2013, April 18; cited 2013 Aug 9]. Available from: http://investor.exactsciences.com/releasedetail.cfm?ReleaseID=757341.

79. ClinicalTrial.gov. Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer (DeeP-C) [Internet]. U.S. National Institutes of Health; 2013 [updated 2013, Jun 18; cited 2013 Aug 9]. Available from: http://prsinfo.clinicaltrial.gov/ct2/show/record/NCT01397747?id=NCT01397747&rank=1).

Description and technical characteristics of technology

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Summary

Aim To describe and review the technical characteristics of iFOBT.

Methods The Project scope is applied in this Domain. Results cards are covered by evidence gathered from basic literature search, hand searched literature, manufacturers web sites, company brochures and information for use, and survey (questionnaire) results. No quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis was performed on different information sources. The assessment elements questions are answered by cooperation of Domain investigators.

Results FITs or iFOBTs are a class of faecal occult blood tests (tests for blood or blood products). They use blood as an indicator of the presence of tumour. FOBTs are recommended for population-based colorectal carcinoma screening (CRC) screening. The target group is asymptomatic people at average risk, of both genders. Regarding the age-range, there is evidence endorsing the provision of CRC screening to average-risk individuals, beginning at age 50, to detect cancers at a favourable stage before they have advanced to a potentially lethal disease state.

The first FOBTs that were developed were guaiac-based (gFOBTs). FITs use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces. New technologies in the field of FOBTs include faecal DNA tests, the use of RNA markers in stool as well as the use of DNA or RNA in plasma, serum and urine. Much work is still ongoing on use of protein biomarkers in blood for CRC screening and early detection.

The advantages of FIT in contrast to gFOBT are: specificity for human Hb, reducing the number of false positive results; no dietetic restrictions necessary; increased sensitivity to human Hb; automated analysis and the possibility to set cut-off limits (the latter applies only to quantitative FIT tests). Disadvantages include sample instability in liquid collection devices, therefore shorter transportation time frame is required; possible additional requirements for packaging of the liquid sample collection devices to meet different MSs postal regulation; and cost of the test. These characteristics should be taken into account in the development of CRC screening programmes in different settings.

A wide range of qualitative and quantitative iFOBT tests is presently available, with varying levels of sensitivity and specificity. Similar to gFOBT, participants collect one or more stool samples, which can be analysed either using automated systems in the laboratory (for some manufacturers) or are read by the naked eye with a positive result indicated by a colour change on a strip. Automated systems can be qualitative (providing dichotomous result) or quantitative (user-defined cut-off levels). In HTAs performed in other countries, automated FITs were considered appropriate for assessment for a population-based screening programme; this approach was also adopted in the present Core HTA. Three iFOBT are presented here, as three analytical platforms using the three sample collection devices: OC-Sensor/OC-Sensor Diana & OC-Sensor Micro, Hem-SP/MagStream HT, FOB Gold/SENTiFOB analyser.

In the framework of a CRC programme using FIT as the primary screening method, users of the technology include people invited to participate in the programme as well as the health professionals who are involved (primary care physicians and nurses, laboratory staff). Parameters that should be taken into account when using FIT in CRC programmes are the material investments needed (procurement and maintenance of laboratory analysers, sample collection devices, refrigerated storage spaces, waste disposal systems and, in some cases, end-of-life disposal), and training needs of the laboratory staff. Laboratory staff training depends on the type of test to be used. Qualification, training and quality assurance processes needed relate to those required in a CRC screening with FOBT. Individuals invited to participate in the programme should be provided with specific instructions on how to use the test kit. It is important that the participant is able to understand written instructions on how to perform these procedures (apart from written material, visual communication instruments and/or oral interventions can be used to facilitate understanding). Furthermore, information about CRC screening risks and benefits, CRC risks, meaning of test results, potential diagnostic tests and potential treatment options should be provided to the patients.

As is the case in every CRC screening programme, several kinds of data need to be recorded. Specifically, records should include: data on each individual and every screening test performed, test results, decision made as a consequence, diagnostic and treatment procedures and subsequent outcome (including cause of death).

Important for practice: In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme.

Introduction

Faecal Immunochemical Tests (FITs), also known as Immunochemical Faecal Occult Blood Test (iFOBTs), are a newer class of Faecal Occult Blood tests (the first FOBTs developed and marketed were gFOBTs). According the EU Guideline for quality assurance in CRC screening and diagnosis (2010), iFOBT have improved test characteristics than gFOBT. iFOBTs have been used for population CRC screening in Japan since 1992. In the US, the first iFOBT (OC-Sensor) has been approved by the FDA (Food and Drug Administration) since 2001. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both, *prevention* (by the removal of adenomas before they had a chance to become malignant, so CRC incidence is reduced) and *earlier diagnosis* of CRC (at early, curable stage).

A wide range of qualitative and quantitative FITs is presently available, with varying levels of sensitivity and specificity. They all use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces.

The older class of faecal occult blood tests, guaiac-based fecal occult blood tests (gFOBTs) has proven characteristics that make them suitable for population CRC screening. The advantages and disadvantages of both, gFOBTs and iFOBTs should be taken into account in the development of CRC screening programmes in different settings, like local labour costs, the mechanism of kit distribution and collection as well as the sample stability characteristics.

The aim of this Domain is to describe and review the technical characteristics of iFOBT.

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC) The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.
Outcomes	**CUR and TEC** • Health problems (target condition) • Epidemiology • Burden of disease • Target population • Current management of the condition • Features of the technology • Life-Cycle • Regulatory status • Utilization • Investments and tools required to use the technology • Training and information needed to use the technology **SAF** • Colonoscopy probability of perforation • Colonoscopy with polypectomy probability of perforation • Colonoscopy probability of death following perforation • Probability of bleeding following colonoscopy • Psychological harms from false-negatives and false-positives (and generally from participating in screening program) **EFF** • Test (FIT and gFOBT) sensitivity for adenomas • Test (FIT and gFOBT) sensitivity for cancer • Test (FIT and gFOBT) specificity for adenomas • Test (FIT and gFOBT) specificity for cancer • Adenoma incidence (detection rates) • Rectal cancer incidence (detection rates) • Colon cancer incidence (detection rates) • CRC incidence (detection rates)

- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
B0001	Features of the technology	What is this technology?	yes	What is FIT?
B0002	Features of the technology	Why is this technology used?	yes	Why is FIT used?
B0003	Features of the technology	What is the phase of the technology?	yes	What is the phase of FIT?
B0004	Features of the technology	Who will apply this technology?	yes	Who will apply FIT?
B0005	Features of the technology	In what place and context is the technology intended to be used?	yes	In what place and context is FIT intended to be used?
B0006	Features of the technology	Are there any special features relevant to this technology?	yes	Are there any special features relevant to FIT?
B0016	Features of the technology	To what population(s) will this technology be used on?	yes	To what population(s) will FIT be used on?
B0017	Features of the technology	Is this technology field changing rapidly?	yes	Is FIT field changing rapidly?
B0018	Features of the technology	Are the reference values or cut-off points clearly established?	yes	Are the reference values or cut-off points clearly established?
B0007	Investments and tools required to use the technology	What material investments are needed to use the technology?	yes	What material investments are needed to use FIT?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology?	yes	What kind of special premises are needed to use FIT?
B0009	Investments and tools required to use the technology	What equipment and supplies are needed to use the technology?	yes	What equipment and supplies are needed to use FIT?
B0010	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use the technology?	yes	What kind of data and records are needed to monitor the use FIT?
B0011	Investments and tools required to use the technology	What kind of registers are needed to monitor the use the technology?	yes	What kind of registers are needed to monitor the use FIT?
B0012	Training and information needed to use the technology	What kind of qualification, training and quality assurance processes are needed for the use or maintenance of the technology?	yes	What kind of qualification, training and quality assurance processes are needed for the use or maintenance of FIT?
B0013	Training and information needed to use the technology	What kind of training is needed for the personnel treating or investigating patients using this technology?	yes	What kind of training is needed for the personnel treating or investigating patients using FIT?
B0014	Training and information needed to use the technology	What kind of training and information should be provided for the patient who uses the technology, or for his family/carer?	yes	What kind of training and information should be provided for the patient who uses FIT, or for his family/carer?
B0015	Training and information needed to use the technology	What information of the technology should be provided for patients outside the target group and the general public?	yes	What information of FIT should be provided for patients outside the target group and the general public?

Methodology description

Domain frame

The Project scope is applied in this domain.

Information sources

- Basic systematic search. Common (basic) literature search strategy was used, run for the whole project and described in COL Appendix 1;

- Additional search for published literature in PubMed and internet search of grey literature using Google search engine;

- Review of the reference lists and bibliographies of studies identified through the basic systematic search;

- Manufacturers web sites;

- Company brochures and Information for use;

- Survey: two questionnaires were administered, to EUnetHTA partners and Manufacturers (more information in COL Appendix 2), with aim to get further information about primary CRC screening methods and tests in different EU countries; please see in COL Appendix 2.

Quality assessment tools or criteria

No quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources.

Analysis and synthesis

Descriptive analysis was performed on different information sources. The assessment elements questions are answered by cooperation of Domain investigators.

Results cards are covered by evidence gathered from basic search (COL Appendix 1), hand searched literature, manufacturers web sites, company brochures and information for use, and survey (questionnaire) results.

Result cards

Features of the technology

Result card for TEC1: "What is FIT?"

View full card

TEC1: What is FIT?

Result

FIT (Faecal immunochemical test) is an alternative name for Immunochemical faecal occult blood test (iFOBT), a class of faecal occult blood tests. Faecal Occult Blood Tests (FOBTs) are tests for blood or blood products. They use blood as an indicator of the presence of tumour {1}.

A wide range of qualitative and quantitative iFOBT tests is presently available, with varying levels of sensitivity and specificity. They all use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces.

Similar to g FOBT, participants collect one or more stool samples. The sampling procedure varies: different sampling systems are available (wooden sticks, brushes) and samples may be applied either to a card (dry method) or to place into a vial (wet method). Samples can be analysed either using automated systems in the laboratory (for some manufacturers) or are read by the naked eye with a positive result indicated by a colour change on a strip {2}. The automated systems can be quantitative or qualitative. Qualitative tests produce a dichotomous result, with individuals categorized as either positive or negative if the amount of Hb in the faecal sample is above or below a specific analytical detection limit set by the manufacturers. In quantitative tests, specificity can be determined by the user {3}. The most frequently used values are 75 or 100 ng/mL. This is important due the fact that by increasing the positive cut-off limit, the test sensitivity and positivity rate decreases and specificity and positive predictive values for CRC detection increase. FIT kits with a visual result are designed as point-of-care devices and are qualitative. They can be adopted for use in clinical laboratories for population-based screening; however they retain a more manual approach than the automated systems.

In their report on the comparison of FITs vs. g FOBTs for population-based colorectal cancer screening in Ontario, CA {4} the FIT Guidelines Expert Panel has considered test processing in laboratories more suitable that point-of-care systems for a population-based screening program. Similarly, the NHS Centre for Evidence-based Purchasing in the UK adopted certain criteria that the iFOBTs had to meet in order to be evaluated for the CRC screening programme in the UK {5}. Only automated systems were included in the evaluation. Regarding staff requirements, more technical knowledge will be required than for gFOB tests. If the increased packing material is required to meet postal regulation, unpacking of iFOBT liquid sampling devices may take longer than for gFOBT.

Potential advantages and disadvantages of iFOBT are given in Table 1.

Table 1. Potential advantages and disadvantages of iFOBT (5)

Advantages of iFOBT	Disadvantages of iFOBT
Automated analysis	Sample instability in liquid collection devices
Specificity for human HB, reducing the number of false positive results	Possible additional requirements for packaging of the liquid sample collection devices to meet different MSs postal regulation
Increased sensitivity to human Hb	Cost of the test
Ability to adjust the cut-off Hb concentration in qualitative iFOBTs (except Hem-SP/MagStream HT method as qualitative method)	

Three iFOBT are presented here, as three analytical platforms using the three sample collection devices: **OC-Sensor/OC-Sensor Diana & OC-Sensor Micro, Hem-SP/MagStream HT, FOB Gold/SENTiFOB analyser.** In brief {6}:

- **OC-Sensor** measures human Hb concentration in faeces samples by latex agglutination using polystyrene latex particles coated with polyclonal anti haemoglobin Ao antibodies. One sample only is recommended as number of separate samples used for assessment. The Diana has a memory capacity for 100 000 test results, with speed of 280 samples per hour analysis. Ten mg of faeces is recommended as quantity that should be collected by sampling device. Advantage is that this test is CE marked for a user defined cut-off (default setting 100 ng/mL), with 20 ng/mL in buffer as limit of detection. The faecal sample is collected into the OC-Auto sampling bottle 3. Analysis should be performed as soon as possible after sample collection; in case of any delay the sample collection bottles should be stored at 2-10C;
- **Hem-SP/MagStream HT (**MagStream Hem-Sp®) is based on magnetic particle agglutination (the magnetic particles are coated with rabbit anti-human Hb antibodies). Two samples are recommended as number of separate samples used for assessment. One disadvantage is that this method is qualitative, and has a non-adjustable cut-off at a Hb concentration equal to or greater than 20 ng/ml. In the presence of human haemoglobin, the particles remain aggregated in a spot with minimal change (positive result). In the absence of human haemoglobin, particles flow down the slope (negative result). MagStream HT, an automated instrument which holds 400 samples has a memory capacity of 2 million test results, with speed of analysis of 960 tests per hour (MagStream HT). 0.3 mg of faeces is recommended as quantity should be collected by sampling device. The faecal sample is collected into the NEW HEMTUBE. Analysis should be performed as soon as possible after sample collection; in case of any delay the sample collection bottles should be stored at 2-10C. Freezing must be avoided;

The FOB Gold use an antigen-antibody agglutination reaction between human haemoglobin and polyclonal anti-human haemoglobin antibodies coated on polystyrene particles. The total reading time is 8 minutes, with speed of analyses of 75 tests/hr

- (SentiFOB). The FOB Gold reagents can be used on any suitable immunoassay automated analyser although the manufacturer provides the SENTiFOB analyser. Advantages of this test is that this test is CE marked for a user defined cut-off, with limit of detection of 14 ng/mL buffer, and measuring range of 15-1000 ng/ml. The faecal sample is collected into the FOB Gold tube. Analysis should be performed as soon as possible after sample collection; in case of any delay the sample tubes should be stored at 2-8 C.

Some of products characteristics are presented in Table 2.

Table 2. Product characteristics of OC-Sensor/OC-Sensor Diana & OC-Sensor Micro, Hem-SP/MagStream HT, FOB Gold/SENTiFOB analyser {5-9}.

Product characteristics	OC-Sensor/OC-Sensor Diana & OC-Sensor Micro	Hem-SP/MagStream HT	FOB Gold/SENTiFOB analyser
Analyser name	OC-Sensor Diana OC-Sensor Micro	MagStream HT	SENTiFOB
Manufacturer	Eiken Chemical Co., Tokyo, Japan, www.eiken.co.jp/en/company/index.html	Fujirebio Inc. Japan, http://www.fujirebio.co.jp/english/index.html	Sentinel Diagnostics SpA, Milan, Italy, http://www.sentinel.it/uk/
Method	Latex agglutination	Magnetic particle agglutination	Latex agglutination (open method)
Sample collection system	OC-Auto sampling bottle 3	New HEMTUBE	FOB Gold tube
Measuring range	50-1050 ng/mL	>20 ng/mL	14-1000 ng/mL
Analyser sample volume	35 µL	25 µL	10 µL
Throughput (claimed/measured)	280 per hour/245 per hour	960 per hour/800 per hour	75 per hour/65 per hour
Usual threshold	175 ng Hb/ml in the buffer	211 pixels (MSR=1.0)	100 ng Hb/ml in the buffer
CE mark	Quantitative measurement	Qualitative measurement	Quantitative measurement
Use in population screening	The Netherlands, Northern Italy, US, Uruguay, France	Japan, France and Slovenia	Italy, France

Different authors {5-8} have compared the analytical performance of 3 iFOB tests: OC-Sensor/OC-Sensor Diana & OC-Sensor Micro, Hem-SP/MagStream HT, FOB Gold/SENTiFOB analyser. With regard to reproducibility and temperature stability, OC-Sensor performed better than Magstream and far better than FOB Gold. For all tests, variability was essentially related to sampling. Detected Hb levels were substantially lower for all tests at temperatures above 20 C. This loss is more important for FOB Gold than for other two tests. Some suggestion are made, like delay between sampling and test processing should be reduced to 3 days, or CRC screening programs should be stopped during the summer in countries with long period of very high temperatures >30 C. Patients should be advised to store faecal samples in the refrigerator at home before forwarding them by post.

Rossum et al. {10} reported that delay in sample return increased false negative iFOBT because of Hb degradation. Compared with no-delay, the adenoma detection rate was significantly decreased after >5 days delay (OR 0.6; 95% CI 0.4-0.9).

Sentinel Diagnostic Spa, manufacturer of FOB Gold NG test was only one who responded on our Survey for Manufacturer and sent documentation for their FIT products. The product leaflet of SENTiFIT pierce Tube (collection tube) writes that the human haemoglobin extracted from the feces sample and obtained according to the recommended collection procedure is stable for 14 days at 2-8 C or 7 days at 15-30 C protected from direct light.

The authors of the NHS Centre Evaluation report in 2009 {5}, concluded that the OC-Sensor/DIANA analyser was the most suitable system for the English CRC population-based screening programme. They reported that even when the faecal collection devices were used by experienced evaluation staff, none of the sampling devices gave reproducible results, contributing to the overall imprecision of the methods. Manufacturers claims for stability of the Hb in faecal samples added to the collection devices and stored at room temperature (23C-26C) prior the analysis were confirmed for the OC-Sensor/DIANA method only. Analytical methods comparisons are presented in Table 3.

Table 3. Analytical methods comparisons for 3 iFOB tests: OC-Sensor/OC-Sensor Diana & OC-Sensor Micro, Hem-SP/MagStream HT, FOB Gold/SENTiFOB analyser {5}

OC-Sensor/OC-Sensor Diana method (quantitative)	Hem-SP/MagStream HT method (qualitative)	FOB Gold/SENTiFOB analyser method (quantitative)
Good imprecision, results consistent with the manufacturers claims	Poor imprecision, results not consistent with the manufacturers claims at low Hb concentration	Poor imprecision, results not consistent with the manufacturers claims at low Hb concentration
Linear in the range 50-500 ng Hb/ml buffer	Not linear since the method is not designed to be linear accross a broad measuring range	Linear in the range 50-500 ng Hb/ml buffer
Identified a problem with samples with very high Hb concentration and did not produced a result		Identified a problem with samples with very high Hb concentration and did not produced a result

According the authors of this report {5}, all 3 analytical platforms are easy to operate and maintain once appropriate training has been received. For all three tests, the liquid samples stored at room temperature for more than three days are not suitable for analysis, due to deterioration of any Hb present. This should be taken in account when sending samples via different MSs postal systems (should be returned within this time). The OC-Sensor/DIANA analyser was the most suitable system for the UK bowl cancer screening programme, despite limited reagent, wash and waste capacity (regular attention will be required in a busy screening laboratory). The FOB Gold/SENTiFOB analyser has a very low sample throughput. The HemSp/MagStream HT has a non-adjustable cut-off, the method is not CE marked for quantitative measurement of human Hb. The system gave negative results for samples that were positive by other methods.

For all three tests sample collection devices should be stored between 2 and 10 C in case of any delay in analysis, so refrigerated storage space is required. The number of analysers required will depend on the laboratory workload; number required for a 5,000 sample per day workload will be 1 for HemSp/MagStream HT; 5 for OC-Sensor/DIANA, and 15 SentiFOB and 1 chemistry analyser for FOB Gold/SENTiFOB. Specialist training is provided by the manufacturers (instructions on routine use and maintance of the analyser). Staff will be required to authorise each batch of results generated from the iFOBT analysers and transfer the data to the bowel cancer screening programme database, if such exists {5}.

Importance: Critical

Transferability: Completely

Result card for TEC2: "Why is FIT used?"

View full card

TEC2: Why is FIT used?

Result

Results {5-8}

FITs /iFOBTs are a class of faecal occult blood tests and one out of few different screening options for colorectal cancer (CRC). The aim of population-based screening for CRC is to reduce mortality through both, *prevention* (by the removal of adenomas) and *earlier diagnosis* of CRC.

Overall, the advantages of FIT in contrast to gFOBT are: specificity for human Hb, reducing the number of false positive results and no dietetic restrictions are necessary; increased sensitivity to human Hb; automated analysis and the possibility to set cut-off limits (the latter applies only to quantitative FIT tests).

According to the EU Guidelines for quality assurance in CRC screening and diagnosis (2010) {6}:

-“iFOBT have improved test characteristics than gFOBT, and they are currently the test of choice for population CRC screening. In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme (Level of evidence II, Grade of recommendation A);

-Maximum period between collection and analysis is significantly shorter than for gFOBT (14-21 days), and screening programmes should adopt the conditions and period of storage described in manufacturers. Instructions for use should be appropriate for local conditions which might expose samples to high temperatures for long period of time (Level of evidence III, Grade of recommendation A);

-The potential for dietary interference is significantly less for iFOBT. With the qualification that a diet peculiar to a particular country or culture may not have been tested or reported, dietary restriction is not indicated for programmes using either gFOBT or iFOBT (Level of evidence II, Strength of recommendation D)“.

Importance: Critical

Transferability: Partially

Result card for TEC3: "What is the phase of FIT?"

View full card

TEC3: What is the phase of FIT?

Result

FITs are a newer class of Faecal Occult Blood tests (the first FOBTs developed and marketed were gFOBTs). According the EU Guideline 2010(6), iFOBTs have improved test characteristics than gFOBT. iFOBTs have been used for population CRC screening in Japan since 1992. In the US, iFOBTs have been approved by the FDA (Food and Drug Administration) since 2001 (OC-Sensor).

Today, a wide range of qualitative and quantitative tests is available worldwide. Over time, manufacturers have developed new sampling methods (brush-sampling vs stick-sampling FIT) with the aim of increasing simplicity of use and acceptability of test by participants {11}.

According to Lin et al. {12}, a new generation DNA test for colorectal cancer screening will combine genetic markers with an immunochemical assay for haemoglobin. A multi-marker faecal DNA test plus FIT, Cologuard has been developed by Exact Sciences Corp. They announced results of preliminary analysis of recently completed DeeP-C pivotal clinical trial in April 2013 (13), registered in ClinicalTrial.gov {14}. No study results posted on ClinicalTrials.gov yet. This study compared “the performance of the Cologuard test to colonoscopy and faecal immunochemical testing or FIT” (according the ClinicalTrial.gov, Primary outcome was Sensitivity and Specificity of the Exact CRC screening test with comparison to colonoscopy, both with respect to cancer; Secondary outcome was to compare the performance of the Exact CRC screening test to a commercially available FIT, both with respect to cancer and advanced adenoma). Exact Sciences planned to submit data from the DeeP-C study to the U.S. Food and Drug Administration as part of its pre-market approval (PMA) submission, and will submit the study's complete data set for publication in a peer-reviewed journal, presentation at a major medical meeting or both.

Importance: Important

Transferability: Completely

Result card for TEC4: "Who will apply FIT?"

View full card

TEC4: Who will apply FIT?

Result

Apart of health professionals (primary care physicians and nurses, laboratory staff), people invited to screening will use this technology.

The EU guidelines for quality assurance in CRC screening and diagnosis {6} state that “people invited to screening need specific and clear instructions on how to use the kit. Factors that enhance accessibility and uptake are the design of a test kit, and simple and clear instructions which should be provided with the test kit. Effective sample collection is critical to the success of a screening programme with FOBT, so the process of collection should be as simple as possible. Physical and mental disabilities in the screened age group could be one of the reasons for non-participation.

Laboratory staff is necessary in settings where a screening programme is based on a FOBT. The training and skills required are dependent on the type of the test (gFOBT or iFOBT, qualitative or quantitative); staffs require supervision by appropriately qualified individual with expertise in clinical biochemistry, and the day-to-day running of the laboratory must be managed by an appropriate skilled scientific officer. Laboratory staff required training in good laboratory practice, training in the performance of the FOBT, and training in the use of the IT system used to record results, in addition to basic understanding of the CRC process. Laboratory Manager required training on managerial skills, internal quality control and external quality assurance; interactions between the laboratory process and the whole screening programme. Individual with expertise in clinical biochemistry which is responsible for the operation of laboratory required training on in-depth understanding of CRC, screening process, performance characteristics of different type of FOBT; in-depth understanding of the technology required to perform the FOBT.

Primary care physicians and nurses in primary care should be informed about national CRC screening programme, to be able to help people invited to screening, if they asked for, in form of answering questions on screening and tests, but not to perform FOBT on an individual basis”.

Importance: Important

Transferability: Partially

Result card for TEC5: "In what place and context is FIT intended to be used?"

View full card

TEC5: In what place and context is FIT intended to be used?

Result

FIT is used in population-based screening for CRC. Faecal occult blood testing for men and women in the range of 50-74 years is the only CRC screening method currently recommended by the EU {15}.

Importance: Important

Transferability: Partially

Result card for TEC6: "Are there any special features relevant to FIT?"

View full card

TEC6: Are there any special features relevant to FIT?

Result

Results {5-9}

iFOBT have improved test characteristics than gFOBT. In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme.

In contrast to gFOBT, iFOBT requires shorter transportation time frame due instability on room temperature (this should be taken in account when sending samples via different MSs postal systems, should be returned within 3 days); new investments in laboratory; staff education (instructions on routine use and maintance of the analyser is provided by manufacturers); all three tests sample collection devices should be stored between 2 and 10 C in case of any delay in analysis, so refrigerated storage space are required. The number of analysers required will depend on the laboratory workload. iFOBT sample collection tubes will require disposal in rigid bins to contain any liquid, which requires different procedure and more manual handling.

Importance: Important

Transferability: Partially

Result card for TEC16: "To what population(s) will FIT be used on?"

View full card

TEC16: To what population(s) will FIT be used on?

Result

FIT is used in the population targeted for colorectal carcinoma screening (CRC). The target group is asymptomatic people at average risk, of both genders. Regarding the age-range, there is evidence endorsing the provision of CRC screening to average-risk individuals, beginning at age 50, to detect cancers at a favourable stage before they have advanced to a potentially lethal disease state. According the Ontario HTA Report {16} persons in whom age is the only risk factor for CRC are considered to be at average risk. Factors that place individuals at higher risk include a family history of CRC or adenoma, personal history of CRC or adenoma, and inflammatory bowel disease. There are other protocols for screening of individuals at higher risk for CRC.

In the European guidelines for quality assurance in CRC screening {6} it is suggested that “in the absence of additional evidence, the age range for a screening programme with iFOBT can be based on the limited evidence for the optimal age range in gFOBT trials. The best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (Level of the evidence IV). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (Level of the evidence VI - B). “

Importance: Critical

Transferability: Partially

Result card for TEC17: "Is FIT field changing rapidly?"

View full card

TEC17: Is FIT field changing rapidly?

Result

This field of faecal tests for CRC screening is changing fast according literature data. In addition to faecal DNA tests, new area of research is use of RNA markers in stool, as well as the use of DNA or RNA in plasma, serum and urine. Much work is still ongoing on use of protein biomarkers in blood for CRC screening and early detection.

For phase of FIT please see Result card TEC3.

Faecal DNA tests represent new group of faecal tests designed to detect molecular abnormalities in cancer or precancerous lesion that are shed into the stool. Two faecal DNA tests were commercially available: PreGen Plus, from 2003 to 2008, and ColoSure (single marker faecal DNA assay for methylated vimentin) the only commercially available test in the US, intended for individuals who are not eligible for more invasive CRC screening. New test showed evolution in the composition of the test, as well in pre-analytical factors and analytic factors in comparison with older faecal DNA tests. Authors of the 2012 AHRQ HTA Report {12} concluded that

faecal DNA tests have insufficient evidence about its diagnostic accuracy to screen for colorectal cancer in asymptomatic, average-risk patients; insufficient evidence for the harms, analytic validity, and acceptability of testing in comparison to other screening modalities. Existing evidence has little or no applicability to currently available faecal DNA testing.

At its website, Epigenomics stated that Septin9 test, the world's first blood-based IVD test for CRC screening, has been available as a CE-marked test kit in Europe and the Middle East since October 2009. For the improved Septin9 test, Epi proColon 2.0, according to the company's press release {17}, the fourth module of the PMA was submitted to FDA, which contained the clinical data generated with the test, including the results of the recently reported head-to-head comparative study of the performance of the Epi proColon® to FIT(18) (with no study results posed yet), previously announced data from a clinical validation study in a cohort of prospectively collected samples and other clinical study results generated during the development of Epi proColon®. On 15 05 2013 they also announced that results of the head-to-head comparative study between its blood-based CRC detection test Epi proColon and FIT will be presented at the workshop of the WEO CRC Screening Committee during conference in Orlando, May 17, 2013 {19}.

Importance: Important

Transferability: Completely

Result card for TEC18: "Are the reference values or cut-off points clearly established?"

View full card

TEC18: Are the reference values or cut-off points clearly established?

Result

Results {5-8,20}

Cut-off limits are important in CRC screening due the fact that, by increasing the positive cut-off limit, the test sensitivity and positivity rate decreases and specificity and positive predictive values for CRC detection increase.

European guidelines {6} state that "the choice of a cut-off concentration to be used in an immunochemical test to discriminate between a positive and negative result will depend on the test device chosen, the number of samples used and the algorithm adopted to integrate the individual test results. Whilst an increasing number of studies are reporting the experience of different algorithms, local conditions, including the effect on sample stability of transport conditions, preclude a simple prescribed algorithm at this time. Adoption of a test device and the selection of a cut-off concentration should follow a local pilot study to ensure that the chosen test, test algorithm and transport arrangements work together to provide a positivity rate that is clinically, logistically and financially acceptable (VI - A)".

Two out of three iFOBT are quantitative tests and have adjustable or user defined cut-off values (OC-Sensor and The FOB Gold); Hem-SP/MagStream HT is qualitative, and has a non-adjustable cut-off value:

- OC-Sensor is CE marked for a user defined cut-off (default setting 100 ng/mL), with 20 ng/mL in buffer as limit of detection.;
- Hem-SP/MagStream HT is qualitative, and has a non-adjustable cut-off at a Hb concentration equal to or greater than 20 ng/ml;
- The FOB Gold is CE marked for a user defined cut-off, with limit of detection of 14 ng/mL buffer, and measuring range of 15-1000 ng/ml.

Van Rossum at al. {20}, using OC-Sensor collection and OC-Micro analyser concluded that cut-off of 75 ng/ml brought optimal results and may be recommended for population screening in Netherlands. They concluded also in settings where colonoscopy capacity is insufficient, a cut-off up to 200ng/ml would result in minimal false negative results for cancer although more for advance adenoma.

Importance: Critical

Transferability: Completely

Investments and tools required to use the technology

Result card for TEC7: "What material investments are needed to use FIT?"

View full card

TEC7: What material investments are needed to use FIT?

Result

iFOBTs are around 10-fold more expensive than gFOBT. In an evaluation of three automated analytical iFOB methods in the UK {5}, investments made by a laboratory for use of FIT, include:

-Analytical platforms (automated analysers): The number of analysers required will depend on the laboratory workload; number required in the evaluation for a 5,000 sample per day workload will be 1 for HemSp/MagStream HT; 5 for OC-Sensor/DIANA, and 15 SentiFOB and 1 chemistry analyser for FOB Gold/SENTiFOB. All analysers required routine prentative maintance visits (part of the service contract, annualy, but depend on the workload). All analysers required a 13 amp power suplly and purified water to wash the cuvettes (OC-Sensor/DIANA) or for preparation of wash solutions (all three) and system solution (SentiFOB). All three have RS 232-C serial interface ports.

-Sample collection devices: for OC-Sensor the faecal sample was collected into the OC-Auto sampling bottle 3; for Hem-SP/MagStream HT (MagStream Hem-Sp®) the faecal sample was collected into the NEW HEMTUBE; for the FOB Gold the faecal sample was collected into the FOB Gold tube.

- Refrigerated storage space

- Clinical waste disposal. iFOBT sample collection tubes required disposal in rigid bins to contain any liquid, which required different procedure and more manual handling.

- End of life disposal: end of life disposal of the products may have financial and/or environmental costs, depending on the regulations in place (e.g. Waste Electrical and Electronic Equipment regulation in the UK).

Importance: Important

Transferability: Partially

Result card for TEC8: "What kind of special premises are needed to use FIT?"

View full card

TEC8: What kind of special premises are needed to use FIT?

Result

Please see Result card TEC6.

Importance: Important

Transferability: Partially

Result card for TEC9: "What equipment and supplies are needed to use FIT?"

View full card

TEC9: What equipment and supplies are needed to use FIT?

Result

Please see Result card TEC7.

Importance: Important

Transferability: Partially

Result card for TEC10: "What kind of data and records are needed to monitor the use FIT?"

View full card

TEC10: What kind of data and records are needed to monitor the use FIT?

Result

The data and records needed that are described refer to the entire CRC screening process, not only for testing with iFOBT.

According the European guidelines (2010) {6}, relevant data on each individual and every screening test performed must be recorded, including the test results, the decision made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death, should be ensured. The data must be linked at the individual level to several external data sources including population register, cancer or pathology registries, and registries of cause of death in the target population, to be able to evaluate the effectiveness of screening.

Legal authorisation should be put in place when the screening programme is introduced in order to be able to carry out programme evaluation by linking the above-mentioned data for follow-up (VI - A).

A database consisting of individual records (one record per person for each screening episode) is essential in order to produce results on screening performance (VI - A).

Quality control procedures for the database should be available and run regularly to check the quality of the data and to correct any data entry errors. (VI - A).

A table should be made to present the test results (positive, negative, or inadequate) by gender and age.

Following Process variables in screening with the faecal occult blood test (FOBT) and other in vitro tests should be applied: Screened/tested; Inadequate test; Positive test; Referral to follow-up colonoscopy.

Following Outcomes variables should be applied to CRC screening performed with any of the currently available primary screening tests; follow-up colonoscopy; lesions; adenomas; advanced adenoma; cancers; severe complications required hospitalizations; 30-day mortality.

Following data tables should be produced: target, eligible, invited, screened/tested at 1st screening and at subsequent screening episodes; inadequate test; positive test or screening; follow-up colonoscopy examination attended; negative follow-up colonoscopy examination; positive follow-up colonoscopy examination; lesion detected; adenoma detected; non-advanced adenoma detected; advanced/high-risk adenoma detected; cancer detected by stage.

Importance: Important

Transferability: Partially

Result card for TEC11: "What kind of registers are needed to monitor the use FIT?"

View full card

TEC11: What kind of registers are needed to monitor the use FIT?

Result

The registers needed are described in detail in the European guidelines for quality assurance in CRC screening {6}: “Relevant data on each individual and every screening test performed must be recorded, including the test results, the decision made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death, should be ensured. The data must be linked at the individual level to several external data sources including population register, cancer or pathology registries, and registries of cause of death in the target population, to be able to evaluate the effectiveness of screening.

Legal authorisation should be put in place when the screening programme is introduced in order to be able to carry out programme evaluation by linking the above-mentioned data for follow-up.”

Importance: Important

Transferability: Partially

Training and information needed to use the technology

Result card for TEC12: "What kind of qualification, training and quality assurance processes are needed for the use or maintenance of FIT?"

View full card

TEC12: What kind of qualification, training and quality assurance processes are needed for the use or maintenance of FIT?

Result

The qualification, training and quality assurance processes are described in detail in the respective European guidelines {6}:

“Laboratory staff is necessary in settings where a screening programme is based on a FOBT. The training and skills required are dependent on the type of the test (gFOBT or iFOBT, qualitative or quantitative); staffs require supervision by appropriately qualified individual with expertise in clinical biochemistry, and the day-to-day running of the laboratory must be managed by an appropriate skilled scientific officer.

Laboratory staff required training in good laboratory practice, training in the performance of the FOBT, and training in the use of the IT system used to record results, in addition to basic understanding of the CRC process.

Laboratory Manager required training on managerial skills, internal quality control and external quality assurance; interactions between the laboratory process and the whole screening programme.

Individual with expertise in clinical biochemistry which is responsible for the operation of laboratory required training on in-depth understanding of CRC, screening process, performance characteristics of different type of FOBT; in-depth understanding of the technology required to perform the FOBT.

All laboratories providing population screening should be led by a qualified clinical chemist trained and experienced in the techniques used for analysis and with clinical quality assurance procedures (Level of evidence VI, Grade of recommendation B).

All laboratories providing screening service should be associated with a laboratory accredited to ISO 15189:2007 Medical laboratories-Particular requirements for quality and competence. Also they should perform Internal Quality Control procedures and participate in appropriate External Quality Assessment Scheme (Level of evidence VI, Grade of recommendation B).

Automated check protocols should be implemented to ensure correct identification of the screen population and complete and accurate recording of individual screening participation and test results. Protocols should be implemented to ensure standardised and reliable classification of the test results (Level of evidence VI,

Grade of recommendation A).

Quality assurance of iFOBT

Manufacturer's Instructions for Use must be followed. Daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit should be performed. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures. Performance data (both internal quality control and external quality assessment data) should be shared and reviewed by a Quality Assurance team working across the programme. (Level of evidence VI, Grade of recommendation B).

All laboratory performance outcomes like uptake, undelivered mail, time from collection to analysis, analytical performance, positivity rates, lots and spoilt kits and technical failure rate, technical performance variability and bias should be each subject to rigorous monitoring (Level of evidence VI, Grade of recommendation A).“

Importance: Important

Transferability: Partially

Result card for TEC13: "What kind of training is needed for the personnel treating or investigating patients using FIT?"

View full card

TEC13: What kind of training is needed for the personnel treating or investigating patients using FIT?

Result

Please see Result card TEC12.

According the Manufacturer of FOB Gold NG assay, simple training is required in order to inform the users about the use of the product and results interpretation. The typical professional laboratory operator is able to use the test in a very short time.

Importance: Important

Transferability: Partially

Result card for TEC14: "What kind of training and information should be provided for the patient who uses FIT, or for his family/carer?"

View full card

TEC14: What kind of training and information should be provided for the patient who uses FIT, or for his family/carer?

Result

Information and education provided about CRC and CRC screening test and procedures is a key component of CRC screening programmes. Three phases in which information can be provided to participants are: Invitation phase (invitation for screening through invitation letters and leaflets); Reporting results page (screening test results are communicated to the participants), and Follow up phase (for people with positive FOBT results).

Personal invitation letters, preferably signed by the GP, should be used. Specific instructions on how to use FOBT kit or perform the bowel cleansing procedure need to be communicated to the patient. Patient should be able to understand written instructions how to perform these procedures. Written material should be clear, visually appealing and motivating.

Recommendations from EU Guidelines {6} on different screening process steps are (see also TEC14-Appendix 1):

“To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions **(VI - A).**

Primary health care providers should be involved in the process of conveying information to people invited for screening **(II - A).**

In the context of an organised programme, personal invitation letters, preferably signed by the GP,

should be used. A reminder letter should be mailed to all non-attenders to the initial invitation **(I - A).**

Clear and simple instruction sheets should be provided with the kit **(V - A).**

Use of a non-tailored leaflet for the general population is advised; the leaflet should be included with the invitation letter. Information about CRC screening risks and benefits, CRC risks (incidence and risks factor), meaning of test results, potential diagnostic tests and potential treatment options should be included **(VI - A)**.

Illustrations may be used, which would be particularly useful for minorities, the elderly or low-literacy participants **(II - A).**

Video/DVD may be a useful component in a multi-modal intervention in addition to written information, and would be particularly useful for the elderly, minorities and low literacy participants **(I - B)**.

For the elderly, increasing the number of components of the multi-modal intervention and the period over which these components are provided may be more effective **(I - B).**

A computer-based decision aid could be used to help both the general population and specific groups to make informed decisions about CRC screening **(I - B)**. The computer-based decision aid should be “user-friendly” and designed to fit with the computer abilities of the target population (general or specific groups).

If possible, all information provided by the screening programme should be available on a specific web site. This information should be regularly updated **(VI - A).**

Patient navigation could be used within CRC screening programmes, particularly to reach subgroups of the population such as the elderly, those with low literacy, and medically underserved patients. When used with minorities, the patient navigator should be from a similar ethnic background and/or live in the same community as the participant **(I - B).**

Verbal face-to-face interventions with a nurse or physician could be used to improve knowledge and participation. They would be useful to reach subgroups of the population such as the elderly, minorities and those with low literacy **(I - A).**

Nurses and primary care practitioners (GPs) should receive adequate training to be able to help people make informed decisions about CRC screening **(VI - A).**

CRC screening programmes should work closely with advocacy groups and the media and provide them with up-to-date, accurate and comprehensive information about CRC and CRC screening **(VI - A).**

A telephone or ideally a verbal face-to-face intervention, e.g. nurse or physician intervention, should be used to inform a patient of a positive screening test result, as obtaining such a result could be a source of psychological distress for the patient. A letter informing the patient should not be used as the only way of notifying a positive result **(VI - A).**

To increase endoscopy follow-up after a positive FOBT and facilitate communication, CRC

screening programmes should, where possible:

- Use a reminder-feedback and an educational outreach intervention targeted to the primary

care physician **(II - A)**;

- Provide patients with a written copy of their screening report **(II - A)**;

- Facilitate patient consultation with a gastroenterologist **(V - B)**;

- Describe the follow-up procedure, make the follow-up testing more convenient and

accessible **(VI - A)**; and

- Use direct contact intervention to address psychological distress and other specific barriers.

(V - B).

Each endoscopy service must have a policy for pre-assessment that includes a minimum data set relevant to the procedure. There should be documentation and processes in place to support and monitor the policy **(III - B).**

The endoscopy service must have policies that guide the consent process, including a policy on withdrawal of consent before or during the endoscopic procedure **(VI - B).**

Before leaving the endoscopy unit, patients should be informed about the outcome of their procedure and given written information that supports a verbal explanation **(VI - A).**

The outcome of screening examinations should be communicated to the primary care doctor (or equivalent) so that it becomes part of the core patient record **(VI - B).**

Ideally, the invitation letter and the letter used for notification of a positive result should be sent with a leaflet and should encourage participants to read it **(VI - A).**

Certain basic information, e.g. logistic/organisational information, description of the screening test, harms and benefits of screening, information about the FOBT kit and the bowel cleansing procedure, must be included in the invitation/result letter in case a person reads only the letter and not the leaflet **(VI - A).** ”

Importance: Critical

Transferability: Partially

Result card for TEC15: "What information of FIT should be provided for patients outside the target group and the general public?"

View full card

TEC15: What information of FIT should be provided for patients outside the target group and the general public?

Result

General information on CRC burden and CRC screening clinical importance and CRC screening methods available.

Importance: Important

Transferability: Partially

Discussion

Some limitations were observed during assessment of domain questions. Authors recognized importance of appropriate stakeholders’ involvement, but only one Manufacturer responded on our questions. Some assessment element questions are overlapping with assessment element questions in Health problem and current use of the technology (CUR) Domain; some should be placed in different order and some are very similar or almost identical in meaning. Authors suggest that assessment elements questions and results cards CUR 23, 24 and 25 should belong to Technical description and characteristics of the technology (TEC) Domain, as well as CUR 27. Referencing to other results cards is used to minimize duplication. Transferability judgement will be mostly appropriately done by HTA doers at national levels, according the core HTA data presented here.

Important for practice: In different settings, individual device characteristics like ease of use by participant and laboratory, suitability for transport, sampling reproducibility and sample stability are important and should be all taken into account when selecting the iFOBT most appropriate for CRC screening programme.

References

1. Young GP, St John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood tests for colorectal cancer screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. The American journal of gastroenterology. 2002;97(10):2499-507. eng.

2. Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Canadian Journal of Gastroenterology. 2012;26(3):131-47. eng.

3. Health Information and Quality Authority. Health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland. Dublin: Health Information and Quality Authority, 2009.

4. Rabeneck L RR, Thompson F, Mills M, Oleschuk C, Whibley AH, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Toronto, ON: Cancer Care Ontario, 2011 Nov 8 Contract No.: Program in Evidence-based Care Evidence-based Series No.: 15-8.

5. NHS Centre for Evidence-based Purchasing. Evaluation report: Immunohistocemical faecal occult blood tests. NHS Purchasing and Supply Agency, 2009 CEP09042.

6. Segnan N, Patnick J, von Karsa L, editors. European guidelines for quality assurance in colorectal cancer screening and diagnosis - First Edition. 1st ed. Luxembourg: Publications Office of the European Union; 2010.

7. Whyte S, Chilcott J, Cooper K, Essat M, Stevens J, Wong R, et al. Re-appraisal of the options for colorectal cancer screening. Report for the NHS Bowel Cancer Screening Programme. Sheffield: University of Sheffield, School of Health and related Research, 2011.

8. Guittet L, Guillaume E, Levillain R, Beley P, Tichet J, Lantieri O, et al. Analytical comparison of three quantitative immunochemical fecal occult blood tests for colorectal cancer screening. Cancer Epidemiol Biomarkers Prev. 2011 2011 Jul;20(7):1492-501. eng.

9. von Karsa L, Patnick J, Segnan N, Atkin W, Halloran S, Lansdorp-Vogelaar I, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis: overview and introduction to the full supplement publication. Endoscopy. 2013;45(1):51-9. eng.

10. van Rossum LGM, van Rijn AF, van Oijen MGH, Fockens P, Laheij RJF, Verbeek ALM, et al. False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening. International Journal of Cancer. 2009;125(4):746-50.

11. Young GP. Fecal immunochemical tests (FIT) vs. office-based guaiac fecal occult blood test (FOBT). Pract Gastroenterol. 2004 2004;28(6):46-56.

12. Lin J, Webber E, Beil T, Goddard K, EP W. Fecal DNA Testing in Screening for Colorectal Cancer in Average-Risk Adults. Rockville, MD: Agency for Healthcare Research and Quality, 2012 Contract No.: AHRQ Publication 12-EHC022-EF.

13. Exact Sciences Corp. Top-Line Data Show Exact Sciences' Cologuard Test Demonstrates 92 Percent Sensitivity in the Detection of Colorectal Cancer. [Internet]. 2013, April 18 [cited 2013 Aug 9]. Available from: http://investor.exactsciences.com/releasedetail.cfm?ReleaseID=757341.

14. ClinicalTrials.gov. Multi-Target Colorectal Cancer Screening Test for the Detection of Colorectal Advanced Adenomatous Polyps and Cancer (DeeP-C) [Internet]. U.S. National Institutes of Health; 2013, Jun 18 [cited 2013 Aug 9]. Available from: http://prsinfo.clinicaltrial.gov/ct2/show/record/NCT01397747?id=NCT01397747&rank=1).

15. Council of the European Union. Recommendation of 2 December 2003 on cancer screening. 2003/878/EC. Off J Eur Union. 2003:34–8.

16. Medical Advisory Secretariat. Screening Methods for Early Detection of Colorectal Cancers and Polyps. Summary of Evidence-Based Analyses. Toronto: Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, 2009 Contract No.: 6.

17. Epigenomics AG. Epigenomics AG submits the fourth module and completes its PMA submission to the FDA for Epi proColon®. [Internet]. Epigenomics AG,; 2013, Jan 7 [cited 2013 Oct 26]. Available from: http://clinicaltrials.gov/ct2/show/record/NCT01580540.

18. ClinicalTrials.gov. Head to Head Study Epi proColon and FIT. [Internet]. U.S. National Institutes of Health; 2013 [updated 2013, Feb 6; cited 2013 Oct 26]. Available from: http://clinicaltrials.gov/ct2/show/record/NCT01580540.

19. Epigenomics AG. Results of Comparative Study between Epigenomics Epi proColon® and FIT to be Presented at Digestive Disease Week. [Internet]. Epigenomics AG,; 2013, Mar 15 [updated 2011; cited 2013 Oct 26]. Available from: http://clinicaltrials.gov/ct2/show/record/NCT01580540.

20. van Rossum LGM, van Rijn AF, Laheij RJF, van Oijen MGH, Fockens P, Jansen JBMJ, et al. Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme. British journal of cancer. 2009;101(8):1274-81.

Safety

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Summary

FIT and gFOBT are non-invasive tests and therefore no direct harms are expected. Indirect harms can be caused by a wrong or delayed diagnosis or by harms related to subsequent colonoscopy. Eventually, psychological impact of the screening (including psychological consequences of false-positive and false-negative test results) and patient discomfort related to the procedures must be considered.The overall number of adverse events depends on sensitivity and specificity of the screening tests.

Subsequent colonoscopies may cause following complications – perforations of the colon, bleeding, infections, pain and discomfort. The false-positive test results may cause anxiety and distress, overdiagnosis and overtreatment. The false-negative test results may delay the detection of illness and the start of treatment.

The onset of harms (both psychological and from subsequent colonoscopies) may be immediate or delayed.

There is no evidence that there are susceptible patient groups that are more likely to be harmed through use of FIT. However, patients with comorbidities can be under higher risk with follow-up colonoscopy.

There are some organisational factors, which can affect the harms. The false-positive test results from gFOBT can be reduced by following dietary and medication restrictions. The FIT samples should be kept in refridgerator and cooling bags should be used when sending samples to clinic.

The risk of false-positive and false-negative test results might be increased if the laboratory personnel is unexperienced (risks of inaccurate interpretation of results). Complications from colonoscopy also may depend on the education and experience of health professional.

Introduction

The safety domain describes unwanted or harmful effects from FIT and gFOBT. As colonoscopy is directly connected to FIT and gFOBT, the unwanted effects from colonoscopy are also described. Indirect harms specific to colorectal cancer screening in vitro are false-positive and false-negative test results, which may cause anxiety and stress, and lead to unnecessary further investigations (eg colonoscopy, which can cause harm in turn) or may cause delay in detection of the illness.

Methodology

Frame

A modified collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description (modified from collection scope)** In CRC screening colonoscopy, that is invasive procedure, is used after positive FIT or gFOBT for approving or disapproving the occult blood test result. In that context colonoscopy is directly connected with using FIT or gFOBT and the harms related with colonoscopy are included in the analysis.
Intended use of the technology (modified from collection scope)	Screening Colonoscopy is considered as gold standard for detecting lesions and colorectal cancer. **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description (modified from collection scope)** The psychological harms from false-positive or false-negative test results are most likely not different using FIT or gFOBT. Thus psychological harms are described without comparison. While gold standard for approving FIT or gFOBT results is colonoscopy, number of other diagnostic methods are available and are considered as comparisons if relevant. The alternative methods are - flexible sigmoidoscopy, computer tomography (CT), barium enema.
Outcomes	**CUR and TEC** • Health problems (target condition) • Epidemiology • Burden of disease • Target population • Current management of the condition • Features of the technology • Life-Cycle • Regulatory status • Utilization • Investments and tools required to use the technology • Training and information needed to use the technology **SAF** • Colonoscopy probability of perforation • Colonoscopy with polypectomy probability of perforation • Colonoscopy probability of death following perforation • Probability of bleeding following colonoscopy • Psychological harms from false-negatives and false-positives (and generally from participating in screening program) **EFF** • Test (FIT and gFOBT) sensitivity for adenomas • Test (FIT and gFOBT) sensitivity for cancer • Test (FIT and gFOBT) specificity for adenomas • Test (FIT and gFOBT) specificity for cancer • Adenoma incidence (detection rates) • Rectal cancer incidence (detection rates) • Colon cancer incidence (detection rates) • CRC incidence (detection rates) • Stage distribution of detected cancers • Rectal cancer specific mortality • CRC specific mortality • Overall mortality • Life years saved **ECO:** • Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening • Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme • Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG) • Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case

- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
C0001	Patient safety	What kind of harms can use of the technology cause to the patient; what are the incidence, severity and duration of harms?	yes	What kind of harms can use of FIT cause to the patient; what are the incidence, severity and duration of harms?
C0002	Patient safety	What is the dose relatedness of the harms to patients?	yes	What is the dose relatedness of the harms to patients?
C0003	Patient safety	What is the timing of onset of harms to patients: immediate, early or late?	yes	What is the timing of onset of harms to patients: immediate, early or late?
C0004	Patient safety	Is the incidence of the harms to patients likely to change over time?	yes	Is the incidence of the harms to patients likely to change over time?
C0005	Patient safety	Are there susceptible patient groups that are more likely to be harmed through use of the technology?	yes	Are there susceptible patient groups that are more likely to be harmed through use of FIT?
C0006	Patient safety	What are the consequences of false positive, false negative and incidental findings brought about using the technology to the patients from the viewpoint of patient safety?	yes	What are the consequences of false positive, false negative and incidental findings brought about using FIT to the patients from the viewpoint of patient safety?
C0007	Patient safety	What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of harmful events?	yes	What are the special features in using (applying/interpreting/maintaining) FIT that may increase the risk of harmful events?
C0008	Patient safety	What is the safety of the technology in comparison to alternative technologies used for the same purpose?	yes	What is the safety of FIT in comparison to alternative technologies used for the same purpose?
C0029	Patient safety	Does the existence of harms influence tolerability or acceptability of the technology?	yes	Does the existence of harms influence tolerability or acceptability of FIT?
C0020	Occupational safety	What kind of occupational harms can occur when using the technology?	yes	What kind of occupational harms can occur when using FIT?
C0040	Environmental safety	What kind of risks for public and environment may occur when using the technology?	yes	What kind of risks for public and environment may occur when using FIT?
C0061	Safety risk management	Is there evidence that harms increase or decrease in different organizational settings?	yes	Is there evidence that harms increase or decrease in different organizational settings?
C0062	Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	yes	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?
C0063	Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?	yes	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?
C0060	Safety risk management	How does the safety profile of the technology vary between different generations, approved versions or products?	no	Irrelevant in the context of outcomes stated in project description (colonoscopy has probably not changed over the past years and psychological harms from false-positives and false-negatives are the same no matter what test is used)
C0064	Safety risk management	How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)?	no	Will be discussed already under Issue C0040

Methodology description

Technology description:

In CRC screening, colonoscopy, that is invasive procedure, is used independently or after positive FIT or gFOBT for confirming or rejecting the occult blood test result. In that context colonoscopy is directly connected with using FIT or gFOBT and the harms related with colonoscopy are included in the analysis.

Use of technology:

Colonoscopy is considered as gold standard for detecting colon lesions and colorectal cancer.

Comparison:

The psychological harms from false-positive or false-negative test results are most likely not different using FIT or gFOBT. Thus psychological harms are described together.

While gold standard for approving FIT or gFOBT results is colonoscopy, number of other screening methods are available and are considered as comparators if relevant. The alternative methods are - flexible sigmoidoscopy, video capsule, computer tomography (CT), barium enema imaging.

Information sources

The domain literature search was used as the main information source. Also the studies from HAS (Haute Autorité de Santé) reports dated 2008 {2} and 2013 {1} were used. Relevant Cochrane systematic reviews were used. Additional searches were done through the Internet engine Google, where guidelines, reports and some free articles/studies on Oxford journals, PubMed etc. were found.

Quality assessment tools or criteria

None.

Analysis and synthesis

Different information sources were used to answer domain questions.

Result cards

Patient safety

Result card for SAF1: "What kind of harms can use of FIT cause to the patient; what are the incidence, severity and duration of harms?"

View full card

SAF1: What kind of harms can use of FIT cause to the patient; what are the incidence, severity and duration of harms?

Method

Domain research was used and completed with other studies used in HAS report dated 2008 and information from HAS recommendation dated 2013. Systematic reviews referenced in HAS report 2008 {3, 8} were used as a basis for this result card.

Result

The screening methods gFOBT and FIT are non-invasive procedures that are therefore not likely to cause any direct harm.

Indirect harm can be caused by a wrong or delayed diagnosis (see Q6) or by harms related to subsequent colonoscopy. Indeed, participants with a positive result of the screening test are referred for further diagnostic evaluation by invasive procedures which may be associated with various adverse events (see point 1 Harms from colonoscopy).

Furthermore, gFOBT and FIT may have a psychological impact related to the procedure itself and related to positive results (see point 2 Psychological harms).

The overall number of adverse events may be influenced by the number of colonoscopies that depends on sensitivity and specificity of the screening test {3}. 1) **Harms from Colonoscopy**

Summary of results:

The overall colonoscopy related morbidity is estimated to 5%. Minor complications such as bloating, abdominal pain or other complications related to bowel preparation have been reported. Major complications are rare and include perforation of the gut and haemorrhage. Complications related to sedation (hypoxia) or cardiovascular complications can be also observed. Infection risks are very rare. {4, 1}

One study also addressed the embarrassment experienced during endoscopy {5}.

The frequency of colonoscopy complications varies from one study to another and results from the different trials are presented further below for completeness of information.

As for the duration of harms Senore et al. {5} found that in about 90% of the cases symptoms were of short duration (arose within two hours from screening and were resolved within four hours).

Summary table of selected references:Author, year	Type of reference	Title	Conclusions
HAS, 2013 {1}	National recommendation	HAS recommendation on colorectal screening and prevention	The overall morbidity related to colonoscopy is estimated to 5%. Major complications are rare.
Medical Services Advisory Committee, 2004 {4}	Assessment report	Faecal occult blood testing for population health screening	Occasional complications are associated with bowel preparation and sedation prior to colonoscopy.
Hewitson P, Glasziou P, Irwig L, Towler B, Watson E., 2007, update 2011 {3}	Cochrane systematic review	Screening for colorectal cancer using the faecal occult blood test, Hemoccult	The rate of perforation during colonoscopy is approximately 1 in 1,400. Major bleedings occurred in 1 out of approximately 1100-1500 procedures.
Quintero et al., 2012 {6}	Article	Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening	Among 24 subjects[1] in the colonoscopy group, 12 (50%) expereinced bleeding, 10 (42%) hypotension or bradycardia, 1 (4%) perforation, and 1 (4%) low blood saturation.

			Among 10 subjects[2] in the FIT group who had subsequent colonoscopy, 8 patients (80%) expereinced bleeding and 2 (20%) hypotension or bradycardia.
Guittet, L., et al., 2007 {7}	Article	Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population	A perforation of the gut occurred in one out of 644 patients screened by colonoscopy (0,2%).
Senore, C., et al., 2011 {5}	Article	Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting	The burden of bowel preparation was associated with a nearly five-fold increase in the occurrence of serious disturbances among people undergoing TC, as compared with FS.

Results from different trials:

- [Cochrane systematic review: Screening for colorectal cancer using the faecal occult blood test, Hemoccult; 2007, update 2011] {3}

A systemic review of literature published up to June 2010 has been done with a primary objective to determine whether screening for colorectal cancer using the faecal occult blood test (guaiac or immunochemical) reduces colorectal cancer mortality. Secondary objective was to evaluate the range of benefits and harms of screening.

Four randomised controlled trials (Nottingham, Funen, Goteborg, Minnesota) involving about 327,000 participants have been included in the review, all of them using Hemoccult test as screening method. In all of the trials, participants with a positive Hemoccult test were referred for further diagnostic evaluation, performed by colonoscopy in all trials except one (Goteborg), in which participants received sigmoidoscopy and double-contrast barium enema.

Among three trials that used colonoscopy as the primary means of further investigation, two reported adverse outcomes in detail (Minnesota, Nottingham) and found that the rate of perforation during colonoscopy is approximately 1 in 1,400.

In the Minnesota trial, of the 12,246 colonoscopies performed at the University of Minnesota hospital there were four perforations of the colon (all requiring surgery) and 11 serious bleeding complications (3 requiring surgery). The Nottingham randomised trial reported that there were seven complications (out of 1,474 procedures) associated with colonoscopy (five perforations, one major bleed, one snare entrapment). Six of these complications required surgery although none of these patients died from the colonoscopy complications.

Although participants from the Goteborg trial mainly received sigmoidoscopy and double-contrast barium enema in further investigation, colonoscopy has been also done in case of repeated failure of other diagnostic methods or for polypectomy. Therefore, adverse outcomes for both flexible sigmoidoscopy and colonoscopy are reported in this trial. One patient's large bowel was perforated during diagnostic endoscopy. Four perforations of the large bowel occurred during endoscopic polypectomy, and one case of bleeding occurred 12 days after polypectomy. No complications occurred in connection with the 1,987 double-contrast barium enemas.

- Quintero et al, 2012: Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening,] {6}

A randomized, controlled trial involving asymptomatic adults compared one-time colonoscopy with FIT every 2 years in a screening setting. Adults with positive result on FIT were further invited to undergo colonoscopy. The study design allowed for crossover between the two study groups. [3]

Major complications occurred in 24 subjects (0.5%)[4] in the colonoscopy group (12 subjects with bleeding, 10 subjects with hypotension or bradycardia, 1 subject with perforation, and 1 subject with low blood saturation) and in 10 subjects (0.1%)[2] in the FIT group in patients who had subsequent colonoscopy (8 subjects with bleeding and 2 subjects with hypotension or bradycardia.

- Guittet, L., et al. (2007). "Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population." {7}

This trial compared the screening performances of the gFOBT and the immunochemical faecal occult blood test (I-FOBT or FIT) in an average risk population sample of 10 673 patients who completed the two tests.

Patients with at least one positive test result were asked to undergo colonoscopy. One perforation was recorded in 644 colonoscopies. (0.2%)

- Senore, C., et al. (2011). "Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting." {5}

The study compared subjects' experiences of sigmoidoscopy and colonoscopy in a screening setting. They especially focused on side-effects other than perforation and bleeding risk, and provided an active follow-up beyond the period spent in the endoscopy unit with a prospective 30-day follow-up after discharge.

Adverse effects associated with the preparation were reported by 15.0%[5] of the interviewees examined with sigmoidoscopy and by 30.1%[3] of those examined with colonoscopy (OR: 2.44; 95% CI: 2.01–2.95). The most common complaints in both groups were abdominal pain, bowel distension and anal irritation, mentioned by 10.1%, 7.7% and 3.2% of people in the sigmoidoscopy group and by 12.8%, 11.1%, and 7.3% of those in the colonoscopy group.

People experiencing more than mild embarrassment were 3.8% and 4.0% for sigmoidoscopy and colonoscopy respectively.

Immediately after the test, some patients reported severe pain (16.6% in the colonoscopy group and 9,5% in the sigmoidoscopy group).

Adverse physical reactions following discharge were reported by 521 (34.7%) people examined with sigmoidoscopy and by 448 (37.4%) of those examined with colonoscopy. In about 90% of the cases symptoms arose within two hours from screening and resolved within four hours.

Bowel distension and abdominal pain were the most common complaints, they were reported as the only symptom by 15.6% and 4.5% of interviewees examined with sigmoidoscopy and by 14.7% and 6.0% of those undergoing colonoscopy screening, and in association by 8.5% of people examined with sigmoidoscopy and by 8.8% of those undergoing colonoscopy.

Patients who underwent sedated colonoscopy were more likely to report feeling dizziness after discharge (3.4%) than those having an unsedated exam (0.8%).

The 30- day admission rate was 1.34% (16/1197), 1.13% (11/976) and 0.88% (12/1363) in the sigmoidoscopy, colonoscopy and FIT arms respectively. In addition, four people (2 in the sigmoidoscopy and 2 in the colonoscopy arm) reported at the phone interview having been referred to an emergency department following onset of abdominal pain (3 cases) or hypotension: they recovered and were discharged within a few hours.

2) **Psychological harms**

Summary of results:

The screening procedures gFOBT or FIT, eventually followed by a colonoscopy, may have a psychological impact related to the procedure itself and related to positive results. Impact of screening on daily life and levels of anxiety after a positive result of the screening test have been reported in several studies. Outcomes of these studies were psychiatric morbidity, anxiety, distress, worry and the effect on daily life {8}.

One study in particular {9} reported quality of life and level of anxiety of participants of a colorectal cancer screening programme that have been tested by FIT or by sigmoidoscopy, concluding that the burden of participating in a CRC screening programme is limited.

- **Results from different trials:**[NHS Centre for Reviews and Dissemination : Diagnostic Accuracy and Cost-Effectiveness of Faecal Occult Blood Tests Used in Screening for Colorectal Cancer: A Systematic Review, 2007] {8}

Three studies have been cited in the NHS systematic review: Parker et al (2002), Mant (1990) et al and Lindholm et al (1997).

In the trial by Parker et al., there was no significant difference in the proportion of participants with psychiatric morbidity, before and three months after FOBT was offered. For people with a false positive FOBT, the highest anxiety levels occurred after notification of a positive test and before colonoscopy. The lowest level of anxiety was experienced the day after colonoscopy and this remained low one month later.

In Mant's paper 68% of people who had a false positive FOBT and filled the questionnaire reported experiencing distress, (62% of these slight distress, 24% moderate distress, and 14% very distressed). Sixty nine percent reported being worried that they may have cancer, and of these 68% reported experiencing slight distress, 24% moderate distress, and 8% were very distressed. Forty three percent of people found the dietary restrictions slightly disruptive, 6% moderately disruptive and 4% very disruptive. Delays in the process caused slight worry for 26% of people, moderate worry for 6%, and 4% were very worried.

In Lindholm's paper 46% of addressed people were worried by the invitation, and refused to participate, and of these, 15% were 'extremely' worried. Sixteen percent of those who participated in the screening reported being 'extremely' worried. For people with a negative FOBT, 19% experienced severe worry, and of these 18% said that their daily life was negatively affected. For people with an initial positive FOBT, 60% experienced severe worry, and 38% said there daily life was negatively affected.

- Kapidzic, A., et al. (2012). "Quality of life in participants of a CRC screening program."{9}

Quality of life and level of anxiety have been studied in Dutch participants of a colorectal cancer screening programme that have been tested by FIT or by sigmoidoscopy. Participants from CRC screening trials were sent a questionnaire, which included validated measures on generic health-related QOL, generic anxiety and screen-specific anxiety. The main research question of the study was whether QOL differed in participants with a positive test result compared with participants with a negative test result.

Thisretrospective questionnaire survey showed slightly worse QOL scores among positive FIT participants compared with FIT negative participants. Screen-specific anxiety was significantly higher among both positive FIT and sigmoidoscopy participants, indicating that a positive test result has a negative impact on participants' emotional well-being, although differences were small and not clinically relevant. A prospective study needs to be conducted, where participants receive questionnaires at different time points during the entire screening process.

[1] 0,5% of the screened population [2] 0.1% of the screened population [3] Among subjects who were assigned to undergo colonoscopy, 5649 subjects accepted the proposed strategy, whereas 1706 requested to be screened by means of FIT. Of the 5649 subjects who agreed to undergo colonoscopy, 4953 actually did so. Among subjects who were assigned to undergo FIT, 9353 subjects accepted the proposed strategy (and a total of 8983 subjects really underwent FIT) , whereas 117 asked to be screened by colonoscopy (and 106 really completed the test). This cross-over resulted in a total of 10611 patients receiving FIT and 5059 completing colonoscopy in a screening setting. Additionnaly, 663 FIT positive patients received colonoscopy. [4] As-screened population [5] Percentage calculated with regards to the total number of patients that completed the 30 days follow-up

Comment

- There is no direct harm caused by either gFOBT or FIT. Indirect harm can be caused by a wrong or delayed diagnosis or by harms related to subsequent colonoscopy. Eventually, psychological impact of the screening can be observed.

- The total number of adverse events may be different between gFOBT and FIT according to the number of colonoscopies which is related to the specificity and sensitivity of the test.

- Population of some analysed studies {6, 5} slightly differs in age from the target population defined by the EU recommendations as they do not cover the entire age range 50-74 years.

- All studies differed with respect to their approach to calculating the % of complications.

- In Kapidzic's study {9} of Quality of life, some patients filled-in the questionnaire up to 5 years after the screening took place, which could have influenced the QoL results. They also indicate having used a Dutch version of PCQ questionnaire for screen-specific anxiety.

Importance: Critical

Transferability: Completely

Result card for SAF2: "What is the dose relatedness of the harms to patients?"

View full card

SAF2: What is the dose relatedness of the harms to patients?

Method

This result card is removed, because it is not relevant.

Frame

This result card is removed, because it is not relevant.

Result

This result card is removed, because it is not relevant.

Comment

This result card is removed, because it is not relevant.

Importance: Unspecified

Transferability: Unspecified

Result card for SAF3: "What is the timing of onset of harms to patients: immediate, early or late?"

View full card

SAF3: What is the timing of onset of harms to patients: immediate, early or late?

Method

Domain research was used and completed with information from HAS report dated 2008 {2} and recommendation dated 2013{1}. Systematic reviews referenced in HAS report {8} were used as a basis for this result card.

Result

Summary of results:

The screening methods gFOBT and FIT are non-invasive procedures that are therefore not likely to cause any direct harm to the participants. Harms can be observed on a psychological basis or can be due to subsequent colonoscopy examination, with different timing.

Summary table of selected references

Author, year	Type of reference	Title	Outcome
HAS, 2013 {1}	National guideline	HAS recommendation on colorectal screening and prevention	Perforation of colon or haemorrhage can be immediate or delayed (7-21 days after colonoscopy).
Senore, C., et al., 2011 {5}	Article	Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting	Bowel distension and abdominal pain were the most common complaints of late onset.
Parker, M. A. et al., 2002 Article referenced in {8}	Article	Psychiatric morbidity and screening for colorectal cancer	Psychological impact can be observed during the whole period of testing. In patients with false positive results, anxiety scores fell the day after colonoscopy and remained low 1 month later.

Results from different trials:1) Physical reactions to colonoscopy

Risks of severe complications such as gut perforation and hemorrhage can be immediate or delayed (7-21 days after colonoscopy). {1}

One study specifically examined the risk of immediate and late reactions other than gut perforation and hemorrhage after colonoscopy and sigmoidoscopy in a screening setting {5}.

Among immediate reactions, patients reported serious reactions following bowel preparation (mainly abdominal pain, bowel distension and anal irritation), severe pain immediately after the exam and embarrassment. {5}

The most common post-procedural complaints were abdominal distension and pain.

2) Psychological impact

Psychological impact can be observed as well during the whole period of testing, including time before testing and time after obtaining the results. In a clinical trial (Parker et al, 2002) a general health questionnaire was sent to 2184 subjects before the offer of screening, and 1541 (70.6%) were returned. Of the 1693 subjects offered the questionnaire 3 months after the offer of screening, 1303 (77%) returned it. Anxiety scores were measured in 100 test positive patients and were highest after notification of a positive test and before investigation by colonoscopy. In patients with false positive results, scores fell the day after colonoscopy and remained low 1 month later. No sustained anxiety has been seen in screening participants.

Comment

Harms can be observed on a psychological basis or can be due to subsequent colonoscopy examination, with different timing.

Importance: Important

Transferability: Completely

Result card for SAF4: "Is the incidence of the harms to patients likely to change over time?"

View full card

SAF4: Is the incidence of the harms to patients likely to change over time?

Method

Domain research was used and completed with information from in HAS recommendation dated 2013 {1}.

Result

As the screening test is non-invasive procedure, no change in direct risk is expected over time. Risk of false negative results may be reduced by a better sensitivity of the test used for screening. Concerning false positive results, they may be reduced by better education and better compliance of the patient. As FIT is specific for human hemoglobine {1}, its use reduces the number of false positive results due to non-compliance of participants related to diet restriction.

Risk of complications of colonoscopy and sigmoidoscopy may be reduced by an experienced endoscopist. {1}

Comment

The reproducibility of the result and the consequent risk of false positive results may be influenced by patient's non-compliance. However, no studies comparing the impact of patient's compliance (diet, education) on the results of FIT and gFOBT are available.

Risk of complications of colonoscopy and sigmoidoscopy may be reduced by an experienced endoscopist. However, data on the reduction of the number of complications related to experience of endoscopist have not been found neither.

Importance: Important

Transferability: Partially

Result card for SAF5: "Are there susceptible patient groups that are more likely to be harmed through use of FIT?"

View full card

SAF5: Are there susceptible patient groups that are more likely to be harmed through use of FIT?

Method

Domain literature search was used.

Result

No susceptible patient goups are known, that would be more likely to be harmed through use of FIT or gFOBT. However there is one study addressing the risk of harm of colonoscopy in patients with co-morbidities.

- Hughes, K., B. Leggett, et al. (2005). "Guaic versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community." {13}

Complications related to colonoscopy are increased if participants with major co-morbidity are included in screening and referred for colonoscopy. One such patient of 92 patients, who underwent colonoscopy, developed heart failure during colonoscopy preparation.

Comment

No other susceptible patient groups were found from literature, that could be more likely to be harmed through use of FIT or gFOBT. One study suggests, that patients with co-morbidities can more likely to be harmed through use of colonoscopy.

Importance: Critical

Transferability: Completely

Result card for SAF6: "What are the consequences of false positive, false negative and incidental findings brought about using FIT to the patients from the viewpoint of patient safety?"

View full card

SAF6: What are the consequences of false positive, false negative and incidental findings brought about using FIT to the patients from the viewpoint of patient safety?

Method

The domain literature search and additional search was used.

Result

False-positive test results may cause anxiety and stress to patients. Also there is the possibility of overdiagnosis (leading to unnecessary investigations or treatment) and the complications associated with treatment. However no studies were found to address the possibility of overdiagnosis. False-negative test results may delay the start of treatment. {8}

Comment

False-positive and false-negative tests may cause anxiety, stress, overdiagnosis and delay in the start of treatment.

Importance: Important

Transferability: Completely

Result card for SAF7: "What are the special features in using (applying/interpreting/maintaining) FIT that may increase the risk of harmful events?"

View full card

SAF7: What are the special features in using (applying/interpreting/maintaining) FIT that may increase the risk of harmful events?

Method

The domain literature search and additional search was used.

Result

The risk of harmful events can be increased due to unexperienced laboratory personnel, who make mistakes, when reading test results{8}. There are many factors infuencing gFOBT test results – food, consumed medications, faecal hydration. FIT test, however does not have dietary or medications restrictions {13}.

- [NHS Centre for Reviews and Dissemination : Diagnostic Accuracy and Cost-Effectiveness of Faecal Occult Blood Tests Used in Screening for Colorectal Cancer: A Systematic Review, 2007] {8}

The accuracy of FOBTs depends upon appropriate performance and interpretation of the test(s). Interpretation of FOBTs may be problematic when they are done by inexperienced personnel. In a retrospective review of questionnaires applied to accredited laboratory personnel (in order to determine their ability to interpret FOBT results), 12% were unable to correctly interpret sample test cards (mainly false-positive results). This finding raised concerns that people with detectable colorectal cancers may be missed, solely because of errors in interpretation. One suggestion to improve test interpretation is the use of tests with automated reading. Alternatively a centralised location for the collection, processing, and interpretation of all tests would facilitate measures to improve consistency.

Guaiac tests are generally best at detecting large, more distal lesions. Because they depend upon peroxidase or pseudo-peroxidase activity in the faeces, and are not specific to the pseudoperoxidase activity of human haemoglobin, many variables are said to influence their results. These include dietary factors, for example animal haemoglobin/myoglobin in red meat, fruits and vegetables high in peroxidase activity (false-positive results), high doses of vitamin C (false-negative results), aspirin or other medication that may cause gastrointestinal bleeding (false-positive results) and faecal hydration. The drying out of the faecal specimen and exposure to high ambient temperature can also result in false negative findings. Conversely rehydration of the sample may deactivate the peroxidases from fruit and vegetables reducing the number of false positive results. A systematic review of five RCTs of CRC screening using a guaiac test (Haemoccult) suggested that dietary restriction during unrehydrated FOBT may not be necessary as it did not appear to affect positivity rates and completion rates. However, the review did not include evidence on the use of more recent guaiac tests such as Haemoccult Sensa, which are believed to be more susceptible to the effects of diet. It also failed to account for dietary differences between countries and ethnic groups

Complications from colonoscopy may depend on the education and experience of health professional {13}.

Comment

The risk of harmful events may be increased due to unexperienced laboratory personnel, dietary and medication restrictions (gFOBT) and education and experience of health professionals.

Importance: Important

Transferability: Completely

Result card for SAF8: "What is the safety of FIT in comparison to alternative technologies used for the same purpose?"

View full card

SAF8: What is the safety of FIT in comparison to alternative technologies used for the same purpose?

Method

The additional literature search was used.

Result

The alternative technologies used for the same purpose are – colonoscopy (not specifically addressed here as covered elsewhere in the document), flexible sigmoidoscopy, computer tomography (CT) and barium enema. As all of the three techniques are invasive, non-invasive FIT and gFOBT tests are safer in terms of colonic perforation, ionizing radiation or sedation performed.

Levin, et al. (2002). Complications of screening flexible sigmoidoscopy {16}

Flexible sigmoidoscopy (FS) is an invasive diagnostic test and can cause perforation in the lining of the bowel, bleeding and infection. Sedation can cause problems with breathing, heart rate and blood pressure. The principal finding of this study was that the rate of complications after FS is modest. Approximately 1 in 5000 screening subjects was hospitalized for a gastrointestinal complication, and 1 in 16,000 was hospitalized for a serious complication. Colonic perforations, serious bleeding, and diverticulitis leading to surgery each occurred in this population less often than in 1 of 50,000 examinations.

Broadstock, (2007). Computed tomographic (CT) colonography for the detection of colorectal cancer – a Technical Brief {17}

Computer tomography has following disadvantages: patients are exposed to ionizing radiation, although low-radiation dose protocols are under investigation. False positives can occur as a result of retained stool in the bowel, diverticular disease (which can produce poorly distensible areas of the colon), or thickened bowel folds. Patients are associated with a very small risk of colonic perforation in CT colonograpy. Both, computer tomography and barium enema, were said to expose patients to ionizing radiation and to be associated with a very small risk of colonic perforation.

Importance: Important

Transferability: Completely

Result card for SAF10: "Does the existence of harms influence tolerability or acceptability of FIT?"

View full card

SAF10: Does the existence of harms influence tolerability or acceptability of FIT?

Method

The domain literature search was used.

Result

Wong et al {15} evaluated the factors associated with choosing immunochemical faecal occult blood test (FIT) or colonoscopy for colorectal cancer (CRC) screening among 3430 Chinese participants taken from a community-based cancer screening programme in Hong Kong and determined that the choice of the colonoscopy test was significantly influenced by the perceived discomfort induced by screening (OR 1.36, 95% CI 1.15–1.59, P < 0.001) . The findings show that those who did not perceive that CRC screening would inflict physical discomfort preferred colonoscopy. The update of this preliminary study {14}which includes 7845 patients also finds that the perception of the cancer screening being uncomfortable or embarrassing were associated with lower odds of choosing colonoscopy over FIT (p<0,001). The perception of risk did not significantly affect the choice of the tests.

Hol et al {12}compared the perceived test burden and acceptability of guaiac-based faecal occult blood test (gFOBT), faecal immunochemical test (FIT) and flexible sigmoidoscopy in a representative sample of the Dutch population randomly invited for the two tests and showed that FIT was perceived as slightly less burdensome than gFOBT due to less reported discomfort during faecal collection and test performance. The vast majority of participants would encourage friends or relatives to undertake either gFOBT or FIT (gFOBT: 96%, 95.8%; p=0.76) and were willing to attend a successive screening round (gFOBT: 94.1%, 94%; p=0.76). A significantly smaller proportion of FS screenees were willing to attend another round (83.8%; p< 0,005). The perceived risk of colorectal screening did not significantly influence the recommendation to friends and/or relatives, or the willingness to return for a successive screening round.

The results of 4 focal groups (n=28) set up to explore the perceptions of colorectal cancer and fecal immunochemical testing among African Americans in a north Carolina Community {11} showed that negative attitudes about FIT were mostly due to embarrassment when returning samples. The multistep instructions were also acknowledged as a potential problem for uptake.

The comparison of the uptake of FIT and gFOBT in 5,464 and 10,668 randomized eligible participants in a screening programme in the Clalit Health Service (Israel) {10} showed that compliance in taking the kits was better (but not statistically significantly better) with gFOBT (37.8% vs. 29.3%; OR 1.43 [95% CI 0.73–2.80]; P = 0.227). Independent factors associated with increased compliance were female gender, age ≥ 60 years and immigrant status.

Comment

The evidence is insufficient in quantity and quality to establish how the existence of perceived harms influences acceptability or tolerability. The findings suggest that the factor that influences acceptability is not so much risk perception but the discomfort of the test procedures {12, 14, 15}. The preference of FIT over colonoscopy can be influenced by the perceived discomfort and embarrassment associated with the latter but there seems to be many other factors involved, like age, educational level, occupational status or family history of colorectal cancer, that should be further explored {14}.

Even though the fewer number of faecal samples required for FIT with respect to gFOBT seems to lead to less discomfort during faecal collection, as the gFOBT has to be performed on three consecutive bowel movements and FIT is a one-sample test, evidence suggests that both tests are equally tolerable {12}. Both tests seem to be equally recommended to their family and/or friends by screening participants but it is not clear how this and other differences, like kit presentation, can influence the acceptance of both tests. Whilst some studies suggest that participation could be similar or even slightly higher with gFOBT {10}, others enhance that patients

receiving immunochemical kits are approximately twice as likely to participate than those receiving the guaiac kit {13}. It would be reasonable to think that persons would prefer the user-friendly characteristics of the immunochemical test (more convenient, less messy, no dietary restrictions) but it must be acknowledged that these tests may be challenging to some people and thus acceptance could depend on the setting {11, 13}.

Importance: Important

Transferability: Partially

Occupational safety

Result card for SAF9: "What kind of occupational harms can occur when using FIT?"

View full card

SAF9: What kind of occupational harms can occur when using FIT?

Method

The domain literature search was used.

Result

We found no studies that addressed occupational harms of FIT and gFOBT.

Universal precaution recommendations include the use of gowns to protect the skin and clothing from contamination with feces during procedures. Gloves should be worn during all procedures. Prolonged use of latex gloves may cause skin sensitivity, contact dermatitis or latex allergy. Both conjunctivitis and systemic infection can also occur from touching the eyes with contaminated fingers or others objects.

Importance: Important

Transferability: Completely

Environmental safety

Result card for SAF11: "What kind of risks for public and environment may occur when using FIT?"

View full card

SAF11: What kind of risks for public and environment may occur when using FIT?

Method

The domain literature search was used.

Result

We found no studies meeting our inclusion criteria that addressed risks for public and environment of fecal immunochemical tests.

Importance: Important

Transferability: Completely

Safety risk management

Result card for SAF12: "Is there evidence that harms increase or decrease in different organizational settings?"

View full card

SAF12: Is there evidence that harms increase or decrease in different organizational settings?

Method

The domain literature search was used.

Result

Only two organisational factors (dietary and medication restrictions, cooling measures) were considered to be potentially relevant, which could affect the harms. The accuracy of FOBTs depends upon appropriate performance and interpretation of the test and the interpretation of FOBTs may be problematic when they are done by inexperienced personnel (see SAF7).

In order to reduce the probability of a false positive result, dietary restrictions are usually recommended when guaiac-based tests are used. FIT tests have no dietary or medication restrictions {13}.

However, FIT test samples were requested in one study {10} to be kept in the refrigerator at home and brought back to clinic using cooling bags.

Importance: Important

Transferability: Completely

Result card for SAF13: "How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?"

View full card

SAF13: How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?

Method

The domain literature search was used.

Result

Safety risks for patients can be reduced by giving special attention to the management of patients with co-morbidities. Also the threshold of positivity of tests can influence the number of colonoscopies performed and thus safety.

Further education of GPs regarding the appropriateness of referrals for gFOBT in patients with major co-morbidities is important, because complications related to colonoscopy are increased in patients with major co-morbidites. {13}

- [NHS Centre for Reviews and Dissemination : Diagnostic Accuracy and Cost-Effectiveness of Faecal Occult Blood Tests Used in Screening for Colorectal Cancer: A Systematic Review, 2007] {8}

Changing the threshold for positivity (e.g. the number of windows required to show blue colouration on a Haemoccult slide) may change both the sensitivity and specificity of the test. Some studies stated that ‘any blue colour’ indicated a positive result, others specified that 2, 3 or more windows had to show a blue colouration to be positive, and some studies retested after what were considered ‘weak’ positive results. These differences in threshold will affect the observed positivity rate of the test, and as such, will impact on the proposed number of colonoscopies that would be required as a result of a screening programme with FOBT.

Importance: Important

Transferability: Completely

Result card for SAF14: "How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?"

View full card

SAF14: How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?

Method

The domain literature search was used.

Result

There were no safety risks for professionals found from literature.

Importance: Optional

Transferability: Completely

Discussion

There are no direct harms caused by either gFOBT or FIT.

Indirect harms can be caused by a wrong or delayed diagnosis or by harms related to subsequent colonoscopy. The total number of adverse events depends on the specificity and sensitivity of the tests and therefore may be different between gFOBT and FIT.

There was limited evidence on different safety issues. Besides, study differences (different populations, different study designs, different approaches in calculating the % of complications) made the interpretation and synthesis of the results difficult.

References

1. HAS recommendation on colorectal screening and prevention 2013 http://www.has-sante.fr/portail/upload/docs/application/pdf/2013-08/referentieleps_format2clic_kc_colon-vfinale_2013-08-30_vf_mel_2013-08-30_12-18-6_653.pdf

2. iIFOBT in the program of organized CRC screening in France, HAS 2008 http://www.has-sante.fr/portail/upload/docs/application/pdf/2008-12/rapport_-_place_des_tests_immunologiques_de_recherche_de_sang_occulte_dans_les_selles_ifobt.pdf

3. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. Cochrane Database Syst Rev 2007;1

4. Medical Services Advisory Committee. Faecal occult blood testing for population health screening. Reference 18 Assessment Report ed. Canberra: MSAC [www.msac.gov.au]; 2004.

5. Senore, C., et al. (2011). "Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting." J Med Screen 18(3): 128-134

6. Quintero, E., et al. (2012). "Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening." N Engl J Med 366(8): 697-706.

7. Guittet, L., et al. (2007). "Comparison of a guaiac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population." Gut 56(2): 210-214.

8. NHS Centre for Reviews and Dissemination. Diagnostic accuracy and cost-effectiveness of faecal occult blood tests used in screening for colorectal cancer: a systematic review. CRD Report 36. York: 2007.

9. Kapidzic, A., et al. (2012). "Quality of life in participants of a CRC screening program." Br J Cancer 107(8): 1295-1301.

10. Birkenfeld, S., R. G. Belfer, et al. (2011). "Factors affecting compliance in faecal occult blood testing: a cluster randomized study of the faecal immunochemical test versus the guaiac faecal occult test." J Med Screen **18**(3): 135-141.

11. Harden, E., A. Moore, et al. (2011). "Exploring perceptions of colorectal cancer and fecal immunochemical testing among African Americans in a North Carolina community." Prev Chronic Dis **8**(6): A134.

12. Hol, L., V. de Jonge, et al. (2010). "Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy." Eur J Cancer **46**(11): 2059-2066.

13. Hughes, K., B. Leggett, et al. (2005). "Guaic versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community." Aust N Z J Public Health **29**: 358-364.

14. Wong, M. C., G. K. John, et al. (2012). "Changes in the choice of colorectal cancer screening tests in primary care settings from 7,845 prospectively collected surveys." Cancer Causes Control **23**(9): 1541-1548.

15. Wong, M. C., K. K. Tsoi, et al. (2010). "A comparison of the acceptance of immunochemical faecal occult blood test and colonoscopy in colorectal cancer screening: a prospective study among Chinese." Aliment Pharmacol Ther **32**(1): 74-82.

16. Levin TR, Connell C, Shapiro JA, Chazan SG, Nadel MR, Selby JV (2002). Complications of screening flexible sigmoidoscopy. Gastroenterology 123: 1786-1792.

17. Broadstock, M. Computed tomographic (CT) colonography for the detection of colorectal cancer – a Technical Brief. NZHTA Technical Brief 2007; 6(6)

Appendices

None.

Clinical Effectiveness

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Summary

The main objective of this EEF domain is to facilitate summarized information on the effectiveness of the use of Fecal Immunochemical Test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC), under conditions of population based colorectal cancer screening, comparing with CRC screening with Guaiac –based fecal occult blood test (gFOBT).

We have not identified any study that compares FIT vs gFOBT in terms of mortality. The identified studies that provided mortality information compared screening using FIT vs no screening and reported only colorectal cancer specific mortality. A randomised controlled trial and three observational studies examined the effect of the use of FIT for colorectal cancer screening versus no screening on colorectal cancer mortality, showing a reduction on CRC mortality. The randomised controlled trial obtained no significant differences for colorectal and colon cancer mortality, but significant for rectal cancer mortality, when compared those FIT based screened vs. those no screened In addition, three Japanese observational studies with high risk of bias found a significant reduction in CRC mortality. Therefore no direct evidence comparing FIT vs gFOBT in the context of a population based colorectal cancer screening program is available.

A high-quality level systematic review studying differences in detection rates between FIT and GFOBT has been identified {10}. This systematic review selected five randomized controlled trials comparing detection rate of advanced neoplasm of FIT vs GFOBT for screening of CRC. The five trials were combined in a meta-analysis using random effects. Colonoscopy was the reference standard. The Pooled detection rates intended to screen cancers and significant adenomas were achieved in 2.23% of individuals with FIT and 1.24% of individuals with GFOBT. The pooled Odds Ratio of detection with FIT vs. with GFOBT was 1.50 (IC 95%: 0.94-2.39). Hence, the FIT have a 50%, but not significant, higher detection rate in comparison with gFOBT for advanced adenomas and cancer.

We identified 5 systematic reviews {10,15,16,17,18} and 3 additional diagnostic cohort trials{19,20,21} directly comparing FIT vs gFOBT. Overall 6 out of the 8 studies in the table conclude that FIT is more accurate and preferable to gFOBT for CRC screening.

The most recent and high quality review {15} analyses the performance characteristics of FIT compared with gFOBT, including two randomized control trials {11,12} and two observational studies {13,14}. In summary, the sensitivity of FIT for detecting CRC and AA compared with a standard gFOBT is superior. In the two randomized control trials, specificity was decreased for CRC and Advanced Adenoma when using FIT compared with gFOBT. On the other hand, these two studies reported higher advanced neoplasia detection rates for FIT compared with gFOBT. The PPV for detecting CRC and Advanced Adenoma using FIT is not different from the standard gFOBT. In general, the positivity rates for FIT using the manufacturer's standard cut-off level in hemoglobin concentration are higher than for gFOBT.

Overall, FIT performance is superior to the standard gFOBT for the detection of CRC and advanced adenomas in a population based screening setting.

Introduction

The Effectiveness domain in the Core HTA considers all relevant questions related to the efficacy and effectiveness of the technology, focusing in the assessment of the health benefits. We primarily consider patient relevant outcomes (mortality, morbidity, quality of life) and performance characteristics of the intervention (accuracy). Also have considered for assessment other related effects of the intervention (change in management).

We selected the relevant Assessment elements and they were translated into research questions. The assessment elements questions for EFF Domain were selected and adapted using as a model the Core Model for Screening Technologies.

The main objective of this EEF domain is to facilitate summarized information on the effectiveness of the use of Fecal Immunochemical Test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and colorectal cancer-CRC), under conditions of population based colorectal cancer screening, comparing with CRC screening with Guaiac –based fecal occult blood test (gFOBT).

Relevant issues and research questions selected

Mortality

D0001. What is the effect of FIT versus gFOBT for CRC screening on overall mortality?

D0002. What is the effect of FIT versus gFOBT for CRC screening on the mortality caused by CRC?

D0003. What is the effect of FIT versus gFOBT for CRC screening due to other causes than CRC?

Morbidity

D0005. How does the use of FIT versus gFOBT for CRC screening modify the symptoms and findings of adenomas and CRC?

D0006. How does FIT versus gFOBT for CRC screening modify the progression of adenomas and CRC?

D0026. How does the use of FIT versus gFOBT for CRC screening technology modify the effectiveness of subsequent interventions?

Change in management

D0020. Does use of FIT versus gFOBT for CRC screening lead to improved detection of adenomas and CRC?

D0022. Does FIT for CRC screening detect other potential health conditions that can impact the subsequent management decisions?

D0023.How does FIT versus gFOBT for CRC screening modifies the need for other technologies and use of resources?

Test accuracy

D1001. What is the accuracy of FIT for CRC screening against reference standard?

D1002. How does FIT compare to gFOBT for CRC screening in terms of accuracy measures?

D1003. What is the reference standard and how likely does it classify adenoma and CRC correctly?

D1005. What is the optimal threshold value of FIT for CRC screening?

D1006. Does FIT for CRC screening reliably rule in or rule out adenomas and CRC?

D1007. How does FIT accuracy vary in different settings?

D1008. What is known about the intra- and inter-observer variation in FIT interpretation?

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).

Intended use of the technology

Screening

CRC screening with faecal inmunochemical test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC).

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC).

Target condition

Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC).

Target condition description

CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease.

Target population

Target population sex: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people.

Target population description

Adults, average risk of CRC, aged 50 years or over.

The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis).

Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population

Comparison

CRC screening with Guaiac –based fecal occult blood test (gFOBT)

Description

CRC screening with Guaiac–based fecal occult blood test (gFOBT)

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet.

Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC)

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme

- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a "new" detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
D0001	Mortality	What is the effect of the intervention on overall mortality?	yes	What is the effect of FIT versus gFOBT for CRC screening on overall mortality?
D0002	Mortality	What is the effect of the intervention on the mortality caused by the target disease?	yes	What is the effect of FIT versus gFOBT for CRC screening on the mortality caused by CRC?
D0003	Mortality	What is the effect of the intervention on the mortality due to other causes than the target disease?	yes	What is the effect of FIT versus gFOBT for CRC screening on the mortality due to other causes than CRC?
D0004	Mortality	What is the mortality related to the diagnostic test?	no	There is no mortality directly associated to FIT or gFOBT
D0005	Morbidity	How does the use of the technology modify the symptoms and findings of the target condition?	yes	How does the use of FIT for CRC screening modify the symptoms and findings of adenomas and CRC?
D0006	Morbidity	How does the technology modify the progression of the target condition?	yes	How does FIT for CRC screening modify the progression of adenomas and CRC?
D0026	Morbidity	How does the technology modify the effectiveness of subsequent interventions?	yes	How does the use of FIT versus gFOBT for CRC screening technology modify the effectiveness of subsequent interventions?
D0008	Morbidity	What is the morbidity directly related to the technology?	no	There is no morbidity directly related to FIT or gFOBT.
D0020	Change-in management	Does use of the test lead to improved detection of the condition?	yes	Does use of FIT versus FOBT for CRC screening lead to improved detection of adenomas and CRC?
D0022	Change-in management	Does the test detect other potential health conditions that can impact the subsequent management decisions?	yes	Does FIT for CRC screening detect other potential health conditions that can impact the subsequent management decisions?
D0023	Change-in management	How does the technology modify the need for other technologies and use of resources?	yes	How does FIT versus FOBT for CRC screening modify the need for other technologies and use of resources?
D0021	Change-in management	How does the use of the test change physicians' management decisions?	no	A positive test must be folowed of new invasive tests for diagnosis (colonoscopy). It is not expected that the use of FIT vs gFOBT change the physician's management decisions. The strategy of performing new invasive diagnostic tests (colonoscopy) following a positive result that is accepted for gFOBT should be applied for FIT.
D0024	Change-in management	Is there an effective treatment for the condition the test is detecting?	no	There is no a need of key information regarding this question for the specific framing of this CORE HTA. There are clear evidences regarding treatment effectiveness for CRC and adenomas, and this ussue would not affect in a relevant way our specific scope.
D1001	Test accuracy	What is the accuracy of the test against reference standard?	yes	What is the accuracy of FIT for CRC screening against reference standard?
D1002	Test accuracy	How does the test compare to other optional tests in terms of accuracy measures?	yes	How does FIT compare to gFOBT for CRC screening in terms of accuracy measures?
D1003	Test accuracy	What is the reference standard and how likely does it classify the target condition correctly?	yes	What is the reference standard and how likely does it classify adenoma and CRC correctly?
D1005	Test accuracy	What is the optimal threshold value in this context?	yes	What is the optimal threshold value of FIT for CRC screening?
D1006	Test accuracy	Does the test reliably rule in or rule out the target condition?	yes	Does FIT for CRC screening reliably rule in or rule out adenomas and CRC?
D1007	Test accuracy	How does test accuracy vary in different settings?	yes	How does FIT accuracy vary in different settings?
D1008	Test accuracy	What is known about the intra- and inter-observer variation in test interpretation?	yes	What is known about the intra- and inter-observer variation in FIT interpretation?
D1004	Test accuracy	What are the requirements for accuracy in the context the technology will be used?	no	Already included within the question G0012 of the ORG domain which is related to quality standards.
D1019	Test accuracy	Is there evidence that the replacing test is more specific or safer than the old one?	no	Regarding specificity, it is already included in the effectiveness domain question D1002. Regarding safety, it is already included within SAF domain.
D0027	Test accuracy	What are the negative consequences of further testing and delayed treatment in patients with false negative test result?	no	Considered as a relevant question more specifically related to SAF domain (C006)
D0028	Test accuracy	What are the negative consequences of further testing and treatments in patients with false positive test result?	no	Considered as a relevant question more specifically related to SAF domain (C006)

D0011	Function	What is the effect of the intervention on global function?	no	Already included as a relevant outcome within SOC domain
D0014	Function	What is the effect of the technology on return to work?	no	Already included as a relevant outcome within SOC domain
D0015	Function	What is the effect of the technology on return to previous living conditions?	no	Already included as a relevant outcome within SOC domain
D0016	Function	How does use of the technology affect activities of daily living?	no	Already included as a relevant outcome within SOC domain
D0012	Quality of life	What is the effect of the technology on generic health-related quality of life?	no	Already included as a relevant outcome within SOC domain
D0013	Quality of life	What is the effect of the technology on disease specific quality of life?	no	Already included as a relevant outcome within SOC domain
D0030	Quality of life	Does the knowledge of the test result affect the patient's non-health-related quality of life?	no	Already included as a relevant outcome within SOC domain
D0017	Patient satisfaction	Was the use of the technology worthwhile?	no	Already included as a relevant outcome within SOC domain (Patient satisfaction, global value)
D0018	Patient satisfaction	Is the patient willing to use the technology?	no	Already included as a relevant outcome within SOC and ORG domains (Patient satisfaction, acceptance)
D0029	Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes?	no	This is a question to be answered with all the information available from all domains. It requires a comprehensive assessment of the overall value of the intervention.

Methodology description

Domain frame/PICO

The project scope is applied in this domain:

Technology	FIT for colorectal cancer screening vs. gFOBT colorectal cancer screening in organized screening program **Description** Procedure of gFOBT: the standard fecal occult blood (FOBT) test can detect small amounts of blood in the stool by submitting a portion of three consecutive bowel movements for testing. The test cannot identify polyps and some diet restrictions need to be considered, as the test is not specific for human blood alone. gFOBT is used for more than 30 years in routine, is widely available and inexpensive. If the test is positive, a colonoscopy will be needed to find the reason for the bleeding. Procedure of FIT: FIT (Fecal Immunochemical Test) for colorectal cancer screening, also called as iFOBT (immunochemical FOBT) screening, is more accurate than FOBT as it only identifies human blood. It needs only one stool sample, thus is more simple to complete. If the test is positive, a colonoscopy will be needed to find the reason for the bleeding. Colorectal cancer screening with faecal inmunochemical test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC) is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Stool samples could be periodically taken and analysed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). To ensure effectiveness, the screening interval in a national screening programme should not exceed two years for gFOBT and three years for FIT. Purpose of use: detect cancer, polyps, nonpolypoid lesions, which are flat or slightly depressed areas of abnormal cell growth and can also develop into colorectal cancer.
Intended use of the technology	Screening CRC screening with faecal immunochemical test (FIT) **Target condition** Adenomas, as non-malignant precursor lesions of Colorectal Cancer. **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. Adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not cause symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the general population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** Target population sex: any. Target population age: 50-74 years. Target population group: Asymptomatic people. **Target population description** Adults (both men and women), average risk of CRC, aged 50 years or over. The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years. The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. EU Council Recommendations suggests only the faecal occult blood test (gFOBT or FIT) for men and women aged 50–74 for CRC screening. Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population.
Comparison	CRC screening with Guaiac – based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect haemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analysed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC). The use of the test is considered under conditions of population based colorectal cancer screening in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states have established nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only gFOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

EFF domain Outcomes

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

Information sources

Answers to the selected research questions of the EFF domain are mainly based in systematic literature search in the following sources {EFF Appendix 1}:

1. A basic literature search for the technology (FIT_technology) (MEDLINE, EMBASE, Cochrane Library: CDSR, DARE, HTA database, CENTRAL).

1. A specific complementary EFF domain search strategy, using the following sources (MEDLINE, EMBASE, Cochrane Library, SCOPUS).

This specific literature search strategy was produced to answer the EEF domain research questions.

We merged the two databases, general and specific, excluding duplicates, and worked with it to answer all research questions. The final selection after deletion of duplicates included a total of 620 studies.

Additional information sources were used to answer specific research questions when the data retrieved through a systematic review did not provide adequate information (hand searching of journals and references in selected studies, trial registers and grey literature).

Retrieved articles were included or excluded according to the PICO adopted for the project scope and related directly to the outcomes selected in the EFF domain. Abstracts resulting from the literature searches were independently assessed by at least two investigators. A final database with 176 selected studies from the merger of the two search strategies used for our EFF domain, after excluding references not directly related to the EFF domain frame and research questions.

Priority was done to the identification of systematic reviews and clinical trials.

For research questions related with issues of mortality, morbidity and change in management the project approach were mainly based in prospective controlled clinical trials, meta-analysis or systematic reviews of clinical trials. Other study types and designs have been considered (observational studies, prognostic studies, registries, statistics) if adequate for some research questions.

For research questions related with test accuracy we searched for diagnostic accuracy reviews, and clinically relevant diagnostic studies comparing FIT and FOBT were selected. Inclusion criteria where: studies that report data on accuracy measures (sensitivity, specificity, positive and negative predictive values, likelihood ratios, SROC and other measures, detection rates), publication date after year 2000, FIT compared with gFOBT or alone, on asymptomatic average risk patients, age 50+ years, data on specific issues relative to selected research questions.

Relevant articles considered to meet inclusion criteria for one selected research question were fully assessed (described, data extraction table, quality assessment) by the investigators. Extraction tables where tailored to research questions issues.

Quality assessment tools or criteria

The quality of the selected studies was analyzed by using the Cochrane risk of bias checklist for randomized controlled trials and for non-randomized studies {1}. To evaluate the quality of systematic reviews we used the 11 items of the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR){2}. Test accuracy studies included in systematic reviews and qualified with QUADAS have also been reported.

Analysis and synthesis

Priority is given to reporting summary effects measures from systematic reviews and randomized clinical trials. When quantitative pooling of results is available or possible from meta-analysis it is presented. When the heterogeneity of studies and nature of data available prevent from pooling on a summary estimate, specific data are described and reported.

Summary informative evidence tables of selected studies are presented once reviewed for methodological quality. Data was synthesized in tables were possible and research questions were answered starting from the best quality of available evidence.

Assessing the accuracy of the screening test we report summary measures from the selected systematic reviews and meta-analysis (pooled sensitivity, pooled specificity, predictive values, likelihood ratios or area under receiver operating characteristic curve), and specific results from other prospective studies once reviewed for methodological quality.

Additional descriptive analysis is presented, interpreted and commented if necessary for the EFF assessment elements.

Result cards

Mortality

Result card for EFF2: "What is the effect of FIT versus gFOBT for CRC screening on overall mortality?"

View full card

EFF2: What is the effect of FIT versus gFOBT for CRC screening on overall mortality?

Method

Refer to domain search and domain methodology section.

Result

We have not identified any study that compares FIT vs gFOBT in terms of mortality. The identified studies that provided mortality information compared screening using FIT vs no screening and reported only colorectal cancer specific mortality. A randomised controlled trial {3} and four observational studies {4, 5, 6, 7} examined the effect of the use of FIT for colorectal cancer screening versus no screening on colorectal cancer mortality or incidence, but not on overall mortality. Tables 1 to 6 and Figure 1 {EFF Appendix 1} extract and evaluate the most important results of the five above mentioned studies. Because of the lack of direct evidence to answer the research question a GRADE profile has not been elaborated.

Importance: Important

Transferability: Completely

Result card for EFF4: "What is the effect of FIT versus gFOBT for CRC screening on the mortality caused by CRC?"

View full card

EFF4: What is the effect of FIT versus gFOBT for CRC screening on the mortality caused by CRC?

Method

Refer to domain search and domain methodology section.

Result

We have not identified any study that compares FIT vs gFOBT in terms of mortality. The identified studies that provide mortality information compared screening using FIT vs no screening. A controlled trial {3} and three observational studies {4, 6, 7} examined mortality effect of the use of FIT for colorectal cancer screening versus no screening. Therefore no direct evidence comparing FIT vs gFOBT in the context of a population based colorectal cancer screening program is available. Because of the lack of direct available evidence to answer the research question a GRADE profile has not been elaborated.

The tables 1 to 5 extract and evaluate the most important results of the four above mentioned studies. Only one of them is a randomised controlled trial{3}, two are case-control studies {6, 7} and one is an observational and comparative retrospective study{4}. The randomised controlled trial compares the use of one round Reverse Passive Hemagglutination (RPHA) immunochemical test along with an individual attribute degree value score versus no screening. This trial, which analyses the screening program conducted in Jiashan (China), presents several bias risks and it is no focused on our specific research question.

First at all, the index test differs from the test consider in our research question because the FIT was used together with a quantitative individual risk assessment method (Attributive Degree Value). On the other hand, the reference standard was initially sigmoidoscopy and colonoscopy only for positive sigmoidoscopies and for positive FIT for those who FIT was repeated. Individuals with a positive FOBT were asked to undergo flexible sigmoidoscopy (FS). If FS failed to detect colorectal lesions, the participants were asked to repeat the FOBT. Those without a lesion found by FS but with a positive repeated FOBT were re-examined by 150-cm colonoscopy to confirm the results. The no use of colonoscopy for all the positive FIT could lead to an underestimation of the colon cancer cases and may explain the better results for detection of rectal but no for colon cancer. Double reference standard can lead to a differential verification bias. That occurs when some of the index test results are verified by a different reference standard. This usually occurs when patients testing positive on the index test receive a more accurate, often invasive, reference standard than those with a negative test result. In this case, the results are overestimated.

The controlled trial is a cluster randomized trial based on townships allocation, with a high risk of bias in several key domains of the Cochrane risk of bias table (randomization, allocation concealment and blinding). Twenty one townships were matched by population size and age distribution into 10 pairs. In each pair, a table of random digits was used to allocate to the screening or to the control group. The unit of analysis was individuals, but there was no inter-cluster correction that would minimize the selection bias risk. On the other hand, there was no participant and personnel blinding, which implies a high risk of performance bias.

This trial obtained no significant differences for colorectal and colon, but significant for rectal cancer mortality, when compared those FIT based screened vs. those no screened. The 8 year cumulative colorectal cancer mortality rate per 1,000 was 2.08 for the FIT group (95% CI: 1.96-2.18) and 2.44 (95% CI: 2.33-2.55) for no screening (p=0.19). For the specific colon cancer mortality the 8 year cumulative mortality rate per 1,000 was 0.90 for the FIT group (95% CI: 0.83-0.97) and 0.83 for the no screening group (95% CI: 0.76-0.90) (p=0.222). The 8 year cumulative rectal cancer mortality rate per 1,000 was significantly different (p<0.05) for the FIT group (1.10; 95% CI: 1.02-1.18) vs the no screening group (1.61; 95% CI: 1.52-1.70).

The rest of the studies are observational retrospective studies with high risk of bias in most of the domains of the Cochrane risk of bias table. Two case-control studies compare, in the context of two different screening programs performed in two Japanese counties, the Odds Ratio of dying due to colorectal cancer for those screened within 1 to 5 years of case diagnosis vs. those no screened. The last one is a retrospective observational study that compares the five years survival rate of 194 screened detected colorectal cancer subjects versus 352 routinely detected (no screening) colorectal cancer at Hirosaki Hospital (Japan). Any of these observational studies provided high quality evidence of the effect of FIT versus gFOBT on the mortality caused by colorectal cancer in the context of a population based colorectal cancer screening program.

Comment

We have observed a similar reduction in CRC mortality in RCT of FIT versus no screening and in RCT of gFOBT vs no screening. If we compare the only one randomized clinical trial on CRC mortality in a population invited to FIT versus no screening {3} with the meta-analysis of four RCT on CRC mortality of gFOBT versus no screening {8}, we observe similar results but with a wide confidence interval. The meta-analysis used the Peto method and effect fixed modelization for obtaining an Odds Ratio of 0.84 (IC 95%: 0.78-0.9). Using the same method for estimating the effect of the unique RCT that compared FIT versus no screening the Odds Ratio would be 0.85 (CI 95%: 0.70-1.03). Table 7 {EFF Appendix 3}.

Importance: Important

Transferability: Completely

Result card for EFF6: "What is the effect of FIT versus gFOBT for CRC screening on the mortality due to other causes than CRC?"

View full card

EFF6: What is the effect of FIT versus gFOBT for CRC screening on the mortality due to other causes than CRC?

Method

Refer to domain search and domain methodology section.

Result

We have not identified any study that compares FIT vs gFOBT in terms of mortality. The identified studies that provided mortality information compared screening using FIT vs no screening and reported only colorectal cancer specific mortality. A controlled trial {3} and three observational studies {4, 5, 7} examined the effect of the use of FIT for colorectal cancer screening versus no screening on colorectal cancer mortality but not on overall mortality. Tables 1 to 5 {EFF Appendix 3} extract and evaluate the most important results of the above mentioned studies. Because of the lack of direct evidence to answer the research question a GRADE profile has not been elaborated.

Importance: Important

Transferability: Completely

Morbidity

Result card for EFF8: "How does the use of FIT for CRC screening modify the symptoms and findings of adenomas and CRC?"

View full card

EFF8: How does the use of FIT for CRC screening modify the symptoms and findings of adenomas and CRC?

Method

Refer to domain search and domain methodology section.

Result

A recent Italian screening programme by biennial immunochemical FOBT reported a retrospective comparison of cancer rate and stages between average risk screening participants and those who did not participate in the screening programme. Although the overall cancer rate was similar in the two populations (1.23 versus 1.20 per 1000 person-years), there were significant differences in TNM stage distribution between the two groups (stage III–IV cancers 0.24 versus 0.74 per 1000 respectively, p = 0.009).

This large cross-sectional study reported that colorectal cancers detected by immunochemical FOBT screening are identified at an earlier pathological stage, with significant prognostic and economic advantages to the populations screened {9}.

Importance: Optional

Transferability: Partially

Result card for EFF10: "How does FIT for CRC screening modify the progression of adenomas and CRC?"

View full card

EFF10: How does FIT for CRC screening modify the progression of adenomas and CRC?

Method

Refer to domain search and domain methodology section.

Result

Compared with standard gFOBT, current evidence from systematic reviews and clinical trials indicates a higher sensitivity for the detection of CRC and advanced adenomas, and higher rates of detection for CRC and advanced adenomas (refer to EFF12, EFF20, EFF22) {10,15,16,17,18}. A superior sensitivity and detection rate of adenomas is a distinguishing performance characteristic of FIT compared with gFOBT, thus proving a greater preventive capacity. If all advanced adenomas and CRC detected are removed progression of lesions could be avoided. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer.

TNM stage distribution of CRC detected in screening programmes using FIT shows an early detection, and early treatment of colorectal lesions before they become symptomatic can reduce morbidity and mortality associated to CRC.

A recent Italian screening programme by biennial immunochemical FOBT reported a retrospective comparison of cancer rate and stages between average risk screening participants and those who did not participate in the screening programme. Although the overall cancer rate was similar in the two populations (1.23 versus 1.20 per 1000 person-years), there were significant differences in TNM stage distribution between the two groups (stage III–IV cancers 0.24 versus 0.74 per 1000 respectively, p = 0.009). This large cross-sectional study reported that colorectal cancers detected by immunochemical FOBT screening are identified at an earlier pathological stage, with significant prognostic and treatment cost advantages to the populations screened {9}. A major goal of a colorectal cancer mass screening programme is to diagnose cancer at an earlier stage, thus permitting curative treatment at lower cost, as the prognosis and cost of late-stage cancer at diagnosis are quite different. In this screening programme most of the screen-detected cancers were diagnosed at a very early stage; 81 per cent were TNM stage I or II and were therefore treated with curative intent, compared with only44·0 per cent of cancers detected within the same age range in the non-screened population.

Comment

It could be a case of lead time bias. Those participants who do not participate in the screening programme are diagnosed after they have signs and symptoms of cancer, so they are in advances TNM stages. If the screening program does not modify the progression, the increase in survival time makes it seem as though screened patients are living longer when that may not be happening (the date of diagnosis is earlier for screened patients).

Importance: Optional

Transferability: Partially

Result card for EFF18: "How does the use of FIT versus gFOBT for CRC screening technology modify the effectiveness of subsequent interventions?"

View full card

EFF18: How does the use of FIT versus gFOBT for CRC screening technology modify the effectiveness of subsequent interventions?

Method

Refer to domain search and domain methodology section.

Result

We have not identified clinical trials or systematic reviews comparing FIT vs gFOBT in terms of the effectiveness of subsequent interventions (colonoscopy and surgery) in the context of population based colorectal cancer screening.

Importance: Optional

Transferability: Not

Change-in management

Result card for EFF12: "Does use of FIT versus FOBT for CRC screening lead to improved detection of adenomas and CRC?"

View full card

EFF12: Does use of FIT versus FOBT for CRC screening lead to improved detection of adenomas and CRC?

Method

Refer to domain search and domain methodology section.

Result

A high-quality level systematic review studying differences in detection rates between FIT and gFOBT has been detected {10). This systematic review selected five randomized controlled trials comparing detection rate of advanced neoplasm of FIT vs gFOBT for screening of CRC. The five trials were combined in a meta-analysis using random effects. Colonoscopy was the reference standard. The Pooled detection rates intended to screen cancers and significant adenomas were achieved in 2.23% of individuals with FIT and 1.24 % of individuals with gFOBT. The pooled Odds Ratio of detection with FIT vs. with gFOBT was 1.50 (IC 95%: 0.94-2.39). Hence, the FIT have a 50%, but not significant, higher detection rate in comparison with gFOBT for advanced adenomas and cancer. The existence of heterogeneity (I2: 70.7%) led to use random effects model.

Importance: Critical

Transferability: Completely

Result card for EFF14: "Does FIT for CRC screening detect other potential health conditions that can impact the subsequent management decisions?"

View full card

EFF14: Does FIT for CRC screening detect other potential health conditions that can impact the subsequent management decisions?

Method

Refer to domain search and domain methodology section.

Result

We have not identified clinical trials or systematic reviews comparing FIT vs gFOBT in terms of other health effects or clinical conditions not included in the project scope and requiring subsequent clinical management decisions. Therefore no direct evidence on other potential health conditions comparing FIT vs gFOBT in the context of a population based colorectal cancer screening program is available.

Importance: Optional

Transferability: Not

Result card for EFF16: "How does FIT versus FOBT for CRC screening modify the need for other technologies and use of resources?"

View full card

EFF16: How does FIT versus FOBT for CRC screening modify the need for other technologies and use of resources?

Method

Refer to domain search and domain methodology section.

Result

All the systematic reviews and available RCTs included reported statistically significantly higher participation rates for FIT compared with gFOBT {10, 11, 15}. This means a higher charge of diagnostic colonoscopies in the population. With respect to FIT performance, compared with standard gFOBT, current evidence indicates a higher sensitivity for the detection of CRC and advanced adenomas, and higher rates of detection for CRC and advanced adenomas. These advantages of FIT are offset by a higher positivity rate (depending on the used cut-off level), which in turn may require a greater number of colonoscopies. A superior sensitivity and detection rate of adenomas is a distinguishing performance characteristic of FIT compared with gFOBT. These performance characteristics change when the cut-off level in hemoglobin concentration is changed, allowing a screening program to select the optimal cut-off for the program (more cancers and pre-malignant lesions detected with the minimum number of colonoscopies required).

Positive rates varies among randomized clinical trials from FIT 5.5% to gFOBT 3.2% {11}; FIT 4.8% to gFOBT 2.8%{12}; FIT 11.2% to gFOBT 7.9% {13} and FIT 3.2% to gFOBT 10.1%{14}. Differences in positive predictive values for CRC or advanced adenoma were no statistically significant.

The total number of colonoscopies needed to confirm positive test results is higher for FIT comparing to gFOBT. In one RCT{11} 20,623 individuals were invited; 10,301 received gFOBT and 10,322 FIT. Tests were returned by 10,993 individuals, 4836 (46.9%) in the gFOBT group and 6157 (59.6%) in the FIT group. To evaluate the outcome in the 456 positives results, a colonoscopy was performed in 383 (84%) patients. Total number of colonoscopies was 103 in the gFOBT group and 280 in the FIT group. Cancer was found in 11 of the G-FOBTs and in 24 of the FIT. Advanced adenomas were found in 46 of the gFOBT and in 121 of the FIT. The number of polyps found with gFOBT was 220 (of which 154 adenomas) and 679 with FIT (of which 470 adenomas). In this RCT the specificity of the FIT for advanced

adenomas and cancer was lower compared with the gFOBT, but the detection rate for advanced adenomas and cancer with the FIT was significantly higher. Consequently, 3 times as many subjects tested with the FIT are referred for a negative colonoscopy. On the other hand, 3 times as many patients with advanced adenomas and 2 times more patients with cancer are left undetected in the gFOBT group compared with the FIT group, ultimately resulting in comparable Positive Predictive Values for both tests.

Importance: Important

Transferability: Partially

Test accuracy

Result card for EFF20: "What is the accuracy of FIT for CRC screening against reference standard?"

View full card

EFF20: What is the accuracy of FIT for CRC screening against reference standard?

Method

We used both basic search done for the whole project and domain search (described in the Domain Methodology section). Furthermore test accuracy issues relative to Research Questions EFF20, EFF22, EFF24, EFF26, EFF28, EFF30 were selected from the above mentioned searches.

Inclusion criteria where: studies that report data on accuracy measures (sensitivity, specificity, positive and negative predictive values, likelihood ratios, SROC and other measures, detection rates), publication date after year 2000, FIT compared with gFOBT or alone, on asymptomatic average risk patients, age 50+ years, data on specific issues relative to selected research questions. Two investigators independently reviewed the titles and abstract. Disagreement was resolved by discussion. See Table 8 {EFF Appendix 3} for included articles. These articles were used, where pertinent, to answer all the above-mentioned Research Questions.

The quality assessment criteria for studies we used for all above mentioned Research Questions are R-AMSTAR {2} {EFF Appendix 2} for systematic reviews and Cochrane risk of bias for observational studies {1}. Two independent reviewers assessed quality and bias. Disagreement was resolved by discussion.

Extraction tables where tailored to research questions issues. Articles covered by systematic reviews that were in our included list were not extracted.

Data was synthesized in tables were possible and research questions were answered starting from the best quality of available evidence.

Result

Very few good quality diagnostic studies comparing FIT versus gFOBT use as reference standard colonoscopy or flexible sigmoidoscopy for all positive or negative results in the index test {10,15}.

Allison et al. {14} and Park et al. {13} studied participants that would receive screening in practice. The reference standards used for each study were different, with Allison et al comparing FIT with gFOBT, and with Park et al comparing FIT with colonoscopy. In both studies, the reference standard and the index test were performed in a short time. In Allison et al, colonoscopy was not used as the comparator to FIT, although participants with a positive test were referred for colonoscopy, and those with a negative test were referred for FS. In Park et al, FIT results were compared directly with colonoscopy results. The index test was independent of the reference standard used.

In the study conducted by Park et al, positivity was slightly higher for FIT (11.2%) than for gFOBT (7.9%), but this difference was not statistically significant. The sensitivity for detecting CRC was statistically significantly increased when using FIT compared with gFOBT (FIT 92.3% versus gFOBT 30.8% [P<0.01]). The sensitivity of FIT (33.9%) compared with gFOBT (13.6%) for detecting advanced adenoma (AA) was significantly higher (P<0.05).

The difference in specificity for both CRC and AA was not statistically significant when comparing FIT (CRC 90.1%; AA 90.6%) with gFOBT (CRC 92.4%; AA 92.4%). The difference in PPV for both CRC and AA was not statistically significant when comparing FIT (CRC 12.8%; AA 23.3%) with gFOBT (CRC 6.7%; AA 13.1%).

In the study conducted by Allison et al, positivity was statistically significantly lower for FIT than the sensitive gFOBT used in the study (FIT 3.2% versus gFOBT 10.1% [P<0.01]). The difference in sensitivity for detecting CRC and AA was not statistically significant for FIT (CRC 81.8%; AA 29.5%) compared with gFOBT (CRC 64.3%; AA 41.3%).The specificity for both CRC and AA was statistically significantly higher for FIT than for gFOBT (CRC FIT 96.9% versus gFOBT 90.1% [P<0.01]; AA FIT 97.3% versus gFOBT 90.6% [P<0.01]). The PPV for both CRC and AA was also statistically significantly higher for FIT compared with gFOBT (CRC FIT 5.2% versus gFOBT 1.5% [P<0.01]; AA FIT 19.1% versus gFOBT 8.9% [P<0.01]). Positive likelihood ratio for distal cancer was 26.7 (95% CI 19.4-36.6) with FIT and 6.5 (4.3-9.6) with gFOBT. Positive likelihood ratio for distal adenomas ≥1 cm was 11.0 (7.9-15.3) with FIT and 4.4 (3.5-5.5) with gFOBT. This measure summarizes how many times more likely patients with the disease will test positive compared with patients without the disease.

In summary, the sensitivity and PPV of FIT for detecting CRC and AA compared with a standard gFOBT is superior. Differences on specificity are not so relevant. Positivity rates for FIT using the manufacturer's standard cut-off level in hemoglobin concentration are higher than for gFOBT.

In a review and meta-analysis {10} seven diagnostic cohort studies in diagnostic patients scheduled for colonoscopy are included. The pooled PPV for detecting advanced colorectal neoplasm was significantly higher for FIT than for gFOBT (0.41 *vs* 0.29, $P < 0.01$). The sensitivity of FIT (0.67, 95% *CI* 0.61–0.73) was superior to that of gFOBT (0.54, 95% *CI* 0.48–0.60), as were the specificities (0.85, 95% *CI* 0.83–0.87 *vs* 0.80, 95% *CI* 0.78–0.82). Figure shows the SROC for FOBT in diagnosing advanced colorectal neoplasm of diagnosed patients, which indicates the mildly higher diagnostic accuracy of FIT.


10936.EFF-20 Figure 1

Figure 1. Summary receiver operating characteristic curve (SROC) showing the diagnostic precision of guaiac-based fecal occult blood test (gFOBT) as Area Under the Curve (AUC) 0.7677, was lower than that of immunochemical fecal occult blood (iFOBT) as AUC 0.8241, for detecting advanced colorectal neoplasm in patients scheduled for colonoscopy.

From: Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ran ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: A meta-analysis. Journal of Digestive Diseases, 2010; 11 (3): 148-60.

Importance: Important

Transferability: Partially

Result card for EFF22: "How does FIT compare to gFOBT for CRC screening in terms of accuracy measures?"

View full card

EFF22: How does FIT compare to gFOBT for CRC screening in terms of accuracy measures?

Method

Please refer to EFF20

Result

We identified 5 systematic reviews {10,15,16,17,18} and 3 additional diagnostic cohort trials {19,20,21} directly comparing FIT vs gFOBT and they are listed in table 9 with R-AMSTAR and risk of bias results. Data reported on accuracy measures are presented in the relative column of above mentioned table, starting from the more robust available evidence.

Overall 6 out of the 8 studies in the table conclude that FIT is more accurate and preferable to gFOBT for CRC screening.

The most recent and high quality review {15} analyses the performance characteristics of FIT compared with gFOBT, including two randomized control trials {11,12} and two observational studies{13,14}. In summary, the sensitivity of FIT for detecting CRC and AA compared with a standard gFOBT is superior. In the two randomized control trials, specificity was decreased for CRC and Advanced Adenoma when using FIT compared with gFOBT. On the other hand, these two studies reported higher advanced neoplasia detection rates for FIT compared with gFOBT. The PPV for detecting CRC and Advanced Adenoma using FIT is not different from the standard gFOBT. In general, the positivity rates for FIT using the manufacturer’s standard cut-off level in hemoglobin concentration are higher than for gBOBT. Please refer to Table 9 for values of accuracy measures.

Overall, FIT performance is superior to the standard gFOBT for the detection of CRC and adenomas. FIT has additional important advantages compared to gFOBT: higher screening participation rates, potential for automation in the laboratory and to select the cut-off level of hemoglobin concentration that defines a positive test. However, the following potential disadvantages are: greater specimen instability and possibly higher positivity rates.

Comment

No merging of available data has been performed do to the wide variability in settings and presented outcomes.

Need for further research:

- More well-designed randomized controlled studies directly comparing guaiac and FIT.
- The use the Standards for Reporting of Diagnostic Accuracy guidelines is recommended for reporting future diagnostic accuracy studies.
- Studies should ideally recruit a representative screening population, use colonoscopy to confirm diagnosis regardless of the FOBT result, measure the detection of CRC and adenomas and report the results separately and combined, and allow outcome assessors access to clinical information that would be available in practice, but blind them to other information.
- Specimen instability issue must be considered in each setting.
- The type of FIT and associated costs, the appropriate haemoglobin cut-off to use, and the capacity for follow-up by colonoscopy or flexible sigmoidoscopy may contribute to deciding if FIT is an appropriate CRC screening tool.

Importance: Critical

Transferability: Partially

Result card for EFF24: "What is the reference standard and how likely does it classify adenoma and CRC correctly?"

View full card

EFF24: What is the reference standard and how likely does it classify adenoma and CRC correctly?

Method

Please refer to EFF20

Result

The reference standard used in most reviews was colonoscopy {10,15,17,22}. Burch et al reported that one study was a diagnostic cohort study in which 3090 patients underwent colonoscopy and an unspecified immunochemical FOBT: for the detection of all neoplasms, sensitivity was 53% and specificity 99.6%; for the detection of CRC, sensitivity was 52.6% and specificity 87.2% {17}.

We found one systematic review reporting accuracy measures for colonoscopy among a total of five colorectal cancer screening methods {22}. It included 130 articles in total (of these 20 were relative to colonoscopy) and the reported mean ± standard deviation sensitivity of colonoscopy for cancer and for large polyps (≥10mm) was respectively 94.7 ± 4.6 % and 92.5± 6.2 % (compared to FOBTs 45.7 ± 26.5% and 18.5 ± 11.8%). Instead the overall specificity of colonoscopy for detecting CRC was 99.8 ± 0.2% (compared to FOBTs 87.6 ± 11.4%). Colonoscopy has the highest sensitivity and specificity of the selected screening methods.

In the remaining reviews the results were not clear. Nevertheless, one of them{15} reported results about one study also included in this review. Park 2010 et al{13} implemented a prospective study in a large population of average- risk people in which everyone underwent colonoscopy after having FIT and gFOBT: confirmed with better evidence the observations of others that FIT has a higher sensitivity for detecting advanced colorectal cancers than gFOBT, and has an acceptable specificity that significantly reduces the need for colonoscopic evaluation in the screened population. FIT results were compared directly with colonoscopy results: the positive rate of gFOBT in patients with adenomas did not differ from the patients with normal colonoscopies (8.0 % vs. 7.3 %); however, the positive rate of FIT at the 75 and 100 ng/ml thresholds was higher in patients with adenomas compared with that of patients with normal colonoscopies (16.9 % vs. 7.5 %, and 14.6 % vs. 7.3% (P < 0.001 and P = 0.002), respectively.

Comment

Further literature research could be done on colonoscopy accuracy measures to gain a more comprehensive view, although most of the studies relative to accuracy measures of FOBTs refer to colonoscopy as the reference standard but do not report what these measures are for colonoscopy itself.

Importance: Critical

Transferability: Completely

Result card for EFF26: "What is the optimal threshold value of FIT for CRC screening?"

View full card

EFF26: What is the optimal threshold value of FIT for CRC screening?

Method

Please refer to EFF20

Result

We found a total of 7 studies relative to cut-off values for the amount of fecal blood that have attempted to define an optimal cut off value or have adopted producers indications and are here below described.

It is know that the positivity rate, specificity and the detection rate of advanced neoplasia varied with the cut-off level. A high-level quality review performed the analysis using different cut-off values in the meta analysis, and the superiority of FIT in the detection of advanced neoplasm was not significantly influenced. Ultimately, data extracted at a cut-off value of 75 ng/mL were considered as an acceptable trade-off between the detection rate and the number needed to scope {10}. Another review reported on 4 studies assessing FITs performances at multiple haemoglobin concentrations cut-off levels that differ from manufacture's recommendations: in general, increasing the cut-off level of haemoglobin concentration the positivity rate decreased and the specificity and PPV increased {15}.

The faecal haemoglobin concentration at first screening predicts subsequent risk of incident colorectal neoplasia: the adjusted hazard ratios increased from 1.43 (95% CI 1.08–1.88) for baseline faecal haemoglobin concentration of 20–39 ng/mL, to 3.41 (2.02–5.75) for a baseline concentration of 80–99 ng/mL (trend test p<0·0001), relative to 1–19 ng/mL {23}. Nevertheless, findings needs to be validated for each kit separately, with a longer term follow-up, since colorectal neoplasia typically takes 10 years to develop, and using a large, population-based longitudinal follow-up study {23}.

Furthermore, f-Hb is related to severity of colorectal neoplastic disease: median f-Hb concentration was higher in those with cancer than those with no (p<0.002) or non-neoplastic (p<0.002) pathology, and those with LRA (p=0.0001); polyp cancers had lower concentrations than more advanced stage cancers (p<0.04). Higher f-Hb was also found in those with HRA than with LRA (p<0.006), large (>10 mm) compared with small adenoma (p<0.0001), and also an adenoma displaying high-grade dysplasia compared with low-grade dysplasia (p<0.009); f-Hb was significantly higher in those with a large compared with a small adenoma (p<0.0001){24}. Nevertheless, these results could be limited by the fact that false negative f-Hb were not taken into account and only participants with a positive result were referred for colonoscopy.

The cut-off level increases detection both for haemoglobin and haemoglobin-haptoglobin: when varying the cut-off level from 2 mcg/ g of stool (recommended by the manufacturer) to 14 mcg/g of stool, sensitivities for advanced adenomas and large adenomas (≥ 1 cm in diameter) ranged 40-24 % and 50-30 % for haemoglobin, and 33-12 % and 41-13 % for haemoglobin-haptoglobin, respectively, whereas specificities ranged 90–97 % for hemoglobin and 91–99 % for haemoglobin-haptoglobin; at cutoff values of 6 mcg/g of stool for hemoglobin and 4 mcg/g of stool for haemoglobin-haptoglobin, the specificity was ~ 95 % for both tests {25}.

A major advantage of FIT is recognized to be the automated and easier to interpret and furthermore, it measures the concentration of haemoglobin in the buffer, thus making it possible to choose the cut-off value. Nevertheless, the effect of different cut-off level in different FIT kit cannot be detected because manufacturers quote the concentration of haemoglobin not in the faeces, but in the buffer solution and this varies between different devices. Therefore, simple comparisons of cut-offs were not possible {19}.

Cut-off level detection is also linked to the colonoscopy capability: when colonoscopy capacity was unlimited, the optimal screening strategy was to administer an annual FIT with a 50 ng/mL haemoglobin cut off level in individuals aged 45–80 years and to offer colonoscopy surveillance to all individuals with adenomas. When colonoscopy capacity was decreasing, the optimal screening adaptation was to first increase the FIT haemoglobin cut-off value to 200 ng haemoglobin per mL and narrow the age range to 50–75 years, to restrict colonoscopy surveillance, and finally to further decrease the number of screening rounds {26}.

Importance: Important

Transferability: Completely

Result card for EFF31: "Does FIT for CRC screening reliably rule in or rule out adenomas and CRC?"

View full card

EFF31: Does FIT for CRC screening reliably rule in or rule out adenomas and CRC?

Method

Please refer to EFF20.

Result

A high-quality review indicated that sensitivities were higher for the detection of CRC, and lower for adenomas, in both the diagnostic cohort and diagnostic case–control studies for both guaiac and immunochemical FOBTs {17}. Another review with lower quality due to unclear design and quality assessment of selected studies, compared sensitivity and specificity of the colorectal cancer mass screening methods: colonoscopy was reported as the one with best sensitivity and specificity while fecal occult blood test with the lowest. The mean ± standard deviation per patient sensitivities and specificity of colonoscopy respectively 94.7 ± 4.6 % and 99.8 ± 0.2% (compared to FOBTs 45.7 ± 26.5% 87.6 ± 11.4%) {22}.

A large population study found that the sensitivity of FIT for non-advanced adenomas, advanced adenomas, and cancer was 10.6%, 28.0%, and 78.6%, respectively. The sensitivity of FIT for advanced polypoid neoplasm (31.1%) was significantly higher than that of nonpolypoid ones (21.1%) (P <.001){27}. Furthermore, the sensitivity of FIT was in relation to neoplasm stage: FIT sensitivity showed stage-dependence and was 28.0% for advanced adenomas, 73.9% for invasive cancer, 66.7% for Tis plus T1 cancers, and 100% for T2 to T4 cancers (P for trend < .001){27}. The specificity was similar in relation with stage: 92.8% for invasive cancer, Tis plus T1 cancer and T2-T4 cancer.

Finally, the sensitivity of FIT for advanced neoplasms was in relation to location and morphology: the sensitivity was significantly lower for proximal polypoid advanced neoplasms compared with distal ones (27.7% vs 31.6%; P < .001) and proximal nonpolypoid advanced neoplasms compared with distal ones (16.2% vs 24.3%; P < .001) {27}. The trend was similar when proximal and distal, polypoid and nonpolypoid advanced adenomas were compared. For invasive cancers, although there was a trend toward lower sensitivity for proximal lesions, the result was not statistically significant {27}.

The I-FOBTs were significantly better than the G-FOBTs in detecting both cancers and advanced adenomas. The detection of cancers was at least twice as high with the I-FOBT as with the G-FOBT, and the number of advanced adenomas was about three to four times as high{19}. The same study also assessed detection according to stage of cancers at diagnosis: the proportion of Tis and stage 1 cancers was higher with I-FOBTs than with the G-FOBT. The differences between I-FOBTs and G-FOBTs, however, were not significant{19}. However, results need to be validated with cut off levels assessed in the faeces and not in the buffer solution {19}.

When applied on as second round test, the results reported here show that, despite a significant decrease in the PPV for CRC, a substantial number of significant lesions were detected; this applies more to advanced adenomas than to cancer cases and appears to be independent of the type of test used in the first round (guaiac FOBT or FIT) {28}.

Comment

FITs capability of reliably ruling in or out adenomas and CRC depends not only on its accuracy measures, but also on threshold and appropriate Mean Sejourn Time. Both of these issues need further research. Also refer to research question EFF15 for other factors influencing accuracy measures.

Importance: Important

Transferability: Partially

Result card for EFF28: "How does FIT accuracy vary in different settings?"

View full card

EFF28: How does FIT accuracy vary in different settings?

Method

Please refer to EFF20.

Result

Many factors affecting the FITs accuracy have been studied. These are reported in the following table.

Effect of variations of different factors on fecal blood detection immunochemical screening

Factor	Results	Conclusions	Reference
Round of detection	A significant decrease was observed in the PPV for advanced neoplasia between the first and second round, from 55% (132/239) to 44% (112/252; P=.017). The PPV for CRC was 8% (20/239) in the first round versus 4% (9/252) in the second round (P=.024). Ten interval cancers were diagnosed.	Despite a significant decrease in the PPV for CRC in a second round of screening, a substantial number of significant lesions are detected in a second screening round. This applies more to advanced adenomas than to cancer cases and appears to be independent of the type of test used in the first round (guaiac FOBT or FIT).	Denters 2012{28}
Temperature	The mean log10 Hb concentration in the low temperature group was significantly higher than those in the high temperature group (0.36 vs. 0.25 ng/ml, p=0.000). An increase in temperature of 1°C reduced the probability of a positive FIT by 3.1 %, but with no effect on detection rate of colorectal neoplasms. High ambient temperature was not a significant risk factor for either the positive FIT result or the detection of colorectal neoplasms. Nevertheless, other Authors* reported the FIT positive rate was significantly lower in summer than in winter, and explained these results as a decrease in fecal hemoglobin values in summer.	Potential instability of fecal hemoglobin at high ambient temperatures should be considered; however, its influence on performance of FIT may be attenuated by the short exposure time of fecal samples to high ambient temperature (i.e., rapid return system).	Cha 2012{29}
Delay between fecal sampling and delivery at the laboratory	Delay in sample return increased false negative immunochemical FOBT's. Mainly precursor lesions, but also colorectal cancer, will be missed due to delayed sample return. The decreased performance of the FIT due to delayed return of the sample was observed to be independent of the cut-off value for positivity of the FIT.	Although selection bias could in a certain measure result in a false negative result, The evidence in this study shows how important it is to control all aspects and logistics of screening protocols. Subjects invited for screening should be adequately informed of the necessity of prompt return of the sample and reporting the date of taking the sample. However, more complicated information and effort, as well as the pressure of prompt return, might also result in decreased participation. The production of a less sensitive hemoglobin stabilizing buffer with improved stability is suggested. Until a less sensitive hemoglobin stabilizing buffer is produced, monitoring delay between fecal sampling and laboratory research should be part of quality control for screening with immunochemical FOBT. Inviting participants to perform a second test when delay is 5 days or more could be considered.	Van Rossum 2009{30}
Diet restrictions	The restricted diet subgroup and unrestricted diet subgroup had showed significant difference for advanced neoplasm detection rate and compliance rate	FIT removes the need for dietary restrictons. However, some FIT advised alcohol and acetylsalicylic acid and similar restriction for 48 h before stool is collected (Rabeneck 2012).	Zhu 2010{10}
Type of care setting	Results demonstrated significant differences in the analytical performance among different FOBT methods.	Highly sensitive and specific FIT methods may be best suited for colorectal cancer screening programs where testing is performed in a central location. Guaiac-based methods are rapid and easy to perform and are suitable for bedside point-of-care testing albeit a high rate of false positive results should be expected.	Tannous 2009{31}
Sampling strategy used: multiple sample from consecutive stools or one sample	Number of samples for FIT: most kits require one sample, Hemoglobin NS-PLUS two samples over two days, HEMOCCULT ICT 3 samples/3days A one-day strategy resulted in an intermediate positive rate.	FIT is superior to gFOBT for participation rate (fewer samples, less stool handling). However, another study in France reported a two day testing (choice based on the fact that CRC bleeding is often intermittent) not to be a barrier to compliance (Faivre 2012)	Rabeneck 2012{15}
Colonoscopy capacity and variation	For all levels of colonoscopy capacity, FIT screening was more effective clinically and in terms of cost compared with gFOBT screening.	FIT should be used at higher hemoglobin cutoff levels when colonoscopy capacity is limited compared with unlimited and is more effective in terms of health outcomes and cost compared with guaiac FOBT at all colonoscopy capacity levels. Increasing the colonoscopy capacity substantially increases the health benefits of FIT screening	Wilschut 2011{26}
Sensitivity left vs right CRC	Sensitivities for subjects with left-vs right-sided advanced neoplasia were 33% (95% CI, 26 – 41%) and 20% (95% CI: 11 – 31%) at a specificity of 95% (overall sensitivity: 29%) and the areas under the receiver-operating characteristics curve were 0.71 (CI, 0.69 – 0.72) and 0.60 (CI, 0.58 – 0.63), respectively.	In conclusion, the immunochemical FOBT in our study was more sensitive for detecting subjects with left-vs right-sided advanced colorectal neoplasia. Our findings may stimulate further research in the field as well as modelling analyses to estimate the potential effect of site-specific test performance on the programmatic sensitivity and the effectiveness of annual or biennial FOBT based screening programmes, in particular with respect to protection from right-sided CRC.	Haug 2011{32}

* Grazzini G, Ventura L, Zappa M, et al. Influence of seasonal variation in ambient temperatures on performance of immunochemical faecal occult blood test for colorectal cancer screening: observational study from Florence district. Gut. 2010;59:1511– 1515.

Importance: Important

Transferability: Completely

Result card for EFF30: "What is known about the intra- and inter-observer variation in FIT interpretation?"

View full card

EFF30: What is known about the intra- and inter-observer variation in FIT interpretation?

Method

Please refer to EFF20.

Result

The development of automated systems for the interpretation of the test has increased the advantage of FITs. Accurate interpretation of gFOBTs is not easy and requires well-run laboratories. An automated FIT is easier to interpret, and minimizes human error in test processing, thus making it a more objective laboratory test with excellent quality control. Furthermore, it measures the concentration of hemoglobin in the buffer, thus making it possible to choose the cutoff value. It is also possible to reinterpret the test in case of a technical problem {19}.

Direct comparison between quantitative and qualitative immunochemical fecal occult blood tests (FOBTs) has been studied. One cohort study reported that quantitative FITs offers advantages in terms of transparency and flexibility regarding the positivity threshold (e.g., specificity can be oriented toward available colonoscopy resources or personal risk profiles) and in terms of a higher level of standardization regarding test analysis and interpretation {25}.

These findings are also confirmed by another cohort study that reported a positivity rates of 8.1% for the qualitative and 2.5% for the quantitative FIT. The detection rate was 5.2% for the qualitative and 14.4% for the quantitative FIT. The odds ratio of a “suspicious cancer and cancer” versus a “normal” result was 2.73 (95% CI=2.22–3.35) for the quantitative compared to qualitative FIT {33}.

Another study about inter-observer variability in interpretation of 5 visually read FOBTs methods (standard guaiac-based method and four immunochemical methods) reported no cases of observer variability except for Hemoccult ITC test this was only minimal (on 1 sample 2 observers recorded a faint band at the cut off and one called the test negative){31}.

Importance: Important

Transferability: Partially

Discussion

With the evidence available for the effectiveness of FIT for CRC screening, it could be argued that it is appropriate to implement FIT instead of gFOBT without direct evidence from high quality RCT on CRC mortality, given that FIT is more sensitive for advanced adenomas and cancer, at least presents equal high specificity and higher detection rates for advanced adenomas and cancer.

Referring to test accuracy assessment, well-designed randomized controlled studies directly comparing FIT and gFOBT are needed. The use the Standards for Reporting of Diagnostic Accuracy guidelines is recommended for reporting future diagnostic accuracy studies. Studies should ideally recruit a representative screening population, use colonoscopy to confirm diagnosis regardless of the FOBT result, measure the detection of CRC and adenomas and report the results separately and combined, and allow outcome assessors access to clinical information that would be available in practice, but blind them to other information. Specimen instability issue must be considered in each setting. The type of FIT and associated costs, the appropriate haemoglobin cut-off to use, and the capacity for follow-up by colonoscopy or flexible sigmoidoscopy may contribute to the evidence of FIT as an appropriate CRC screening tool.

Despite the differences in the design and heterogeneity of selected studies the analysis shows that FIF is more accurate and performs better than gFOBT in detecting advanced adenoma and CRC.

FIT has additional important advantages compared to gFOBT: higher acceptance and screening participation rates, needs a smaller number of stool samples, has no need for dietary restriction, potential for automation in the laboratory and to select the cut-off level of hemoglobin concentration that defines a positive test. However, potential disadvantages are greater specimen instability and possibly higher positivity rates.

Global balance between total health benefits and harms and costs is out of the scope of the EFF domain. The global impact of false positive screening results and false negative screening results, the potential effects of over-diagnosis and over-treatment have not been considered. This global balance could be obtained in a comprehensive view of all pieces of information produced by all domains of the CoreHTA and could need the design of specific analytical modeling.

References

1. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011.

2. Kung J, Chiappelli F, Cajulis OO, Avezova R, Kossan G, Chew L, et al. From Systematic Reviews to Clinical Recommendations for Evidence-Based Health Care: Validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for Grading of Clinical Relevance. Open Dent J. 2010; 4:84-91.

3. Zheng S, Chen K, Liu X, Ma X, Yu H, Chen K, et al. Cluster randomization trial of sequence mass screening for colorectal cancer. Dis Colon Rectum. 2003; 46(1):51-8.

4. Wada T, Saito H, Soma Y, Koeda J, Kawaguchi H, Tanaka M, et al. Survival benefit for patients with colorectal cancer detected by population-based screening program using an immunochemical fecal occult blood test. Int J Oncol 1996; 9:685-91.

5. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. Br J Cancer 2003; 89(1):23-8.

6. Saito H, Soma Y, Nakajima M, Koeda J, Kawaguchi H, Kakizaki R, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncol Rep 2000;7:815-9.

7. Saito H, Soma Y, Koeda J, Wada T, Kawaguchi H, Sobue T, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. Int J Cancer 1995; 61:465-9.

8. Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (Hemoccult): An update. Am J Gastroenterol 2008; 103(6):1541-9.

9. Parente F, Marino B, DeVecchi N, Moretti R, Ucci G, Tricomi P, et al. Colorectal Cancer Screening Group. Faecal occult blood test-based screening programme with high compliance for colonoscopy has a strong clinical impact on colorectal cancer. Br J Surg 2009; 96(5):533-40.

10. Zhu MM, Xu XT, Nie F, Tong JL, Xiao SD, Ran ZH. Comparison of immunochemical and guaiac-based fecal occult blood test in screening and surveillance for advanced colorectal neoplasms: A meta-analysis. J Dig Dis 2010; 11(3):148-60.

11. Van Rossum LG, van Rijn AF, Laheij RJ, van Oijen MG, Fockens P, van Krieken HH, et al. Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population. Gastroenterology 2008; 135(1):82-90.

12. Hol L, Wilschut JA, Van Ballegooijen M, van Vuuren AJ, Van Der Valk H, Reijerink JCIY, et al. Screening for colorectal cancer: Random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels. Br J Cancer 2009; 100(7):1103-10.

13. Park DI, Ryu S, Kim YH, Lee SH, Lee CK, Eun CS, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010; 105(9):2017-25.

14. Allison JE, Sakoda LC, Levin TR, Tucker JP, Tekawa IS, Cuff T, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. J Natl Cancer Inst 2007; 99(19):1462-70.

15. Rabeneck L, Rumble RB, Thompson F, Mills M, Oleschuk C, Whibley A, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. Can J Gastroenterol 2012; 26(3):131-47.

16. Fecal occult blood test for colorectal cancer screening: an evidence-based analysis. Ont Heal Technol Assess Ser. 2009; 9(10):1-40.

17. Burch JA, Soares-Weiser K, St John DJB, Duffy S, Smith S, Kleijnen J, et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: A systematic review. J Med Screen 2007; 14(3):132-7.

18. Fecal immunochemical tests for colorectal cancer screening: a systematic review of accuracy and compliance. CADTH Technol Overv 2010; 1(3):e0117.

19. Faivre J, Dancourt V, Denis B, Dorval E, Piette C, Perrin P, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. Eur J Cancer 2012; 48(16):2969-76.

20. Raginel T, Puvinel J, Ferrand O, Bouvier V, Levillain R, Ruiz A, et al. A Population-based Comparison of Immunochemical Fecal Occult Blood Tests for Colorectal Cancer Screening. Gastroenterology 2013; 144: 918-925.

21. Wong CKW, Fedorak RN, Prosser CI, Stewart ME, Van Zanten SV, Sadowski DC. The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer. Int J Colorectal Dis 2012; 27 (12):1657-64.

22. Allameh Z, Davari M, Emami MH. Sensitivity and specificity of colorectal cancer mass screening methods: A systematic review of the literature. Iran J Cancer Prev 2011; 4(2):88-105.

23. Chen LS, Yen AMF, Chiu SYH, Liao CS, Chen HH. Baseline faecal occult blood concentration as a predictor of incident colorectal neoplasia: Longitudinal follow-up of a Taiwanese population-based colorectal cancer screening cohort. Lancet Oncol 2011; 12(6):551-8.

24. Digby J, Fraser CG, Carey FA, McDonald PJ, Strachan JA, Diament RH, et al. Faecal haemoglobin concentration is related to severity of colorectal neoplasia. J Clin Pathol 2013; 66(5): 415-419.

25. Haug U, Hundt S, Brenner H. Quantitative immunochemical fecal occult blood testing for colorectal adenoma detection: evaluation in the target population of screening and comparison with qualitative tests. Am J Gastroenterol 2010; 105(3):682-90.

26. Wilschut JA, Habbema JD, van Leerdam ME, Hol L, Lansdorp-Vogelaar I, Kuipers EJ, et al. Fecal occult blood testing when colonoscopy capacity is limited. J Natl Cancer Inst 2011; 103 (23):1741-51.

27. Chiu HM, Lee YC, Tu CH, Chen CC, Tseng PH, Liang JT, et al. Association Between Early-Stage Colon Neoplasms and False-Negative Results from the Fecal Immunochemical Test. Clin Gastroenterol Hepatol 2013; 11(7):832-8.

28. Denters MJ, Deutekom M, Bossuyt PM, Stroobants AK, Fockens P, Dekker E. Lower risk of advanced neoplasia among patients with a previous negative result from a fecal test for colorectal cancer. Gastroenterology 2012; 142(3):497-504.

29. Cha JM, Lee JI, Joo KR, Shin HP, Park JJ, Jeun JW, et al. Performance of the fecal immunochemical test is not decreased by high ambient temperature in the rapid return system. Dig Dis Sci 2012; 57(8):2178-83.

30. Van Rossum LGM, van Rijn AF, Van Oijen MGH, Fockens P, Laheij RJF, Verbeek ALM, et al. False negative fecal occult blood tests due to delayed sample return in colorectal cancer screening. Int J Cancer 2009; 125(4):746-50.

31. Tannous B, Lee-Lewandrowski E, Sharples C, Brugge W, Bigatello L, Thompson T, et al. Comparison of conventional guaiac to four immunochemical methods for fecal occult blood testing: implications for clinical practice in hospital and outpatient settings. Clin Chim Acta. febrero de 2009; 400(1-2):120-2.

32. Haug U, Kuntz KM, Knudsen AB, Hundt S, Brenner H. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. Br J Cancer 2011; 104(11):1779-85.

33. Park MJ, Choi KS, Lee YK, Jun JK, Lee HY. A comparison of qualitative and quantitative fecal immunochemical tests in the Korean national colorectal cancer screening program. Scand J Gastroenterol 2012; 47(4):461-6.

Appendices

APPENDIX 1. Search strategies and flow chart.

APPENDIX 2. Revised Assessment of Multiple Systematic Reviews (R-AMSTAR)

APPENDIX 3. Evidence tables of studies, description of studies, quality assessment.

Costs and economic evaluation

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Summary

Cost-effectiveness studies generally find that both FIT and FOBT have relatively favourable ICERs when compared with no screening. Although neither type of screening modality is always more cost effective than the other, cost-effectiveness models tend to suggest FIT has more favourable ICERs. However, it should be noted that, compared to gFOBT, the added test sensitivity of FIT is accompanied by a need for a higher capacity in undertaking diagnostic colonoscopies. Therefore, there is increased up-front resource use, potential harm and cost associated with these colonoscopies which will normally be undertaken when screening using FIT (in comparison to gFOBT). FIT also lacks direct evidence from randomised trials concerning its effect on mortality. With the advent of increasingly expensive treatments, the cost-effectiveness both of FIT and gFOBT is likely to increase. On the other hand, although FIT is likely to detect more asymptomatic cancers than gFOBT, this increased test sensitivity increases diagnostic testing costs and also increases the possible dangers associated with screening-induced colonoscopy.

Introduction

Colorectal cancer (CRC) is the second most frequent malignancy in developed countries. The overall burden of disease in Europe caused by CRC is high due to both, a high incidence rate and a high mortality. Estimates show that over 450,000 people were diagnosed with, and over 223,000 died of, CRC in Europe in 2008. Hence, the number of new CRC cases was nearly 51 per 100,000 Europeans and the mortality of CRC was over 25 per 100,000 Europeans {1}. Screening and detecting adenomas or polyps in an average risk population has the potential to reduce the individual, social and financial burden of disease.

The aim of this Cost and economic evaluation domain is to summarise the results of a systematic literature search concerning the costs and cost-effectiveness of immunochemical versus guaiac-based faecal occult blood tests used for CRC screening. This is done to gain insight into the results and the study design of published cost-effectiveness models and support decision making on screening. The domain reviews published cost-effectiveness studies that include a (direct or indirect) comparison of a Faecal Immunochemical Test (FIT) and a Guaiac-based Faecal Occult Blood Test (gFOBT) {2}.

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC) The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.
Outcomes	**CUR and TEC** • Health problems (target condition) • Epidemiology • Burden of disease • Target population • Current management of the condition • Features of the technology • Life-Cycle • Regulatory status • Utilization • Investments and tools required to use the technology • Training and information needed to use the technology **SAF** • Colonoscopy probability of perforation • Colonoscopy with polypectomy probability of perforation • Colonoscopy probability of death following perforation • Probability of bleeding following colonoscopy • Psychological harms from false-negatives and false-positives (and generally from participating in screening program) **EFF** • Test (FIT and gFOBT) sensitivity for adenomas • Test (FIT and gFOBT) sensitivity for cancer • Test (FIT and gFOBT) specificity for adenomas • Test (FIT and gFOBT) specificity for cancer • Adenoma incidence (detection rates) • Rectal cancer incidence (detection rates)

- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a "new" detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
E0001	Resource utilization	What types of resources are used when delivering the assessed technology and its comparators (resource use identification)?	yes	What types of resources are used when delivering FIT and its comparators gFOBT and no screening(resource use identification)?
E0002	Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators (resource use measurement)?	yes	What amounts of resources are used when delivering FIT and its comparators gFOBT and no screening (resource use measurement)?
E0003	Unit costs	What are the unit costs of the resources used when delivering the assessed technology and its comparators?	yes	What are the unit costs of the resources used when delivering FIT and its comparators gFOBT and no screening?
E0005	Outcomes	What are the incremental effects of the technology relative to its comparator(s)?	yes	What are the incremental effects of FIT relative to its comparator(s)gFOBT and no screening?
E0006	Cost-effectiveness	What is the incremental cost-effectiveness ratio?	yes	What is the incremental cost-effectiveness ratio (FIT versus gFOBT; FIT versus no screening; gFOBT versus no screening)?
E0007	Cost-effectiveness	What is the appropriate time horizon?	yes	What is the appropriate time horizon?
E0008	Cost-effectiveness	What is the method of analysis?	yes	What is the method of analysis?
E0004	Indirect Costs	What is the impact of the technology on indirect costs?	no	the indirect costs are not considered because the study is carried out from the perspective of the health care payer/system; furthermore, if QALYs are used as outcome measure, there is discussion in the scientific community, that there might be double counting; additionally the decision makers, responsible for the implementation of a screening technology, are mainly interested in the costs for the health care system

Methodology description

The following elements will be assessed within the domain "Cost and Economic Evaluation" (ECO):

Result card	Topic	Research question
ECO1	Resource use	What types of resources are used when delivering FIT and its comparator gFOBT?
ECO2	Resource use	What amounts of resources are used when delivering FIT and its comparator gFOBT?
ECO3	Unit costs	What are the unit costs of the resources used when delivering FIT and its comparator gFOBT?

ECO4	Outcomes	What are the incremental effects of FIT relative to its comparator gFOBT?
ECO5	Cost-effectiveness	What is the incremental cost-effectiveness ratio (FIT versus gFOBT)?
ECO6	Cost-effectiveness	What is the appropriate time horizon?
ECO7	Cost-effectiveness	What is the method of analysis?

Indirect costs are not covered to any great extent in this domain because a health-care payer perspective has been adopted in most of the studies found. The main reason for exclusion of indirect costs may be that most decision makers consider only health care resource costs in the base case for the evaluation of screening programmes and studies that include indirect costs are rare. With respect to this domain, decision makers who are responsible for implementing a screening program should be aware that the studies focus is almost entirely on the direct costs for the health care system, with little attention to potential wider economic impacts. Further details related to impact on budgets can be found from results card ORG7, from the Organisational aspects -domain.

Information sources

A systematic literature search was conducted using the CRD, Cochrane and PubMed databases to identify studies that are based on cost-effectiveness models comparing FIT with gFOBT.

The results of the “Survey for retrieving information on the use of technology in European countries” did not yield enough information on the costs of screening using FIT and gFOBT and were therefore not included in the analysis.

Quality assessment tools or criteria

In the systematic literature review, the focus was on cost-effectiveness studies published in peer reviewed journals. Reviews, letters, comments, etc., were not considered for inclusion in the analysis of evidence, although HTA reports as well as other literature were used to gain a further perspective (see, e.g., {5, 6}). The search strategy was validated by achieving consensus among the investigators and reviewers of the ECO domain. The quality of the included studies was not formally assessed here, the reasons being that cost-effectiveness studies are generally aimed at providing an input into informed decision making and that there are both strengths and weaknesses in existing checklists {7}. These studies are often highly context specific (i.e., specific to the country, population, health care system, perspective, etc. in which the decision is being made). As a consequence, a study on cost-effectiveness considered as high-quality according to a reporting-quality checklist (such as {8, 9}) but may not be highly relevant for a decision maker in a different decision-making or policy context. On the other hand, a study classed by a checklist as ‘low-quality’ might include the best available evidence for a specific decision-making situation and, therefore, make a relevant contribution to informing the decision.

Analysis and synthesis

A systematic literature search was conducted using different scientific databases (CRD, Cochrane and PubMed) in June 2013. The search was specifically aimed at identifying peer-reviewed literature containing cost-effectiveness models focusing on population-based colorectal cancer (CRC) screening using FIT vs. gFOBt. Studies comparing other screening strategies (e.g., flexible sigmoidoscopy or computed tomographic colonography) with only one of the two relevant strategies, either FIT or gFOBT, were excluded as well as studies that were not based on decision-analytic modelling. Articles that solely report clinical outcomes and studies looking only at costs were excluded since the primary aim of this domain is to gain insight into the results and the study design of published cost-effectiveness models.

After the systematic literature was completed, extensive citation tracking and non-systematic searching was conducted. This additional search was essential because, at this point in time, a general consensus is lacking about one or more standard terms used for the relatively new immunochemical screening technology. In the literature different terms or abbreviations for screening for CRC with an immunochemical faecal occult blood test are used and some of these were only identified on the basis of the systematic search results; the most common are FIT (faecal immunochemical test), iFOBT (immunochemical faecal occult blood test) or FOBT with HemeSelect, which is a specific immunochemical test. The latter term is often used in older studies (until 2000), whereas FIT is frequently used in the most recent studies. The detailed search strategies can be found in the Appendix.

Figure 1: Literature search

The decision to exclude studies was based on main two criteria: (1) the study does not compare a guaiac-based faecal occult blood test with an immunochemical based faecal occult blood test and (2) the study does not include a cost-effectiveness model. Other reasons for exclusion were a lack of relevance for the European context, focus on a different disease, or the published work being case studies, congress presentations, editorial letters, etc. (see the Appendix for detailed selection criteria). After screening the abstracts and evaluation of the full texts, 16 relevant articles {10-25} could be identified and included in the review. {26-37}

The results presented in this domain are a review of the included models but do not include a meta-analysis. A meta-analysis, amongst other things, would neglect the fact that the costs (result cards 1-3), incremental effects (result card 4) and as a consequence the cost-effectiveness (result card 5) ratios are influenced by the study design (type of model, perspective, time horizon, population etc.) and the input parameters (sensitivity, specificity, compliance rate, etc.) {38}. Building a generic cost-effectiveness model for Europe was regarded as not feasible within the time constraints of this pilot Core HTA, due to the need to allow for the modelling of different health-care systems and the epidemiological differences found in European countries. It was therefore considered more useful to provide a comprehensive overview of the existing published cost-effectiveness models as support and starting point for country-specific models developed in national reports.

Result cards

Resource utilization

Result card for ECO1: "What types of resources are used when delivering FIT and its comparators gFOBT and no screening(resource use identification)?"

View full card

ECO1: What types of resources are used when delivering FIT and its comparators gFOBT and no screening(resource use identification)?

Method

Nine articles from the systematic review of the literature outlined in the domain methodology section were used to identify what types of resources are used when delivering FIT and its comparator gFOBT. The remaining seven included studies did not identify the exact types of resources needed for the two tests.

Result

In general, articles and studies that mention the type of costs and resources, divide those into the screening costs (organization, invitation and procedure, including the material resources), diagnostic follow-up in case of positive results and costs of treatment and care (in case of detected disease). The results of each of the included studies are presented below:

Berchi et al. s' (2010) {11} study of cost-effectiveness analysis of the optimal threshold of an automated immunochemical test for colorectal cancer screening (study looks at only 1 round of screening), conducted from June 2004 to December 2005 in Calvados (France), identified the following costs, related to cancer management: (a) the costs of organizing the campaign; (b) the costs of offering screening tests including the costs of purchasing, distributing, and interpreting the tests; (c) the costs of performing confirmatory colonoscopies; (d) the costs of treating screened tumors.

In an earlier study Berchi et al. (2004) {12} undertook a cost-effectiveness analysis of two strategies for the screening of colorectal cancer in France (in a study taking a 20-yeartime-horizon) where resource use is presented from the perspective of the screening organizer, i.e., the Social Security Service. Therefore, the modeling of costs included all direct costs related to screening, diagnosis and management of cancer. This included the costs of organizing the screening campaign (public information, running costs), costs of purchasing, distributing and interpreting the tests, costs of explorations performed in individuals with a positive test, costs of diagnosing cancers in individuals with a negative test, the costs of treating cancers and the costs of follow-up.

A Canadian report from 2009 (Heitman et al., 2009) {14} tried to identify what was the cost-effectiveness of FIT in colorectal cancer screening of average risk individuals in comparison with FOBT and colonoscopy, and a strategy of no screening (report included a lifetime horizon). The investigators specified a cost-effectiveness study conducted from the perspective of the publicly funded health care system. The implementation of this perspective seems to be inconsistent, because relevant costs included were direct health care costs as well as patient time and transport costs according to recent guidelines (REF: Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies: Canada). Societal costs (costs due to lost productivity) were excluded in the primary analysis. They assumed that gFOBT and FIT screening would be requested during a person's annual visit to the general practitioner. As a result, they only considered the costs of the gFOBT and FIT kit and related laboratory and processing costs when estimating the direct cost of gFOBT and FIT. The total cost of gFOBT and FIT also included the relevant non-medical costs (patient, caregiver time and travel costs) according to CADTH guidelines. It is likely that higher costs would occur, particularly if a screening program is organized outside the regularly scheduled medical visits. They also mentioned the direct costs for colonoscopy, which includes: the non-physician costs (capital, nursing, drug, and cleaning costs) and the physician-related fees for the procedure.

In their study Heitman et al. (2010) {15} performed an incremental cost-utility analysis using a Markov model. Their study was based on an economic evaluation of CRC screening in average risk North American individuals, over a lifetime time-horizon. Heitman et al. included into an economic evaluation the non-physician costs (capital, nursing, drugs, and cleaning costs) and the physician fees for the procedure into the overall screening costs. Because they assumed that stool-based screening would be offered at a person's annual visit to their general practitioner, they only considered the costs of the screening kit and related laboratory/processing costs. For all screening modalities, the authors included the relevant patient and caregiver time and travel costs (non-medical costs), on the basis of available surveys for flexible sigmoidoscopy, colonoscopy, both FOBTs, and computed tomographic colonography (CTC). The nonmedical costs of FIT and fecal DNA were assumed to be the same as gFOBT. In the base case, they did not consider the capital costs of initiating or administering a screening program and thus assumed that screening would be opportunistic in all strategies. They have also considered the costs of treatment.

Lejeune et al. (2010) {17} examined cost-effectiveness of screening for colorectal cancer in France (Burgundy) using gFOBT versus FIT (time-horizon: 20 years, or until age of 85, or until death) and divided the costs into:

1. the costs of organizing the screening program, including labor and equipment (similar for gFOBT and FIT screening programs).
2. the costs of informing and inviting the population (similar for gFOBT and FIT screening programs). This also includes the design and printing of the invitation letter and of the information leaflet sent at the beginning of each screening campaign, the manpower for preparing the mail and postage, the training cost of general practitioners (GPs), and the cost of informing the entire medical profession.
3. the distribution costs, including the costs for screening conducted during a regular consultation with a GP (taking into account the purchase price of the test kit and a special fee paid to GPs according to the number of tests received at the central analysis center, therefore, depending on participation in the screening program), the cost of the test sent by mail if the screening test was not performed during the medical phase (test kit, letter, envelope, instruction for use, stamp), and the cost of a reminder letter.
4. the cost of test revelation in a centralized analysis center included overhead costs, capital expenditure, running costs, and labor. The process cost also included the cost of sending test results to the participants and to their GPs.
5. the costs of a colonoscopy performed after a positive test.
6. the costs of the follow-up after large adenoma resection.
7. the costs of the follow-up of treated CRCs.
8. the average costs of treatment of CRC by stage.

Parekh et al. (2008) {18} in their study, which was modelled on a US population, examined in detail the potential impact of imperfect adherence on the effectiveness and cost-effectiveness of screening strategies (time horizon: until age 100 or death). They included the costs of screening, diagnostic testing, treatment of possible complications (e.g. ruptures from colonoscopies) and CRC care. If F-DNA, gFOBT or FIT test were positive, colonoscopy followed with polypectomy and biopsy as

necessary. If colonoscopy was normal after a positive non-invasive test, the non-invasive test was assumed to be false positive and screening resumed in 10 years with the primary screening strategy.

A Dutch study that took a 10-years time-horizon and referred to a cost-effectiveness analysis and Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests, carried out by van Rossum et al. (2011) {19} also considered only direct healthcare costs. The costs of the two FOBTs consisted of costs that were independent and dependent on the type of test. Ignoring the differences in participation between the FIT and gFOBT, costs independent of the type of test were costs related to the invitation for screening (e.g. letters and information brochures), basic administration of the tests, feedback of test results to the patient and postal charges. The costs which are directly dependent on the type of test were costs of the test itself and costs for laboratory analyses. To represent the costs of the actual test kits they used retail prices. The costs of the laboratory analysis of the FOBTs were based on costs for administration, laboratory work and correspondence of test results for returned tests only. Consequently, participation rates influenced the total costs of each screening strategy. A complete test kit of Hemoccult-II (gFOBT) includes a number of tests and the test developer solution. OC-Sensor testing materials (FIT) are made available separately and were, therefore, calculated for returned tests only. The costs of the automated analyzer OC-micro, used for the analysis of the OC-Sensor, were also included into the costs of a returned FIT given the assumption of 100,000 tests per year and depreciated over 3 years. All other clinical costs for the follow-up of positive FOBT results (e.g., CRC surgery) were given as charges and directly derived from the Dutch Health Care Authority database (NZA). The NZA is the supervisory body for all the healthcare markets in the Netherlands and supervises both healthcare providers and insurers in the curative markets and in the long-term care markets.

Sharp et al.'s (2012) {20} study is based on cost-effectiveness of population-based screening for colorectal cancer: a comparison gFOBT, FIT and flexible sigmoidoscopy (time-horizon: cohort entered simulation at age 30 until age 100 or death) and evaluated in Ireland. The study included direct costs, valued in 2008 Euros, associated with screening and cancer management. Costs of gFOBT and FIT kits and associated processing were estimated following discussion with the National Cancer Screening Service, test suppliers, and laboratory staff, and using Department of Health and Children salary scales. They do not specify the types of resources included in their study, only stating at the end that their model did not incorporate the costs of establishing the infrastructure to implement population-based screening for colorectal cancer. The model was developed from a third-party payer perspective, in this case a provincial organization that decides on funding for a provincial screening program for colorectal cancer. Therefore, lost productivity costs, which would be necessary to give a wider societal perspective, were not incorporated.

Wilschut et al. (2011) {24} undertook a cost-effectiveness analysis, comparing Fecal Occult Blood Testing (gFOBT and FIT) when colonoscopy capacity is limited, and depicted the different cost components in more detail. Their study is based on 30 years time-horizon. In their analysis they included (a) the screening costs for FOBT screening such as organizational costs, costs of test kits, costs of analysis of the tests (that includes material and personnel needed during the process of registration, analysis, and authorization of returned tests) and (b) the costs of CRC treatment divided into three clinically relevant phases of care: initial treatment, continuous care, and terminal care.

Zauber et al. (2010) {5} undertook research on the cost-effectiveness of colonoscopy and included several types of resources within their cost-effectiveness analysis: costs that occur during procedures, costs of tests associated with CRC screening, costs of complications of screening, and treatment costs. These costs included the facility charges (as applicable) and physician services charges. Thus beneficiaries' copayments are not reflected in the analysis. They also conducted an analysis from a modified societal perspective, by including direct costs borne by beneficiaries as well as estimated patient time costs, but excluding costs caused by lost productivity caused by early death or disability.

From this literature it could be concluded that organized screening contains:

- the costs of screening (organization of screening, screening procedure etc.). However, some studies {11, 12, 14, 15} only considered the costs of FIT/gFOBT kits and related laboratory and processing costs, because they have assumed that gFOBT and FIT screening would be requested during a person's annual visit to the general practitioner.
- the costs of diagnostic follow-up in case of positive results
- the costs of treatment in case of detected disease (the costs of all 4 stages: stage I, stage II, stage III and stage IV) (the treatment costs of possible complications (e.g. ruptures from colonoscopy) were also included)
- non-medical costs (patient/ caregiver time and travel costs)

In general, the types of resources used when undertaking FIT and gFOBT screening will be similar, due to the similarity of the alternative screening procedures. The resources used for screening include those necessary for the organization of screening (e.g., sending invitation, distributing the kits, sending re-invitation, and possibly collecting the samples), those for the screening procedure (e.g., laboratory analysis, sending information concerning results, and diagnostic follow-up in case of positive results), and those for treatment in case of detected disease. This results card (ECO1) summarises the types of costs included in the literature. Attention should be drawn to fact that the majority of studies failed to mention costs associated with lost or re-gained productivity. Only six studies mentioned costs associated with lost productivity, but none of these included such costs into the analysis. The exclusion of productivity-related costs has both economic and ethical dimensions, and is a matter which is subject to much methodological debate.

Importance: Important

Transferability: Completely

Result card for ECO2: "What amounts of resources are used when delivering FIT and its comparators gFOBT and no screening (resource use measurement)?"

View full card

ECO2: What amounts of resources are used when delivering FIT and its comparators gFOBT and no screening (resource use measurement)?

Method

Eighteen different articles from the systematic review of the literature outlined in the domain methodology section were used to identify estimates of the amounts of resources that are used when delivering FIT and its comparators gFOBT and no-screening.

The term “resources” refers to the natural units of health care services used. After reviewing the studies it can be concluded that majority of studies mainly focused on the estimation of financial resources {10-12, 16-19, 21, 22, 25}. Nevertheless, there are some studies which also mentioned other types of resources used, namely: the number of screening tests {13-15, 30}, colonoscopies (COL) {13-15, 20, 23, 24, 30}, computed tomographic colonographies (CTC) {30}, polypectomies {13, 14, 20}, number of ultrasounds (TUS), number of persons receiving PET scan, MRI scan, CT scan, pre-operative radiotherapy and undergoing colorectal resection {30}.

Result

By comparing estimates of financial resources that would be used when delivering FIT and its comparator gFOBT, it can be summarized that the amount of resources used are approximately at the same level. Studies {11, 13, 17, 20-22, 25} have shown that the amounts of resources, when delivering FIT, can be slightly higher in comparison with gFOBT. Some other studies reported similar costs – depending also on specificity of the test or the different types of thresholds (i.e. positivity threshold to determine the optimal cut-off) {10, 11, 15}.

Van Ballegooijen et al. (2003) indicated that FIT at 95% specificity level (462,794,391 $) is more expensive than gFOBT Hemoccult II (205,556,566 $) but less expensive in comparison to gFOBT Hemoccult – SENSA (775,643,892 $). FIT at 98% specificity level is the least expensive strategy; total costs are estimated to 83,110,600 $ (results per 1 million individuals, age 65-79 at the beginning of the screening program) {10}.

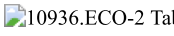
Results of Berchi et al.’s study (2010) indicates that screening with FIT at a 20 ng/ml (1,555,041 €) and 55ng/ml cut-off level (1,119,406 €) is more expensive than gFOBT (907,805 €) – if comparing only total costs. However, FIT can be less expensive if using thresholds at 93ng/ml (713,764 €) and 148ng/ml (192,702 €) – if comparing only total costs. Berchi et al. concluded that at a threshold of 93 ng/ml screening with FIT would cost € 94,041 less than one round of screening with gFOBT and would allow the detection of four additional advanced tumors. At a threshold of 75 ng/ml one round of screening with FIT would cost €6,282 less than one round of screening with gFOBT and would allow the detection of forty-two additional advanced tumors. For both thresholds, the positivity rate of FIT was lower than that of gFOBT. Consequently, FIT enabled the detection of a higher number of tumors without substantially increasing the risk associated with confirmatory colonoscopy. The threshold at which FIT and gFOBT positivity rates were almost identical was 67 ng/ ml. Using this threshold, screening with FIT resulted in more advanced cancers screened than screening with gFOBT, but was also more costly (€863 per advanced tumor screened) {11}.

In one of the previous studies Berchi et al. (2004) mentioned that the total annual cost of organizing the campaign, which had been assessed by the Social Security Department, amounts to 63,256 €. They also conclude that FIT can be slightly more expensive in comparison to gFOBT. Five biennial screening campaigns cost 230 € per targeted individual (including refusals) with FIT and 177 € per targeted person with gFOBT. With ten biennial screening campaigns, the costs per targeted individual were 316 € for FIT and 234 € for gFOBT {12}.

Hassan et al. (2011) displayed the use of resources for a cohort of 100,000 subjects that were invited to screening. (In order to project the simulation outcomes on the French population; a steady state for population size and age distribution was assumed, as represented by the year 2010 French census data. The model outputs reflected all persons aged 50–100 years of age at a given point in time in the steady state, as opposed to a cohort aging from 50 to 100 years over 50 years.) Besides financial resources they presented also the number of colonoscopies, total number of screening tests and number of polypectomies. They indicated that the number of colonoscopies (COL), which were performed as a screening strategy every 10 years, amounted 153,862. COL performed after annual FIT screening were estimated to 89,265, after biennial FIT screening 56,827, after annual gFOBT screening 38,219 and after biennial gFOBT 21.160. The number of total screening tests after annual FIT screening was estimated to 615,237, after biennial FIT screening 346.930, after annual gFOBT screening 772,361 and after biennial gFOBT screening 425,987. They indicated that 22,168 polypectomies have been performed after the colonoscopy, 22,639 number of polypectomies after annual FIT screening, 14,683 number of polypectomies after biennial FIT screening, 10,833 after annual gFOBT screening and 6,005 after biennial gFOBT screening. They estimated that the amount of resources that is required for FIT is higher than the amount that is necessary when screening with gFOBT. The estimated costs for delivering FIT biennially are 90,851,477 € (909 € per individual) and increase to 108,657,236 € (1087 € per individual), when delivering the screening with FIT annually. The presented data stands for a cohort of 100,000 French subjects. If the gFOBT screening method is used, the necessary amount of resources for biennially screening amounts to 79,359,152 € (794 € per individual) and for annually screening – 88,132,104 € (881 € per individual) {13}.

A Canadian report from 2009 (Heitman et al.) {14}mentioned number of performed colonoscopies and polypectomies and also number of FIT and gFOBT screening tests (i.e., test kits, as well as colonoscopies, polypectomies performed after the results of primary screening test). The results are indicated in the table below:

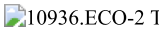
Table 1: Results of Heitman et al. (2009) {14}



hey came to the conclusion that FIT tests differ in methods (type of assay and collection) and test performance. Given the heterogeneity of the available FIT tests, they modeled three independent scenarios: one representing studies reporting “lower” test performance (FIT-low), one representing studies with “mid-range” test performance (FIT-mid), and one representing studies with “high” test performance (FIT-high). Their use of FIT-low, FIT-mid, and FIT-high represents a spectrum of FIT sensitivity and specificity, which in their opinion may be the result of differences in the testing kits and collection methods. The results were based on 100,000 people screened and indicated that the amount of resources (i.e. the costs of screening and CRC management) are equal among gFOBT and FIT-low (1,820 CAN$ in average per patient). This could be due to the fact that approximately the same number of tests (FIT and FOBT) were used and similar number of cancer was detected. If screening is delivered with FIT-mid (1,730 CAN$ in average per patient) the costs are lower, while with FIT-high (1,920 CAN$ in average per patient) the costs are higher. This could be due to smaller number of FIT’s used and due to further treatment (higher number of colonoscopies, polypectomies and colonoscopy complications). The data seem to suggest a better detection of advanced adenomas and CRC with two or three days of fecal sampling compared with one day {14}.

Heitman’s et al. study, published one year later (2010), indicated the number of screening tests required (during the lifetimes for hypothetical cohort of 100.000 average risk patients), number of colonoscopies and base case costs of screening and managing CRC. The study compared FIT-low, FIT-mid and FIT-high with gFOBT-low and gFOBT-high. Using base case estimates, over the lifetimes of a 100,000 patient cohort, the estimations showed that in general the FIT screening option is less expensive in comparison to the gFOBT strategy. Screening with FIT-low amounts to 2,005 CAN$ (on average per patient), with FIT-mid to 1,833 CAN$ (on average per patient) and with FIT-high to 2,004 CAN$ (on average per patient). On the other hand screening with gFOBT-low amounts to 2,195 CAN$ (on average per patient) and with gFOBT-high 2,084 CAN$ (on average per patient). The data on the base case costs as well as on number of screening tests required, are presented also in the following table {15}:

Table 2: Results of Heitman et al. (2010) {15}



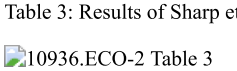
Heresbach et al. (2010) were the only ones (compared to other studies), who outlined the comparison between screening costs and overall costs. The results of the study were based on a cohort of 100,000 individuals from 50-74 years, observing a time horizon of 30 years. In the study by Heresbach et al. total costs of the strategy that uses FIT are higher in comparison to the overall/total costs of strategy that uses gFOBT. They estimated that invitations to FOBT screenings structurally cost much more than those for CTC screening, the latter induced a much higher expenditure associated with the cost of the screening procedure itself. However, FIT generated much more colonoscopy costs. The increase in the total cost of COL-P and COL-S relative to no screening was 48,951,079 € with FIT and 28,348,797 € with CTC. Fewer cancers were prevented by FIT than by CTC, which induced more costs of CRC treatments. On the whole, gFOBT was the least costly competing strategy (13,583,934 €) and FIT the most expensive one (28,560,396 €). When comparing only the amount of resources that are necessary for screening (invitation and the screening procedure) it can be seen that the invitation to FIT screening and FIT procedure amounted slightly less in comparison to gFOBT's invitation and procedure. Invitation to FIT screening amounted 1,717,911 €, in addition the FIT screening procedure amounted 3,037,266 €, while the invitation to gFOBT screening amounted 1,767,118 € and the gFOBT screening procedure – 3,880,590 € {16}.

Lejeune et al. (2010), similar to the studies mentioned above, concluded in their economic modeling study that costs for screening with FIT over a time period of 20 years (in a cohort of 100,000 persons over 50) are higher in comparison to gFOBT screening. The costs for FIT screening amounted to 78,579,147 € in comparison to gFOBT, which amounted to 74,608,067 € {17}.

Sharp et al. (2012) defined the use of resources on financial ones as well as on the screening-related endoscopic procedures. They indicated that FIT screening is a little bit more expensive than gFOBT screening. But the costs differ only slightly. Costs of FIT screening and CRC management per person was 1,114 € (age 55-74), in comparison to gFOBT, where the costs of screening and CRC management per person amounted to 1,107 € (age 55-74). They presented that in case of gFOBT at 55-74 years (over the entire lifetime of cohort, i.e. 10 screening rounds, rated per 100.000 population) 3.386 colonoscopies have been required, while for FIT screening 34.632 colonoscopies have been required. As regards polypectomy they have indicated that 1.215 polypectomies have been required after the gFOBT screening and 9.486 polypectomies after FIT screening {20}.

In one of the later studies Sharp et al. (2013) estimated the screening-related resource use for biennial gFOBT (at 55-74 years) and biennial FIT (at 55-74 years) as it is presented in the table below. They made a comparison between the first year of screening and the 10th year of screening {30}.

Table 3: Results of Sharp et al. (2013) {30}



It can be concluded from the table above that after FIT screening scenario higher number of colonoscopies and colonographies has been implemented. The numbers are higher for FIT screening also within CRC work-up and treatment. As regards the number of screening tests in year 1 the number of kits sent out and processed was the same for gFOBT and FIT screening scenario, while in year 10 the number of kits sent out and processed was a little lower within FIT screening scenario {30}.

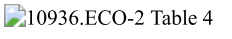
Sobhani et al. (2011) indicated the expected costs for an individual at age 50, using FIT screening, as to 694 €, in comparison to gFOBT, where the expected costs are slightly lower – 584 € per individual. The expected costs for an individual at age 50 after 24 years (3-sample Oc-Sensor) for a cut-off level of 50ng/ml are 1,141 € and for a cut-off level of 100ng/ml 1,593 € gFOBT was estimated to be the cheapest screening test, with expected costs for an individual after 24 years of 1,120 € {21}.

Two US studies {22, 25} also indicated that the costs of FIT screening is comparable to gFOBT screening, but that FIT is still slightly more expensive. Telford et al. have estimated that the costs of FIT, performed annually (over the lifetime of 100,000 individuals, who commence screening at age 50 years) amount to 65,429,821 CAN$, whereas gFOBT, also performed annually (over the lifetime of 100,000 individuals, who commence screening at age 50 years) amounts 63,139,823 CAN$. They have estimated that the strategy of screening with FIT amounts to 1,437 CAN$ per person (in 2007) and with gFOBT to 1,415 CAN$ (in 2007) {22}.

Zauber et al. estimated that FIT screening costs 2,688,092 US$ (per 1,000 50 year olds), whereas gFOBT screening costs 2,369,426 US$ (per 1,000 50 year olds) if Hemoccult II is used and 2,615,292 US$ (per 1,000 50 year olds) if Hemoccult-SENSA is used {25}.

Wilschut et al. (2011) also presented the amount of screening resources, but only for FIT screening. Information on screening resources can be evident from the following table {24}:

Table 4: Results of Wilschut et al. (2011) {24}



Their results showed (as also indicated in the table) that FIT screening (cut-off at 50ng/ml) amounts to 493€ per 1,000 individuals aged 45–80 years during the year 2005. For an unlimited capacity, it was most beneficial to screen intensively with the lowest FIT hemoglobin cutoff level for referral to colonoscopy set at 50 ng hemoglobin per mL for those aged 45–80 years with an annual screening interval and offering colonoscopy surveillance to all individuals with adenomas. The colonoscopy demand with this strategy was 49 colonoscopies per 1000 individuals. To optimally adapt screening when capacity was limited to 40 colonoscopies per 1000 individuals, individuals with a FIT hemoglobin measurement between 50 and 75 ng hemoglobin per mL were no longer referred to colonoscopy and individuals between ages 45 and 50 years were no longer invited. This decreased the demand to 36 colonoscopies per 1000 individuals. If capacity was limited to 20 colonoscopies per 1000 individuals, the next step was to further increase the FIT hemoglobin cutoff to 200 ng/mL and to stop screening 5 years earlier at age 75. Also surveillance colonoscopies in individuals with only one or two non-advanced adenomas were cancelled. If colonoscopy demand had to decrease even further, it became efficient to greatly reduce the number of screening rounds by first narrowing the age range to 60–80 years and lengthening the screening interval to 2 years (11 rounds) to reach a demand of 10 colonoscopies per 1000 individuals, and then to narrow the age range to 60–69 years every 3 years (four rounds) for a final capacity of five colonoscopies per 1000 individuals {24}.

Parekh et al. (2008) estimated that the costs of FIT screening amounts to 2,428 US$, per person, whereas the costs of gFOBT screening amounts to 2,683 US$ per person. The results are presenting CRC cases and costs per 100,000 persons from age 50 – 100 years {18}.

Van Rossum et al. (2011) concluded that over a period of 10 years, an average person aged between 50 and 75 years would cost the healthcare system, €327 with G-FOBT and €301 with FIT screening. These costs included CRC-related costs {19}.

The last study, which found FIT screening to be less expensive than gFOBT screening, is the study of Whyte et al. (2012). They concluded that FIT screening amounts to 530 £ per person (age 60-74) over a lifetime, whereas gFOBT screening amounts to 558 £ per person. They also indicated the endoscopy resource use requirements for a cohort of 649,400 individuals – all 50 years-old, monitoring the data for year 2010. The results showed that after biennial gFOBT screening strategy (population of 60-74 year-olds) 38.242 screening colonoscopies and 21.030 surveillance colonoscopies have been performed. In case of FIT screening strategy (population of 60-74 year-olds) 117,681 screening colonoscopies and 43,254 surveillance colonoscopies have been performed {23}.

The review made on amount of resources revealed that the majority of studies mentioned mainly financial resources, although some studies specified also other types of resources used, namely: the number of screening tests, colonoscopies, colonographies, polypectomies, number of ultrasounds, number of receiving PET scan, MRI scan, CT scan, pre-operative radiotherapy and undergoing colorectal resection.

By comparing the amount of other (i.e. non-financial) types of resources it can be concluded that in studies that mentioned those type of resources the numbers of screening tests used were higher within gFOBT screening strategy in comparison to FIT screening strategy {13-15, 30}. In addition, all studies indicated that the number of colonoscopies and polypectomies performed after the primary screening test were higher after FIT screening strategy in comparison to gFOBT screening strategy {13-15, 20, 30}.

As regards the financial resources, the majority of studies revealed that FIT screening can be slightly more expensive than gFOBT screening {11-13, 17, 20-22, 25, 27; 10 and 14 – depends on the test performance and specificity). However, a few studies presented later revealed just the opposite {15, 16, 18, 19, 23}, thus that FIT screening is less expensive than gFOBT screening {15, 16}. The reason for this hasn't been directly highlighted in the studies. Nevertheless it could be concluded that the costs vary according to the cut-off values and test sensitivities of FOBTs (i.e. FIT and gFOBT). Some studies, for example, indicated that FIT should be used at higher hemoglobin cut-off levels when colonoscopy capacity is limited. This means, if FIT is used at a low cut-off value, a higher number of colonoscopies will be required which consequently results in higher total costs of screening (and vice versa). Van Rossum et al. {19}, for example, indicated that colonoscopy costs have a relatively high impact on the total screening costs because the relative screening costs of gFOBT screening compared to FIT screening is lower in terms of the costs of follow-up colonoscopies.

Summary table of type of resources and estimated or assumed amounts of resources used when delivering FIT and its comparator gFOBT:

Comment

All costs presented in the results use a discount rate of 3% {10, 13, 16-19, 21, 24, 25}, 3.5% {23}, 4% {20} or 5% {12, 22} in their base case analysis; further details can be found under ECO6.

Importance: Critical

Transferability: Not

Unit costs

Result card for ECO3: "What are the unit costs of the resources used when delivering FIT and its comparators gFOBT and no screening?"

View full card

ECO3: What are the unit costs of the resources used when delivering FIT and its comparators gFOBT and no screening?

Method

Thirteen different articles from the systematic review of the literature outlined in the domain methodology section were used to identify the unit costs (according to the standard definition used in health economic evaluation, a unit cost is the cost of natural resource unit, e.g. cost of test kit; in some situations, it can also be the cost of the medical resources required to treat a certain stage of disease, e.g. cost of the resources required to treat metastatic colon cancer) of the resources used when delivering FIT and its comparator gFOBT.

The unit costs of resources used were not presented in every study. The studies that did mention the unit costs are presented below.

Result

Heitman et al. (2010) in their study concludes that gFOBT screening, when comparing overall costs, is slightly more expensive in comparison to FIT screening. Nevertheless, when comparing unit costs in the study from 2010 and also in the report of 2009, it can be seen that the unit costs for FIT are slightly higher than the unit costs for gFOBT. Unit costs for FIT are 19 CAN$ (i.e. base case: direct health care costs including costs of the kit and the processing), whereas unit costs for gFOBT amount to 12 CAN$ (the test of the kit costs 5 CAN$ and processing costs 7 CAN$). They also specified non-medical costs, which included patients and caregivers time and travel costs, but excluded productivity losses, and in both cases amount to 36 CAN$. Heitman et al. indicated also the unit costs for diagnostic follow-up and further treatment. They estimated that diagnostic colonoscopy (includes physician costs of diagnostic colonoscopy – 327 CAN$ and nonphysician costs of colonoscopy – 530 CAN$) amounts 857 CAN$, while therapeutic colonoscopy (includes physician costs of therapeutic colonoscopy – 401 CAN$ and nonphysician costs of colonoscopy – 598 CAN$) amounts to 999 CAN$. The authors also presented the total cost of managing CRC, which amount for stage I on average to 25,049 CAN$, for stage II on average to 36,143 CAN$, for stage III on average to 96,768 CAN$ and for stage IV on average to 134,014 CAN$ {15}.

Van Ballegooijen et al. (2003) revealed that FIT has a unit cost of approximately 13 $ (i.e. when specificity is 98% and sensitivity 70%), whereas a gFOBT Hemoccult II has a unit cost of approximately 4.50 $ (i.e. when specificity is 98% and sensitivity 40%). But rather than providing an estimate of the unit cost of FIT, van Ballegooijen et al. used a threshold analysis to estimate the unit cost at which FIT could be considered to be as equally cost effective as gFOBT. Van Ballegooijen et al. also made estimations on the average number of colonoscopy, which follows a positive screening result. The estimated costs for colonoscopy were based on information provided by CMS (i.e. Centers for Medicare and Medicaid Services) on Medicare payment rates for 2002 for colonoscopy procedures and polypectomy

procedures performed in free standing clinic settings, on outpatient hospital settings and ambulatory surgical settings. The weighted average payment across these settings was 646$ for diagnostic colonoscopy and 683 $ for diagnostic colonoscopy together with biopsy {10}.

Berchi et al. (2004) indicated the following annual cost per individual {12}:

- organization of screening campaign – 0.38 €;
- FIT test – 8.84 € (i.e. purchasing, distribution, revelation of the test);
- gFOBT test – 10.98 € (i.e. purchasing, distribution, revelation of the test);
- colonoscopy – 457.35 €;
- treatment(1) of stage A – 17,579 €;
- treatment of stage B – 21,858 €;
- treatment of stage C – 31,110 €;
- treatment of metastasized cancer – 17,384 € .

Heresbach et al. (2010) reported that the screening test proposal in both screening alternatives (FIT and gFOBT) costs 2.1 €. In addition to that, FIT costs 8.84 €, whereas the gFOBT is a little more expensive and it costs10.98 €. They have estimated that CTC (computed tomographic colonography) procedure costs 128.7 €, Colonoscopy without polypectomy costs 779 €, Colonoscopy with polypectomy of nonadenomatous polyps 1561 € and Colonoscopy with polypectomy of adenomatous polyps 3,610 € on average. They have calclated that the colorectal cancer treatment costs 17,000 € on average in stage I, 22.000 on average in stage II, 30,700 on average in stage III and 36,600 on average in stage IV {16}.

The results of the study by van Rossum et al. (2011) indicated that the participation-independent costs(2) of the FOBTs were: €5.20 for gFOBT and €4.39 for FIT. Compared with the manually operated and evaluated gFOBT, the automated analyzer (OC-Sensor micro) reduced operation and evaluation time for the FIT with more than 90%. When assuming 100% participation of individuals in performing the test, one gFOBT overall cost €9.63 and one FIT cost €8.50. The actual participation was 47% for gFOBT and 60% for FIT. Therefore, the overall cost according to intention to screen for one gFOBT was €7.06 and for one FIT €6.22. Van Rossum et al. also presented the screening costs, which are independent of the type of test and the participation rate, as equal for FIT and gFOBT, i.e. 2.40 €. They presented equal screening costs also for screening that is independent on the type of test and depending on participation. Those costs amount to 3.04 € for both tests. The differences that they identified were only among the test specific invitation costs that are independent of participation (FIT costs 1.35 €; gFOBT costs 2.80 €) and among test specific costs that depend on participation (1.71 € for FIT and 1.39 € for gFOBT). Van Rossum et al. also presented colonoscopy and treatment costs. They have estimated that the average costs for colonoscopy (Including polypectomy and pathology) amounts 921 €. They divided the treatment base costs to a costs for surgery (12,366 €), chemotherapy (12,731 €), Surgery and chemotherapy metastasis (23,097 €) and Radiotherapy (5,710 €) {19}.

Lejeune et al. (2010) concluded that FIT is more expensive as gFOBT. Distribution costs per FIT test performed amount to 18 €, whereas for gFOBT these costs amount to 11.8 €. They also identified costs of revelation per test performed, which amounts 5 € for FIT and 4.5 € for gFOBT. They have also presented costs relative to positive tests and concluded that diagnostic colonoscopy on average costs 526 €, while colonoscopy together with polypectomy costs 641 €. They have also indicated the treatment cost: 17,596 € for stage I, 20,472 € for stage II, 29,013 € for stage III and 35,059 € for stage IV {17}.

Some other studies came to similar conclusions (i.e. that FIT unit costs are higher than gFOBT's). Parekh et al. (2008) assumed that the base case costs of FIT amount to 22 $ (for each cycle of FIT – i.e. per year), whereas for gFOBT they amount to15 $ (for each cycle – i.e. per year). Parekh et al. also indicated that the costs of colonoscopy costs on average 920 €. They concluded that the base case value for localized cancer stage amounts 51,000 €, base case value for regional cancer stage amounts 98,000 € and base case value for distant cancer stage amounts 200,000 € {18}.

Sharp et al. (2012) indicated that the costs for one FIT kit (i.e. cost per kit dispatched/per individual invited to participate in screening) amounts to 3.75 €, whereas a gFOBT kit costs less – 1.70 €. They claim that the costs of FIT processing/ analysis (i.e. costs per kit completed and returned/ cost per screening participant) amount to 11.60 €, in comparison to gFOBT, where the costs amount to 7.81 €. They indicated that cost of colonoscopy amounts 650 €, while cost of CTC amounts 550 €. They have calculated that the lifetime cost of stage I CRC-screen-detected amounts 22,885 €, of stage II 36,377 €, of stage III 48,032 € and of stage IV 35,799 € {20}.

Sobhani et al. (2011) compared FIT and gFOBT alternatives and concluded that the costs for the screening program, the invitation of the population and the distribution of the tests are the same for both tests. A screening program costs 1.26 € for both tests, inviting the population amounts to 0.65 € and the distribution amounts to 9.32 €. Sobhani et al. (2011) estimated that the gFOBT purchase costs 4 € and gFOBT analysis 3.2 €. He made the same assumption for FIT tests. They have calculated that the colonoscopy, performed in case of positive results, would cost 526 € on average, colonoscopy with polypectomy – 641 €. They have also made a calculation for the phase of treatment, where the stage I amounts 17,596 €, stage II 20,472 €, stage III 29,013 € and stage IV 35,059 € {21}.

Telford et al. (2010) concluded that the FIT test is more expensive than gFOBT test. The costs of the FIT kit ranges between 10 and 40 CAN$, whereas the gFOBT kit ranges between 5 and 20 CAN$ {22}.

Zauber (2010) identified the base case costs for FIT to be 22.22 US$ (payer is CMS - Center for Medicare and Medicaid Services) and modified societal costs to be 39.22 US$ (these costs include beneficiary costs (copayments) and time costs in addition to the payer costs). They identified the base case costs for gFOBT to be 4.54 US$ (payer is CMS) and modified societal costs to be 21.54 US$. Telford et a.l also made an estimation for colonoscopy and further treatment. They indicated that colonoscopy costs between 200 and 2000 €, cost of cancer care in year 1 for stage I ranges between 5,000 and 30,000 €, for stage II between 20,000 and 50,000 €, for stage III 30,000 – 100,000 € and for stage IV 50,000 – 500,000 € {22}.

Wilschut et al. (2011) also came to the conclusion that the unit costs of FIT are more expensive than of gFOBT. Costs for FIT invitation (organization and test kit), according to their data, amount to 14.85 €, whereas for gFOBT they amount to 14.05 €. They have also identified costs per attendee (personnel and material costs for

analysis) to 4.37 € for FIT and 1.90 € for gFOBT. They have estimated that the colonoscopy costs are 303 € without polypectomy and 393 € with polypectomy. Initial treatment in stage I was estimated to be 12,500 € initial treatment in stage II was estimated to be 17,000 €, initial treatment in stage III was estimated to be 21,000 € and in stage IV to 25,000. All 4 treatment scenarios had also additional costs both for continuing treatment after the first year and in the event of terminal care due to either CRC or other causes. {24}.

From the studies that present the unit costs it could be summarized that the ratio of the price between FIT's and gFOBT's unit costs usually corresponds to the ratio of the overall amount of resources (i.e total strategy costs) between those two screening strategies. This means, if FIT unit costs are higher compared to the gFOBT unit costs, the total amount of resources for a FIT screening strategy are higher in comparison to a gFOBT screening strategy. Nevertheless, there are some exceptions (e.g. {15}) that are presented above. In addition, if FIT is used at a low cut-off value, a higher number of colonoscopies will be required which consequently results in higher total costs of screening (and vice versa). Van Rossum et al. {19}, for example, indicated that colonoscopy costs have a relatively high impact on the total costs of a screening strategy. The unit costs of colonoscopy and further treatment are comparable between studies. The colonoscopy costs on average amounts to 600 €, while further treatment costs increase with the cancer stages.

Author (year), Country	Study design	Included costs	FIT	FOBT	Colonoscopy	Treatment/management
van Ballegoijen et al. (2003), USA	Use of MISCAN-COLON micro-simulation model	Direct costs including a co-payment from the patient	**$13**	**$4.50**	**$646** **$683**	
			Hemocult II		*Diagnostic colonoscopy (weighted average payment) **Diagnostic colonoscopy together with biopsy (weighted average payment)	
Berchi et al. (2004), France	State-transition model (Markov process)	Direct costs based on French health care insurance contracts	**€8.84**	**€10.98**	**€457.35**	**€17,579*** **€21,858**** **€31,110***** **€17,384******
						*Treatment of stage A **Treatment of stage B ***Treatment of stage C ****Treatment of metastasized cancer
Heitmann et al. (2010), Canada	Markov model, with calibration against the efficacy and effectiveness outcomes from the literature	Direct costs derived from the Canadian health care system, costs of patient time and transport costs	**CAN$ 19**	**CAN$ 12**	**CAN$ 857*** **CAN$ 999****	**CAN$ 25,049*** **CAN$ 36,143**** **CAN$ 96,768***** **CAN$ 134,014******
			including costs of the kit and processing	including costs of the kit and processing	*diagnostic colonoscopy **therapeutic colonoscopy	*Managing CRC at stage I **Managing CRC at stage II ***Managing CRC at stage III ****Managing CRC at stage IV
Heresbach et al. (2010), France	State-transition model (Markov process)	Direct costs obtained from French health care system	**€ 8.84**	**€ 10.98**	**€ 128.7*** **€ 779**** **€ 1561***** **€ 3610******	**€ 17,000*** **€ 22,000**** **€ 30,700***** **€ 36,600******

					*CTC (computed tomographic colonography) procedure (on average) **Colonoscopy without polypectomy (on average) ***Colonoscopy with polypectomy of nonadenomatous polyps (on average) ****Colonoscopy with polypectomy adenomatous polyps (on average)	on average: *Treatment of CRC at stage I **Treatment of CRC at stage II ***Treatment of CRC at stage III ****Treatment of CRC at stage IV
Lejeune et al. (2010), France	State-transition model (Markov process)	Direct costs based on French health care insurance contracts	**€ 23**	**€ 16,3**	**€ 526*** **€ 641****	**€ 17,596*** **€ 20,472**** **€ 29,013***** **€ 35,059******
					*diagnostic colonoscopy (on average) **colonoscopy together with polypectomy (on average)	*Treatment of CRC at stage I **Treatment of CRC at stage II ***Treatment of CRC at stage III ****Treatment of CRC at stage IV
Parekh et al. (2008), USA	State-transition model (Markov process)	Direct costs derived from Medicare fee schedule	**€ 22**	**€ 15**	**€ 920**	**€ 51,000*** **€ 98,000**** **€ 200,000*****
			per year	per year		*base case value for localized cancer stage **base case value for regional cancer stage ***base case value for distant cancer stage
van Rossum et al. (2011), Netherlands	State-transition model (Markov process)	Direct costs based on Dutch health care charges and retail prices)	**€ 12,89**	**€ 14,63**	**€ 921**	**€ 12,366*** **€ 12,731**** **€23,097*** **€ 5,710******
			dependent costs of the test, assuming 100 % participation (costs of the FOBT itself and costs for laboratory analyses	dependent costs of the test, assuming 100 % participation (costs of the FOBT itself and costs for laboratory analyses	including polypectomy and pathology) (on average	*costs for surgery **costs for chemotheraphy ***cost of surgery and chemotheraphy metastasis ****radiotheraphy
Sharp et al. (2012), Ireland	State-transition model (Markov process), with calibration against the efficacy and effectiveness outcomes from the literature	Direct costs based on Health Service Executive	**€ 3.75*** **€ 11.60****	**€ 7.81*** **€ 1.70****	**€ 650*** **€ 550****	**€ 22,885*** **€ 36,377**** **€ 48,032***** **€ 35,799******
			*FIT kit (costs per kit dispatched/ per	*gFOBT kit (costs per kit dispatched/	*colonoscopy	*Lifetime costs of stage I

			individual invited to participate in screening) **FIT processing/analysis (costs per kit completed and returned/ costs per screening participant)	per individual invited to participate in screening) **gFOBT processing/analysis (costs per kit completed and returned/ costs per screening participant)	**CTC	CRC-screen-detected *'Lifetime costs of stage II CRC-screen-detected ***Lifetime costs of stage III CRC-screen-detected ****Lifetime costs of stage IV CRC-screen-detected
Sobhani et al. (2011), France	State-transition model (Markov process)	Direct costs based on literature	**€ 18.43**	**€ 18.43**	**€526*** **€641****	**€ 17,596*** **€ 20,472**** **€ 29,013***** **€ 35,059*****
			costs for the screening programme, the invitation of the population and the distribution of the tests are the **same** for FIT and gFOBT: Screening programme Inviting the population Distribution Purchase costs Analysis		*Colonoscopy in case of positive results (on average) **Colonoscopy with polypectomy (on average)	*Treatment of CRC at stage I **Treatment of CRC at stage II ***Treatment of CRC at stage III ****Treatment of CRC at stage IV
Telford et al. (2010), Canada	State-transition model (Markov process)	Direct costs based on data from the Provincial Ministry of Health	Between 10 and 40 CAN$	Between 5 and 20 CAN$		
Wilschut et al. (2011) Netherlands	Use of MISCAN-COLON micro-simulation model	Direct costs derived from the Dutch health care system	**€ 19.22**	**€ 15.95**	**€ 303*** **€ 393****	**€ 12,500*** **€ 17,000**** **€ 21,000***** **€ 25,000******
			Costs per invitation (organizational costs and test kit) Costs per attendee (personnel and material costs for analysis)		*Colonoscopy **Colonoscopy with polypectomy	*Treatment of CRC at stage I **Treatment of CRC at stage II ***Treatment of CRC at stage III ****Treatment of CRC at stage IV
Zauber (2010), USA	Use of MISCAN-COLON micro-simulation model	Direct costs derived from Medicare fee schedule excluding co-payments borne by the patient	**$ 22.22**	**$ 4.54**	**$ between 200 and 2,000**	**$ between 5,000 and 30,000*** **$ between 20,000 and 50,000**** **$ between 30,000 and 100,000***** **$ between 50,000 and 500,000******
			base-case costs	base-case costs		*Treatment of CRC at stage I **Treatment of CRC at stage II ***Treatment of CRC at stage III ****Treatment of CRC at stage IV

[1] Costs of treating cancers with regard to diagnostic stage (i.e. A, B, C and metastasized stage) were estimated using data from the Digestive Tumour Registry of Calvados and Social Security data on reimbursements for treating all CRCs incident in the Department of Calvados during the period 1st September 1997 to 31st August 1998. They were constituted of: hospital care (both public and private) and care given in the medical departments of retirement homes; outpatient care (specialised or non-specialised medical consultations, medical and paramedical acts); transportation for medical reasons; medical purchases such as pharmaceutical products and prosthesis (colostomy bags); and assistance provided to patients such as daily payments and other allowances (disability with or without recourse to a third person). [2] The costs of the FOBTs consist of costs that were independent and dependent on the type of test. Ignoring the differences in participation between the types of test, costs independent of the type of test were costs related to the invitation for screening as letters and information brochures, basic administration of tests, feedback of test results to the patient and postal charges. Costs dependent on the type of test were costs of the FOBT itself and costs for laboratory analyses.

Importance: Optional

Transferability: Not

Outcomes

Result card for ECO4: "What are the incremental effects of FIT relative to its comparator(s)gFOBT and no screening?"

View full card

ECO4: What are the incremental effects of FIT relative to its comparator(s)gFOBT and no screening?

Method

The effectiveness of the screening methods for CRC is elaborated in the Clinical Effectiveness domain. The incremental effectiveness of FIT versus gFOBT presented here is based on the results of the systematic literature review of cost-effectiveness studies using decision analytic modelling.

Result

There are differences in the output measures used by the included cost-effectiveness studies. Eight studies are using life-years gained as the measure of effectiveness {10, 12, 13, 16-19, 25}, six are using Quality adjusted life years (QALY) {14, 15, 20-24} and one is using the intermediate outcome “detected advanced tumours” {11}. Since there are different study designs (type of model, perspective, time horizon, population, etc.) and input parameters (sensitivity, specificity, compliance rate, etc.) the results of the models are not necessarily comparable.

Life-years gained when using FIT instead of gFOBT:

- In general the results of the cost-effectiveness modelling show that using FIT instead of gFOBT increases the life-years per person. The incremental effects range from 0.041 life-years gained per person over a lifetime if annual screening is performed from age 65 – 79 {10}, to 0.003 life-years-gained after 10 years if only one round of screening is performed in a cohort of 50-75 year-olds {19}.
- There are two different types of guaiac-based tests, which are frequently used as comparators in cost-effectiveness studies: Hemoccult II and Hemoccult SENSA. The effect on life-years gained of the latter, Heoccult SENSA, is estimated to be similar to that of the immunochemical tests {10, 25}.
- Most studies using life-years gained as the measure for effectiveness are based on data from the USA and France {10, 12, 13, 16-18, 25}. Only one study is based on data from the Netherlands {19}.

Table 5: Incremental effects of FIT vs. gFOBT in life-years gained (LYG):

Author (year)	Life-years gained [1]	Comparators	Screening age	Participation rate	Discount rate	Country
van Ballegooijen et al. (2003) {10}	0.041	FIT 98%-specificity vs. gFOBT (Hemoccult II); annual	65-79	100%	3%	USA
	0.04	FIT 95% specificity vs. gFOBT (Hemoccult II); annual				
	0.0008	FIT 98% specificity vs. gFOBT (Hemoccult Sensa); annual				
	0.00003	FIT 95% specificity vs. gFOBT (Hemocult Sensa); annual				
Berchi et al. (2004) {12}	0.0198	FIT vs. gFOBT; after 20 years; biennial	50-74	43.7%	5%	France
Hassan et al. (2011) {13}	0.01707	Annual FIT vs. biennial gFOBT	50-74	Adherence[2]: 40%; compliance[3]: 100%	3%	France
	0.01337	FIT vs. gFOBT; biennial				
Heresbach et al. (2010) {16}	0.02744	FIT vs. gFOBT; after 30 years; biennial	50-74	42%	3%	France
Lejeune et al. (2010) {17}	0.01329	FIT vs. gFOBT; after 20 years; biennial	50-74	55%	3%	France
Parekh et al. (2008) {18}	0.00919	FIT vs. gFOBT; annual;	50-80	100%	3%	USA
van Rossum et al. (2011) {19}	0.003	FIT vs. gFOBT; after 10 years; 1 round of screening	50-75	gFOBT: 47% FIT: 60%	3%	Netherlands
Zauber (2010) {25}	0.0144	FIT vs. gFOBT (Hemoccult II); annual	50-80	100%	3%	USA
	-0.00005	FIT vs. gFOBt (Hemoccult Sensa); annual				

(1) Per person when using FIT instead of gFOBT (over a lifetime if not stated otherwise)

(2) Attending initial screening

(3) Attending subsequent rescreening

QALYs gained when using FIT instead of gFOBT:

All included cost-effectiveness studies that used QALYs as effectiveness measure support the results of the studies using life-years gained as the endpoint. The results of the comparison between FIT and gFOBT range from 0.036 QALYs gained per person over a lifetime by screening a cohort of 50-75 year-olds annually with FIT instead of gFOBT {22}, to 0.01 QALYs gained over a lifetime when annually screening a population of the same age with a low performance FIT instead of a gFOBT {14}. The study with the highest QALY gain also assumes the highest compliance with the screening strategies (75%). The smallest differences between the effectiveness of FIT and gFOBT occur when the test performance (sensitivity) is assumed to be low. The studies using QALYs as effectiveness measure are based on data from Canada {14, 15, 22}, England {23}, France {21} and Ireland {20}. Wilschut et al. (2011) {24} does not give the estimated effects of FIT and gFOBT and hence does not allow an estimation of the incremental effects.

Table 6: Incremental effects of FIT vs. gFOBT in Quality Adjusted Life-years (QALYs):

Author (year)	QALYs gained (1)	Comparators	Screening age	Participation rate	Discount rate	Country
Heitman et al. (2009) (2) {14}	0.020	FITmid vs. gFOBT; annual;	50-74	adherence: 68%; compliance: 63%	5%	Canada
	0.020	FIThigh vs. gFOBT; annual;				
	0.010	FITlow vs. gFOBT; annual;				
Heitman et al. (2010) {15}	0.035	FIThigh vs. gFOBThigh; annual;	50-75	Adherence(3): 68%; compliance(4): 63%	5%	Canada
	0.011	FITlow vs. gFOBTlow; annual;				
Sharp et al. (2012) {20}	0.016	FIT vs. gFOBT; biennial;	55-74	53%	4%	Ireland
Sobhani et al. (2011) {21}	0.013	FIT vs. gFOBT; biennial;	50-75	57.3%	3%	France
Telford et al. (2010) {22}	0.036	FIT vs. gFOBT; annual;	50-75	73%	5%	Canada
Whyte et al. (2012) {23}	0.016	FIT vs. gFOBT; biennial;	60-74	adherence: 54%; compliance: 85%	3.5%	England

(1) Per person when using FIT instead of gFOBT (over a lifetime).

(2) The time horizon is not clearly stated in the published article but it seems likely to be over a lifetime.

(3) Attending initial screening

(4) Attending subsequent rescreening

Increase in detected advanced tumours when using FIT instead of gFOBT:

One cost-effectiveness study uses detected advanced tumours as effectiveness measure {11}. This is an intermediate outcome that is used in clinical studies, and can only be assumed to be correlated with the final outcomes, life-years and QALYs gained. The results of this study show that the higher the cut-off level of the FIT (ranging from 20 – 148 ng/ml) the less effective FIT becomes compared to gFOBT (incremental effects ranging from 188 more detected tumours by FIT compared to gFOBT to 99 less detected by FIT). The reason for this is that the positive predictive value increases with the cut-off level, which means that a higher cut-off level reduces unnecessary follow-up colonoscopies but it also reduces the chance that a tumour is found if the level of blood in the stools is low (e.g. 20ng/ml).

Overall, the FIT seems to be more effective than gFOBT irrespective of the outcome measure used. The only exception is Zauber (2010) who compared FIT with a specific gFOBT (Hemoccult SENSA) and estimated that this specific gFOBT is marginally more effective (at the 5th decimal place) than FIT {25}.

Comment

The transferability of a model´s results depends on similarities and dissimilarities of the relevant settings. Important model parameters that should be comparable are the age range, the rate of compliance and the discount rate. Furthermore, the basic demography of the model country and the country-specific epidemiology should be considered when transferring results from one setting to another.

Importance: Critical

Transferability: Partially

Cost-effectiveness

Result card for ECO5: "What is the incremental cost-effectiveness ratio (FIT versus gFOBT; FIT versus no screening; gFOBT versus no screening)?"

View full card

ECO5: What is the incremental cost-effectiveness ratio (FIT versus gFOBT; FIT versus no screening; gFOBT versus no screening)?

Method

The incremental cost-effectiveness ratio (ICER) of FIT versus gFOBT is based on the studies identified through the systematic literature search described above. In most of these studies the incremental cost-effectiveness ratio (ICER) was already calculated and explicitly given. For the remaining studies the incremental costs and effects of FIT versus gFOBT was calculated and divided to obtain the ICER:

ICER= DCosts/D Effects

For the estimation of the overall costs of the different screening technologies most of the cost-effectiveness models adopted a payer's perspective and hence only included the direct costs of the screening programme, the follow-up tests and the treatment of a detected adenoma or cancer. Heitman et al. (2009 and 2010) {14, 15} also added indirect costs of the patient time and of the transport.

Result

The 16 identified studies all contained an estimation of either cost-effectiveness (effects are measured in life-years gained) {10, 12, 13, 16-19, 25} or cost-utility (effects are measured in QALYs) {14, 15, 20-24}, based on health-economic models.

The calculated ICERs varied across the studies as was expected due to the different modelling structures and parameter assumptions. However, given that the studies were undertaken in different settings (countries and health-care systems) and used data from different points in time the result that FIT was estimated to be 'dominant' or have a relatively low incremental cost-effectiveness ratio (ICER), is consistent across almost all the studies.

The consequences of screening for colorectal cancer can potentially occur throughout the participants' remaining lifetime. Hence, the time horizon for a study modelling the costs and effects of different screening strategies for CRC should be over a lifetime, if sufficient information is available to support such an approach. If a life-time horizon is not taken or not possible, then there is a potential that important costs and/or effects will be ignored. For the reason being that costs of a screening occur immediately, whereas the effects (life years / QALYs gained) usually occur later in life, a shorter time horizon might underestimate the cost-effectiveness of a technology. There are three studies included in this review that use shorter than lifetime time horizons (10 {19}, 20 {11, 12, 17} and 30 years {16, 24}).

Costs per life-year gained when using FIT instead of gFOBT:

In one third of the reported ICERs (four of 12) FIT dominates gFOBT, meaning that FIT is associated with lower costs and higher effects than gFOBT (see table below). However, most of these studies were based on US-data {10, 18}. One model estimated that FIT was dominated by gFOBT if used in a screening population of 50-80-year-olds {25}; this is the study were Hemeoccult SENSA was used, which is assumed to have effects similar to those of FIT, and to cost less than FIT. The remaining estimates of the ICER are ranging between around 3,000 € and 17,500 € per life-year gained {10, 12, 13, 16, 17, 25}. The publication date of the studies does not seem to play a significant role in the differences between the ICERs.

Table 7: Incremental Cost Effectiveness Ratios (ICERs) using life years gained

Author (year)	ICER[1] (=ΔCosts/ Δlife-year gained)	Comparators	Screening age	Costs included	Discount rate	Country
van Ballegooijen et al. (2003) {10}	FIT **dominates** gFOBT	FIT 98% specificity vs. gFOBT (Hemoccult II and Hemoccult Sensa); annual	56-79	Direct costs derived from Medicare fee schedule including co-payments born by the patient (in 2002 US Dollars)	3%	USA
	FIT **dominates** gFOBT	FIT 95% specificity vs. gFOBT (Hemoccult Sensa); annual				
	6,400 US$ per LYG (**~ 4,700** €)	FIT 95% specificity vs. gFOBT (Hemoccult II)				
Berchi et al. (2004) {12}	**3,000**€ per LYG	FIT vs. gFOBT; after 20 years; biennial	50-74	Direct costs based on French health care insurance contracts (in 2003[b] Euros)	5%	France
Hassan et al. (2011) {13}	**8,600** € per LYG	FIT vs. gFOBT; biennial	50-74	Direct costs based on French health care insurance contracts (in 2010[b] Euros)	3%	France
	17,600 € per LYG	Annual FIT vs. biennial gFOBT				
Heresbach et al. (2010) {16}	**5,500** € per LYG	FIT vs. gFOBT; after 30 years; biennial	50-74	Direct costs obtained from French health care system (in 2005/07[a] Euros)	3%	France
Lejeune et al. (2010) {17}	**3,000** € per LYG	FIT vs. gFOBT; after 20 years; biennial	50-74	Direct costs based on French health care insurance contracts (in 2006 Euros)	3%	France
Parekh et al. (2008)	FIT **dominates**	FIT vs. gFOBT; annual;	50-80	Direct costs derived from Medicare fee schedule (in 2006 US Dollars)	3%	USA

{18}	gFOBT					
van Rossum et al. (2011) {19}	FIT **dominates** gFOBT	FIT vs. gFOBT; after 10 years; 1 round of screening	50-75	Direct costs based on Dutch health care charges and retail prices (in 2009[a] Euros)	3%	Netherlands
Zauber (2010) {25}	**22,100** US$ per LYG (**~ 16,400** €)	FIT vs. gFOBT (Hemoccult II)	50-80	Direct costs derived from Medicare fee schedule excluding co-payments borne by the patient (in 2007 US Dollars)	3%	USA
	FIT **is dominated by** gFOBT	FIT vs. gFOBT (Hemoccult SENSA); annual				

1. year of price based on referenced literature
2. year of price not given, and assumed to correspond to year prior to publication

Costs per QALY gained when using FIT instead of gFOBT:

All of the studies that used QALYs as a measure of effectiveness were conducted recently, i.e., between 2009 {14} and 2012 {20} (see table below).

Half of the estimated ICERs based on the included models show that FIT dominates gFOBT {14, 15, 23, 24}. The settings (Canada, England and the Netherlands), the screening age (50-74, 60-74 and 45-80) and the assumed base-case discount rates (3%, 3.5% and 5%) vary across these studies. Two of the ICERs where FIT dominated gFOBT were estimated from a model that included costs for patient time and transport to the screening {14}. The ICERs of the remaining four studies {14, 20-22} range between around 400 € and almost 9,000 € per QALY which is well below one often-suggested ICER threshold of 50,000 US $ (around 36,960 €).

Table 7: Incremental Cost Effectiveness Ratios (ICERs) using QALYs

Author (year)	**ICER** [1] **(= ΔCosts/ ΔQALY gained)**	**Comparators**	**Screening age**	**Costs-included**	**Discount rate**	**Country**
Heitman et al. (2009) [2] {14}	FIT **dominates** gFOBT	FIT-**low** vs. gFOBT; annual	50-74	Direct costs derived from the Canadian health care system, costs of patient time and transport costs (in 2007 CAN Dollars)	5%	Canada
	FIT **dominates** gFOBT	FIT-**mid** vs. gFOBT; annual				
	5,000 CAN$ per QALY (**~ 3,600** €)	FIThigh vs. gFOBT; annual				
Heitman et al. (2010) {15}	FIT **dominates** gFOBT	FIT-mid, -low and -high vs. gFOBT low and high	50-75	Direct costs derived from the Canadian health care system, costs of patient time and transport costs (in 2007 CAN Dollars)	5%	Canada
Sharp et al. (2012) {20}	**400** € per QALY	FIT vs. gFOBT; biennial;	55-74	Direct costs based on Health Service Executive (in 2008 Euros)	4%	Ireland
Sobhani et al. (2011) {21}	**8,800** € per QALY	FIT vs. gFOBT; biennial	50-75	Direct costs based on literature (in 2010 Euros)	3%	France
Telford et al. (2010) {22}	**600** CAN$ per QALY (**~ 400** €)	FIT vs. gFOBT; annual	50-75	Direct costs based on data from the Provicial Ministry of Health (in 2007 CAN Dollars)	5%	Canada
Whyte et al. (2012) {23}	FIT **dominates** gFOBT	FIT vs. gFOBT; biennial;	60-74	Direct costs based on data from the National Health Service	3.5%	England
Wilschut et al. (2011) {24}	FIT **dominates** gFOBT	FIT (at all cut-off levels) vs. gFOBT; after 30 years; annual	45-80	Direct costs derived from the Dutch health care system (in 2010[a] Euros)	3%	Netherlands

1. year of price not given, and assumed to correspond to year prior to publication

[1] Numbers are rounded to full hundreds (exact estimates can be found in the Appendix “Study Designs and Results”

[2] The time horizon is not clearly stated in the published article but it seems likely to be over a lifetime.

[1] Numbers are rounded to full hundreds (exact estimates can be found in the Appendix “Study Designs and Results”

Comment

Adjustment of price levels:

The results of the cost-effectiveness models were not adjusted to one price level or one point in time. Since most studies (12 of 16) were conducted in or after 2008 this might cause non-significant changes to the ranking of the ICERs in the tables but is unlikely to change the overall order dramatically.

Sensitivity analyses:

An analysis of the robustness of the results was not given by all studies, especially not on the gFOBT-vs.-FIT ICER since the primary aim of some studies was to compare not only FIT and gFOBT but also other screening strategies, or no screening at all.

1. *Studies life years gained as the outcome measure:*

The result of the study of van Ballegooijen et al. (2003) revealed that FIT with a 98% specificity dominates gFBOT (Hemeoccult II) and that this holds even if the compliance rate decreases from 100% to 60% for gFOBT and 90% for FIT {10}.

In a Monte Carlo simulation Parekh et al. (2008) shows that FIT dominates a no screening strategy in 100% of the simulations whereas gFOBT dominates a no-screening strategy in only around 95% of the simulations {18}. A direct comparison of FIT and gFOBT using a Monte Carlo simulation was not conducted.

Van Rossum et al. (2011) present the results of a deterministic sensitivity analysis, with the result that only very low CRC incidence and very high estimated costs of colonoscopy have a negative impact on the cost-effectiveness of FIT {19}.

Another deterministic sensitivity analysis was conducted by Berchi et al. (2004) using different assumptions about the participation rate, the costs of gFOBT, costs of colonoscopy, costs of CRC treatment, quality of FIT and natural history of disease {12}. The results suggest a robustness of the finding that FIT is more effective but also more costly than gFOBT.

Lejeune et al.'s (2010) sensitivity analysis also shows that FIT remained more effective and more costly for all parameter variations, but that the ICER increases if the price for gFOBT is decreased by 50% or if the sensitivity of FIT decreases. The ICER decreases if the price for FIT decreases by 50%, if the participation rate of FIT is increased by 10%, if the lead time associated with FIT increases or if FIT`s sensitivity increases {17}.

A probabilistic sensitivity analysis of the model designed by Heresbach et al. (2010) shows that FIT is more effective than gFOBT in 97.8% and dominant in 8.9% of the simulations {16}.

Hassan et al. (2011) also conducted a probabilistic sensitivity analysis with the result that annual FIT had the highest net-benefit in 20% of the simulations, compared to other strategies such as sigmoidoscopy every five years, of colonoscopy every 10 years which had the highest net-benefit in 40% and 26% of the simulations respectively {13}.

In the publication of Zauber (2010) no sensitivity analysis is reported {25}.

1. *Studies using QALYs gained as the outcome measure:*

The univariate sensitivity analysis of Heitman et al. (2009) showed that changing the costs or the screening interval (biennial instead of annual) did not change the dominance of FIT-mid (representing studies with "mid-range" test performance) over gFOBT {14}.

In the study published by Heitman et al. one year later (2010) no sensitivity analysis of the direct comparison of FIT versus gFOBT was published, but the probabilistic analysis shows that in nearly 100% of the simulations FITmid was cost saving and more effective compared to no screening, but no direct comparison of {15}.

The results of the model presented by Whyte et al (2012) are highly sensitive to several model parameters such as uptake, endoscopy costs and FIT thresholds. In the probabilistic sensitivity analysis FIT remains cost-effective compared to gFOBT at an assumed willingness-to-pay threshold of 20,000 £ {23}.

Wilschut et al. (2011) conducted a deterministic sensitivity analysis on different parameters. FIT (50ng/ml) for the age group 45-80 years remained most cost-effective when attendance rate increased to 100%, quality of life loss was taken into account, fatal complications decreased, FOBT costs and colonoscopy costs were halved, and when complication and treatment costs were halved or doubled. FIT (50ng/ml) for the age group 50-80 years became more cost-effective for all other parameter changes {24}.

In the one-way sensitivity analysis of Sharp et al. (2012) the most influential parameters were the discount rate, the costs of the tests and the costs of managing CRC. The ICERs for FIT and gFOBT compared to no screening always remained below the chosen notional cost-effectiveness threshold (45,000 € per QALY). The probabilistic sensitivity analysis showed that uncertainty was greatest for FIT, but all cost-effectiveness ratios remained below the notional threshold and the incremental QALY gains for FIT exceeded those for gFOBT in most simulations {20}.

The model of Telford et al. (2010) was sensitive to variations in the sensitivity of the tests to detect advanced adenoma, the costs of the test, the compliance with screening and the costs of cancer care. The probabilistic sensitivity showed that the ranking of strategies did not change and that no strategy was dominant {22}.

In the model of Sobhani et al. (2011) the participation rate seems to have a very high impact on the results, whereas changing the compliance rate for colonoscopy did not change the results much. Throughout the one-way sensitivity analyses the 3-sample FIT with a cut-off level of 50ng/ml was consistently the most cost-effective choice {21}.

It is difficult to provide an overall statement on the robustness of the ICER estimations because neither the methods of sensitivity analysis nor the reporting of the results are standardised. The matter is further complicated by that fact that in some of the studies FIT is not directly compared to gFOBT but both are compared to no screening. As a consequence, the sensitivity analyses focus on the robustness of the cost-effectiveness compared to no screening.

In conclusion, the deterministic sensitivity analyses of the *studies using life years gained as the outcome measure* show that the model results are quite robust, especially to changes in compliance and participation rate, but might be sensitive to other assumptions, such as that the CRC incidence is very low, the costs of a colonoscopy or a gFOBT is very high or that the sensitivity of FIT decreases. The probabilistic sensitivity analyses suggest that the results are rather robust.

The sensitivity analyses of the *studies using QALYs gained as the outcome measure* show no common pattern and therefore no qualified statement about influential parameters can be given.

Six studies reported the result of a deterministic sensitivity analysis {10, 12, 17, 19, 21, 24}, four used a probabilistic method {13, 15, 16, 18}and four studies used both, a deterministic and a probabilistic analysis {14, 20, 22, 23}. Only one study did not report a sensitivity analysis {25}.

Importance: Critical

Transferability: Partially

Result card for ECO6: "What is the appropriate time horizon?"

View full card

ECO6: What is the appropriate time horizon?

Method

The systematic review of the literature, outlined in the domain methodology –section, was used to form the description of the time horizons used in the studies found (see table **"**Study designs and results" in Appendix). The appropriateness of the time horizon relates to three main considerations:

1. the extent to which a study can be considered comparable to other studies on the same topic
2. data availability and decision-making context
3. the discount rate

Result

In studies of technologies with a potential for life-long consequences, the time horizon of cost-effectiveness analysis would ideally be over the remaining lifetime. However, the relevant time horizon will also depend on the availability of appropriate data, as well as on the availability of appropriate statistical or mathematical models, in order to estimate costs and outcomes. In the cost-effectiveness studies located, the majority use a time period over which most of the significant economic and health consequences of the intervention could become apparent. In order to do this, they invariably link intermediate endpoints to final endpoints and/or extrapolate evidence on effectiveness. One approach when undertaking an economic evaluation with a time horizon of the remaining lifetime of the modelled cohort, is that costs and effects can be measured alongside a trial and then, when appropriate, be extrapolated using modelling (e.g., by synthesizing trial-based information with information on costs and effects from other studies).

Although some of these models may not describe reality with full face validity, they may be able to offer a useful method of making relative cost-effectiveness comparisons between different screening modalities.

The main differences and similarities between the studies with respect to the stated time horizons and discount rate(s) can be found from the Appendix (see table "Study designs and results").

Importance: Unspecified

Transferability: Unspecified

Result card for ECO7: "What is the method of analysis?"

View full card

ECO7: What is the method of analysis?

Method

The systematic review of the literature outlined in the domain methodology section and many of the details concerning the method of analysis can be found from the other results cards within this domain. In this result card we will focus on the types of modelling used, the two broad categories can be classed as modelling on the basis of a single study, such as in {11, 12} and those using a stage-based or natural history modelling approach using multiple sources of evidence (i.e., most others). We also draw on one overview of the cost-effectiveness literature {6} and on one earlier HTA {5}.

Result

Single-study-based economic evaluations have the potential advantage of the internal validity of the trial design and the advantage of joint collection of data on both resource use and effectiveness. However, the aims of the underlying trials and economic evaluations, may differ in significant respects, which can lead to problems concerning the suitability or comparability of trial-based economic analyses. Despite the aims of single-study-based economic evaluations generally being somewhat different than model-based economic evaluation, trial-based economic analyses may provide individual-level analysis of the impact of the screening technology and its comparator(s). On the other hand, it should be kept in mind that in many instances modelling is needed, e.g., to estimate final outcomes from the intermediate outcomes measured during a trial, or to extrapolate to the envisaged population. As an alternative to single-study-based economic evaluations, 'stage-shift models' or 'natural-history models' can be used to synthesise information from numerous studies and sources.

Stage-shift models (sometimes referred to as 'shallow' models) generally compare the distribution of disease stages associated with screening (e.g., observed in screening trials) with the distribution of disease stages at diagnosis (at a later point in time) seen in the absence of a screening programme (e.g., observations from cancer registers or screening-trial comparator arms) {39}. In the case of CRC, relevant stages could include absence of disease, pre-cancerous lesions, different stages of cancer. In stage-shift models the effect of screening is modelled by shifts to less severe stages, e.g., using information that, given systematic screening, proportionally more people will be diagnosed with pre-cancerous lesions or at an early stage of cancer that may be more operable or still curable. One common feature is that modelling starts at the time of the first screening and models estimate costs and effects as a function of disease stage at screening or diagnosis.

An alternative to stage-shift models is to use 'natural-history models' to estimate the development of cancer and its precursor stages in a population that is followed from an early age onwards (e.g., starting in young adulthood or at birth). For each member of the modelled cohort, the development of disease is tracked, i.e., the model determines at each point in time whether the person remains disease free, has a precursor lesion, or has developed a certain stage of cancer. Such epidemiological models of the natural history of the disease, sometimes referred to as 'deep models', have the advantage of serving as a basis for 'applying' or 'plugging-in' a diverse range of screening strategies, diagnostic procedures, treatments, and associated costs and effects. One limitation is that extensive epidemiological data of high quality are required. Natural-history models also usually cover the early stages of the disease process and there are often gaps in knowledge that hinder modelling. On the other hand, lead-time and length-time issues (e.g., the question whether screening participants may encounter a net survival benefit or beneficial treatment, or whether he/she is only diagnosed earlier), may be efficiently addressed using natural-history models, if suitable input data are available.

The differences and similarities between the studies with respect to the type of model used can be found from the Appendix (see table "Study designs").

Importance: Unspecified

Transferability: Unspecified

Discussion

The general limitation of model-based cost-effectiveness studies is that models represent a simplification of a complex reality. This limitation is clearly present in the Costs and economic evaluation domain where we included studies that use modelling to estimate the costs, effects and cost-effectiveness of colorectal cancer. For instance, many cost-effectiveness studies make the simplifying assumption that all colorectal cancers develop from adenomas, although this is unlikely to be the case {5}. A series of trade-offs have to be made, for instance, between complexity and transparency. Many of these models have been to some extent validated, or calibrated, against, e.g., estimates of efficacy in terms of CRC incidence or mortality from randomised trials and other literature. However, as there is no general means to validate or calibrate models in terms of their estimates of cost or cost effectiveness, readers should focus on their potential face validity given the inputs used, the extent to which models were transparently documented, and whether appropriate sensitivity analyses were performed. The benefit of model-based studies is that it allows the comparison of different screening tests where economic evaluations based on end-to-end trials might not be feasible. It enables researchers to put the two comparators in the same context (e.g. assuming the same quality of follow-up tests or cancer treatment), and therefore limit the analysis to the actual outcomes of the tests.

Issues relevant to numerous domains within this Core model include sensitivity and specificity, participation rate, age of the population to be screened, screening interval, different FIT thresholds. Below we highlight some of the issues from the literature which have some of the strongest effects on the estimates of cost and cost effectiveness.

It should be noted that the review presented in this domain is complicated by the fact that a majority of studies compare many screening modalities (e.g. faecal DNA test, flexible sigmoidoscopy, computed tomography colonoscopy, colon capsule endoscopy {13-15, 18, 20, 22, 23, 25}), rather than just FIT and FOBT. A difference is also discernible between those studies with a North American focus and those with a European focus. One of the main ways in which European studies may differ markedly from those in the US is in terms of the lower European *level* of health care and social care costs. For instance, the cost of testing kits, diagnostic procedures and both curative and palliative treatment may all be substantially higher in the US. The rate of *increase* in costs may also differ between Europe and the US, many studies have not incorporated the probable cost pressures caused by the new forms of chemotherapy {6}. Another culturally-specific issue is the pattern of adherence to screening protocols, for example, FOBT participation rates in Finland during the roll-out of a national screening programme were as high as 71% {40}, while in Italy adherence as part of a randomised controlled trial was recorded as 27% on average {41}. Most of the studies included in the review do not take into account that adherence, i.e., the level of participation in screening and post-screening protocols, may differ quantitatively {10-16, 18, 21-23, 25}, e.g., may depend on the screening modalities in question. However, even when studies do not assume perfect adherence relatively favourable estimates of cost-effectiveness are reported in base-case analyses {6}.

Given the use of a health-care payer perspective in many studies, when analysing costs, they naturally do not include costs which are borne by the patient or costs borne outside the health care system. Hence, in the studies found, many of the costs borne by individuals, which may vary according to the screening modality used, has not been taken into account in many models {5}. A variety of health-care-payer perspectives on costs was predominant in the studies found. It could also be informative if a societal perspective, which may include costs falling more widely both inside and outside the health-care system, would also have been investigated. It should be noted that the choice of a restricted perspective, such as the perspective of a health-care-payer, may affect both the ability to provide information on either static or dynamic economic efficiency, and the ability of estimates of cost-effectiveness to be usefully compared to analyses of other technologies which use a different or broader perspective.

There is still a dearth of information concerning health-related quality of life both for screening participants, as well as for individuals who undergo diagnosis and or treatment. One small-scale, now decades old, study of health-related quality of life amongst colorectal cancer patients is widely used in the estimates found in this literature review.

The choice between FIT and FOBT is complicated as both FIT and gFOBT are often used as generic names for a number of tests, for which the sensitivity and specificity, for example, vary. FOBT has had versions called Hemoccult ®, Hemoccult II and Hemoccult SENSA and FIT has been used with low-mid-high or other quantitative thresholds. The situation is complicated even further by the fact that there are different approaches of measuring the sensitivity and specificity of a screening test {33}.

Although a discount rate of 3% was widely used for both costs and benefits {10, 13, 16-18, 21, 24, 25}, in many of the studies reviewed here the rate of discount for costs and/or benefits was one of the parameters most influential on the resulting ICERs and, together with the chosen time horizon, careful consideration should be given to the applicability of the values used in the analysis {40}. The use of thorough sensitivity analyses concerning variations in discount rates is particularly advisable when a time horizon of extended duration is used.

It should also be remembered that estimates of the overall cost burden of initiating and maintaining a screening programme is usually considered to be beyond the scope of the ECO domain (see, e.g. {30}). The Core Model considers such costs within the Organisational domain.

Potential future research needs in the light of this systematic review:

- Trial-based economic evaluations of FIT versus gFOBt, no screening, or opportunistic screening, with both mortality and morbidity endpoints (one such study, currently underway in Finland, is comparing gFOBT to no screening)
- Thorough and transparent sensitivity analyses concerning variations in, e.g., discount rates and adherence

References

1. Ferlay J SH, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. 2010 [cited 2013 September]; Available from: http://globocan.iarc.fr

2. Colon; E. Prevention and screening [cited 2013 05.06.]; Available from: http://www.europacolon.com/preventionandscreening.php?Action=Preventionandscreening;

3. Institute; NC. Tests to Detect Colorectal Cancer and Polyps 2013 [cited 2013 05.06.]; Available from: http://www.cancer.gov/cancertopics/factsheet/detection/colorectal-screening#r13

4. (eds); SNPJvKL. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition. 2013 [cited 2013 05.06.]; Available from: http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=ND3210390

5. Health Information and Quality Authority of Ireland. Health technology assessment (HTA) of a population-based colorectal cancer screening programme in Ireland: Health Information and Quality Authority of Ireland (HIQA); 2009 2009-03-25.

6. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening – An overview. Best Practice & Research Clinical Gastroenterology. 2010;24(4):439-49.

7. Walker DG, Wilson RF, Sharma R, Bridges J, Niessen L, EB B. Best Practices for Conducting Economic Evaluations in Health Care: A Systematic Review of Quality Assessment Tools. : Rockville (MD); 2012.

8. Damian G. Walker, Renee F. Wilson, Ritu Sharma, John Bridges, Louis Niessen, Eric B. Bass, et al. Best Practices for Conducting Economic Evaluations in Health Care: A Systematic Review of Quality Assessment Tools. Baltimore, MD: Johns Hopkins University Evidence-based Practice Center

2012.

9. Don Husereau, Michael Drummond, Stavros Petrou M, Chris Carswell, David Moher, Dan Greenberg, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health. 2013;15(2).

10. Ballegooijen v, Habbema, Boer, Zauber, Brown. A comparison of the cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in the Medicare population; 2003.

11. Berchi, Guittet, Bouvier, Launvoy. Cost-effectiveness analysis of the optimal threshold of an automated immunochemical test for colorectal cancer screening: performances of immunochemical colorectal cancer screening. Int J Technol Assess Health Care. 2010;26(1).

12. Berchi C, Bouvier V, Reaud JM, Launoy G. Cost-effectiveness analysis of two strategies for mass screening for colorectal cancer in France. Health Econ. 2004 Mar;13(3):227-38.

13. Hassan, Benamouzig, Spada, Ponchon, Zullo, Saurin, et al. Cost effectiveness and projected national impact of colorectal cancer screening in France. Endoscopy. 2011;43(9).

14. Heitman, Au, Hilsden, Manns. Fecal Immunochemical Testing in Colorectal Cancer Screening of Average Risk Individuals: Economic Evaluation. Ottawa; 2009.

15. Heitman SJ, Hilsden RJ, Au F, Dowden S, Manns BJ. Colorectal cancer screening for average-risk North Americans: an economic evaluation. PLoS Med. 2010;7(11):e1000370.

16. Heresbach D, Chauvin P, Grolier J, Josselin JM. Cost-effectiveness of colorectal cancer screening with computed tomography colonography or fecal blood tests. Eur J Gastroenterol Hepatol. 2010 Nov;22(11):1372-9.

17. Lejeune C, Dancourt V, Arveux P, Bonithon-Kopp C, Faivre J. Cost-effectiveness of screening for colorectal cancer in France using a guaiac test versus an immunochemical test. Int J Technol Assess Health Care. 2010 Jan;26(1):40-7.

18. Parekh M, Fendrick AM, Ladabaum U. As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. Aliment Pharmacol Ther. 2008 Apr;27(8):697-712.

19. Rossum v, Rijn v, Verbeek, Oijen v, Laheij, Fockens, et al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. Int J Cancer. 2011;128(8).

20. Sharp L, Tilson L, Whyte S, O'Ceilleachair A, Walsh C, Usher C, et al. Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. Br J Cancer. 2012 Feb 28;106(5):805-16.

21. Sobhani I, Alzahouri K, Ghout I, Charles DJ, Durand-Zaleski I. Cost-effectiveness of mass screening for colorectal cancer: choice of fecal occult blood test and screening strategy. Dis Colon Rectum. 2011 Jul;54(7):876-86.

22. Telford JJ, Levy AR, Sambrook JC, Zou D, Enns RA. The cost-effectiveness of screening for colorectal cancer. CMAJ. 2010 Sep 7;182(12):1307-13.

23. Whyte S, Chilcott J, Halloran S. Reappraisal of the options for colorectal cancer screening in England. Colorectal Dis. 2012 Sep;14(9):e547-61.

24. Wilschut JA, Habbema JD, van Leerdam ME, Hol L, Lansdorp-Vogelaar I, Kuipers EJ, et al. Fecal occult blood testing when colonoscopy capacity is limited. J Natl Cancer Inst. 2011 Dec 7;103(23):1741-51.

25. Zauber AG. Cost-effectiveness of colonoscopy. Gastrointest Endosc Clin N Am. 2010 Oct;20(4):751-70.

26. Haug U, Knudsen AB, Kuntz KM. How should individuals with a false-positive fecal occult blood test for colorectal cancer be managed? A decision analysis. Int J Cancer. 2012 Nov 1;131(9):2094-102.

27. Labianca R, Beretta GD, Mosconi S, Milesi L, Pessi MA. Colorectal cancer: screening. Ann Oncol. 2005;16 Suppl 2:ii127-32.

28. Lejeune C, Arveux P, Dancourt V, Fagnani F, Bonithon-Kopp C, Faivre J. A simulation model for evaluating the medical and economic outcomes of screening strategies for colorectal cancer. Eur J Cancer Prev. 2003 Feb;12(1):77-84.

29. Robinson MHE, Marks CG, Farrands PA, Whynes DK, Bostock K, Hardcastle JD. Is an immunological faecal occult blood test better than Haemoccult? A cost-benefit study. european Journal of Surgical Oncology. 1995;21.

30. Sharp, Tilson, Whyte, O`Ceilleachair, Walsh, Usher, et al. Using resource modelling to inform decision making and service planning: the case of colorectal cancer screening in Ireland. BMC Health Service Research. 2013;March 19(13).

31. Castiglione, Zappa, Grazzini, Sani, Mazzotta, Mantelli, et al. Cost analysis in a population based screening programme for colorectal cancer: comparison of immunochemical and guaiac faecal occult blood testing. Journal of Medical Screening. 1997;4(3).

32. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of Screening for Colorectal Cancer in the General Population. Journal of the American Medical Association. 2000;284(15).

33. Gyrd-Hansen D. Fecal Occult-Blood Tests - A cost-effectiveness Analysis. International Journal of Technology Assessment in Health Care. 1998;14(2).

34. Ladabaum U, Song K. Projected national impact of colorectal cancer screening on clinical and economic outcomes and health services demand. Gastroenterology. 2005 Oct;129(4):1151-62.

35. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel ancer in Australia. MJA. 2011;194(4).

36. Sonnenberg A, Delco F, Inadomi JM. Cost-effectiveness of Colonoscopy in Screening for Colorectal Cancer. Annals of Internal Medicine. 2000;133(8).

37. Whynes DK. Cost-effectiveness of faecal occult blood screening for colorectal cancer: results of the Nottingham trial. Critical Reviews in Oncology/Hematology. 1998;32.

38. Anderson R. Systematic reviews of economic evaluations: utility or futility? . Health Economics. 2010;19(3).

39. Connor R, Chu K, Smart C. Stage-shift cancer screening model. Journal of Clinical Epidemiology. 1989;42(11).

40. Malila N, Oivanen T, Malminiemi O, Hakama M. Test, episode, and programme sensitivities of screening for colorectal cancer as a public health policy in Finland: experimental design. Bmj. 2008;337:a2261.

41. Lisi D, Hassan C, Crespi M, Group AS. Participation in colorectal cancer screening with FOBT and colonoscopy: an Italian, multicentre, randomized population study. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2010 May;42(5):371-6.

Appendices

- Systematic literature search

- Selection Criteria

- Study designs and results

Ethical analysis

Authors: Gottfried Endel

Summary

A comparison of tests with identical test characteristic, similar accuracy and identical types of consequences pose no specific ethical problems. If a regional health care system has already decided to implement a population based screening for colorectal cancer the main ethical issues are already decided. A choice of the screening test for occult blood in faeces is very similar to the decision which product to choose, if there are different vendors.

The variability of ICERs in ECO5 shows that the tests are really very similar. They both dominate no screening but the indirect comparison of the two tests varies considerably. Even so most models attribute dominance to FIT some are favorable for gFOBT. To address these uncertainties an appraisal of the HTA information with

application of regional values and experiences has to be done. There the usual framework for decisions in the respective health care system can be applied. This should also cover the question of opportunity cost if the decision imposes a financial impact on the sytem.

Introduction

Questions addressing (population) screening activities need a special approach in ethical analysis. There are the following points with a framework different from usual treatment interventions:

- The health care system recommends an intervention. So it is a system responsibility to provide the information needed for an informed consent to participate. The best available evidence and open information about uncertainty has to be made available.
- The intervention addresses asymptomatic = “healthy” people. So issues of safety, quality and harm reduction have first priority. This influences the approach to a risk / benefit balance.
- As it is a recommendation of the health care system the quality of the service provision has to be monitored and the results have to be evaluated. Results have to be published and data has to be made available.
- The use of public resources needs special legitimating and proof of evidence.

There is also no information in medical literature about the basics of a health care system. The challenge in a core HTA is to be specific on an European level but according to the organization of health care in the member states only to outline the questions and principles addressed so they can be applied on the local level.

In the case of the comparison of Fecal Immunochemical Test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and colorectal cancer-CRC), under conditions of population based colorectal cancer screening, comparing with CRC screening with Guaiac –based fecal occult blood test (gFOBT) only the questions of the effectiveness and safety of the test in combination with the economic consequences are of interest. These questions are covered in the corresponding domains.

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC) The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a

nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
F0001	Principal questions about the ethical aspects of technology	Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?	yes	Is FIT a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?
F0002	Principal questions about	Can the technology challenge religious, cultural or moral convictions or beliefs of some	no	This would only be relevant between organized and opportunistic screening.

	the ethical aspects of technology	groups or change current social arrangements?		But it's no question between two tests.
F0003	Principal questions about the ethical aspects of technology	What can be the hidden or unintended consequences of the technology and its applications for different stakeholders.	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0006	Autonomy	Can the technology entail special challenges/risk that the patient/person needs to be informed of?	yes	Can FIT entail special challenges/risk that the patient/person needs to be informed of?
F0004	Autonomy	Does the implementation or use of the technology challenge patient autonomy?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0005	Autonomy	Is the technology used for patients/people that are especially vulnerable?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0007	Autonomy	Does the implementation challenge or change professional values, ethics or traditional roles?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0010	Beneficence/nonmaleficence	What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the risks and benefits in practice and how?	yes	What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing FIT? Who will balance the risks and benefits in practice and how?
F0011	Beneficence/nonmaleficence	Can the technology harm any other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0012	Justice and Equity	What are the consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?	yes	What are the consequences of implementing / not implementing FIT on justice in the health care system? Are principles of fairness, justness and solidarity respected?
F0013	Justice and Equity	How are technologies presenting with relevantly similar (ethical) problems treated in health care system?	yes	How are technologies presenting with relevantly similar (ethical) problems treated in health care system?
F0017	Questions about effectiveness and accuracy	What are the proper end-points for assessment and how should they be investigated?	yes	What are the proper end-points for assessment and how should they be investigated?
F0018	Questions about effectiveness and accuracy	Are the accuracy measures decided and balanced on a transparent and acceptable way?	yes	Are the accuracy measures decided and balanced on a transparent and acceptable way?
F0008	Human Dignity	Does the implementation or use of the technology affect human dignity?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0009	Human integrity	Does the implementation or use of the technology affect human integrity?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests which are equivalent in this respect.
F0014	Rights	Does the implementation or use of the technology affect the realisation of basic human rights?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.
F0016	Legislation	Is legislation and regulation to use the technology fair and adequate?	no	This would only be relevant between organized and opportunistic screening. But it's no question between two tests.

Methodology description

The project scope is applied in this domain. The ethical dimension of questions already covered in other domains adds only minor extensions to the findings there.

Information sources

The discussion of ethical issues is based on the results of the other domains and addresses in a discursive manner of coherence analysis (CA) according to the methodological recommendations for these domain aspects which were already covered but not scrutinized with regards to ethical aspects included. This methodological approach is chosen to minimize overlap and to take into account the potential of regional differences in values and opinions regarding potential marginal differences for ongoing programs.

Nevertheless a literature search was performed to find ethical discussions comparing these two tests or comparing two very similar tests in general. The search in pubmed and google sholar produced no literature addressing these issues. Articles on ethical issues for the questions of

- screening versus no screening
- screening with tests of very different risks for patients (FOBT versus colonoscopy)
- organized population based screening versus no screening or opportunistic screening

were identified. Also a framework for ethical questions in public health referred to some common questions of screening but did not expand the comprehensive methodological guidance available for the core model.

Quality assessment tools or criteria

As the goal on the level of the core HTA is to define the framework for the ethical analysis only criteria for the application of this framework will be defined. The quality assessment than can be done by using these criteria in the local scope. There the specific answer to the questions of the element cards have to be found by gathering the local information necessary.

As mentioned as method CA was chosen. The main idea of CA is to reflect upon the consistency of ethical argumentations or broader theories on different levels, without prescribing which facts, arguments or principles are prima facie relevant. It is a procedural, pragmatic approach, i.e. describes a procedure of approaching moral issues without claims of providing direct answers on “right or wrong”. This supports regional adaptation by focusing discussions on the value given special criteria in the specific context of the own health care system.

The criteria to consider coming from the effectiveness domain are:

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality

- Overall mortality
- Life years saved

The criteria to consider coming from the safety domain are:

- Harms from colonoscopy
- Psychological harms

The criteria to consider coming from the economic domain are:

- Cost effectiveness
- ICER
- LYG
- QUALY

Analysis and synthesis

The main sources for the ethical analysis are the results of the other domains. As shown in the EUNetHTA member survey of the domain on current use of the technologies CRC screening programs are widely ongoing in Europe. So the discussion of isolated aspects will be provided and no attempt is done to produce a synthesis fitting all different regional conditions and frameworks. The isolated aspects may – if appropriate – support the local adaptation of the assessment.

Result cards

Principal questions about the ethical aspects of technology

Result card for ETH1: "Is FIT a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?"

View full card

ETH1: Is FIT a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?

Method

Results of the CUR domain and the member survey done there answer this question perfectly.

Result

Table 1: “Overview of CRC screening practices in European countries” in CUR show that FIT is already used in several regions. So no new far reaching consequences on health care are to be expected.

Importance: Important

Transferability: Completely

Autonomy

Result card for ETH2: "Can FIT entail special challenges/risk that the patient/person needs to be informed of?"

View full card

ETH2: Can FIT entail special challenges/risk that the patient/person needs to be informed of?

Method

Results from EFF and SAF domain answer this question perfectly. As there are only minor differences between the two tests and the consequences are identical common professional practice will be the same for both tests.

Result

The comparison between the two tests show no special challenges or risks for patients.

Importance: Important

Transferability: Completely

Beneficence/nonmaleficence

Result card for ETH3: "What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing FIT? Who will balance the risks and benefits in practice and how?"

View full card

ETH3: What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing FIT? Who will balance the risks and benefits in practice and how?

Method

Results from EFF and SAF domain answer this question perfectly. As there are only minor differences between the two tests and the consequences are identical no important differences in benefits and risks have to be taken care of.

Result

The key question is whether to implement a population based screening using the detection of fecal blood. Minor differences in sensitivity and specific do not shift the balance of risks and harms.

Importance: Important

Transferability: Unspecified

Justice and Equity

Result card for ETH4: "What are the consequences of implementing / not implementing FIT on justice in the health care system? Are principles of fairness, justness and solidarity respected?"

View full card

ETH4: What are the consequences of implementing / not implementing FIT on justice in the health care system? Are principles of fairness, justness and solidarity respected?

Method

Results from EFF and SAF domain answer this question perfectly. As there are only minor differences between the two tests and the consequences are identical no important differences in benefits and risks have to be taken care of.

Result

The key issue is the implementation as population based screening. The choice of the test does not influence issues of justice. An indirect question with regard to justice can arise from differences in cost of the two tests. Cost differences in this program are opportunity costs for other potential interventions in the field of screening or in the wider field of health care or public health. So only the indirect consequences of the budget impact of a decision between the two tests may influence fairness or solidarity. This indirect impact was outside of the scope of the assessment. In an indirect way such questions are included in economic evaluations as willingness to pay threshold.

Importance: Important

Transferability: Partially

Result card for ETH5: "How are technologies presenting with relevantly similar (ethical) problems treated in health care system?"

View full card

ETH5: How are technologies presenting with relevantly similar (ethical) problems treated in health care system?

Method

Results from EFF, SAF and ECO domain answer this question perfectly.

Result

Technologies with very similar benefits and risks in the same field of diseases are usually compared with methods of health economic evaluations. Either the regional health care system has a system with a more or less explicit willingness to pay framework or the appraisal process has to clarify if an increase in test accuracy (calculated into live years gained –LYG, quality adjusted life years gained – QUALY, incremental cost per LYG or QUALY) is seen as “good value for money”. This willingness to pay consideration may look at

- Burden of disease – the epidemiology as documented in CUR domain
- Severity and prognosis of disease – disease stages detected as shown in EFF domain
- Follow up and treatment as discussed in EFF, SAF, ECO and ORG domain

Usually this considerations are guiding decisions on diagnostic tests in health care and in treatment.

Importance: Optional

Transferability: Not

Questions about effectiveness and accuracy

Result card for ETH6: "What are the proper end-points for assessment and how should they be investigated?"

View full card

ETH6: What are the proper end-points for assessment and how should they be investigated?

Method

The endpoints are outlined in the PICO question documented in the common scope of the assessment as well as in the PICO descriptions of the different domains.

Result

The rational of the assessment is clearly described in the scoping and in the CUR domain. Both tests address the same endpoints so they have the same context and there are no differences with regard to the choice of endpoints.

Importance: Optional

Transferability: Completely

Result card for ETH7: "Are the accuracy measures decided and balanced on a transparent and acceptable way?"

View full card

ETH7: Are the accuracy measures decided and balanced on a transparent and acceptable way?

Method

The rational of the assessment is clearly described in the scoping and in the CUR domain. Both tests address the same endpoints so they have the same context and there are no differences with regard to the measurement of endpoints.

Result

As shown in the EFF domain the study designs are quite different. But it is no systematic difference between gFOBT and FIT but the differences can be found in both groups. With FIT the additional question of cut off values arise. This may complicate implementation as well as critical appraisal or meta analysis of studies. As no modeling of the impact of the two tests was done the sensitivity of the results for a shift of the cut off value is unclear. So uncertainty is not quantified and appraisal processes can address this question.

Importance: Important

Transferability: Partially

Discussion

The comparison of two tests to detect occult blood in faeces poses no serious ethical problems. The main issues regarding screening arise in the field of autonomy of the individual – which should be taken care of with objective information -, the measurement of benefits and harms – as done in the domains of EFF and SAF – and justice – this is addressed mostly in the ECO domain.

As the characteristics of the tests, their consequences and the informational content in a population based screening are structural identical ethical considerations for the marginal differences are not necessary. The information documented in the other domains suffices to support an appraisal process on the regional level. This appraisal

to apply the framework of the regional values used in a specific health care system may address uncertainties which remain although with this collection of HTA information at hand.

Organisational aspects

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Summary

The manner in which CRC screening is carried out varies significantly from country to country within the EU, both in terms of organization and the screening test chosen. A screening program of one sort or another has been implemented in 19 of 27 EU countries. Results have shown that some countries have organized screening and some countries have the opportunistic one. European guidelines compared those two screening types and, according to the reviewed evidence, showed that organised screening programmes achieve better coverage of the target population including hard to- reach or disadvantaged groups that opportunistic. It is also more cost-effective and provides greater protection against the harms of screening, including over screening, poor quality and complications of screening, and poor follow-up of participants with positive test results.

The most frequently applied method in Europe is testing stool for occult bleeding (fecal occult blood test, FOBT). In 2007, gFOBT (which in 2003 was the only test recommended by the Council of the European Union) was used as the only screening method in twelve countries (Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and United Kingdom). In six countries, two types of tests were used: FIT and FS in Italy, and gFOBT and colonoscopy in Austria, Cyprus, Germany, Greece, and Slovak Republic. Since then FIT is becoming increasingly popular. For example: Slovenia, since 2009, when national CRC screening programme FIT has been adopted, uses FIT technology. According to the survey, implemented among 11 European countries (i. e. Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia), it is seen that only 6 countries (Russia, Lithuania, Italy, Scotland, Spain and Slovenia) out of 11 uses FIT technology. Other countries, which participated to the survey, use gFOBT technology, with exception of Austria (excluding the Burgenland that uses FIT technology), who uses colonoscopy as a primary screening method. In addition to that Luxembourg indicated that FIT is relatively new technology and isn't widely accepted in their country. All countries stated that FIT and gFOBT screening are free of charge for target population and founded by the country.

FIT screening, like other screening methods, have to follow specific procedure: from identifying target population, sending invitation, re-invitation where it is necessary, delivering kits (The test kit may be delivered by mail, at GPs' offices or outpatient clinics, by pharmacists, or in other community facilities, and in some cases with the support of volunteers.), collecting samples (via e-mail, or through volunteers for example – like in some countries), laboratory examination and follow up.

National screening programme gives criteria based on risk information about who should receive screening invitations. The target population for a CRC screening programme includes all people eligible to attend screening on the basis of age and geographical area of residence. According to Table 1 and Table 2 (see ORG1), some differences about the target population exist between European countries. In general, people who are between 50 and 75 are invited to the screening. Table 1 offers also information on operational characteristics.

Several studies found FIT as a better option in comparison to gFOBT, due to the fact that FIT:

· Has no need for dietary restriction that results in better screening participation;

· Needs a smaller number of stool samples than gFOBT;

· Shows a greater relative sensitivity than gFOBT;

· Shows a greater sensitivity for the detection of advanced adenomas than gFOBT;

· Has a higher recall rate than most gFOBTs;

· Has a PPV similar to those obtained with most gFOBTs;

· Provides an opportunity of using a numeric threshold to find the most appropriate balance between sensitivity and specificity (i.e. between detection rate and positivity to the test); and

· Allows the opportunity to balance recall and detection rates providing each country with the tools to implement a colorectal cancer screening programme that will meet local healthcare expectations within available resources.

· But still, it has a major problem with sample instability, and collected samples should preferably be kept cool and returned immediately for analysis;

As regarding the participants' and important others' involvement into screening process and their own care and treatment, it has been showed (according to one study) that the attitudes towards CRC screening are strongly correlated with participation. Some other studies revealed participants' low awareness of the faecal occult blood test before they received the invitation for screening. Two of the major factors that influence the participation in screening programme are therefore an increasing knowledge and provision of more accessible screening programmes.

The success of a colorectal cancer screening programme depends on specially trained individuals committed to implementation, provision and evaluation of a high quality, efficient service. The multidisciplinary team that is responsible for a colorectal screening programme within FIT screening method includes:

· Administrative, clerical staff,

· Epidemiologists,

· Laboratory staff,

· Primary care physicians,

· Nurses and also

· Public health specialists.

Where screening tests are positive and further examination, treatment or care are necessary, the team also includes:

· Endoscopists,

· Radiologists,

· Pathologists and

· Surgeons.

But quality assurance cannot be achieved without a proper communication – in all levels. Cancer and screening communication messages must be therefore designed and delivered to match the communication skills, needs, and pre-dispositions of specific audiences. A key component of CRC screening programmes is, therefore, the information and education provided about CRC and CRC screening tests and procedures.

Communication among professionals is essential in order to ensure that all the information coming from the prognostic tests is available quickly and is correctly interpreted. To achieve and maintain an effective communication between the various professionals of a colorectal multidisciplinary team it is essential that they participate to different training courses, which should be focused on good inter-professional communication. Joint courses given for the multidisciplinary team may facilitate this goal. Good communication should be carried out between the members of the screening team with agreed terminology, regular meetings and clinical discussions.

Although colorectal cancer screening is recommended by major policy-making organizations, rates of screening remain low. Studies examine different communication tool options to increase knowledge on colorectal cancer screening and also to its participation. Studies also examine how communication factors influence CRC screening.

Literature provided little information on the impact of de-centralisation/ centralisation on implementation of FIT. Nevertheless some general conclusions about advantages and disadvantages of centralized and/or decentralized systems could be drawn; studies reveals that decentralized clinics and activities provide better access to health campaigns, who offers more information and knowledge to the participants and therefore influences on individuals participation to the screening. In the other hand in the centralized services the development of teams of different disciplines are more easily to arrange, they achieve economies of scale and can make better efficient use of a scarce resource and they also provide better outcomes for patients under the care due to the larger team of specialist professionals, for example – for cancer survival.

For implementation of FIT several investments are needed: a) material: e.g. equipment for screening, premises, office material for posting invitations and re-invitations, IT equipment and other office devices such as printers, and b) human resources: administrative and health personnel, investment in education of personnel and their training. Every country needs to assess their costs independently using cost-effectiveness analyses or other economic evaluation method. Investments that are needed for implementation of FIT are therefore country specific.

Data of budget impact of the implementation of FIT for the different payers were, by the literature review, not found. The existing studies examine only cost-effectiveness of performing FIT. The study of cost-effectiveness is important due to its impact on the payers' decision about budget allocation and about the amount of financial resources that they will invest in the national screening programme and into a new technology. Although it has been expected that the information on the budget impact is going to be obtained through a survey, it can be concluded that information obtained from the survey were not sufficient for the budget impact analysis. In addition to that only two countries have indicated the costs that are related to the screening (i.e. Lithuania and Slovenia). We believe that further research and in-depth studies would be necessary to indicate the budget impact of the implementation of FIT for the payers.

According to the insight that was gained through the literature review, it can be concluded that the most critical points in management are:

· To ensure that all eligible target population is invited and well informed about the colorectal cancer, colorectal cancer screening and the screening process;

· To ensure that screening process is conducted strictly according to the rules of procedure (the quality of process depend also on the communication, coordination etc.);

· To ensure an adequate and timely follow-up or treatment for those, who needs it;

· To ensure the availability of data (data management system);

FIT method has been, among patients, well accepted. The studies have shown that FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden. There are little information about the acceptance of FIT by health personnel and the organization. Nevertheless it has been demonstrated that the higher acceptability of FIT among patients is an important argument for choosing FIT in preference to gFOBT as the screening method for a nation-wide screening programme, apart from additional arguments regarding test performance characteristics. The additional information from the survey is going to enhance and backed the data on acceptance of FIT by health personnel and the organization.

Wide spectrums of stakeholders are engaged in planning and implementation of FIT. Usually stakeholders, involved in that process, vigorously defend their many interests, including patients, health professionals, politicians and industry. Little information exists about the interest groups/ stakeholders, who are or have to be taken into account in the planning / implementation of FIT. Only two reports were found – UK and Australian – to be relevant to this question. In addition, some information was gained through the survey.

For reaching quality assurance of FIT testing a consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures.

Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures.

The prime importance of quality assurance should also be included in basic training of the staff that is engaged in screening process.

Quality assurance is strongly connected to the monitoring. All aspects of the cancer screening programme should be monitored and evaluated. Quality standards need to be set for every step along the screening pathway and an appropriate monitoring framework is required to determine if the standards are being met. Standards will apply at a number of levels: to procedures; individuals; teams; institutions and overall systems.

In the case of FIT cancer screening programme, where screening is based on a laboratory test, it is self-evident that an adequate monitoring system should be present in laboratories.

All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 Medical laboratories - Particular requirements for quality and competence. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS).

Of fundamental importance is also the complete and accurate recording of all relevant data on each individual and every screening test performed - including the test results, the decisions made as a consequence, diagnostic and treatment procedures and the subsequent outcome, including cause of death.

In order to be able to evaluate the effectiveness of screening, the data must be linked at the individual level to several external data sources including population register, cancer or pathology registries, and registries of cause of death in the target population. Therefore, legal authorisation should be put in place when the screening programme is introduced in order to be able to carry out programme evaluation by linking the above-mentioned data for follow-up.

Introduction

The organisational domain considers what types of resources (material, human skills, knowledge, money, etc.) must be mobilised and organised when implementing a technology, and what changes or consequences the use can cause in an organisation and a health care system as a whole. The issues include e.g. quality and sustainability assurance, centralization, communication, managerial structure and acceptance. There are three levels to consider regarding organizational aspects: intra-organizational, inter-organizational and health care system level. The levels of approach can also be divided into micro level (patient interaction), mezzo level (health care organization and community) and macro level (health policy).

The growing focus of organizational issues in health technology assessment (HTA) indicates a recognition that many decisions on resource allocation in provision of technologies are of crucial importance. Organizational aspects in HTA influence the behaviour of managers and health professionals. Also policy makers on the national level need knowledge on organizational aspects, when making decisions on the use of technologies. Organizational aspects in HTA may clarify challenges and barriers in implementing health technologies {1}.

In this core HTA the objective is to assess the organisational effects of FIT (Fecal immunochemical Test) for colorectal cancer screening, also called as iFOBT (immunochemical FOBT) screening, compared with the guaiac-based fecal occult blood test (gFOBT) for colorectal cancer screening, both within organized screening program.

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC) The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
G0001	Process	What kind of work flow, participant flow and other processes are needed?	yes	What kind of work flow, participant flow and other processes are needed?
G0002	Process	What kind of involvement has to be mobilized for participants and important others?	yes	What kind of involvement has to be mobilized for participants and important others?
G0003	Process	What kind of staff, training and other human resources are required?	yes	What kind of staff, training and other human resources are required?
G0004	Process	What kind of co-operation and communication of activities have to be mobilised?	yes	What kind of co-operation and communication of activities have to be mobilised?

G0012	Process	What kind of quality assurance is needed and how should it be organised?	yes	What kind of quality assurance is needed and how should it be organised?
G0005	Structure	How does de-centralisation or centralization requirements influence the implementation of the technology?	yes	How does de-centralisation or centralization requirements influence the implementation of FIT?
G0006	Structure	What kinds of investments are needed (material or premises) and who are responsible for those?	yes	What kinds of investments are needed (material or premises) and who are responsible for those?
G0007	Structure	What is the likely budget impact of the implementation of the technology for the payers (e.g. government)?	yes	What is the likely budget impact of the implementation of FIT for the payers (e.g. government)?
G0008	Management	What management problems and opportunities are attached to the technology?	yes	What management problems and opportunities are attached to FIT?
G0013	Management	What kind of monitoring requirements and opportunities are there for the technology?	yes	What kind of monitoring requirements and opportunities are there for FIT?
G0009	Management	Who decides which people are eligible for the technology and on what basis?	no	In comapring gFOBT and FIT in organized screening the eligibility of the population is the same as it is based on incidence and prevalence.
G0010	Culture	How is the technology accepted?	yes	How is FIT accepted?
G0011	Culture	How are the other interest groups taken into account in the planning / implementation of the technology?	yes	How are the other interest groups taken into account in the planning / implementation of FIT?

Methodology description

Domain frame

The project scope is applied in this domain.

Technology	FIT for colorectal cancer screening vs. gFOBT colorectal cancer screening in organized screening program **Description** Procedure of gFOBT: the standard fecal occult blood (FOBT) test can detect small amounts of blood in the stool by submitting a portion of three consecutive bowel movements for testing. The test cannot identify polyps and some diet restrictions need to be considered, as the test is not specific for human blood alone. gFOBT is used for more than 30 years in routine, is widely available and inexpensive. If the test is positive, a colonoscopy will be needed to find the reason for the bleeding {2, 3}. Procedure of FIT: FIT (Fecal Immunochemical Test) for colorectal cancer screening, also called as iFOBT (immunochemical FOBT) screening, is more accurate than FOBT as it only identifies human blood. It needs only one stool sample, thus is more simple to complete. If the test is positive, a colonoscopy will be needed to find the reason for the bleeding {2, 3}. Colorectal cancer (CRC) screening with faecal inmunochemical test (FIT) for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC) is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). To ensure effectiveness, the screening interval in a national screening programme should not exceed two years for gFOBT and three years for FIT {4}. Purpose of use: detect cancer, polyps, nonpolypoid lesions, which are flat or slightly depressed areas of abnormal cell growth and can also develop into colorectal cancer.
Intended use of the technology	Screening CRC screening with faecal immunochemical test (FIT) **Target condition** Adenomas, as non-malignant precursor lesions of Colorectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. Adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not cause symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the general population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** Target population sex: any. Target population age: 50-74 years. Target population group: Asymptomatic people. **Target population description** Adults (both men and women), average risk of CRC, aged 50 years or over. The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years. The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. EU Council Recommendations suggests only the faecal occult blood test (gFOBT or FIT) for men and women aged 50–74 for CRC screening {4}. Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population.
Comparison	CRC screening with Guaiac – based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analysed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC). The use of the test is considered under conditions of population based colorectal cancer screening in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states have established nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only gFOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

ASSESSMENT ELEMENTS

Question number	ID	Topic	Issue	Relevant	Research questions or rationale for irrelevance
ORG1	G0001	Process	What kind of work flow, participant flow and other processes are needed?	yes	What kind of work flow, participant flow and other processes are needed?
ORG2	G0002	Process	What kind of involvement has to be mobilized for participants and important others?	yes	What kind of involvement has to be mobilized for participants and important others?
ORG3	G0003	Process	What kind of staff, training and other human resources are required?	yes	What kind of staff, training and other human resources are required?
ORG4	G0004	Process	What kind of co-operation and communication of activities have to be mobilised?	yes	What kind of co-operation and communication of activities have to be mobilised?
ORG5	G0005	Structure	How does de-centralisation or centralization requirements influence the implementation of the technology?	yes	How does de-centralisation or centralization requirements influence the implementation of FIT?
ORG6	G0006	Structure	What kinds of investments are needed (material or premises) and who are responsible for those?	yes	What kinds of investments are needed (material or premises) and who are responsible for those?
ORG7	G0007	Structure	What is the likely budget impact of the implementation of the technology for the payers (e.g. government)?[1]	yes	What is the likely budget impact of the implementation of FIT for the payers (e.g. government)?
ORG8	G0008	Management	What management problems and opportunities are attached to the technology?	yes	What management problems and opportunities are attached to the FIT?
ORG9	G0010	Culture	How is the technology accepted?	yes	How is FIT accepted?
ORG10	G0011	Culture	How are the other interest groups taken into account in the planning / implementation of the technology?	yes	How are the other interest groups taken into account in the planning / implementation of FIT?
ORG11	G0012	Process	What kind of quality assurance is needed and how should it be organised?	yes	What kind of quality assurance is needed and how should it be organised?
ORG12	G0013	Management	What kind of monitoring requirements and opportunities are there for the technology?	yes	What kind of monitoring requirements and opportunities are there for FIT?

Information sources

Organisational aspects are rarely covered in clinical studies or HTA reports so the current analysis required several activities. Systematic review of the literature was not enough to answer the research question of this domain. So grey literature and national guidelines were added. Since some organizational aspects are very much linked to country contexts, it is useful to integrate results with the experience of local experts in the area. For this purpose the results of the survey was used.

Quality assessment tools or criteria

In the systematic literature review, only studies with organizational aspect, published in peer reviewed journals were selected. Reviews, letters, comments, etc., were not considered for inclusion in the analysis of evidence. These studies are often highly context specific (i.e., specific to the country, population, health-care system).

Hereinafter exclusion and inclusion criteria are presented in more detail:

Exclusion criteria:

a) Formal exclusion criteria

· Studies not published in English

· Duplicates

· Studies irrelevant for the European context

b) Thematic exclusion criteria

· Different research question

· Different disease or clinical focus (e.g. other diseases than colorectal cancer)

· Other intervention (i.e. no comparison between FIT and gFOBT)

c) Study design

· Congress presentation, posters, „Comments“, „Letters“ etc. (i.e.. „Abstracts“, not based on any actual primary study)

· Case studies

· Studies not focusing on human medicine (e.g. animal studies) or in-vitro Studies

Inclusion criteria:

· Basic requirements fulfilled (none of the above exclusion criteria is applicable)

· HTA / systematic Review

· Study presents an organizational aspect

To summarize, inclusion criteria for ORG domain were:

1. The studies compared a guaiac-based faecal occult blood test (gFOBT) with an immunochemical based faecal occult blood test (FIT),
2. The studies considered the organizational aspect,
3. The studies were relevant for the European context.

Analysis and synthesis

Literature search was conducted in May 2013. Descriptive analysis was performed on different information sources. The assessment elements questions were answered by Principal investigator and complemented and reviewed by investigators. Literature search was specifically aimed at identifying peer-reviewed literature containing organizational aspect on population based colorectal cancer screening using FIT and gFOBT. After systematic literature was completed, non-systematic searching for other literature (grey literature) and survey were conducted. The details of all three steps in this process of information searching are described below:

1. A literature search and review of the results

A systematic literature search was conducted in May 2013. Published literature was obtained by searching: ACADEMIC SEARCH COMPLETE (EBSCO), WILEY ONLINE LIBRARY, SCIENCE DIRECT, SPRINGER LINK, ERIC (EBSCO) and JSTOR. Additional searches were done through the Internet engine Google, where guidelines, reports and some free articles/ studies on Oxford journals, PubMed etc. were found.

The search was performed using key words of each identity card (i.e. each research question). More detailed description of literature (key words) are described in Appendix 1 (i.e. search strategies).

2. Grey literature and national guidelines searches

Grey literature was searched for the ORG1, ORG5, ORG6, ORG10 and ORG12 assessment elements. Details of the searches are covered in those elements and the identified literature is included in the domain references. Grey literature was not searched for any other assessment element.

32 relevant articles/studies were found, one international guidelines and two international reports. In addition, two publications were found, one national report and one national guidelines (through an Internet engine Google). Six other grey resources ware found through an Internet engine Google. We also used EUnetHTA WP4 CORE HTA basic document, published on EUnetHTA intranet, as a background document.

3. A survey

The survey for retrieving information on the use of technology in European countries has been implemented. 11 European countries have participated to the survey: Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia.

Institutions that participated to the survey are listed in table below (Table 1):

Table 1: Institutions that participated to the survey

Country	Institution
Austria	Ludwig Boltzmann Institute for Health Technology Assessment
Russia	National Center for Health Technology Assessment - NCHTA
Luxembourg	Cellule d'expertise médicale
Lithuania	State Health Care Accreditation Agency under the Ministry of Health
Italy	• Laziosanità – ASP (Agenzia di Sanità Pubblica della Regione Lazio è l'organo strumentale della Regione in materia sanitaria) • Veneto Region
Scotland	Healthcare Improvement Scotland
Spain	Andalusian Agency for Health Technology Assessment - AETSA
Romania	National School of Public Health, Management and Professional Development - NSPHMPD
France	HAS
Croatia	Agency for Quality and Accreditation in Health Care and Social Welfare
Slovenia	National Institute of Public Health

A survey gives answers on question ORG7 and the supplement to the answers on following questions: ORG5, ORG6 and ORG10. The survey gives additional information also to the questions ORG1 and ORG9.

[1] This question should be included in the ECO domain.

Result cards

Process

Result card for ORG1: "What kind of work flow, participant flow and other processes are needed?"

View full card

ORG1: What kind of work flow, participant flow and other processes are needed?

Method

The domain methodology was used for this question (analysis of selected studies extracted from the basic literature search). Two reports, one document with guidelines and four articles were found to be relevant to this question. We found additional information by an internet search of grey literature performed on 21 June 2013 via the search engine Google. It was performed by investigator using the phrase: “Slovenian colorectal cancer screening programme”. One grey literature source is referred to in these results, more precisely a presentation, prepared by Institute of Public Health of Slovenia.

Frame

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Result

With FOBT, stool samples are analysed for the presence of occult blood. FOBTs are either guaiac-based (gFOBT) or immunochemical tests (FIT). gFOBTs investigate the presence of any blood, whereas FIT are specific for human blood {4}.

The specific policy of a screening programme determines the target age and gender and possibly the geographical area, the screening test and screening interval, and further diagnostics and treatment for those who need them. European guidelines compare opportunistic screening and organized screening. The evidence shows that organised screening programmes achieve better coverage of the target population including hard to- reach or disadvantaged groups. It is also more cost-effective and provides greater protection against the harms of screening, including over screening, poor quality and complications of screening, and poor follow-up of participants with positive test results {4}.

Organized screening should generally include a regional or national team responsible for the implementation, quality assurance and reporting of results. Comprehensive guidelines, rules and a quality assurance structure should be available. Population-based screening requires the identification and personal invitation of each person in the eligible target population (by an office or special agency) {5, 6}.

Organised CRC screening is a multi-step process including {4}:

- Identification of the target population;
- Recruitment of eligible subjects;
- Delivery of screening test;
- Reporting of screening test results;
- Reassurance of people with negative results and information on the timing of the next test;
- Recall of people with unsatisfactory/inadequate screening test
- Follow-up of people with positive tests, i.e. diagnostic procedures and treatment needed, including a fail-safe system to make sure this actually happens; and
- Registration, monitoring and evaluation of the entire programme.

The manner in which CRC screening is carried out varies significantly from country to country within the EU, both in terms of organization and the screening test chosen. A screening program of one sort or another has been implemented in 19 of 27 EU countries. The target group contains approximately 136 million individuals suitable for CRC screening (aged 50 to 74 years). Of this number, 43% individuals come from 12 countries where CRC population screening is performed or being prepared on either national or regional levels (i.e. Cyprus, Finland, France, Hungary, Italy, Poland, Portugal, Romania, Slovenia, Spain, Sweden and the United Kingdom) {4, 5, 6}.

Testing stool for occult bleeding (fecal occult blood test, FOBT) is the most frequently applied method. In 2007, gFOBT (which in 2003 was the only test recommended by the Council of the European Union) was used as the only screening method in twelve countries (Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and United Kingdom). According to the data of European Guidelines {4}, EU report on implementation of the Council Recommendation on cancer screening {5} and Zavoral et. al. {6}, two types of tests was used in six countries: FIT and FS in Italy, and gFOBT and colonoscopy in Austria, Cyprus, Germany, Greece, and Slovak Republic . Since then FIT is becoming increasingly popular. For example: Slovenia, since 2009, when national CRC screening programme FIT has been adopted, uses FIT technology (which is followed by colonoscopy in case of positive screening results) {7}.

Another study, executed by the International Colorectal Cancer Screening Network, also compares screening programs on international level. The study identifies 43 organized screening programs, of which 28 of them used FOBT as their primary screening modality. Of these, 16 used guaiac tests, 9 used immunochemical tests and 3 used both kinds of tests. The country comparison in this study, which observed 15 European countries – 13 of them are part of EU 27 –, reveals that there are 10 EU countries who used gFOBT and 3 EU countries, which used FIT (Italy, Netherlands and Hungary) {8}. The report on colorectal cancer in Europe and Australia {9} confirms that FIT method is used in Italy, Netherlands and Hungary, furthermore, this report indicates that FIT is also used in 2 more European countries (Czech Republic and Spain), including Australia {9}. According to Spanish study of Ascunce et al. (2010) it can be confirmed that Spain is using gFOBT, as well as FIT technology for CRC screening. In more detail the data from the study indicated that CRC screening had been implemented in 6 regions (out of 17), {10}

The survey, implemented among 11 European countries (i. e. Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia), indicated that only 5 countries (Russia, Lithuania, Italy, Spain and Slovenia) out of 11 uses FIT technology. Other countries, which participated to the survey, use gFOBT technology, with exception of Scotland who uses gFOBT and FIT only in case if individuals are required to repeat the test or do the retest. One of the exceptions is also Austria (excluding the Burgenland that uses FIT technology), who uses colonoscopy as a primary screening method. In addition to that Luxembourg indicated that FIT is relatively new technology and isn't widely accepted in their country. All countries stated that FIT and gFOBT screening requires no additional costs for target population and is founded by the country.

Most programs using gFOBt collected six stool samples (two samples from three consecutive bowel movements), whereas programs using FIT collected only one or two stool samples (one sample per bowel movement). Regardless of the number of samples taken, most programs defined a test as positive when any of the samples was considered positive. However, England and Spain defined gFOBT test as positive when at least five of the six samples were positive on first tests, or for borderline tests (1–4 samples positive), on repeat testing (any of 12 samples positive on two further tests). Scotland defined a test as positive when at least five of the six samples taken were positive, or when 1–4 of the six samples and a subsequent FIT were positive {8}.

In the following eight states: Belgium, Denmark, Estonia, Ireland, Lithuania, Luxembourg, Malta, and the Netherlands, CRC screening has not been implemented yet, but according to the data of European guidelines Denmark and the Netherlands are currently in the decision process for implementing a CRC screening programme {4, 5, 6}.

Identifying a target population (see Figure 2)

Participation in screening (see Figure 3)

Testing protocol

The test kit may be delivered by mail, at GPs' offices or outpatient clinics, by pharmacists, or in other community facilities, and in some cases with the support of volunteers. The studies review in European guidelines shows no evidence that any of these strategies may have an impact on the proportion of inadequate samples, provided that clear and simple instruction sheets are included in the kit {4}.

The choice of the provider should aim to maximise accessibility, taking into account local conditions, settings and cultural factors {4}.

According to study review, mailing of the FOBT kit with instructions, together with the invitation letter and the information leaflet, is effective in increasing participation rates. These results are consistent with previous reports indicating that the GP's letter and mailing of FOBT kits represent the most important factors for improving compliance. Mailing of the FOBT kit might not always represent a cost-effective strategy, if the baseline participation rate and the expected increase in participation are low. Compared to mailing a second FOBT kit to all non-responders, mailing a recall letter with a test order coupon resulted in a substantial decrease in the programme costs, but also in a significant decrease in participation. The authors of the trial suggested, however, that the spared costs might be allocated more efficiently to communication interventions that might have a higher impact on compliance. Several test providers close to the target population should be available when the subject is required to reach health or community facilities to get the kit {4}.

Volunteers or non-health professionals may also be involved in the distribution and collection of kits. Delivery of kits may represent in this case an additional opportunity for counselling, for conveying information about the programme and for providing instructions for test utilisation. Subjects contacted at home by a trained non-health professional, who delivered the kit and collected the sample from the participant's home showed a substantially higher completion rate of FIT, as compared to the group who received the kit by mail with an invitation from their primary care physician {4}. Programs Using Mailed Contact and Screening Kit include those that make direct contact with individuals who are determined to be eligible for CRC screening, and place a screening kit in the hands of potential respondents. Countries that are using this method are, according to the study of Swan et. al., the following: Croatia, Finland, France, Italy, Spain and UK. Programs Using Office Visit Contact, which rely on providers in

the health system to offer CRC screening to individuals who are determined to be eligible for CRC screening, are implemented in Latvia, Czech Republic, Germany and Poland {11}.

Community volunteers, who have received some general training by the programme staff, have been involved in the kit distribution in the context of ongoing organised programmes and their involvement has been consistently associated with high participation rates. As no randomised comparison is available, it is difficult to dissociate their specific effect from other characteristics of the communities or target populations involved. Sustainability over time represents an important issue to be taken into account when planning to use volunteer support. The modalities adopted for stool collection, storage and shipping of the sample to the laboratory are mainly dependent on the characteristics of the test adopted, i.e. its stability at environment temperature. Based on these considerations mailing of the samples may be an option that can be implemented more easily for guaiac than for immunochemical tests, which need to be processed faster. The haem moiety used in gFOBTs is more stable than the globin moiety used in FITs. Transport of a dried sample, which is used for most guaiac test kits, provides greater stability than that in wet buffer which is usually used for immunochemical tests. The acceptable time period between sampling and testing is defined by the product manufacturers in their Instructions For Use (IFU). For gFOBTs the maximum time period is usually between 14 and 21 days; for FIT it is much less {4}.

Accessibility of the collection facilities remains an important goal, but the logistics of the sample handling may promote reducing the number of collection facilities in order to ensure an appropriate storage or timely shipping to the laboratories {4}.

When samples are collected, they are sent to the laboratory examinations. Laboratories must strictly follow the procedure's protocol, under the constant monitoring, in order to reach quality assurance standards.

Detailed protocols on handling the stool samples must be available and followed through the whole process. Identification and tracing of the sample through the entire process should be ensured by adopting appropriate labelling allowing the sample and patient's ID code to be linked. Automated check protocols should be implemented in order to avoid mismatching of the results. All data, including test results, should have a regular backup system. An operational definition for an inadequate screening test should be made explicit in the programme protocol, taking into account the characteristics of the test (i.e. the stability and the storage requirements of the tests) as well as the testing procedure adopted (i.e. the number of samples or of cards required). Protocols should be in place to define the appropriate test and the algorithm used to classify a test result (as negative or positive). For quantitative or semi-quantitative [1]FITs, an explicit definition of cut-off levels for haemoglobin concentration should be defined. Protocols or rules for combining results when using multiple samples, the number of samples that are needed to evaluate the test result, etc. must be in place. When using a quantitative test, provision should be made to record the information concerning the actual amount of haemoglobin, both for tests classified as negative and for those classified as positive. Some people may present with clinical conditions such as inflammatory bowel disease (Crohn's disease or haemorrhagic recto-colitis), which may explain a positive FOBT result. In such cases, if no cancers were detected, then the screening results should be classified as negative for the purposes of the screening programme. These patients should then be referred for treatment in the appropriate clinical setting {4}.

There are some differences between FIT and gFOBT. Nevertheless European experts agree it is difficult to draw simple conclusions from the variety of different tests and study settings, it can be concluded that FIT in comparison with gFOBT:

- Has no need for dietary restriction;
- Has a major problem with sample instability, and collected samples should preferably be kept cool and returned immediately for analysis;
- Provides a greater participation rate than gFOBT;
- Needs a smaller number of stool samples than gFOBT;
- Shows a greater relative sensitivity than gFOBT;
- Shows a greater sensitivity for the detection of advanced adenomas than gFOBT;
- Has a higher recall rate than most gFOBTs;
- Has a PPV (positive predictive value) similar to those obtained with most gFOBTs;
- Provides an opportunity of using a numeric threshold to find the most appropriate balance between sensitivity and specificity (i.e. between detection rate and positivity to the test); and
- Allows the opportunity to balance recall and detection rates providing each country with the tools to implement a colorectal cancer screening programme that will meet local healthcare expectations within available resources {4}.

Several providers of bowel preparation close to the target population should be available when the subject is required to reach health or community facilities to get the preparation. Organisational options include the possibility of having the enema administered at the endoscopy unit. Clear and simple instruction sheets should be provided with the preparation {4}.

The potential reduction of mortality through cancer screening can only be achieved if subjects with abnormal findings receive timely and appropriate follow-up for detected abnormalities. The ascertainment of interval cancers represents a key component of the evaluation of a screening programme. The documentation and evaluation process requires forward planning and linkage between screening registries and cancer registries, including data on causes of death, with no losses to follow-up. Data collection and reporting should cover information on colorectal cancer appearing in the target population. Methods of ascertainment and follow-up may differ across countries and screening programmes depending on the availability and accessibility of data and of existing data sources: cancer/pathology registries, clinical or pathology records or death records/registries {4}.

Defining the relevant healthcare professionals

Depending on each country's health system and culture, different health professionals can be involved in kit delivery and stool sampling collection or in delivering bowel preparation for endoscopy screening (i.e. GPs, nurses, paramedics, pharmacists, volunteers from no-profit organisations, etc.), as well as in performing colonoscopy, sigmoidoscopy when offered as a screening test (i.e. GPs, nurses gastroenterologists,). Each country should follow quality assurance standards for the facilities and establish minimum training requirements for each type of professional, fulfilling the present guidelines {4}.

[1] Quantitative FIT - adjustable cutoff point and high throughput analysis; Semi-quantitative nature of test permits adjust ment of the cutoff value for the detection of colorectal cancer (CRC) in an effort to optimise screening programmes for specific populations and health-care practices;

Comment

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Importance: Critical

Transferability: Completely

Result card for ORG2: "What kind of involvement has to be mobilized for participants and important others?"

View full card

ORG2: What kind of involvement has to be mobilized for participants and important others?

Method

Analysis of selected studies extracted from the basic literature search. Two articles and one document with guidelines were relevant to this question.

Frame

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Result

A Netherlands study found that attitudes towards CRC screening strongly correlated with participation. People who considered screening to be ineffective, those expressing anxiety and those who are not familiar with CRC screening tests were less likely to participate. Knowledge of CRC and screening is therefore a positive predictor of participation. According to the study, having acquaintances affected by CRC increased screening participation. Researches also indicated that CRC screening participants are more often engaged in other health-promoting interventions, such as regular dental visits and other forms of cancer screening; those who are more familiar with health prevention are more likely to participate in screening. Italian study also indicates that physical health below average was a positive predictor of FOBT screening participation. A possible explanation may be that those of worse physical health may worry more about their health or are more familiar with health care and therefore are more inclined to participate. The fact that the absence of abdominal complaints is the main reason for non-participation in FOBT screening, and

that insufficient knowledge significantly correlates with non-participation highlights the need of adequately informing the target population, including making individuals aware that CRC symptoms mostly occur late in the course of the disease and CRC can be present without symptoms. This Netherlands study reveals that only 12% of non-participants had made an informed choice on non-participation. So, screening organisations should focus on adequate information provision to the target population by for example suitable information brochures, information meetings, and media coverage, as this will affect the two of the most important parameters for the success of screening: informed choice and participation {13}.

Another study showed participants' low awareness of the faecal occult blood test before they received the invitation for screening. Awareness of bowel cancer was mainly through past experience or family history or was work-related. Data suggested that demography and cultural issues such as age, sex, taboo, attitudes, altruism, so-called ostrich syndrome, and stoicism can affect behaviour and decisions. Knowledge and awareness were identified as factors in breaking some of the cultural barriers affecting uptake {14}.

According to several studies one of the major factors that influence the participation in screening programme is increasing knowledge. Therefore it is highly important to make a screening programmes and information about screening easily accessible. Different strategies for making screening programme easily accessible are used. The most widely used strategy is to consider the size of the population and the patients' geographic distribution and to establish local screening centres for better availability. Also mobile screening vans can be used for more distant areas.

Selection and management of the participants through the screening process needs to be well organized. Participants must receive complete information about benefits and risks, as well as pros and cons of participation in screening programme. Patient, who decides to participate in the screening process, needs to be aware and consider the screening protocol. According to the data of European guidelines the test kit may be delivered by mail, at GPs' offices or outpatient clinics, by pharmacists, or in other community facilities, and in some cases with the support of volunteers, who can deliver the kits and collect samples {4}.

In order to reduce the probability of a false positive result, dietary restrictions are usually recommended when guaiac-based tests are used. More recent randomised trials have demonstrated that better compliance can be achieved using FIT compared to a gFOBT test, because FIT does not require modification of a subject's diet and sampling is limited to one or two bowel movement. In order to enhance compliance European guidelines therefore recommend testing procedures that require no or only minor dietary restrictions {4}.

Distribution of task is also presented in the picture below (i.e. Figure 4):

Comment

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Importance: Critical

Transferability: Completely

Result card for ORG3: "What kind of staff, training and other human resources are required?"

View full card

ORG3: What kind of staff, training and other human resources are required?

Method

Analysis of selected studies extracted from the basic literature search. One report and one document with guidelines were relevant to this question.

Frame

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Result

Depending on each country's health system and culture, different health professionals can be involved in kit delivery and stool sampling collection or in delivering bowel preparation for endoscopy screening (i.e. GPs, nurses, paramedics, pharmacists, volunteers from no-profit organisations, etc.). Each country should follow quality assurance standards for the facilities and establish minimum training requirements for each type of professional, fulfilling the present guidelines {4}.

All staff involved in the delivery of a colorectal cancer screening programme must have knowledge of the basic principles of colorectal cancer screening. To achieve this it would be appropriate for them to attend a course of instruction at an approved training centre prior to the commencement of the programme. Updating knowledge as part of continuing medical education should be encouraged. Participation in training courses should be documented and certificates of attendance issued based on the levels of skill attained and evaluated. Specific training requirements in terms of quality and volume should determine eligibility for any certification or accreditation process which must be applied only to centres with sufficiently skilled personnel {4}.

The success of a colorectal cancer screening programme is dependent on specially trained individuals committed to implementation, provision and evaluation of a high quality, efficient service. The multidisciplinary team that is responsible for a colorectal screening programme includes {4}:

- Administrative and clerical staff (A colorectal screening programme can be run under the umbrella of a screening programmes division associated with the national or regional health department where this exists. This allows the colorectal screening programme staff to benefit from the experience gained from other screening programmes. In the UK, the organisation of the colorectal screening programmes is overseen by a programme manager who reports to a national or regional screening coordinator responsible for all screening programmes. In addition to a programme manager each centre that is responsible for sending out invitations and/or organising screening tests for those who accept the invitations is overseen by a screening manager who is responsible for the efficient operation of the screening programme and managing the staff of the screening centre. The staffing of the screening centre depends on the structure of the programme itself; e.g. if it is a centralised programme, staff are required for identifying individuals to be invited, sending out invitations, replying to those who have undergone testing and, where appropriate, organising further investigations for those with positive tests.);

- Epidemiologists (As many disciplines contribute to providing data required for monitoring and evaluating of a colorectal screening programme it is essential that a designated individual with relevant epidemiological expertise oversees the collection and analyses the data required for evaluation. Assessing a programme's impact on colorectal cancer mortality is only possible if adequate provision has been made in the planning process for adequate collection and analysis of data. Basic Training: The individual overseeing data collection and analysis requires training in clinical epidemiology and statistics. Specific training: Training for epidemiologists involved in a colorectal cancer screening programme focuses on:
  - Colorectal cancer epidemiology (incidence, prevalence, mortality, trends);
  - Screening theory (pre-clinical disease, lead time, selection, length bias);
  - Colorectal cancer screening terminology (sensitivity, specificity, positive predictive value etc);
  - The colorectal screening programme (organisation, current screening modalities);
  - Ethical and confidentiality issues;
  - Setting up a colorectal cancer screening programme (identification and an invitation of target population, call-recall system, follow-up system);
  - Strategies for data collection and management (use of appropriate databases, individual files,
  - computerised archives, linkage to appropriate registries, classification of screening outcomes, quality control procedures and data collection);
  - Statistical analysis and interpretation of results (performance indicators for evaluation, predictors of the impact of screening, assessing screening impact and effectiveness, cost-effectiveness calculations); and
  - Presentation of data and report writing.);
- Laboratory staff (In the case of FOBT cancer screening programme, where screening is based on a laboratory test, it is self-evident that an adequately staffed laboratory is necessary. It is similarly self-evident that the training and skills required by the laboratory staff are dependent on the type of test (guaiac or immunochemical, qualitative or quantitative). The laboratory staff require supervision by an appropriately qualified individual with expertise in clinical biochemistry, and the day-to-day running of the laboratory must be managed by an appropriately skilled scientific officer. When faecal occult blood testing is being used as the primary test for a colorectal screening programme it is essential that this be done with appropriate internal quality control (IQC) and external quality assurance (EQAS); and this requires centralisation, either on a national or regional basis, of the testing process. Delegation to individual practitioners is not appropriate. The training required for the laboratory staff should include the following:
  - A basic understanding of colorectal cancer and the benefits of early diagnosis (a basic understanding of the colorectal cancer screening process);
  - Training in good laboratory practice;
  - Training in the performance of the faecal occult blood test (the specific training will depend on whether a guaiac or immunochemical test is used and whether it is a qualitative or quantitative test); and
  - Training in the use of the IT system used to record results.

In addition, the training required by the Laboratory Manager includes:

- Managerial skills;
- An appreciation of internal quality control and external quality assurance; and
- A thorough understanding of the interactions between the laboratory process and the whole screening programme.

An individual with expertise in clinical biochemistry is ultimately responsible for the operation of the laboratory and requires training in the following:

- An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);
- An in-depth understanding of the colorectal cancer screening process (including screening theory and especially the potential benefits and harms of screening and the prime importance or quality assurance);
- Extensive knowledge of performance characteristics of different types of faecal occult blood test; and
- An in-depth understanding of the technology required to perform the faecal occult blood test.;
- Primary care physicians (There is ample evidence for the importance of involving primary care physicians in the implementation of colorectal cancer screening programmes. The role of primary care physicians in colorectal cancer screening will vary widely from one European country to another. In some instances the general practitioner (GP) is required to invite the target population, in some instances they are required to encourage their patients to participate in a centrally organised screening programme and in some instances they may not play a direct role in the screening programme but will clearly be required to answer questions on screening posed by their patients. It must be emphasised however, that general practitioners should not be encouraged to perform faecal occult blood tests on an individual basis as it is impossible to ensure adequate quality assurance for the performance of the test. The training required of general practitioners working in an area where there is an active screening programme should include the following:
  - A thorough knowledge of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis);
  - An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and
  - A thorough knowledge of the organisation of the local screening programme and the role of GPs within the programme.
- *Endoscopists (Endoscopists carrying out colonoscopy as the investigation following a positive primary screening test, are central to the delivery of a successful screening programme. It is essential that they be skilled in complete examination of the colonic mucosa and in recognising both cancers and pre-cancerous lesions (i.e. adenomas). It is also essential that they be skilled in biopsy and polypectomy technique such that they can carry out lower gastrointestinal endoscopy safely and effectively. Different countries will employ different types of health professionals to undertake endoscopy, including medically qualified gastroenterologists, medically qualified surgeons, nurse endoscopists and, in some instances, endoscopists who have neither a formal medical nor a nursing qualification);*
- *Radiologists (While the majority of European countries will employ colonoscopy as either the main investigative technique for a positive test or as the primary screening test, radiology expertise is required to investigate the colon in those individuals in whom a complete follow-up or surveillance colonoscopy is not achievable.);*

- *Pathologists (Pathologists working within a colorectal cancer screening programme require full training in the histopathology of gastrointestinal disease with specific emphasis on colorectal cancer. These pathologists should be skilled in the following areas:*
  - *The interpretation of biopsies taken from benign and malignant tumours of the colon and rectum;*
  - *The preparation and histological interpretation of endoscopic polypectomy specimens; and*
  - *The preparation and histological interpretation of surgical resection specimens.*

They also need the following training requirements:

- *Good knowledge of the disease processes that can affect the colon and their histological appearances;*
- *An ability to distinguish between benign and malignant biopsy specimens;*
- *An ability to distinguish between benign and malignant polypectomy specimens;*
- *An ability to access the risk factors associated with recurrence after endoscopic excision of malignant polyps;*
- *An appreciation of immunohistochemistry where it relates to histological interpretation of colorectal tumours; and*
- *The ability to prepare a colorectal resection specimen, with particular emphasis on harvesting lymph nodes and assessing the circumferential resection margin.*
- *Surgeons (Most cancers and a small proportion of large adenomas detected within a colorectal screening programme will require surgical excision, and it is important that this be carried out as effectively and safely as possible. The beneficial effect of early detection of colorectal cancer is dependent on low mortality and morbidity rates associated with the subsequent surgery. It is now recognised that both short- and long-term results of surgery for both rectal and colon cancer are highly surgeon-dependant and there is now good evidence that specialisation associated with high volume is associated with improved results. It is therefore mandatory that all screen-detected cancers requiring surgery are treated by surgeons who specialise in colorectal surgery, preferably with a particular interest in cancer. It is also essential that these surgeons work in multidisciplinary teams with access to oncologists experienced in both adjuvant and palliative treatment of colorectal cancer. It follows that surgeons treating patients with screen-detected colorectal cancer should be fully trained and possess the appropriate qualifications for a colorectal surgeon. In addition to the specialist training that this entails, surgeons working within a colorectal screening programme have the following training requirements:*
  - *An understanding of the basic principles of screening, with particular reference to colorectal cancer; and*
  - *An understanding of the significance of pT1 cancers with reference to the need for completion surgery.*

Screen-detected cancers may be particularly suitable for laparoscopic resection, and it is essential that any surgeon utilising this technique is fully trained and, where appropriate, accredited. While some surgeons may be in a position to obtain appropriate training for laparoscopic surgery within their own institutions, this may not always be the case; and it is essential that surgeons wishing to carry out laparoscopic colorectal surgery should attend the appropriate courses and obtain the appropriate training wherever this is available.;

- Nurses (Nurses have important roles throughout the colorectal screening pathway, from the initial contact with the screening invitees through diagnostic endoscopy both as an endoscopy nurse or as a nurse endoscopist, to the care of the patient requiring surgery. The importance of these roles will vary from country to country and indeed from region to region within countries. The nursing skills required to care for screening patients are essentially the same as those required to care for symptomatic colorectal patients in many situations. However, the specialist colorectal nurse may have a specific role to play, particularly in counselling individuals with positive screening tests. Such nurses are fully qualified and have experience in specialist colorectal nursing. The training requirements for nurses in a colorectal cancer screening programme include the following:
  - An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and importance of stage at diagnosis);
  - An in-depth understanding of the colorectal screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance); and
  - Advanced communication skills.

Appropriate courses should be available for nurses involved specifically in colorectal cancer screening programmes to address these issues, including adequate training to be able to help people make informed decisions about CRC screening.

- Public health specialists (Considering the different healthcare environments, public health specialists with adequate epidemiological knowledge or equivalent expertise are recommended. These professionals are needed from the onset, to ensure that the programme includes a population-based information system that monitors each step of the screening process. They will then be responsible for gathering data and for ongoing monitoring in order to identify problems that need intervention. These public health specialists can be based at a national or regional level, whereas the other health professionals who are providing screening services are needed in each area.. The role of the public health specialist in a colorectal cancer screening programme is to ensure coordination of the component parts of the screening programme in such a way as to optimise delivery of the programme to the target population. This will include endeavouring to maximise uptake by means of health promotion initiatives and addressing inequality issues. The role of the public health physician may vary from country to country and from region to region within countries, but public health specialists are well placed to act in a coordinating role. Public health specialists engaging in colorectal cancer have the following training requirements:
  - An in-depth understanding of colorectal cancer (diagnosis, treatment, prognosis, staging and the importance of stage at diagnosis);
  - An in-depth understanding of the colorectal cancer screening process (including screening theory and particularly the potential benefits and harms of screening, and the prime importance of quality assurance);
  - A full understanding of the mechanisms whereby colorectal cancer screening is delivered in their population; and
  - Training in effective health promotion.

Public health specialists should therefore have training in and an understanding of basic epidemiology, statistics and communication. Courses or the ability to visit screening centres can provide this specific training.

Criteria for personnel and training

All staff involved in the delivery of a colorectal cancer screening programme requires knowledge of the basic principles of colorectal cancer screening. The need for specialist training in screening differs between the different disciplines and is most important for those involved in the delivery of the service and diagnosis, e.g. laboratory staff, endoscopists, radiologists, pathologists and nurses. The surgical treatment of screen-detected cancer and post-operative treatment is not performed differently according to whether a cancer is screen detected or symptomatic, but there are certain considerations for the surgeon to take into account when treating a screen-detected cancer. Professional requirements of oncologists are not discussed in this chapter because; stage for stage, their role in the treatment of screen-detected disease is no different from that in symptomatic disease {4}.

According to the Report on the implementation of the Council Recommendation on cancer screening, very high level of adequate training is reported in the European level. Twenty (i.e. Austria, Belgium, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherland, Poland, Slovakia, Slovenia, Spain, Sweden, UK) out of 22 responding Member States (91%) reported that screening programme personnel is adequately trained at all levels to ensure that they are able to deliver high quality screening{5}.

Comment

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Importance: Critical

Transferability: Completely

Result card for ORG4: "What kind of co-operation and communication of activities have to be mobilised?"

View full card

ORG4: What kind of co-operation and communication of activities have to be mobilised?

Method

Analysis of selected studies extracted from the basic literature search. Seven articles were found to be relevant to this question and one document with guidelines.

Frame

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Result

Communication is the primary tool for educating people about cancer risks and motivating them to seek out screening for early detection of cancer. Promotion of early cancer detection and screening often involves the use of communication campaigns, educational materials, and behavioural intervention programs {14}. There are positive effects of intrapersonal, interpersonal, group, organizational, and societal communications on cancer screening behaviours {15}.

Within the communication it is extremely important that the information is transferred and communicated to the information’s receiver in a proper way. Cancer communication messages must be therefore designed and delivered to match the communication skills, needs, and pre-dispositions of specific audiences. To influence entrenched health behaviours, messages need to be relevant and compelling, with health information that provides direction and rationale for making the best health-related decisions and adopting health-preserving behaviours {14}. A key component of CRC screening programmes, therefore, is the information and education provided about CRC and CRC screening tests and procedures: people who use CRC screening services should receive, through an appropriate communication, accurate and accessible information that reflects the most current evidence about the CRC screening test and its potential contributions to reducing illness as well as information about its risks and limitations {4}.

Co-operation and communication activities take place at different levels and between several actors. If we focus only on screening process itself, the following two relationships are the most important: a) patient/ participant and health personnel (i.e. medical and administration personnel), b) health personnel in intra- and inter-organizational level.

Provision of balanced, unbiased and quantified information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risk factors) is crucial for helping patients in making informed decisions. It is important that scientific evidence is used to develop patient information materials, and that this evidence is easily accessible for public consultation {4}. Several countries have patient information materials available on the national institution's web site. Receiving balanced, unbiased and quantified information related to CRC and CRC screening may be not sufficient for patients to make informed decisions; patients need also to be able to understand the information provided, to make a decision and to carry out their decision. Barriers/obstacles to informed decision making (IDM) may exist and may be related to:

· the setting and the organisation of the CRC screening programme, such as the access and the availability of the screening service and the access and the availability of the screening information,

· the knowledge, attitudes and practice of the CRC screening provider(s) and

· the patient themselves: age, gender, physical or mental health problems, occupation, education or abilities to read or understand information.

To ensure participation in screening process and its suitable embodiment, with adequate communication process, European guidelines highlight the following recommendations {4}:

· Developing communication strategies for an organised CRC screening programme is important to ensure that as many of the target population as possible receive the relevant information to be able to make informed decisions about whether or not they wish to attend for CRC screening.

· Any framework developed to communicate CRC screening information must enable subjects to make an informed decision and should be underpinned by the four ethical principles of autonomy, non-maleficence, beneficence and justice;

· CRC screening programmes should provide balanced, quantified and unbiased information about CRC (e.g. incidence, risk factors and symptoms) and CRC screening (benefits, harms and risks). Scientific evidence should be used to develop patient information materials and should be easily accessible for public consultation.

· CRC screening programmes should identify the barriers, needs and facilitators to informed decision making of their target population (including specific groups). The information materials produced, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, and the intervention(s) used must conform to these identified information needs and facilitators. The public should be involved in the entire process; from identifying barriers, needs and facilitators to developing information materials.

· To communicate CRC screening information, including written instructions on how to use the FOBT kit or perform the bowel cleansing procedure, the language and text format used should be easy to understand and illustrations may be used. Ideally, written information (including written instructions) should not be the only source of information and should be complemented by visual communication instruments and/or oral interventions.

Organised screening programmes generally have three distinct "communication" phases throughout the CRC screening process, where information (general or person-specific information) can be provided to participants. For a CRC FOBT screening programme the following figure illustrates these three phases and the corresponding communication tools {4}:

· The invitation phase: people are invited to participate in screening. Information for this screening phase is generally provided through invitation letters and leaflets. Written instructions on how to use the FOBT kit are usually provided with the kit;

· The reporting results phase: people are notified of the results of their screening test. Information conveyed during this phase may be very sensitive and the communication tools must be carefully crafted to address the people‘s information needs;

· The follow-up phase: only for people with a positive FOBT result, who require further assessment (colonoscopy). Usually information about colonoscopy is notified at the same time as positive results. This phase also involves information about management of the colonoscopy procedure;

In the invitation phase different contact strategies can be used: mailed contacts, mailed contacts and screening kits, office visit or all three together.

Figure 5: Communication tools in FOBT-CRC screening

Communication among professionals is essential in order to ensure that all the information coming from the prognostic tests is available quickly and is correctly interpreted. To achieve and maintain an effective communication between the various professionals of a colorectal multidisciplinary team it is essential that they participate to different training courses, which should be focused on good inter-professional communication. Joint courses given for the multidisciplinary team may facilitate this goal. Good communication should be carried out between the members of the screening team with agreed terminology, regular meetings and clinical discussions {4}. What is also extremely important is that the tasks among health personnel are clearly organized. The study of Rowe et al. indicates that the lack of communication and teamwork between the nurses and residents highly affected the rates of implementation of colorectal cancer screening {16}.

Although colorectal cancer screening is recommended by major policy-making organizations, rates of screening remain low. Studies examine different communication tool options to increase knowledge on colorectal cancer screening and also to its participation.

The study of Yoo et. al. {15} utilizes the Health Belief Model (HBM) that predicts individuals’ cancer screening behaviours. Building on the HBM, the study investigated how communication factors influence CRC screening. They have found out that media use for health information and interpersonal health communication had direct effects on both perceived CRC threat and positive expectations for CRC screening. The mass media has the capacity to disseminate effective, large scale, strategic messages for the promotion of cancer prevention. While mass communication is relatively more important in increasing awareness and knowledge of cancer-related risks, interpersonal communication channels provide rapid and continuous feedback, making them instrumental in persuading people to engage in a specific behaviour, including cancer-preventive behaviours. New communication technologies, especially the Internet, can be understood as integrated communication outlets that combine the broad reach of mass communication with the persuasive capabilities of interpersonal communication. The result of this study reveals that although communication factors were not found to have a direct impact on the stool blood test, they indirectly influenced the stool blood test through their influence on key components of the HBM. The use of mass media for obtaining health information positively affected perceived CRC threat that, in turn, led to positive expectations for CRC screening which finally resulted in the use of the stool blood test. In addition, mass media use for obtaining health information positively influenced the use of new media for seeking health information which, in turn, created positive expectations for colon cancer screening. The positive expectations ultimately resulted in the use of the stool blood test. Because communication factors are crucial determinants of these perceptions, it is essential to produce effective communication messages, which outline the risk of CRC as well as the benefits of CRC screening. The lack of awareness of the need for CRC screening and lack of knowledge about CRC is still the greatest barriers that make individuals do not be screened. Thus, health care providers need to be educated regarding appropriate communication approaches to encourage people to get screened for CRC. In addition, health campaign researchers should develop a variety of risk communication strategies to promote CRC screening. Irrespective of the evidence of positive impact of mass media and new media on individual’s behaviour, certain concerns about effective communication of colon cancer still persist. With the explosive growth of communication channels and the subsequent abundance of health information available to the general public, it may be difficult for people to judge the quality of the information they are exposed to. The Internet, in particular, has a strong potential to disseminate inaccurate or misleading cancer information. On the Internet, half of the links on CRC are commercially oriented – containing information on goods or private health services – while less than 1% of the available colon cancer information is being provided by healthcare professionals. The problem of cancer information overload is as overwhelming for the general public as well as physicians or patients. Because of the overwhelming amount of cancer information, individuals who paid less attention to, and who are less trusting of cancer information may overlook critical cancer information, and may not believe important or credible information. Therefore, those who are overwhelmed with cancer prevention information may require cancer messages that are structured as clearly, and as accurately as possible.

Kim et. al. in their study developed a patient-directed, computer-based decision aid about colorectal cancer screening and investigate whether it could increase patient interest in screening. A computer-based aid, which they have developed, differs from several other decision aids for CRC screening in that patients were able to interact with the aid via its modular format and choose to view information based on their knowledge needs. It is interactive and takes approximately 25 minutes of patient time. This computer-based decision aid on colorectal cancer screening increased patient interest in screening and subjectively improved knowledge about screening options {17}. The exactly same results were found from the study of Miller et. al. Through a randomized controlled trial they have measured the effectiveness of a web-based colorectal cancer screening in a mixed-literacy population. The results have shown that the CRC screening decision aid, called CHOICE (Communicating Health Options through Interactive Computer Education) increased test preferences and patients’ readiness to receive screening, irrespective of literacy level {18}.

A study of Cueva et. al. {19} reveals interesting interpersonal communication tool to provide CRC screening information, model ways to talk about CRC screening, increase comfort with talking about CRC, and encourage healthy lifestyle choices. It is called: “Readers’ Theatre”, a 25 minutes long script that was developed with and for Alaska Native and American Indian Community Health Workers (CHWs) and the people in their communities. Readers’ Theatre, within the context of this study, was the coming together of a group of adults to read aloud a written theatre script. Participants eagerly embraced this CRC Readers’ Theatre as a cancer communication tool. Readers’ Theatre created a comfortable, supportive environment of trust for adult learners to ask questions and discuss concerns, making learning relevant and meaningful. As reported by participants, Readers’ Theatre increased their knowledge, comfort talking about CRC, and appeared to serve as a catalyst for positive intent to change behaviour. The power of Readers’ Theatre as an innovative health communication tool lies in its ability to connect with people both

affectively and cognitively, to share information in culturally respectful ways, to offer diverse perspectives, to actively engage participants in cancer-related conversations, and to serve as a springboard for action.

As already mentioned, patients are more likely to be screened, if this is recommended by the primary health provider. Therefore it is of great importance that providers have the information and access to the latest screening guidelines. The results, presented in the study of Redmond et. al. on effective communication of colorectal cancer screening information to primary care providers suggests that an effective dissemination of colorectal cancer screening information requires multiple approaches, which includes: e-mail from a trusted source, scientific journal articles, professional conferences and media campaigns. In addition, the information is well received when delivered periodically by trusted sources, such as medical colleagues, professional organizations and societies, and national research and advocacy agencies. Importantly, providers indicated that they would prefer receiving colorectal cancer screening update prior to the public to be best prepared for questions they receive from their patients. An ideal partner to venue and disseminate information is through comprehensive national programmes {20}.

Comment

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Importance: Critical

Transferability: Completely

Result card for ORG11: "What kind of quality assurance is needed and how should it be organised?"

View full card

ORG11: What kind of quality assurance is needed and how should it be organised?

Method

Analysis of selected studies extracted from the basic literature search. One article, one report and one document with guidelines were found to be relevant to this question.

Frame

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Result

Adequate quality assurance requires substantial efforts, due to the complexity of the screening process which extends from identification and invitation of the target population, to performance of the screening test and, if necessary, diagnostic work-up and treatment of screen detected lesions; and aftercare {5}.

According to the European guidelines {4}, European external quality assessment scheme should be developed to facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening.

Rigorous analytical quality assurance procedures must be adopted by laboratories providing gFOBT and FIT analysis for population screening. To minimise analytical and procedural variability, the number of laboratories used for population screening should be small {4}.

All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007, Medical laboratories - Particular requirements for quality and competence. The laboratory should be led by a qualified clinical chemist who is trained and experienced in the techniques used for analysis and in clinical quality assurance procedures. The laboratory staff should be appropriately trained and competent in the use of the analytical device/ instrumentation, quality control and assessment procedures and associated information technology {4}.

Quality assurance of FIT testing

Consistency in analytical performance must be assured by the adoption and application of rigorous quality assurance procedures. Manufacturer’s Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures {4}.

Nevertheless prevention of delays of return samples to laboratory is one of the factors that contributes to quality assurance of FIT testing, Roon et al. (2011) in their study indicated that both positivity rate and detection rate of FITs do not decrease with prolonged sample return times up to 10 days. This means that a delay in sending the FIT back to the laboratory, of ups to at least 1 week, does not necessitate repeat sampling in case of negative result. this data also supports the use of FIT-based screening as a reliable tool for nationwide CRC screening programs {45}.

Quality assurance of gFOBT testing

Whilst an immunochemical test is recommended, programmes that adopt a traditional guaiac test need to apply additional laboratory quality procedures. To minimise variability and error associated with visual test reading, including manual results input, the following procedures should be considered {4}:

- Use of appropriate temperature for artificial lighting and neutral-coloured walls in the reading laboratory;
- Use of a national laboratory training programme to prosper consistency of interpretation;
- A blinded internal QC check each day for each analyst prior to commencing testing;
- Adoption of a monitoring programme to identify operator related analytical performance (e.g. positivity variability and bias); and

- Double entry of test results.

Analytical quality assurance – Internal Quality Control (IQC) and External Quality Assessment Schemes (EQAS)

For those laboratories using visually read gFOBTs, the design of the test kit will influence the reliability of analysis. Reproducibility in detecting the blue gFOBT colour in the presence of dark faecal pigments depends on good staff training and experience but can be improved by other factors. The visual acuity and colour perception of the reader should be professionally checked and monitored. The colour of the test card surrounding the sample, the colour of surrounding walls and the colour temperature and brightness of artificial lighting all should be considered. The opportunity for errors due to operator fatigue should be minimised by enforcing periodic work breaks. The competence of staff to perform visual tests should be checked before they commence each batch of analysis, typically using preloaded test kits with known positivity that is hidden from the operator. A rigorous monitoring system should be adopted to identify staff, who has spot positivity rates which are markedly different to the mean or who exhibit marked variability {4}.

Most gFOBTs and point-of-care FIT devices have a means of checking the integrity of the device and reagents by way of a quality control check integral to the device. For gFOBT, this control can check whether guaiac has been applied across the whole of the test area and whether the hydrogen peroxide reagents are working correctly. Point-of-care FIT devices provide a similar check of reagent integrity but are unsuitable for population screening {4}.

The case for automation in population screening programmes is a strong one, and should significantly influence the choice of an acceptable occult blood testing system. Automated FIT analysis will require internal quality control procedures appropriate to the chosen technique and instrument. As a minimum, laboratories should adopt the manufacturers' instructions for use, and give consideration to what additional internal quality control measures can be used to check instrument accuracy and imprecision throughout the period of analysis. Good analytical performance is particularly important at the selected cut-off concentration, and quality control measures should reflect that requirement {4}.

Participation in an external quality assessment scheme (EQAS) is seen as mandatory for tests performed in a clinical laboratory. Participation in an EQAS enables assessment of bias between participating laboratories, and is particularly important for a national screening programme utilising several laboratories. The availability of an EU-wide EQAS is desirable. National population screening programmes should have quality assurance procedures that enable oversight of the analytical performance of all screening laboratories. Satisfactory performance in an EQAS provides an objective criterion of competence {4}.

Quality assurance and staff

The prime importance of quality assurance should also be included in basic training of other staff involved in screening process, not just those in laboratories: public health specialists, administrative and clerical staff, general practitioners, nurses, endoscopists, who must be strongly engaged in quality assurance, and also radiologist. In addition, quality control of surgery is particularly important within a screening programme, as it is essential that individuals with lesions detected at screening are afforded the highest possible standards of care. The pathologist has an essential role in the quality assurance of surgery by assessing the completeness of tumour excision in surgical resection specimens {4}.

Achieving and maintaining high quality at every step in the screening process requires an integrated, population-based approach to health service delivery. This approach is essential in order to make screening accessible to those in the population who may benefit and in order to adequately monitor, evaluate and continuously improve performance {5}.

In the case of positive FOBT result the follow-up phase is necessary. Participants with positive feedback require further assessment (colonoscopy). Usually information about colonoscopy is notified at the same time as positive results. The information provider is usually so called patients navigator (PN). This is an individual whose role has been described as providing individualized assistance (by telephone and/or by direct contact) to a patient to both educate and help them overcome healthcare system barriers related to, for example, doctors' offices, clinics, hospitals, outpatient centres, payment systems. Social and logistical services provided by patient navigators could be for example facilitating communication among patients/family members/survivors/healthcare providers, coordinating care among providers, facilitating appointments and follow-up appointments, and facilitating access and transportation to services facilities. Patient navigators could be trained community health workers/advisors who have close ties to the local community or trained social workers/health professional/volunteers or belong to a specific organization {4}.

According to the manufacturer's information on the FIT technology (FOB Gold/ SENTiFOB analyser), the FOB Gold® NG assay is a IVD laboratory test for professionals use, so a simple training is required in order to inform the users about the use of the product and results interpretation. The typical professional laboratory operator is able to use the test in a very short time.

Comment

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Importance: Critical

Transferability: Partially

Structure

Result card for ORG5: "How does de-centralisation or centralization requirements influence the implementation of FIT?"

View full card

ORG5: How does de-centralisation or centralization requirements influence the implementation of FIT?

Method

Analysis of selected studies extracted from the basic literature search. Four articles were found to be relevant to this question and one publication. We found additional information by an internet search of grey literature performed on 16 May 2013 via the search engine Google. It was performed by investigator using key words specific to this question ("impact of centralization/ dencetralization on colorectal cancer screening", "centralized vs. decentralized health care environments", "centralized vs. decentralized health care system", "centralized or decentralized health services", "impact of centralization/ decentralization on health preventive programmes"). One grey literature source is referred to in these results.

Frame

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Result

The factors that speak in favor of centralized services are the following {21}:

a) development of teams of different disciplines are easily to arrange in larger establishments,

b) large units achieve economies of scale and can make most efficient use of a scarce resource and

c) better outcomes for patients under the care of more specialized professionals.

Although the organizational theory includes several disadvantages of decentralization: (a) the risk of sub-optimality as decentralized entities focus on their own performance rather than the entire organization, b) lack of coordination, c) inappropriate diversity in practices and standards especially in personnel management and d) reduced comparability and predictability at the system level) {22}, there is still a significant advantage for the basic interventions as screening. Decentralized clinics and activities provide better access to health campaigns, which offer more information and knowledge to the participants {23}. Regarding implementation of FIT and participation in screening, centralization might reduce participation in screening, especially in countries with practices like in France {24}, where the individuals from the target population are first invited to consult their family physician before they receive the screening test by mail. Centralization might also reduce the awareness of screening meaning for health, because the access to information is not as good as in decentralized system. There is consistent evidence that centralisation of cancer screening services increased patient travel costs, time and distance {25}. The negative impact is mostly felt by those with low incomes, poor access to transport, by elderly and disabled {21}. Centralization impact that is related to access of the information about the screening could easily be overcome with mobile screening vans, which can be used for more distant areas.

Survey, implemented among 11 European countries, has shown that countries have its health system organized in a different way. Austria, Italy (i.e. decentralized in regional level) and Spain have decentralised health system. In Spain, every single region has its own organization. The Spain also indicated that they don't have information about the influence of each Regional Health System on the screening phases. The Russian healthcare system is a mixture of centralized and decentralized features. The decision making regarding health policy issues, key national health and reimbursement programs is centralized and supported by significant federal budget funds. Implementation of important health programs is the obligation of regional and municipal health authorities. Centralization of the healthcare system affects all CRC screening phases. Lithuania has semi-centralized health-care system. Lithuania indicated that there is a national legislation act, concerning the CRC screening programme, defining screening services and implementation procedures. The implementation results of this programme are provided by the Colon Cancer Early Detection Program Funding Coordination Group. The Coordination Group indicates results of the programme at least once a year. Programme implementation reports are provided to the Ministry of Health and to the National Health Insurance Fund under the Ministry of Health. Scotland indicated that the advice on screening programmes is provided to all devolved administrations by the UK National Screening Committee. Screening policy is set by the Scottish Government Health Directorates. Romania has stated that National Unit for the Management of Screening Programmes under Ministry of Health is responsible for the planning, implementation and monitoring. The tests are performed by Accredited Laboratories. National screening programme in France is organized around departmental management structures that coordinate all activities, provide training to general practitioners, manage invitations based on data of the national health insurance, track results and assure transmission of data to the In VS (Institute national de Veille Sanitaire - French Institute for Public Health Surveillance). Slovenia has a centrally organized program. Preparations started in 2006, when the Ministry of Health has approved the national program and has been granted funding of public funds through the Health Insurance (Health Insurance Institute of Rep. Slovenia). In 2008 a pilot study was made and in 2009 the program became operational at the state level. The Central Unit, at the Institute of Public Health of Slovenia, is responsible for the planning, organization, implementation, tracking, monitoring and data collection. The colonoscopy preparation and implementation is performed by clinics/health centres and colonoscopy authorized centres (this is decentralized).

Program organization in Croatia is related to their country division into 20 counties plus the capital city of Zagreb. There is one public health institute in each county and city. In each local public health institute there is a coordinator nominated for the National Screening Program. At the national level, a coordinator from the Croatian National Public Health Institute has been nominated, and all 22 coordinators are members of the Committee for Program Performance. An Expert Committee has also been nominated by the Minister of Health and Social Welfare with the main task to evaluate professional qualification of colonoscopists included in the National Program and to attend to other issues during the program performance {26}.

Comment

Literature provides little information on the impact of de-centralisation or centralisation on implementation of FIT.

Importance: Critical

Transferability: Partially

Result card for ORG6: "What kinds of investments are needed (material or premises) and who are responsible for those?"

View full card

ORG6: What kinds of investments are needed (material or premises) and who are responsible for those?

Method

Analysis of selected studies extracted from the basic literature search. Four articles were found to be relevant to this question. We found additional information by an internet search of grey literature performed on 19 May 2013 via the search engine Google. It was performed by investigator using key words specific to this question ("health expenditure for colorectal cancer screening in Europe", "cost for colorectal cancer screening in Europe", "financial investment in colorectal cancer screening in Europe" etc.). One grey literature source is referred to in these results.

Frame

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Result

For implementation of FIT several investments are needed: a) material: e.g. equipment for screening, premises, office material for posting invitations and re-invitations, IT equipment and other office devices such as printers, and b) human resources: administrative and health personnel, investment in education of personnel and their training.

Every country needs to assess their costs independently using cost-effectiveness analyses or other economic evaluation method. Investments that are needed for implementation of FIT are therefore country specific.

Screening programs are usually financed by central or local government – depends from a country {27}.

Explicit allocation of resources from the national budget to adult screening seemed to be standard within countries offering colorectal screening programmes. LSE Health (London School of Economics in Health) in 2008 concluded in their report that of countries, who participated in some form of screening, explicit funding allocation was noted in Australia, France, Netherlands, Poland, Romania and the UK. Concrete values were only reported for six countries. In the Netherlands, spending for the 2005 IKA pilot was reported to be €700,000; this was based on a population of 32,000. CRC screening expenditure was €4.2 million in Poland (2005-2006), while the pilot programme in Romania was allocated €185,000. Finally, although explicit CRC resource allocation was reported in Germany and the Czech Republic, no information was available regarding funding amounts {9}.

The Netherland's study of van Rossum et. al. (2010) indicates the actual costs of FIT and gFOBT screening. The participation-independent costs of the FOBTs were: €5.20 for G-FOBT and €4.39 for I-FOBT. Compared with the manually operated and evaluated G-FOBT, the automated analyser (OC-Sensor micro) reduced operation and evaluation time for the I-FOBT with more than 90%. When assuming 100% participation, one G-FOBT overall cost €9.63 and one I-FOBT cost €8.50. The actual participation was 47% for G-FOBT and 60% for I-FOBT. Therefore, the overall cost according to intention to screen for one G-FOBT was €7.06 and for one I-FOBT €6.22 {28}.

University of Nottingham made a study on the cost of screening for colorectal cancer. They have concluded that one clerical officer and two clerical assistants (at a total cost of £18 909 per annum) would be sufficient to handle the necessary administration in a more general setting, assuming the appropriate computer software were to be available. In addition, a consultant surgeon acts as overseer to the entire screening project, and would presumably continue to do so in the general setting. This input amounts to one session per week and is accordingly costed at one tenth of the cost of employing the consultant (£38 400 per annum). Again, they initially presumed that the furnished office accommodation at zero opportunity cost, and free access to the existing mainframe computer should be provided. There would be an additional requirement for a local IT budget, covering, for example, the purchase of terminals, a printer, disks and tapes, and lines to the mainframe. Experience suggests that a test processing rate of 60 tests per hour is feasible, and employing the nurse for the necessary length of time is necessary (total annual cost of state registered nurse = £9132). The current cost of a three day Haemoccult test is £1-13, including reagent (based on the purchase price of one pack of 50 tests). Each test costs £0-41 to send (including postage, stationery, and instruction leaflet). Returned unused tests are assumed to be discarded rather than reused. According to this study the computing equipment necessary to operate the screening system would entail an expenditure of the order of £25 000. Administrative staff would need to be in post for perhaps six months before the programme became operationalized, at a cost of some £10 000, and the nurse responsible for test development would require a short period of training (costing, perhaps £2000) {29}. According to another UK study, performed by Sharp et. al. (2012), the cost for FIT kit (cost per kit dispatched (i.e., cost per individual invited to participate in screening) is 3.75 €, the cost for FIT processing/analysis (cost per kit completed and returned (i.e., cost per screening participant)) amounts 11.60 €. Study reveals that for biennial FIT implementation at age 55–74 40.17 € per person is required {30}. Screening process also requires some other health personnel: laboratory staff and general practitioner, who give appropriate information about the screening to the patients.

International survey, implemented among 11 European countries, also indicates some information about the screening costs. Only two countries out of 11 reported on screening cost, i.e. Lithuania and Slovenia.

Lithuania indicated that the unit cost of FIT kit is 8,57 LTL, which implies that for 111,366 number of kits (the data refers for the period from July 2011 until July 2012) they have spent 954.406.62 LTL. They have indicated that FIT processing/analysis per participating person (completed and returned kit) amounts 23,20 LTL, which, for the number of 111,366, amounts 2.583.947,34 LTL. In case of positive screening results: 40.091.803 colonoscopies examinations without anaesthesia (per participating person), 2.206 colonoscopies examinations with anaesthesia and 1.392 colonoscopy biopsy examination and evaluation have been performed in above mentioned time period. The unit cost for colonoscopy examination was 124,22 LTL (without anaesthesia), 202,83 LTL (with anaesthesia) and 126,09 LTL (colonoscopy biopsy examination and evaluation). They have also indicated the costs of cancer treatment for different cancer stages. Unit cost for stage I has been estimated to 2.543,80 LTL, while 199 numbers of treatments have been necessary in above mentioned time period. Unit cost for stage II has been estimated to 4.076,49 LTL, while 311 numbers of treatments have been necessary in above mentioned time period. Unit cost for stage III has been estimated to 5.073,03 LTL, while 364 numbers of treatments have been necessary in above mentioned time period. Unit cost for stage IV has been estimated to 7.459,48 LTL, while 399 numbers of treatments have been necessary in above mentioned time period.

Slovenia provided data for year 2012. They have indicated that in 2012 - 280.686 individuals have been invited to the screening. The unit cost for the invitation letter amounts 2,12 €, which amounted in total 597.727,96 € for the invitation letters. The unit cost for FIT kit costs 6,54 €, which for 126.971 screening participants amounted 830.390,34 €. They have also indicated labour costs (total per year for all employees) in GP's office, which amounted 310.645,05 €. Material costs (total per year) in GP's office was estimated to 57.023,64 €, while laxatives (Movi Prep) amounted to 116.991.30 € (the unit cost of laxative is 13,64 €; 8.577 number of laxatives have been used in 2012). Labour costs in laboratory was estimated to 155.322,52 € per year 2012. FIT processing/analysis per participating person was estimated to 261.243,38 € (the unit cost of FIT processing/analysis is 1,60 €; 163,114 number of FIT kits was analysed in 2012). After a positive screening result 9016 number of colonoscopies was implemented in 2012. A unit cost for colonoscopy examination per participating person amounts 217,21 €, which in 2012 amounted 1.958.350,82 € in total. They have also reported on 35 DRG (diagnosis related group) cases, which in 2012 amounted 146.982,84 € (unit cost of DRG case ranges between 0,58 to 7,01 €). In 2012 also 6.004 pathohistologic medical tests was performed, which amounted 643.628,80 € (the unit cost is 107,20 €).

Comment

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Importance: Critical

Transferability: Partially

Result card for ORG7: "What is the likely budget impact of the implementation of FIT for the payers (e.g. government)?"

View full card

ORG7: What is the likely budget impact of the implementation of FIT for the payers (e.g. government)?

Method

Analysis of selected studies extracted from the basic literature search. Two articles were identified to be relevant to this question. Survey gave additional information on this question.

Frame

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Result

Budget impact analysis (BIA) of the implementation of FIT as a new technology was not found by the literature review. On the other hand literature search did provide information on importance of BIA and guidance for developing BIA. It was noticed that countries on their national level have already perform some BIA of a new technology but since those reports were note prepared precisely for FIT technology they weren't included into this document.

Budget impact analysis in combination with cost study and economic evaluation play a crucial part in the comprehensive assessment of a health technology and may inform reimbursement decisions. Reimbursement may be withheld from a cost-effective health technology if it has a high budgetary impact. Conversely, a cost-ineffective technology may receive reimbursement if its budgetary impact is limited. This is because the opportunity cost of adopting such a technology is low (little other activity would need to be displaced) and the adoption may meet other important objectives of a decision-maker such as equity {31}. The methodology of budget impact analysis is still developing. While cost-effectiveness analyses (CEAs) are well accepted, the same progress has not been made for BIA. In 2005 Task Force was established by International Society for Pharmacoeconomics and Outcomes Research (ISPOR) to develop and present guidance on methodologies for those undertaking such analyses or for those reviewing the results of such analyses. The BIA is important, along with the CEA, as part of a comprehensive economic evaluation of a new health technology. A BIA starts with providing all relevant epidemiological, clinical and economic information of the disease. More precisely, it should be performed using data that reflect, for a specific health condition, the size and characteristics of the population, the current and new treatment mix, the efficacy and safety of the new and current treatments, and the resource use and costs for the treatments and symptoms as would apply to the population of interest. The Task Force recommended that budget impact analyses be generated as a series of scenario analyses in the same manner that sensitivity analyses would be provided for CEAs. In particular, the input values for the calculation and the specific cost outcomes presented (a scenario) should be specific to a particular decision-maker's population and information needs. Sensitivity analysis should also be in the form of alternative scenarios chosen from the perspective of the decision-maker. The primary data sources for estimating the budget impact should be published clinical trial estimates and comparator studies for efficacy and safety of current and new technologies as well as, where possible, the decision-maker's own population for the other parameter estimates. Suggested default data sources also are recommended. These include the use of published data, well-recognized local or national statistical information and in special circumstances, expert opinion. Finally, the Task Force recommended that the analyst use the simplest design that will generate credible and transparent estimates. If a health condition model is needed for the BIA, it should reflect health outcomes and their related costs in the total affected population for each year after the new intervention is introduced into clinical practice. The model should be consistent with that used for the CEA with regard to clinical and economic assumptions {32}.

The survey, implemented among 11 European countries (i. e. Austria, Russia, Luxembourg, Lithuania, Italy, Scotland, Spain, Romania, France, Croatia and Slovenia), indicated that only 6 countries (Russia, Lithuania, Italy, Scotland, Spain and Slovenia) out of 11 uses FIT technology. In addition to that Luxembourg indicated that FIT is relatively new technology and isn't widely accepted in their country. All countries stated that FIT screening is free of charge for target population and founded by the country. Not all country indicated the payers. In Spain for example the payer are Regional Health Services; Russia has stated that reimbursement is provided under the program for Mandatory health Checks. CRC checks in high risk population and patients with CRC symptoms are covered under the Health Service State Guaratees Program. In Scotland FIT is supplied by NHS (National Health Service). Slovenia also stated that FIT is covered by compulsory Health insurance. In addition, only two countries indicated the costs that were related to the screening (i.e. Lithuania and Slovenia).

Unfortunately information obtained from the survey was not sufficient for the budget impact analysis. Data from the survey could present only one part of BIA. In addition, BIA is very country specific and therefore one general model of BIA of FIT couldn't be applicable to all countries. Nevertheless there are some general guidance that each country should stick to, when preparing their own BIA.

We believe that further research and countries' in-depth studies would be necessary to indicate the budget impact of the implementation of FIT for the payers.

Comment

Data of budget impact of the implementation of FIT for the different payers was, by the literature review, not found.

Importance: Critical

Transferability: Partially

Management

Result card for ORG8: "What management problems and opportunities are attached to FIT?"

View full card

ORG8: What management problems and opportunities are attached to FIT?

Method

Analysis of selected studies extracted from the basic literature search. Three articles were found to be relevant to this question and one document with guidelines.

Frame

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Result

According to the insight that was gained through the literature review, it can be concluded that the most critical points in management are:

- To ensure that all eligible target population is invited and well informed about the colorectal cancer, colorectal cancer screening and the screening process;
- To ensure that screening process is conducted strictly according to the rules of procedure (the quality of process depends also on the communication, coordination etc.);
- To ensure an adequate and timely follow-up or treatment for those who need it;
- To ensure the availability of data (data management system);

i-FOBT requires assurance of consistency in analytical performance by the adoption and application of rigorous quality assurance procedures. Manufacturer's Instructions for Use must be followed. Laboratories should perform daily checks of analytical accuracy and precision across the measurement range with particular emphasis at the selected cut-off limit. Rigorous procedures need to be agreed and adopted on how internal quality control data is interpreted and how the laboratory responds to unsatisfactory results. Performance data, both internal quality control and external quality assessment data, should be shared and reviewed by a Quality Assurance team working across the programme. Sufficient instrumentation should be available to avoid delays in analysis due to instrument failure or maintenance procedures {4}.

The problem can occur in relation to the inappropriate implementation of screening, which can result in grossly misleading results {4}. Another challenge is related to an insufficient participation to an appropriate follow-up diagnostic evaluation in cases with a positive fecal occult blood test (FIT) result {33}.

The problem can also represent a limited amount of financial, technical, staff and time resources.

Therefore in an organized screening program, besides a health care team, a management team acts an important role for its implementation {8, 27}. In colorectal cancer, multidisciplinary management is strongly recommended. In the UK for example (already mentioned in ORG3), the organisation of the colorectal screening programmes is overseen by a programme manager, who reports to a national or regional screening coordinator responsible for all screening programmes {4}.

The professional and organisational managers of a screening programme must have sufficient authority and autonomy, including an identified budget and sufficient control over the use of resources to effectively control the quality, effectiveness and cost-effectiveness of the programme and the screening service. The institutional structure must facilitate effective management of quality and performance {4}.

One of the management opportunities could also be located within the development of a European external quality assessment scheme that would facilitate Europe-wide quality assurance of occult blood testing and enhance the reproducibility of testing within and between countries providing population screening {4}.

Comment

Literature provides little information about European countries' perspective on the management problems and opportunities attached to FIT.

Importance: Critical

Transferability: Partially

Result card for ORG12: "What kind of monitoring requirements and opportunities are there for FIT?"

View full card

ORG12: What kind of monitoring requirements and opportunities are there for FIT?

Method

Analysis of selected studies extracted from the basic literature search. Three studies, one document with guidelines and one international report were found to be relevant to this question. We found additional information by an internet search of grey literature performed on 23 May 2013 via the search engine Google. It was performed by investigator using the key words, specific to this question: "colorectal cancer screening and monitoring", "monitoring in colorectal cancer screening" etc. Two additional sources have been found: one report and one document with national guidelines.

Frame

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Result

All aspects of the cancer screening programme should be monitored and evaluated. Quality standards need to be set for every step along the screening pathway and an appropriate monitoring framework is required to determine if the standards are being met. Standards will apply at a number of levels: to procedures; individuals; teams; institutions and overall systems. These standards, and their monitoring, are an essential ethical requirement for all screening programmes, to ensure that harms are minimised and benefits are maximised for participants {39}.

Maintaining high-quality of the screening service requires continuous supervision and rigorous scientific reporting. Attention must be paid to performance at each step in the screening process from information and invitation to performance of the screening test, assessment of abnormalities, and diagnosis and treatment of lesions detected in screening {46}.

Key points at this stage are {46}:

- Supervision of all steps in the screening process.

- Ability to exclude bad performers.
- Testing grounds for new technologies.
- Monitoring the benefits and harms of screening.
- Scientific publication of outcome.

European Council Recommendations on cancer screening (2003) indicates that all countries should {5}:

(a) regularly monitor the process and outcome of organised screening and report these results quickly to the public and the personnel providing the screening;

(b) adhere to the standards defined by the European Network of Cancer Registries in establishing and maintaining the screening databases in full accordance with relevant legislation on personal data protection;

(c) monitor the screening programmes at adequate intervals.

Regular, systematic monitoring, evaluation and EU-wide status reporting would promote the exchange of information on successful developments between Member States and would identify weak points requiring improvement {5}.

With regard to specific recommendation 3 (a) in the Council Recommendation (i.e. to regularly monitor the process and outcome of organised screening and report these results quickly to the public and the personnel providing the screening), only 55% of the responding Member States reported that the process and outcome of organised screening is monitored regularly by an independent peer review and 59% indicated that the results are reported quickly to the general public and to screening staff {5}.

Monitoring programme performance in UK

UK have designed a national IT system – the bowel cancer screening system (BCSS) – has been designed and built by to support the BCSP (bowel cancer screening programme). The system offers a range of functions that enable programme hubs and screening centres to manage the programme. These functions include: a) selection of screening subjects, b) call and recall, c) logging receipt of test kits and test kit results, d) booking SSP clinic appointments, e) recording of colonoscopy and histopathology results, f) letter production, g) reporting programme activity {41}.

The BCSS provides a series of strategic reports that contain statistics about programme activity (e.g. count of letter types sent, FOB test results count). Programme hubs are expected to report regularly to the national office on programme activity {41}.

All screening centres are required to use this system, which is provided free of any licensing charge. Programme hubs and screening centres will be required to work towards meeting the national standard for cancer waiting times (the 62 day wait) for patients who are diagnosed with bowel cancer through the screening programme. All patients diagnosed with cancer are included in the 31 day wait target {41}.

France

The France's program established monitoring centres that are responsible for program implementation within specified districts. Individuals in the national health registry who are eligible for CRC screening receive biennial mailed screening invitations from local monitoring centres. Initially, recipients are directed to visit their primary care physician for a free in office FOBT. If the test is not completed within three months of invitation, the program sends a reminder with an FOBT kit {11}.

Laboratory accreditation and quality monitoring

In the case of FIT cancer screening programme, where screening is based on a laboratory test, it is self-evident that an adequate monitoring system should be present in laboratories.

One of the reasons of FITs development is to provide for large scale development in the laboratory where quality assurance of test development is much easier to monitor and control. Laboratory development is preferred in many countries, especially for mass screening when many tests must be done and quality assurance is vital {34}.

All laboratories providing screening services should be associated with a laboratory accredited to ISO 15189:2007 Medical laboratories - Particular requirements for quality and competence. The laboratories should perform Internal Quality Control (IQC) procedures and participate in an appropriate External Quality Assessment Scheme (EQAS) {4}.

Outcome monitoring: All aspects of laboratory performance in respect of the screening test should be part of a rigorous quality assurance system. Uptake, undelivered mail, time from collection to analysis, analytical performance (internal QC and external QA), positivity rates, lost & spoilt kits and technical failure rate, technician performance variability and bias should each be subject to rigorous monitoring {4}.

Data collection and monitoring

There is a special need to monitor performance of programmes using new tests. The monitoring and evaluation of the programme therefore require that adequate provision has to be made in the planning process for the complete and accurate recording of all the relevant data. Achieving this goal is dependent on the development of comprehensive systems for documentation of the screening process, monitoring of data acquisition and quality, and accurate compilation and reporting of the results. The information system should be designed to support the implementation of the different steps of screening, to record screening findings of each individual, to identify those detected with abnormalities, to monitor that the recommended action has been taken and to collect information about assessments and treatment. For the purposes of impact evaluation this information should be linked to several external data sources, and legal authorisation to be able to achieve this should be secured: population registries, for estimating population coverage and to identify people in the target population in relation to their screening history; cancer or pathology registries, for cancer follow-up and for quality assurance purposes and feed-back to clinicians; and cause of death register for individuals in addition to population statistics, for assessing vital status and cause of death for final effectiveness evaluation {4}.

The design of the information system should take into account the views and data requirements of all groups involved in the screening programme. A wide range of consultation and participatory planning is important to improve programme evaluation, through common definition of data elements, indicators and standards. The programme should ensure that professionals involved in screening receive timely feedback on programme and individual performance. Rapid publication of the monitoring results is important as screening units and other actors need the information to run their activity and to implement quality assurance and training efforts {4}.

For monitoring the programme, tables presenting performance indicators should be produced at regular intervals (at least annually) by age and gender and by type of screening test using the collected data {4}.

Screening organization

A number of indicators can be used to monitor the organizational performance of a screening programme {4}:

• Time interval between completion of test and receipt of results: The time interval between performing a test and receipt of results will affect patient outcomes in terms of anxiety and potentially screening outcomes in terms of stage of diagnosis of disease. The time interval between completion of test and receipt of results by the subject should be as short as possible, (acceptable standard: >90% within 15 days).

• Time interval between positive test and follow-up colonoscopy: timely procedure is not critical in the context of primary screening but it is very important when endoscopy is performed following a previous positive screening test. A delayed procedure may not be critical biologically, but it can cause unnecessary anxiety for the screenee. To ensure that patient anxiety is not unnecessarily increased, it is recommended that follow-up colonoscopy after positive screening be performed as soon as reasonably possible but no later than within 31 days of referral. Follow-up colonoscopy after positive screening (any modality) should be scheduled within 31 days of referral (an acceptable standard is >90%, >95% is desirable).

• Time interval between positive endoscopy (CS or FS) and start of definitive management: The interval between the diagnosis of screen-detected disease and the start of definitive management is a time of anxiety for the patient and affords the opportunity, if prolonged, for disease progression. For these reasons, standards aimed at minimising delay have set the maximum interval at 31 days. The time interval between the diagnosis of screen-detected disease and the start of definitive management should be minimised. Acceptable standard: >90%, desirable >95% within 31 days.

• Time interval between consecutive primary screening tests: The time interval between two consecutive primary screening tests will affect the coverage of the programme by invitation/screening. The interval between two consecutive primary screening tests should be monitored to remain within an acceptable level (depending on the screening interval). People should be re-invited according to the date of their last test and not that of their last invitation.

Management of people with positive test results and fail-safe mechanism

In order to ensure timely and appropriate assessment, an active follow-up of people with an abnormal screening test result should be implemented, using reminders and computerised systems for tracking and monitoring management of these patients {4}.

In order to achieve these aims it is recommended to identify a coordination board that is responsible for regularly auditing the programme and taking necessary actions (including indications about the specific organisational changes which are necessary to meet the desired quality standards) {4}.

Considering the different healthcare environments, public health specialists with adequate epidemiological knowledge or equivalent expertise are recommended. These professionals are needed from the onset, to ensure that the programme includes a population-based information system that monitors each step of the screening process. They will then be responsible for gathering data and for ongoing monitoring in order to identify problems that need intervention. These public health specialists can be based at a national or regional level, whereas the other health professionals who are providing screening services are needed in each area. Public health specialists should have training in and an understanding of basic epidemiology, statistics and communication. A European training programme on monitoring and evaluation of screening programmes would be desirable {4}.

Comment

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Importance: Critical

Transferability: Partially

Culture

Result card for ORG9: "How is FIT accepted?"

View full card

ORG9: How is FIT accepted?

Method

Analysis of selected studies extracted from the basic literature search. Five articles were found to be relevant to this question.

Frame

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Result

Acceptance of FIT by patients

Young and Cole in their study (2007) found out that FITs overcome most of the disadvantages presented by gFOBT, are superior to gFOBT in terms of participation as well as performance and concluded that FIT should replace gFOBT in two-step screening. FIT technology simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling tools such as brushes or probes rather than a wooden spatula, and is possible with collecting fewer fecal samples. Most branded versions of FIT require fewer than three fecal samples, the recommended number for gFOBT {33}. In study of Cole et. al. (2003) the removal of dietary restrictions has been shown to enhance participation in screening with FIT relative to gFOBT, by 28% {35}. Changing to a brush-sampling method also simplifies the process and enhances participation by 30%. Together, these two advances increase population participation by 66% {34}.

Another population-based study compares perceived test burden and willingness to return for a successive screening round among gFOBT, FIT and FS (flexible sigmoidoscopy) in an average-risk population. All three screening tests were well accepted among participants, given the large proportion of screenees willing to return

for successive screening rounds and the positive recommendation for screening that most subjects intended to give their family and/or friends. FIT was perceived as slightly less burdensome than gFOBT screening due to less reported discomfort during faecal collection and test performance. The number of faecal samples required may explain the difference in discomfort during faecal collection, as gFOBT had to be performed on three consecutive bowel movements and FIT was a one-sample test. The authors concluded that gFOBT, FIT and FS are well accepted screening tests among participants. FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden. Both FOBTs were better accepted than FS screening {36}. Better acceptance of FIT in comparison to gFOBT was also observed in Allison's study {37}.

Acceptance of FIT by personnel and organization

There are little information about the acceptance of FIT by health personnel and the organization. Nevertheless, it has been demonstrated that the higher acceptability of FIT among patients is an important argument for choosing FIT in preference to gFOBT as the screening method for a nation-wide screening programme, apart from additional arguments regarding test performance characteristics. Therefore, the Dutch Health Council recently recommended introducing a nation-wide FIT-based CRC screening programme {36}.

The survey result gave additional information. Scotland indicated that FIT test is new in the country and not widely accepted by doctors. Therefore patients can choose between FOBT and colonoscopy.

Comment

There are little information about the acceptance of FIT by health personnel and the organization.

Importance: Critical

Transferability: Partially

Result card for ORG10: "How are the other interest groups taken into account in the planning / implementation of FIT?"

View full card

ORG10: How are the other interest groups taken into account in the planning / implementation of FIT?

Method

Analysis of selected studies extracted from the basic literature search. Two articles were found to be relevant to this question. We found additional information by an internet search of grey literature performed on 23 May 2013 via the search engine Google. It was performed by investigator using key words specific to this question ("professional involved in FIT screening", "stakeholders' participation in FIT screening", "stakeholders' engagement in FIT screening", "partners' participation in FIT screening", "the role of manufacturers in FIT screening", "the role of municipalities in FIT screening", "the role of pharmacists in FIT screening" etc.). Five grey literature sources are referred to in these results.

Frame

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Result

Wide spectrums of stakeholders are engaged in planning and implementation of FIT. Usually stakeholders, involved in that process, vigorously defend their many interests, including patients, health professionals, politicians and industry {38}. New Zeland's report from University of Otago agrees that the relevant stakeholders have to be included already in the early process, when screening program is in stage of designing. Key stakeholders in their specific area include Consumers, Maori, Pacific people, Surgeons, Gastroenterologists, Pathologists, Laboratories, Academics, radiation specialists, oncologists, Potential providers of any services such as laboratories, private specialists, FOBT manufacturers General practitioners, National Screening Unit Cancer NGOs, DHBs, Ministry of Health, Treasury, Minister of Health {39}. That involvement of a wide range of stakeholders is essential, confirms also a study of Geddies et. al., who claim that those, who participate in health policy decision making may range from senior government and administrative officials, trained methodologists and clinicians, program managers, or community stakeholders {40}. UK has also defined roles and responsibilities of stakeholders in their bowel cancer screening programme. Main stakeholders that have been mentioned are:

- national office (for example: they develop quality assurance (QA), develop and monitor the effectiveness of QA etc.),
- strategic health authorities (SHAs), who have the role of coordination of the process of selection of screening centres and recommendation of potential centres to the national office to ensure that their responsible populations are included in the screening programme,
- primary care trusts (PCTs), who are involved in the process of selecting proposed screening centres and are responsible for securing and funding the treatment of cancers detected by the screening programme,
- general practice (screening centres are responsible for disseminating information about the screening programme to primary care teams, e.g. through PCTs, practice visits or regular GP/practice manager meetings; once screening has begun, some people receiving invitations and test kits may want the opportunity to discuss the screening process with their GPs),
- program hubs (their main roles are: manage call and recall for the screening programme, provide a telephone helpline for people invited for screening, despatch and process test kits, send test result letters and notify GPs, book the first appointment at an SSP (specialist screening practitioner) clinic for patients with an abnormal test result),
- screening centres (their roles are: arrange colonoscopy appointments for patients with an abnormal test result or who are scheduled for polyp surveillance, ensure appropriate follow up or treatment for patients after colonoscopy etc. and also provide information about the screening programme for the local health community, promote the screening programme to the general public in their locality, provide information and support for local people in completing the FOB test (on referral from the programme hub), ensure that data are collected to enable audit and evaluation of the screening programme) and
- acute trusts (provide endoscopy services, but which will not be developing into screening centres) {41}.

Spanish study of Carballo and Munoz-Navas (2012) indicated that one of the main reasons of thriving and active population based screening of high quality in Spain was also a good collaboration between key institutions, which are integrated in pre-existing Cancer Screeing Program Network (CSPN). The CSPN is formed by the people in charge of cancer screening programs in the Autonomous regions, who are experts in Public Health; its main objective is the exchange of experiences between managers of population based programs of early cancer detection. They organize the CSPN annual meeting, to which specialists in digestive disorders, pathologists, radiologists, surgeons, primary care physicians and oncologists participate. In 2007 this special meeting was dedicated to establish the necessary recommendations for the planning and setting up of demographically-based organized programs for the prevention of CRC {42}.

Some literatures have also been found on the importance and the role of pharmacists. In Canada pharmacists help those, who do not have a health care provider to access screening for colorectal cancer by: dispensing program-branded FOBT kits to eligible unattached participants, providing information about the importance of screening for colorectal cancer etc. {43, 44}.

Survey, implemented among 11 European countries, has also provided some important results. Only 5 countries indicated the stakeholder's involvement (Austria, Italy, Scotland, France and Slovenia). Only 3 countries out of those five mentioned use FIT technology (Scotland, Italy and Slovenia). Scotland indicated that stakeholders in their country include NHS Education Scotland, Healthcare Improvement Scotland, 14 territorial NHS Boards, NHS National Services Scotland, Central Legal Office, Information Services Division, National Services Division, Health Facilities Scotland, Bowel Cancer UK. Italy only mentioned the important role of GPs, who advise the target population about the relevance/importance of screening. Slovenia indicated the following 5 important stakeholders:

1. NIPH (National Institute of Public Health) Slovenia as Svit leading program.
2. Authorized contractual partners: Histopatological centres, colonoscopy centres.
3. Payer: Health Insurance Institute of Rep. Slovenia.
4. Tenders for promotions program (web pages, IT support).
5. Pharmaceutical industry: Tenders for iFOBT, laxative Movi Prep, laboratory materials.

Comment

Little information exists about the interest groups/ stakeholders, who are or have to be taken into account in the planning / implementation of FIT. No study was found that would indicate general information on each stakeholder's involvement or their interaction that could be referred to all European countries. Stakeholders' involvement and role are, naturally, country specific due to specific countries programme, but little information was found also among grey literature.

Importance: Important

Transferability: Not

Discussion

Based on the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition and on the Report on the implementation of the Council Recommendation on cancer screening – First Report, sufficient overview of organizational aspect of FIT has been given. We have substantiated and strengthen the answers with several studies and also other resources that have been found on the web site. However those two documents on all the other resources were not enough to gain a complete insight into countries' specific organizational situation and also for gaining an insight into the budgetary issues.

The current overview can be therefore used as a starting point for further – country specific – examination. For this purpose an international survey was executed.

References

1. Eunetha (WP4 Core HTA). HTA Core Model online; 2012.

2. National cancer institute [Internet]. Tests to Detect Colorectal Cancer and Polyps [cited 2013-05-06]; Available on: http://www.cancer.gov/cancertopics/factsheet/detection/colorectal-screening#r13;

3. Europa Colon [Internet]. Prevention and screening [cited 2013-05-06]; Available from: http://www.europacolon.com/preventionandscreening.php?Action=Preventionandscreening;

4. Segnan N, Patnick J, von Karsa L (eds). European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis - First Edition [cited 2013-05-06]; Available from: http://bookshop.europa.eu/is-bin/INTERSHOP.enfinity/WFS/EU-Bookshop-Site/en_GB/-/EUR/ViewPublication-Start?PublicationKey=ND3210390; 2010.

5. Von Karsa et. al. Cancer Screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening – First Report [cited 2013-05-06]; Available from: http://ec.europa.eu/health/archive/ph_determinants/genetics/documents/cancer_screening.pdf; 2008.

6. Zavoral, Miroslav et. al. Colorectal cancer screening in Europe. World J Gastroenterol 2009; 15(47): 5907-5915.

7. Institute of Biostatics and Analysis [Internet]. National colorectal cancer screening programme in Slovenia – Svit Programme. II. European colorectal cancer days – Brno 2013 - prevention and screening: Stakeholder Meeting [cited 2013-06-21] Available from: http://www.crcprevention.eu/res/file/presentations/06-novak-mlakar.pdf

8. Benson, S. Victoria et. al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: the International Colorectal Cancer Screening Network. International Journal of Cancer 2011; 130: 2961–2973.

9. Kanavos, Panos et. al. [Internet] Colorectal cancer in Europe and Australia: challenges and opportunities for the future [cited 2013-05-19]. Available from: http://www.tumori.net/it3/brochures/documenti/ColorectalCancerReport.pdf, 2008.

10. Ascunce N. et al. Cancer Screening in Spain. Annals of Oncology 2010. 21 (3):iii43-iii51.

11. Swan, Heidi et. al. International Colorectal Cancer Screening Programs: Population Contact Strategies, Testing Methods and Screening Rates [cited 2013-05-06]; Available from: http://www.practicalgastro.com/pdf/August12/Swan.pdf; 2012.

12. Van Dam L. et. al. What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy? European Journal of Cancer 2013 [cited 2013-05-14]; Available from: http://dx.doi.org/10.1016/j.ejca.2013.03.007;

13. Azodo, P. Ijeoma. Participation in bowel cancer screening: an exploration of the processes involved. The Lancet 2012; 380: S24.

14. Kreps, G.L. The impact of communication on cancer risk, incidence, morbidity, mortality, and quality of life. Health Communication 2003; 15: 2, 163-171.

15. Yoo, Woohyun et. al. Influence of communication on colorectal cancer screening: Revisiting the Health Belief Model. Journal of Communication in Healthcare 2013; vol. 6 no. 1: 35-43.

16. Rowe, Sara et. al. Health Care Providers' Perspectives of an Intervention Designed to Improve Colorectal Cancer Screening Rates in Family Medicine Residency Clinics – A Qualitative Study. J Canc Educ 2012; 27: 695–702.

17. Kim, Jane. et. al. Development and initial testing of a computer-based patient decision aid to promote colorectal cancer screening for primary care practice. BMC Medical Informatics and Decision Making 2005, 5:36.

18. Miller Jr, P. David et. al. Effectiveness of a Web-Based Colorectal Cancer Screening Patient Decision Aid A Randomized Controlled Trial in a Mixed-Literacy Population. Am J Prev Med 2011; 40(6): 608–615.

19. Cueva, Melany et. al. Readers' Theatre: A Communication Tool for Colorectal Cancer Screening. J Canc Educ 2012; 27: 281–286.

20. Redmond, Jennifer et. al. Effectively Communicating Colorectal Cancer Screening Information to Primary Care Providers: Application for State, Tribe or Territory comprehensive cancer control coalitions. American Journal of Health Education 2012; 43, 4; ProQuest pg. 194.

21. Royal College of General practitioners. Trend towards centralisation of hospital services, and its effect on access to care for rural and remote communities in the UK. Rutal and remote health 2005; 5:390.

22. Saltman, B. Richard, et. al. [Internet] Decentralization in health care [cited 2013-05-16]; Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/98275/E89891.pdf; 2007.

23. UCLA Newsroom [Internet]. Centralized health care more cost-effective, offers better access to preventive services [cited 2013-05-16]. Available from: http://newsroom.ucla.edu/portal/ucla/centralized-health-care-systems-171264.aspx; 2010.

24. Poncet, Florence et. al. Determinants of participation in organized colorectal cancer screening in Isere (France). Clinics and Research in Hepatology and Gastroenterology 2013; 37: 193—199.

25. Ke, K. M. et. al. The costs of centralisation: a systematic review of the economic impact of the centralisation of cancer services. European Journal of Cancer Care 2012; 21: 158–168.

26. Katičić, M. et. al. Results of National Colorectal Cancer Screening Program in Croatia (2007-2011). World J Gastroenterol 2012; 18(32): 4300-4307.

27. Benson, S. Victoria et. al. Colorectal cancer screening: A comparison of 35 initiatives in 17 countries. Int. J. Cancer 2008; 122: 1357–1367.

28. Van Rossum, G. M. Leo et. al. Colorectal cancer screening comparing no screening, immunochemical and guaiac fecal occult blood tests: a cost-effectiveness analysis. Int. J. Cancer 2011; 128: 1908–1917.

29. Walker, A. et. al. The cost of screening for colorectal cancer. Journal of Epidemiology and Community Health 1991; 45: 220-224.

30. Sharp, L. et. al. Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. British Journal of Cancer 2012; 106: 805 – 816.

31. Simoens, Steven. Health Economic Assessment: A Methodological Example. Int. J. Environ. Res. Public Health 2009; 6: 2950-2966.

32. Mauskopf, J.A. et al. Principles of Good Practice for Budget Impact Analysis: Report if the ISPOR Task Force on Good Research Practices – Budget Impact Analysis. Value in Health 2007; 10 (5): 336-347.

33. Rao, K. Sandhya. Challenges in the Management of Positive Fecal Occult Blood Tests. J Gen Intern Med 2009; 24(3): 356–60.

34. Young, P. Graeme; Cole, Stephen. New Stool Screening Tests for Colorectal Cancer. Digestion 2007; 76: 26–33.

35. Cole SR, Young GP, Esterman A, Cadd B, Morcom J: A randomized trial of the impact of new fecal hemoglobin test technologies on population participation in screening for colorectal cancer. J Med Screen 2003; 10: 117–122.

36. Hol, L. et. al. Screening for colorectal cancer: Comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy. European journal of cancer 2010; 46: 2059 –2066.

37. Allison, E. James [Internet]. The Role of Fecal Occult Blood Testing in Screening for Colorectal Cancer [cited 2013-05-20]. Practical gastroenterology 2007; 3: 20-32. Available from: http://www.practicalgastro.com/pdf/June07/June07AllisonArticle.pdf;

38. Atun, Riftat et. al. [Internet] Analysis of National Cancer Control Programmes in Europe [cited 2013-05-19]. Available from: http://spiral.imperial.ac.uk/bitstream/10044/1/4204/1/Cancer%20Control%20vf2.pdf

39. Shaw, Caroline et. al. [Internet] Next Steps Towards a Feasibility Study for Colorectal Cancer Screening in New Zealand: Report for the Ministry of Health [cited 2013-05-23]. Available from: https://www.google.si/url?sa=f&rct=j&url=http://www.health.govt.nz/system/files/documents/pages/next_steps_towards_a_feasibility_study_for_colorectal_cancer_screening_in_new_zealanoDT4vJveU5kA; 2008.

40. Geddie, Hannah, et. al. A prospective multiple case study of the impact of emerging scientific evidence on established colorectal cancer screening programs: a study protocol. Implementation Science 2012, 7: 51.

41. Public Health Resource Unit [Internet]. Guidance for public health and commissioners [cited 2013-05-23]. Available from: http://www.cancerscreening.nhs.uk/bowel/publications/nhsbcsp03.pdf, 2008.

42. Carballo F. and Munoz-Navas M. Prevention or cure in times of crisis: the case of screening for colorectal cancer. Reviesta Espanola de Enfermedades Digestivas 2012; 104 (10): 537-545.

43. Cancer Care Ontario [Internet]. ColonCancerCheck Information for Pharmacists [cited 2013-05-23]. Available from: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=33442

44. Canadian Pharmacists Association [Internet]. Ontario pharmacists participate in Canada's first province-wide screening program for colorectal cancer Pharmacists. Canadian Pharmacists Journal / Revue des Pharmaciens du Canada 2008; 141: 159. [cited 2013-05-23]. Available from: http://cph.sagepub.com/content/141/3/159.full.pdf+html.

45. Van Roon H. C. et al. Are Fecal Immunochemical Test Characteristics Influenced by Sample Return Time? A Population-based Colorectal Cancer Screening Trial. The American Journal of Gastroenterology 2011. 107: 99-107.

46. Lynge, Elsebeth et. al. Determinants of successful implementation of population-based cancer screening programmes. European journal of cancer 2012; 48: 743 –748.

Appendices

Appendix 1:

Appendix 2:

Social aspects

Authors: Pseudo275 Pseudo275, Pseudo108 Pseudo108

Summary

The two systematic reviews, both published in 2012 (Vart et al. 2012 and Hassan et al. 2012) found that overall participation rate/rate of adherence resulting from their meta-analysis is significantly higher with FIT than with g-FOBT. All other socio-economical association, but not gender, and reasons for a better compliance need to be better investigated. Contextual socio-cultural variables seem to affect compliance, but ad hoc comparative cross national studies should be performed.

Introduction

The social domain deals with the impact the two tests can have on patients. The patient is considered both as an “individual” with his/her own psychology, emotion, perceptions, skills and capacities and as a “social subject”, an individual who is part of a community or/and a group - characterized by e.g. geographical location, religion, ethnicity, socio-economic status, age, gender etc. - with which he/she shares values, believes, experiences and culture. From an individual point of view barriers to compliance can be inconvenience of the process, embarrassment, repugnance to manipulating stool, discomfort with the procedure of the test, lack of perceived risk to develop a cancer, fear of diagnosis, but also an individual lack of understanding and a need of information/communication provided by health providers on the technology. A specific economic status, age, ethnic group etc. can also be independent variables for compliance with one test or another, this suggesting different screening paths for different groups or/and different ad hoc educational program. Patterns of adherence by age or sex or both, ethnicity or socioeconomic status were reported in many programs that used these tests (Vernon S. W, et al. 1997).

Social, cultural and psychological variables could affect satisfaction with and acceptance of gFOBT and FIT and thus the compliance with the tests and with their procedure (uptake, use, return). It is important to consider these aspects when designing a screening program as a higher or lower compliance in a first round population screening can affect the overall participation in the program and also the effectiveness of the screening program. In this context willingness of individuals to perform the screening test has as equal importance as the diagnostic accuracy of the test, because without participation no detection is possible (Hassan et al. 2012).

Methodology

Frame

The collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population

Comparison

CRC screening with Guaiac –based fecal occult blood test (gFOBT)

Description

CRC screening with Guaiac–based fecal occult blood test (gFOBT)

The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet.

Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC)

The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.

Outcomes

CUR and TEC

- Health problems (target condition)
- Epidemiology
- Burden of disease
- Target population
- Current management of the condition
- Features of the technology
- Life-Cycle
- Regulatory status
- Utilization
- Investments and tools required to use the technology
- Training and information needed to use the technology

SAF

- Colonoscopy probability of perforation
- Colonoscopy with polypectomy probability of perforation
- Colonoscopy probability of death following perforation
- Probability of bleeding following colonoscopy
- Psychological harms from false-negatives and false-positives (and generally from participating in screening program)

EFF

- Test (FIT and gFOBT) sensitivity for adenomas
- Test (FIT and gFOBT) sensitivity for cancer
- Test (FIT and gFOBT) specificity for adenomas
- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
H0001	Major life areas	Which social areas does the use of the technology influence?	yes	Which social areas does the use of FIT and gFOBT influence?
H0002	Major life areas	Who are the important others that may be affected, in addition to the individual using the technology?	yes	Who are the important others that may be affected, in addition to the individual using gFOBT and FIT?
H0004	Major life areas	What kind of changes may the use of the technology generate in the individual's role in the major life areas?	no	We do not think that the screening of crc will provide major role-changes. This could be relevant with a positive screening result, but not for the screening participation.
H0003	Major life areas	What kind of support and resources are needed for the patient or citizen as the technology is introduced?	no	This part is better treated in Organisational and costs domains.
H0010	Major life areas	What kind of social support and resources are needed for the providers as the technology is introduced?	no	Better to be trated in the organisational domain.
H0011	Major life areas	What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?	no	In many countries the FOBT or FIT tests are already used as screening. There are no experiences about any reactions or consequences on the overall societal level.
H0012	Individual	Are there factors that could prevent a group or persons to participate?	yes	Are there factors that could prevent a group or persons to participate?
H0006	Individual	How do patients, citizens and the important others using the technology react and act upon the technology?	yes	How do patients, citizens and the important others using FIT or gFOBT react and act upon them?
H0005	Individual	What kind of physical and psychological changes does the implementation and use of the technology bring about and what kind of changes do patients or citizens expect?	no	Relevant if we had to focus on the whole screening process. Further gFOBT and FIT do not cause harms.
H0007	Communication	What is the knowledge and understanding of the technology in patients and citizens?	yes	What is the knowledge and understanding of FIT or gFOBT in patients and citizens?
H0008	Communication	How do patients and citizens perceive the information they receive or require about the technology?	yes	How do patients and citizens perceive the information they receive or require about FIT and gFOBT?
H0009	Communication	What influences patients' or citizens' decisions to use the technology?	yes	What influences patients' or citizens' decisions to use FIT or gFOBT?
H0013	Communication	What are the social obstacles or prospects in the communication about the technology?	yes	What are the social obstacles or prospects in the communication about gFOBT and FIT?

Methodology description

Domain frame

We will focus on the social, cultural and psychological variables that can affect the uptake – use and return of gFOBT and FIT - and will look for studies aimed at collecting evidence that tried to verify those associations or at collecting more in depth information on psychological barriers to the use of the two tests.

For some research questions we could not find any evidence, and this is highlighted in each related result card. For other research questions we detected an intra-domain overlap, so we chose to subsume evidence in only one of the two research questions and result cards that we had judged to overlap (see each single result cards for more information on intra-domain overlapping).

We could find evidence for 4 research questions/assessment elements out of the 8 we initially had selected. Result cards we filled are described below.

The first is SOC7 - AE H0001 (Which social areas does the use of FIT and gFOBT influence?). In this Result card we included evidence on how characteristics of the tests and their procedure are perceived by individual in his/her daily life (e.g. more or less burdensome according to impact on individual's major life areas such as lifestyle and daily activities).

SOC14 - AE H0009 (What influences patients or citizens decisions to use FIT or gFOBT?) is a question that points out how societal influences can affect compliance and participation. In this result card we summarized evidence about influence of social identity (e.g. ethnicity) and of the group to which individual belongs (defnied by age, or socio-economic status, gender etc.) on compliance and participation.

The SOC10 – AE H0006 (How do patients, citizens and the important others using FIT or gFOBT react and act upon them?) contains the evidence on different compliance and participation rates with one test or the other as it is also about satisfaction (thus compliance and participation) of citizens using the technology.

SOC11- AE H0007 (What is the knowledge and understanding of FIT or gFOBT in patients and citizens?) is a result card were we report studies that provide information on understanding of the technology by patients related to communication or information provided by health care providers (information leaflets, invitation letters). This research question (and result card) overlaps with ORG domain, where – at least in the case of a screening program - more information can probably be found.

Information sources

A specific search for the social domain was conducted in the traditional databases. No mix with the literature of other domains was done. For the Search Strategy see Appendix 1.

Inclusion criteria:

We included all secondary and primary studies that where about target population (50-64 years and 65+ years; male and female; healthy/asymptomatic population; compared FIT vs gFOBT and measured/dealt with outcomes related to the social domain (e.g. compliance , participation rates associated with socio-demographical variables etc.). We included RCTs and observational studies and qualitative social studies, also if related to just one of the two technologies at stake.

A list of all the studies we selected for the full text reading is provided in the Appendix 2, with reasons for exclusion.

Quality assessment tools or criteria

As a measurement tool to assess the methodological quality of systematic reviews we used AMSTAR (at least 6 score). For primary studies we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS). See appendix 4 and 5 for both instruments applied to selected primary and secondary studies.

Analysis and synthesis

All abstracts from the domain specific literature search were screened by both ALS and IW, on the basis of the previously agreed inclusion criteria. Disagreement on inclusions were discussed. We read in double full articles of all the selected records, and extracted information/data from them on the basis of each single assessment elements using ad hoc extraction sheets. After this we refined which study had to be included and, for each of them, and independent data extraction was performed.

When a systematic review was relevant for answering a specific result card's question and was judged of good quality, this was our main source of information. To this we added information and data from the studies we had selected that were not included in the systematic review itself. Not all the studies and systematic reviews had relevant information and data for each single result card/assessment element. When studies were relevant, data and information from each of them where extracted and reported in the relevant result card.

Overall results

Included studies

Elevent 11records (Birkenfeld et al. 2011, Cole et al. 2003, Federici et al. 2005, Hassan et al. 2012, Hawley et al. 2008, Hol 2010a and Hol 2010b, Hughes et al. 2005, Levi et al. 2011, van Rossum et al. 2010, Vart et al. 2012) were included in the analysis of the social domain. Nine (9) primary studies (8 RCTs and one prospective observational study) and 2 systematic reviews (Hassan et al. 2012, Vart 2012). The complete list of all included studies and extraction of their characteristics can be found in Appendix 3. No qualitative social studies were included.

The two studies by Hol published in 2010 refer to the same population based trial, but describe results of different "line of research" made on the same cohort. Both were included as they provided evidence for different result cards (compliance and socio-economic factors affecting it).

The two Israeli studies published in 2011 (Birkenfeld et al. and Levi et al) are based on the same population, but as above, the Birkenfeld at al. article aimed at verifying if socio economic status impacted on compliance within the same population-based study described in Levi et al.). We included both Hol's and both Levi's and Birkenfeld as, although based on same population, they reported results on different social outcomes we included in our focus.

Year of publication

The studies were published in 2003 (Cole et al., 2003), 2005 (Federici et al 2005, Hughes et al 2005), 2008 (Hawley et al 2008), 2010 (Hol et al 2010a and Hol et al. 2010b, van Rossum 2010), 2011 (Birkenfeld et al. 2011, Levi et al. 2011), and 2012 (Hassan et al. 2012, Vart et al. 2012). None of the studies had a huge gap between study conduction and study publication.

Country

Three of the primary studies were from the Netherlands (Hol et al. 2010a and Hol et al. 2010b, van Rossum et al. 2010) two of the studies were from Israel (Birkenfeld 2011, Levi 2011 but same population from which they published two articles on different outcomes), 1 from the USA (Hawley 2008,), two from Australia (Cole 2003, Hughes 2005) and one from Italy (Federici 2005). The two systematic reviews (Hassan 2012, Vart 2012) were included studies from Australia, Italy, Netherlands, USA, Israel. Hassan 2012 included 14 studies in their meta-analysis, 4double with our search results (Federici 2005, van Rossum 2008, Hoffmann 2010, Hol 2010, Levi 2011,), whereas two included in Hassan were excluded by us (Segnan 2007 and Quintero 2012 due to no comparison of FIT versus gFOBT). Vart included 7 studies in their metanalysis, among them we did not include just Hoffman due to target population (male and veterans), while Hol 2009 was not retrieved with our search strategy, which on the other hand included two other Hol's studies both published in 2010, which are based on the same cohort of healthy Dutch people.

Funding

Ten studies provided information about funding of the research, in two studies the funding was unclear or not mentioned (Hawley 2008, Federici 2005). Three studies reported a funding from companies (Birkenfeld 2011, Cole 2003, Levi 2011), four studies reported a funding by official organisations (Hassan 2012, Hol 2010a, van Rossum 2008, Vart 2012) and two studies (Hol 2010b, Hughes 2005) reported mixed official and company funding.

	Official funding	**Funding from companies**
Birkenfeld, et al. 2011		Eiken Japan provided the OC-MICROTM instrument, reagents and partial financial support for administration.
Cole, et al. 2003		Grant support: Hemoccult SENSA and FlexSure OBT cards were purchased from Beckman Coulter Inc. (Palo Alto CA, USA). Enterix Inc. (Portland ME, USA) provided InSure test kits. Grants from the Bushell Foundation and Enterix Inc. provided part support for salaries (SC, BC).

Federici et al. 2005	Not applicable	Not applicable
Hawley et al. 2008	Unclear	Unclear
Hol 2010a (44)	This trial was funded by the Dutch Cancer Society (EMCR 2006-3673), and the Dutch Ministry of Health, Health Care Prevention Program–Implementation (ZonMw 2006-5877).	
Hol 2010b (46)	This trial was funded by the Dutch Cancer Society (EMCR 2006-3673), the Dutch Ministry of Health, Health Care Prevention Program–Implementation (ZonMw 2006-5877),	Olympus Medical Systems Europe GmbH, Hamburg, Germany and Eiken Chemical Co., Tokyo, Japan.
Hughes et al. 2005	This research was funded by Queensland Health. The pathology laboratory at Townsville General Hospital, which provided analysis of Hemoccult-II kits at a greatly reduced fee.	In addition, funding was subsidised by Enterix (Inc), which made the !nform FOBT kit and its analysis available at a highly discounted rate.
Levi et al. 2011		Eiken Japan provided the OC-MICROTM instrument, reagents and partial financial support for administration.
Van Rossum et al. 2008	Netherlands organization for Health Research and Development (ZonMW: number 50-50115-98-060, project 63000004)	
Hassan et al. 2012	This study was partially funded by the Italy Ministry of Health, through a project coordinated by the Agenzia Nazionale per i Servizi Sanitari and conducted by Laziosanità: 'Strumenti e metodi per il governo dei processi di innovazione tecnologica, clinica ed organizzativa nel SSN – Un sistema integrato di ricerca', sub-project 'Analysis of the impact of professional involvement in evidence generation for the HTA process' grant no. I85J07000080001.	
Vart et al. , 2012	This research was funded via studentship provided by The Guildford Tumour Screening (G.U.T.S) charity for part fulfilment of the degree PhD Health Psychology at the University of Surrey	

Trial registration (RCTs)

One study provided a trial registration number (van Rossum 2008).

Basic population data

SYSTEMATIC REVIEWS

Vart 2012	Number of included studies was 7; (Cohorts ranged from 1818 (Cole 2003) to 20623 (van Rossum 2008).	50+	n.a.	screening population	n.a.	n.a.	population based program setting	FIT	gFOBT
Hassan 2012	Five studies compared g-FOBT with FIT, including 59 729 randomised subjects Number of included studies was 5	50-74 (4x), 50-75 (4x); 55-64 (3x); 50-54/65-69 (1x); 50-80 (1x); 50-69 (1x)	male 49.5%; female 50.5% (own calculation of all studies included in the meta analysis)	no exclusions	n.a.	n.a.	population screening	FIT/gFOBT/endoscopy	FIT/gFOBT/endoscopy

PRIMARY STUDIES

Birkenfeld 2011	16132 [10668 (gFOBT) + 5464 (FIT)]	60-74	43,1% male; 56,9% female	asymptomatic	10,8% immigrants	34% high SES, 36,6% medium SES, 29,4% low SES	Israel	primary care clinic registrees, setting population-based like	FIT	gFOBT
Cole 2003	1818 (3 groups of each 606)	50-69	49,5% male, 50,5% female (own calculation of table 1)	no exclusions	Exposure of this population to screening was low by US standards and prior participation in screening had been less than 20%.	Exposure of this population to screening was low by US standards and prior participation in screening had been less than 20%.	Australia	population screening	FIT	gFOBT
Federici 2005	7320	50-74	Guaiac 46.9% men FIT 45.8% men	average risk	no	no	Italy	population screening	FIT	gFOBT
Hawley 2008	*220*	*50-80*	*not specified, proportion controlled in the analysis*	*asymptomatic*	*74 white, 60 Africans, 78 Hispanic*		*USA, Michigan*	*None. Diverse hypothetical scenarios. Southern urban*	*FOBT, COL, SIG, FIT, V-COL*	
Hol 2010a	852	50–74	45.3% male (FOBT), 50.6% male (FIT), 50.7% (FS)	asymptomatic	5% non Cuacasian	no	NL	population screening	FIT	FOBT, FS
Hol2010b	15111	50-74	participation OR for Women 1.1 (0.9 to 1.4) (FOBT) 1.3 (1.1 to 1.4)(FIT) 0.9 (0.8 to 1.0)(FS)	asymptomatic	n.a.	n.a.	NL	population screening	FIT	FOBT, FS
Hughes 2005	3358	50-74	51.2% female	asymptomatic	no	no	Australia	population screening	FIT	FOBT, FS
Levi 2011	12,539 (4,657 FIT; 7,880 G-FOBT)	mean age FIT: 60.4, mean age FOBT 61.3	45.4% male for FIT, 42.6% male for FOBT	asymptomatic	n.a.	SES controlled	Israel	population screening	FIT	FOBT
van Rossum 2008	Out of 20.623 people the test was sent to 10.993 tests were returned	50-75 years (50.4% with GFOBT and 51.7% with IFOBT aged < 60)	**47.8% (GFOBT) and 48.8% (IFOBT) male**	asymptomatic	n.a.	n.a.	Netherlands	population based program setting	FIT	gFOBT

Result cards

Major life areas

Result card for SOC7: "Which social areas does the use of FIT and gFOBT influence?"

View full card

SOC7: Which social areas does the use of FIT and gFOBT influence?

Method

We used the SOC domain literature search and selected records according to explicit criteria (see domain methodology section). Systematic review by Vart et al. provided answers to SOC7 domain question. Vart included 7 studies: Cole et al., 2003; Federici et al., 2005; Hoffman et al., 2010; Hol et al. 2009, Hughes et al., 2005; Levi et al., 2011 van Rossum et al 2008. We had selected 4 more primary studies Birkenfeld et al. (2011), Hawley et al. (2008), Hol L, De Jonge et al (2010) and Hol L, De Jonge et al (2010) (which are not the same study by Hol included by Vart et al, as this is Hol, Wilschut J.A et al. 2009) and 1 further systematic review (Hassan et al., 2012). Among the studies Vart et al. included, there is just Hoffman which we decided to exclude as being not being on our target population as it involved just veterans (male and with potential specific health history related to being in the army).

In reporting results we start from the Vart systematic review and add the primary studies we selected that were not included in Vart review and answered to this specific SOC7 question.

Result

Having the two tests implies a change in one's own daily activities and routine which can affect the patient's willingness to participate to the whole program or/and his/her compliance with test. The tests differ in the procedure of sampling and keeping stools. A procedure that breaks daily routines and social areas – such as lunch time - can be less acceptable and affect compliance with tests and overall participation to the screening.

Systematic review by Vart et al. (2012) beside a meta-analysis of participation rates, gives an exploratory synthesis of tests characteristics and a qualitative analysis of all authors claims about possible effects that certain tests characteristics have on enhancing or diminishing compliance with tests and thus with screening participation. Vart et al. highlights that the procedure for the tests has 4 main steps:

1)dietary and drugs assumption restrictions before the test;

2)collecting faecal samples;

3)test kit return;

4)sample storage.

The first of them can be seen as a social activity (food-dietary restriction), while the others are less "social" and more related to the individual psychology.

Vart et al. explain that just 5 studies (Cole et al., 2003; Federici et al., 2005; Hoffman et al., 2010; Hughes et al., 2005; Levi et al., 2011) cited the possible determinants for higher participation in the FIT or g-FOBT groups. A description of the explanations given in the above 5 studies is provided below. All explanation and claims are reported by Vart as they can be seen as authoritative hypothesis, but ad hoc studies should be performed to prove that they are sound.

Four studies claimed that FIT was more acceptable because it did not require dietary or medicinal restrictions (Cole et al., 2003; Federici et al., 2005; Hoffman et al., 2010; Hughes et al., 2005). One of these studies reported that participation increased by 28% when these restrictions were removed (Cole et al., 2003). However, about "medical restriction", Federici et al. (2005) asked the FIT group to abstain from anticoagulant use, thus enforcing medical restriction also in this group, and this was not reported to impact on the higher participation rate for that group. Two studies (Cole et al., 2003; Federici et al., 2005) claimed participation was higher in the FIT group because this test required fewer samples than the g-FOBT. This characteristics makes the FIT test more convenient since lessens the aversion to handle faecal samples, which can be a psychological barriers to the use of the test. Four studies stated that FIT was more readily used because the sampling was simpler (Cole et al., 2003; Federici et al., 2005; Hoffman et al., 2010; Hughes et al., 2005). Cole et al. stated that the FIT, using brush sampling, combated inconvenience and aversion to the manipulation of faecal samples: in Cole's study participation significantly increased by 30% if the sampling procedure was simplified, i.e. by allowing a sample to be taken from the toilet water, in addition to taking fewer samples. Participation further improved to 66% if these factors were combined with the removal of dietary or medical restrictions. Hughes et al. (2005) concluded that participants must have preferred the FIT because it is more 'user-friendly', convenient, and less messy. Federici et al. (2005) stated participation was higher in the FIT group because they did not have to handle their faeces with a paper sampler, as in the g-FOBt group. Hoffman et al. (2010) claimed that the FIT was easier to perform as a reason for a higher compliance and participation to the FIT and added that their findings suggest that less faecal manipulation makes the test more acceptable. Vart et al. highlights that FIT did not have a better rate of participation just in one of the selected studies, the one by Levi et al. (2011). Vart et al reports Levi et al's explanation for that, who claim that this could be due to the fact that participants were requested to keep the FIT refrigerated and return the samples to the clinic in a cooling bag due to Israel hot climate. Moreover, according to Levi et al.'s, participants in their study were required to take the same amount of samples for the FIT as the g-FOBt, and the authors state that this could be a added possible explanation as to why the FIT was not as favorable in this study.

Vart et al highlights that the method of test kit return and storage was not cited as a predictor of response rate in any of the other studies. Authors state that although three studies (Cole et al., 2003; Federici et al., 2005; Hughes et al., 2005) discussed the reasons for a higher participation in the FIT group claims that it was because FIT is easier to complete, they did not ask participants directly why they preferred a particular test, and they interpreted possible reasons for higher participation in the FIT group from previous literature. Other studies either did not discuss reasons for different participation rates (Hol et al., 2009), or claimed that the reasons were not apparent (van Rossum et al., 2008). Therefore, absolute conclusions as to why the FIT participation rate was mostly found to be significantly higher than g-FOBt cannot be drawn.

Three studies that were not included in Vart'systematic review where useful to answer the question of this Result card: Birkenfeld et al (2011), Hol L, De Jonge et al (2010) and L Hol, Van Leerdam M.E. ,(2010), while study by Hawely et al. (2008) and Hassan systematic review (2012) did not provide data and information for this results card.

The Birkenfeld et al. study (2011) was conducted in Israel on the same population as Levi's et al (2011). In this study, a higher participation rate for the FIT than G-FOBT is not demonstrated (as already happened with Levi et al.'s) . Authors state that they believe reasons for this difference with international results that usually favor Fit vs GFOBT are the familiarity of the population with G-FOBT and the procedure needed for keeping the FIT in the refrigerator and bring the samples to the clinic in a cooling bag. The overall participation rate with the FIT was 3.2% lower that with G-FOBT. Once the kit was dispensed, the compliance was 15.8% higher in the FIT arm. However data on "overall compliance" in table 4 p. 139 of Birkenfeld 2011 show that FIT was performed by 23,1% and gFOBT by 24.6% (p=0.036). There were some inconsistencies between text and tables in these two studies including the same population for different aspects.

The study by Hol L, De Jonge et al (2010).involved a representative sample of the Dutch population (aged 50–74 years) who was randomized be invited for gFOBT, FIT and FS screening. A random sample of participants of each group was asked to complete a questionnaire about test burden and willingness to return for CRC screening. Screeners rated overall embarrassment during gFOBT and FIT equally (0.07 versus 0.06; p = 0.30) . A larger proportion of gFOBT than FIT screenees described the test as uncomfortable (0.15 versus 0.11; p = 0.02), mainly due to more discomfort while collecting faeces and performing the test. FIT was perceived as slightly less burdensome than gFOBT due to less reported discomfort during faecal collection and test performance. The number of faecal samples required may explain the difference in discomfort during faecal collection, as the gFOBT had to be performed on three consecutive bowel movements and FIT was a one-sample test.

Hol L., Van Leerdam ME (2010) shows that gFOBT screening performed without dietary restrictions remains associated with a lower uptake than FIT screening. A more demanding sampling procedure and the number of consecutive bowel movements that had to be collected (three for gFOBT vs one for FIT) seem likely explanations for the difference in participation rate.

Importance: Important

Transferability: Partially

Result card for SOC8: "Who are the important others that may be affected, in addition to the individual using gFOBT and FIT?"

View full card

SOC8: Who are the important others that may be affected, in addition to the individual using gFOBT and FIT?

Method

None of the included studies reported about important others

Frame

None of the included studies reported about important others

Result

None of the included studies reported about important others

Comment

None of the included studies reported about important others

Importance: Unspecified

Transferability: Unspecified

Communication

Result card for SOC11: "What is the knowledge and understanding of FIT or gFOBT in patients and citizens?"

View full card

SOC11: What is the knowledge and understanding of FIT or gFOBT in patients and citizens?

Method

We used the SOC domain literature search and selected records according to explicit criteria (see domain methodology section). Four of the selected primary studies provided answers/information to this result card giving details of the information given to the participants. Two studies refer to the same collective – Hol L., ME van Leerdam et al. 2010 et Hol L. de Jionge V. et al 2010. Same population is also in Levi et al. and Birkenfeld et al, but Levi took a subgroup of Birkenfeld and reported

with different outcomes so we include both for this result card. In reporting results of the various studies we start by describing studies that were published previously, and then describe the more recent.

Result

Cole et al (2003) sent a letter of invitation accompanied by an information sheet on screening for colorectal cancer and a stool sample collection kit with relevant instructions. Reminders were sent by mail six weeks after the initial mail-out if a completed collection card had not been received. Participants were advised of the results (positive or negative).

In Hol et al studies (2010) same population, and two different studies, all individuals were sent a pre-invitation letter containing information on CRC screening. All information was made available via a dedicated website (www.dikkedarmkankerpreventie.nl; accessed 3 September 2009), mailings and information sites of the municipality offices, regional newspapers and national and regional broadcasting.

In the Israeli study by Levi et al. (2011) those willing to participate were instructed how to prepare the FOBTs and were asked to bring it back to the clinic. The kits were then transported to a central laboratory. The patients with positive tests were referred to a consultant gastroenterologist with a recommendation to perform colonoscopy. Hemoccult SENSATM (HOS) Cards were provided at the primary care clinic. Patients willing to participate in the study received an oral explanation and written instructions about test preparation. Patients were requested to follow the manufacturer's instructions on diet and use of medications before and during the preparation for G-FOBT. They applied stool on six windows of three cards and brought them back to the clinic where they were provided. Then, the cards were collected and checked at the central laboratory of the CHS. OC-MICRO (FIT) This FIT: 14 Patients willing to participate in the study received an oral explanation and written instructions about the test preparation. They were given the kit for fecal sampling and requested to prepare three consecutive daily samples without any limitation of diet or medication. The patients were instructed to keep the samples in the refrigerator and bring the samples back to the clinic using a cooling bag provided with the kits. Samples were refrigerated at 4 C until developed within 2 weeks of preparation.

Birkenfeld study (2011) verbal explanation and written instructions about the test preparations were given. Individuals received a kit for faecal sampling and were requested to prepare three consecutive daily samples without any limitation of diet or medications. In the FIT arm participants were instructed to keep the samples in their refrigerator and bring the samples back to the clinic using a cooling bag provided with the kits. For FOBT, participants were provided with cards (Hemoccult SENSATM, Beckman Coulter, Fullerton, CA) at the primary care clinic and were requested to follow the manufacturer's instructions on diet and use of medications before and during preparation of the gFOBT. They applied stool on six windows of three cards and brought the cards back to their clinic. The cards were then collected. Participants in the study received a verbal explanation and written instructions about the test preparations. They received a kit for faecal sampling and were requested to prepare three consecutive daily samples without any limitation of diet or medications. Participants were instructed to keep the samples in their refrigerator and bring the samples back to the clinic using a cooling bag provided with the kits. The samples were refrigerated at 4oC. All individuals participating to the whole study were informed and asked whether they wanted to participate, but did not have to sign an informed consent.

Comment

According to the information (only) available on a website ("All information was made available via a dedicated website (www.dikkedarmkankerpreventie.nl") it should be proved whether the equal access could be guaranteed, especially for persons in the target group for crc (like about 60 years old): do they all have/use internet?

Importance: Important

Transferability: Partially

Result card for SOC12: "How do patients and citizens perceive the information they receive or require about FIT and gFOBT?"

View full card

SOC12: How do patients and citizens perceive the information they receive or require about FIT and gFOBT?

Method

None of our included studies provided information on this topic.

Frame

None of our included studies provided information on this topic.

Result

None of our included studies provided information on this topic.

Comment

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for SOC14: "What influences patients' or citizens' decisions to use FIT or gFOBT?"

View full card

SOC14: What influences patients' or citizens' decisions to use FIT or gFOBT?

Method

We used the SOC domain literature search and selected records according to explicit criteria (see domain methodology section). Four of the selected primary studies provided answers/information to this result card. In reporting results of the various studies we start by describing studies that were published previously, and then describe the more recent.

Result

We detected a huge overlap with the issue of SOC14 and SOC6. We decided to subsume SOC6 and SOC14 into one only result card (SOC14). Five (5) of our included primary studies provided information on this topic.

In the Australian study by Cole et al, 2003, a pool of 4000 potential invitees aged 50–69 years was randomly selected using postcodes that represented a broad range of socio-economic index. Exposure of this population to screening was low: prior participation in screening had been less than 20%. The study compares gFOBT and two types of FIT: FlexSure OBT and InSure. Both did not require drug or diet restrictions, but InSure had a simplified procedure to sampling stools. It needed two rather than three stools and invitee were asked to sample the stool by brushing the surface of the stool while immersed in toilet bowl water. The content of the brush is transferred by touching one of the two windows of the sample card, and the second stool is separately sampled onto the other window. FelxSure OBT provided to sample three stools (one card per stool) using a spatula similar to that for Hemoccult, keeping the stool clear of toilet bowl water. Three randomized cohorts of 606 invitees were offered a screening test by mail in 2001. The first 606 were allocated to the gFOBT (Hemoccult SENSA), the second 606 to the FIT (FlexSure OBT) and the third 606 to the FIT (InSure).

For gender, univariate analysis indicated a trend to better participation to screening in women, but this was not statistically significant or confirmed in the multivariate analysis (see fig. 1). Authors conclude that interaction between gender and participation needs more detailed exploration. Univariate analysis also indicated a trend to better participation in those aged 60–69 years than in those in the previous decade but again, this was not statistically significant. Socioeconomic status showed not to be a confounding factor in the study by Cole et al. although authors highlight that other studies showed an influence of this variable. The reasons why these associations were not seen in the Australian study remain might be related to complex cultural factors that vary between populations.

Fig. 1 Table from Cole et al. 2003, p. 121

The Hughes et al study (2005) involved a rural Queensland community in Unites States, with a population of 15,000 of which 4,200 were aged 50 or over. Overall, 1,219 kits were completed and returned for analysis, with a participation rate of 36.3%. Participation was significantly higher with the immunochemical kit ($\chi 2=20.7$, $p<0.001$), and women were significantly more likely to comply with testing than men ($\chi 2=24.8$, $p<0.001$). For those receiving the gFOBT, participation progressively increased with increasing age (27% among those 50-59; 32% among those 60- 69; and 35% among those 70-74 years). In contrast, among recipients of FIT participation by the youngest (47%) and oldest (49%) age groups were similar (OR=0.98; 95% CI 0.74-1.28 comparing 50-59 year-olds and 70- 74 year-olds), whereas persons aged 60-69 (40%) were less likely to participate (OR=0.73; 95% CI 0.56-0.96 relative to 70-74 year olds). (see Fig.1).

Fig.1 Table from Hughes et al study (2005), p-361

The association between participation and age was significant at the multivariate level with younger age groups, particularly the 60-69 year olds, less likely to comply compared with the 70-74- year age group. However, there was evidence of interaction between age and kit type (p=0.01; see Figure 2). For those receiving the guaiac test, participation progressively increased with increasing age (27% among those 50-59; 32% among those 60- 69; and 35% among those 70-74 years). In contrast, among recipients of the immunochemical test, participation by the youngest (47%) and oldest (49%) age groups were similar (OR=0.98; 95% CI 0.74-1.28 comparing 50-59 year-olds and 70-74 year-olds), whereas persons aged 60-69 (40%) were less likely to participate (OR=0.73; 95% CI 0.56-0.96 relative to 70-74 year olds).

Fig 2. Table form Hughes et al study (2005), p-361

In the Hawley et al (2008) a purposive sampling from waiting areas of 3 community health centers was done and patients aged 50-80 recruited. This study is about the declared intention to participate in hypothetical secnarios and its not a community based trial directly comparing screening with different test. Respondents were asked to rate 8 hypothetical CRC screening tests scenarios. Patients demographics included race/ethnicity (White, Hispanic, African Americans) educational attainment, gender and age.

The study found an importance of the variable race/ethnicity. Hispanic patients were significantly more likely to prefer the FOBT and the BE scenarios compared with Withes. African Americans were significantly more likely to prefer the SIG and the Virtual–Colonoscoy scenarios and less likely to prefer FIT compared with whites.

Those with less education were more likely to prefer FOBT than Colonoscopy. Compared to white persons, Hispanics preferred FOBT to endoscopic tests and less likely FIT; African Americans preferred the endoscopic tests to FOBT and FIT.

Fig 3. Table form Hawley et al (2008) , p. 14

In their 2010 paper, Hol, van Leerdam M.E. et al compared three days of gFOBT without dietary restrictions with one day of FIT (OC-Micro) and flexible sigmoidoscopy (FS) in a representative sample of Dutch population (n=15011) randomized by age, gender and SES (using postal code). High SES and living in a rural area were associated with increased attendance in all screening arms. The age specific participation rate to gFOBT screening was significantly higher in women than in men aged 50-59 years (OR, 1.6; CI, 1.4 to 2.0 while no difference was seen in the other age groups (60-64 years and 65-74 years). Independent predictors for higher participation to Fit screening were female sex and age 60-64 years, while a low participation rate was especially found among men ages 50-55 years (gFOBT, 37% and FIT, 51%).

Birkenfeld et al. (2011) aimed at better understanding if demographic and socioeconomic factors might affect patients compliance with tests uptake. Subject from Israeli population related to Calalit health service and their primary area clinics were clustered according to socioeconomic status (SES), using clinic quarter as a proxy of socio-economical status. Clinics from each SES were then randomly allocated into either the FIT or gFOBT arm. Results showed that age above 60 years and female gender were independent predictors of increased attendance/compliance in both arms.

Comment

Demographic variables such as age, socio economic status seem to affect participation with one test or another, but this hypothesis would need further research. Moreover associations also can change according to the different countries the study has been done, this suggesting the importance of context specific variables. There is evidence that female gender is an independent variable for higher participation to screening with both tests.

Importance: Important

Transferability: Partially

Result card for SOC15: "What are the social obstacles or prospects in the communication about gFOBT and FIT?"

View full card

SOC15: What are the social obstacles or prospects in the communication about gFOBT and FIT?

Method

We detected a huge overlap with the issue SOC11 and therefore subsumed SOC15 and SOC11 into one results card at SOC11

Result

We detected a huge overlap with the issue SOC11 and therefore subsumed SOC15 and SOC11 into one results card at SOC11

Comment

See SOC11

Importance: Unspecified

Transferability: Unspecified

Individual

Result card for SOC6: "Are there factors that could prevent a group or persons to participate?"

View full card

SOC6: Are there factors that could prevent a group or persons to participate?

Method

We detected a overlap with the issue SOC14 and therefore subsumed SOC6 and SOC14 into one results card at SOC14

Frame

We detected a overlap with the issue SOC14 and therefore subsumed SOC6 and SOC14 into one results card at SOC14

Result

We detected a overlap with the issue SOC14 and therefore subsumed SOC6 and SOC14 into one results card at SOC14

Comment

We detected a overlap with the issue SOC14 and therefore subsumed SOC6 and SOC14 into one results card at SOC14

Importance: Unspecified

Transferability: Unspecified

Result card for SOC10: "How do patients, citizens and the important others using FIT or gFOBT react and act upon them?"

View full card

SOC10: How do patients, citizens and the important others using FIT or gFOBT react and act upon them?

Method

We used the SOC domain literature search and selected records according to explicit criteria (see domain methodology section). Systematic review by Vart et al. provided answers to the SOC10 domain question. Vart included 7 studies: Cole et al., 2003; Federici et al., 2005; Hoffman et al., 2010; Hol et al. 2009, Hughes et al., 2005; Levi et al., 2011 van Rossum et al 2008). We had selected 5 more primary studies Birkenfeld (2011), Hawley (2008), Hol et al (2010a) and Hol et al. 2010b (which are not the same study by Hol included by Vart et al, as this is Hol, Wilschut J.A et al. 2009) and a further systematic review (Hassan 2012). Among the studies Vart included, there is just Hoffman which we decided to exclude as not being on our target population as it involved just veterans (male and with potential specific health history related to being ion the army). In reporting results we start from the Vart systematic review and add to information from primary studies that were not included in Vart review and that we judged to answer this specific SOC710 question.

Result

This result card deals with how patients react upon Fit and gFobt both in terms of compliance with the two tests and participation to the screening and in terms of patients' preferences, satisfaction, perceptions of the pros and cons of having one tests or the other. Seven (7) of our included records provided data on participation to a screening program with Fit and/or gFOBT and compliance with those tests: systematic reviews by Vart et al. (2012) and Hassan et al (2012), and 5 primary studies that were not included in the Vart et al.'s review (Hughes 2005, Federici, 2005, Hol. L., V. de Jonge et al. 2010, Hol, van Leerdam M.E. 2010, Birkenfeld 2011). Specifically the study by Hol. L., V. de Jonge et al. 2010, gives an insight to aspects related to preferences and satisfaction with the tests. Below a detailed descriptions of the above studies is provided for the participation/compliance item and for the satisfaction/preferences topic.

Systematic review by Vart et al (2012) is namely about comparing participation rates between Fit and gFOBT. According to Vart et al. overall the participation rate was found to be significantly higher with FIT than with g-FOBT. Vart highlights that only Levi et al. (2011) reported a better compliance for g-FOBt, but context specific variables (related to hot climate in Israel causing a more complex procedure to store stools) with FiT could help to explain this diversity. Vart et al explains that notwithstanding this heterogeneity among studies, since six out of the seven included studies drew similar conclusions, authors thought a meta-analysis was useful and justified because it increased the statistical precision of the point estimate.

Authors highlight that all studies included in the meta-analysis defined the "participation rate" as the "number of completed test kits returned". Three studies specified a time line for participation rates, i.e. number of test kits returned within 12 weeks (Cole et al., 2003), within 90 days of the participant agreeing to take part in the study (Hoffman et al., 2010), or the number of participants returning a gFOBT by the end of the study (van Rossum et al., 2008).

Four studies reported the use of reminders sent to non-responders 2 weeks (van Rossum et al., 2008); 6 weeks (Cole et al., 2003; Hol et al., 2009) and 8 weeks (Hughes et al., 2005) after the initial invitation, if a completed kit had not been returned. When the seven studies were pooled together, the participation rate was significantly higher in the FIT groups (48.1%) than in the G-FOBT (39.2%) groups (RR 1.21; 95% CI 1.09–1.33) with a quite large heterogeneity within studies (I2=95%) (See below). Authors' conlcusions support hypothesis that the implementation of FIT test instead of gFOBT is likely to increase participation in CRC screening.

Fig.1

Forest Plot by Vart et al. meta-analysis (Vart et al. 2012, p.91)

Birkenfeld et al. 2011 is a Israeli study and its results does not show the same huge diversity due to context specific variables of the other Israeli study by Levi et al (see the Forest Polt in Fig.1). In this study there were 5,464 and 10,668 eligible participants in the FIT and gFOBT arms respectively. Compliance in taking the kits was better (but not statistically significantly better)

with gFOBT (37.8% vs 29.3%; odds ratio [OR] 1.43 [95% CI 0.73–2.80]; P ¼ 0.227). Authors themselves tried to give an explanation of their out of line results. Their design was indeed much more demanding for the FIT arm than for the gFOBT one although the latter provided the usual dietary restrictions. The Fit arm had indeed to take three samples, keeping them in the refrigerator and bring the samples back using cooling bags. This more demanding procedure was related to the hot climate in Israel that could degraded samples taken with FIT. Anyways Kit return was higher in the FIT arm (65.0% vs. 78.9%; OR 0.45 [95% CI 0.24–0.83], P ¼ 0.021) and the overall uptake of gFOBT and FIT was comparable (OR 0.996 [95% CI 0.46–2.17], P ¼ 0.99).

In the other systematic review performed by Hassan et al. the aim was to compare the participation rates among different CRC screening options and to assess the effect of such differences on the detection rates of advanced neoplasia. Indeed authors themselves highlights that the effectiveness of a screening depends not only on the sensitivity for colorectal neoplasia but also on population attendance. Thus the impact of adherence and compliance on the effectiveness of a screening strategy is paramount and a low participation diminish the efficacy of a CRC screening as a whole.

Their study specifically aimed to address two questions. The first is related to our topic, as authors aim at understanding if, when equally offered to a screening population, the screening tests differ with regard to adherence to the CRC screening. To answer this question, Hassan et al. meta-analysed 5 studies (see fig. 2) about attendance rate with g-FOBT vs. FIT. Final results showed that FIT resulted in a higher uptake compared with g-FOBT (RR: 1.16; 95% CI: 1.03, 1.3). Authors highlight that inter-study heterogeneity (I2) was 96% and that such heterogeneity appeared to be related only to one series (the already mentioned Levi et al study). The exclusion of Levi's was shown to result in a I2 equal to 0%. The detection rate for advanced neoplasia and cancer with FIT was also superior to g-FOBT at both PP (RR: 1.94, 95% CI: 1.37, 2.76, I2: 56%; RR: 1.67, 95% CI: 1.01, 2.8, I2: 0%) and ITT analyses (RR: 2.28, 95% CI: 1.68, 3.10, I2: 43%; RR: 1.96, 95% CI: 1.2, 3.2, I2: 0%).

Fig.2

Forest Plot by Hassan et al. meta-analysis (Hassan et al. 2012, p.935)

Federici et al. (2005) conducted a cluster-randomized trial to evaluate the effect of the type of test (gFOBT vs FIT) on screening compliance. The principal outcome was the percentage of returned tests. A sample og 130 general practitioners who consented to participate in the trial was selected. A sample of GP's patients 50 –75-year-old were then randomly divided into 2 groups: one to be screened at the GP's office and the other to the nearest gastroenterology ward. The FIT test had a compliance of 35.8% and the guaiac of 30.4% (relative risk [RR] 1.20; 95% confidence interval [CI] 1.02–1.44). The difference was mostly due to a higher probability of returning the sample: 93.8% and 88.6% for immunochemical and guaiac, respectively (RR 1.06; 95% CI 1.02–1.10). Authors stated that compliance is more likely with FIT than gFOBT, and this difference is independent of the provider.

In the study by Hughes et al. (2005) conducted in a small, rural community of the north Queensland (USA), overall, 1,219 kits were completed and returned for analysis. Participation was significantly higher with the immunochemical kit ($\chi 2$=20.7, p<0.00). In accordance with bivariate results, persons receiving an immunochemical kit were approximately twice as likely to participate than those receiving a guaiac kit.

The Dutch population-based randomised screening trial described by Hol L., Van Leerdam ME - 2010 involved a random sample of the Dutch population aged 50–74 years that was asked to participate in a randomised screening trial. Of the 15 011 subjects who were randomised prior to invitation to one of the three tests 670 were excluded from analysis (4.5%; 608 subjects met one of the exclusion criteria, 43 had moved away and 19 had died). The overall participation rate was 48.0% (CI, 47.1 to 48.7%). In total, 49.5% (CI, 48.1% to 50.9%) attended gFOBT, 61.5% (CI, 60.1% to 62.9%) FIT and 32.4% (CI, 31.1% to 33.7%) FS screening. This demonstrated a 12% higher participation rate to FIT than gFOBT screening.

In the study by Hol. L., V. de Jonge et al. 2010, authors describe results of the survey about the "perceived burden" of FIT, gFOBT and FS, which was undertaken involving the same cohort of people of Hol L., Van Leerdam ME (2010) and Hol L.(2009)..Durimg the Dutch population-based randomised screening trial (described by Hol L., Van Leerdam ME - 2010) a further random sample of screenees (481 gFOBT participants, 659 FIT participants and 1124 FS participants) was asked to participate in the questionnaire study on acceptance and burden of the screening test they underwent. Patients who used gFOBT and FIT were asked to complete a single questionnaire 1 week after the test was received at the laboratory, but before the screened received the test result. Embarrassment and discomfort resulting were measured by three separate items that were adapted from earlier studies and related to three stages of the procedure (collecting faeces, performance of the test and returning the test to the laboratory), each with three response options (not, quite or very embarrassing/unpleasant).

For the "Embarrassment, discomfort, and pain" issue, respondents rated "overall embarrassment" during gFOBT and FIT equally (0.07 versus 0.06; p = 0.30). A larger proportion of gFOBT than FIT screenees described the test as "uncomfortable" (0.15 versus 0.11; p = 0.02) due to more discomfort while collecting faeces and performing the test. For "Overall acceptance" significantly less FIT than gFOBT described the test as burdensome(p = 0.05), whereas FS was more often reported to be burdensome than gFOBT (p < 0.001) and FIT (p < 0.001). According to authors, FIT slightly outperforms gFOBT with a lower level of reported discomfort and overall burden.

Importance: Unspecified

Transferability: Unspecified

Discussion

The two systematic reviews, both published in 2012 (Vart et al. 2012 and Hassan et al. 2012) found that overall participation rate/rate of adherence resulting from their meta-analysis is significantly higher with FIT than with g-FOBT. Hassan et al. included two more studies (Cole et al 2003 and Hughes et al. 2005), this may be due to different search strategy, but this does not change final result.

Both studies' authors highlight that inter-study heterogeneity in their meta-analysis is higher, but is related only to one included study, Levi et al (2011). The exclusion of Levi et al resulted in a reduction in the I2 e from 96% to to 0% (Hassan et al.2012). Result of the Israeli population based study show that contextual socio-cultural and/or geographical variables might affect compliance.

Reasons for FIT outperforming gFOBT (or the opposite, in the case of Isreali studies) in compliance rate needs to be better investigated via qualitative studies and quantitative designs that confirm any interpretative hypothesis. For the moment all we found in the literature are conjectures and authors' opinions. Socio-demographical and ethnicity variables seem to have a part in affecting compliance with one test or another, but more research seem to be needed to confirm this.

In some cases, such as socio economic status, studies give, , conflicting results. In the Australian study by Cole et al, socioeconomic status showed not to be a confounding factor, while in Birkenfeld this association was verified. More evidence is also needed to evaluate the importance of age as studies gave inconsistent result, both in term of overall compliance to screening and in terms of compliance broken down by age groups when comparing FIT and gFOBT. On the other side, as regard to gender, results of quite all studies that focused on this variable (Hughes, 2005; Hol, van Leerdam M.E 201; Birkenfeld 2011) showed that female gender were independent predictors of increased attendance/compliance in both arms. The study by Hughes et al. 2005, which is about the "intention to participate" (scenarios) seem to show differences among different ethnic group in preferring FIT versus gFOBT and other CRC screening methods, but yet this association should need further evidence.

References

Birkenfeld, S., et al. (2011). "Factors affecting compliance in faecal occult blood testing: a cluster randomized study of the faecal immunochemical test versus the guaiac faecal occult test." J Med Screen 18(3): 135-141.

Cole, S. R., et al. (2003). "A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer." J Med Screen 10(3): 117-122.

Federici, A., et al. (2005). "The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial." J Med Screen 12(2): 83-88.

Hassan, C., et al. (2012). "Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test." Aliment Pharmacol Ther 36(10): 929-940.

Hawley, S. T., et al. (2008). "Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients." Med Care 46(9 Suppl 1): S10-16.

Hol, L., et al. (2010). "Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy." Eur J Cancer 46(11): 2059-2066.

Hol, L., et al. (2010). "Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy." Gut 59(1): 62-68.

Hughes, K., et al. (2005). "Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community." Aust N Z J Public Health 29(4): 358-364.

Levi, Z., et al. (2011). "A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study." Int J Cancer 128(10): 2415-244.

Vernon, S.W. Participation in Colorectal Cancer Screening: a review , Journal of the National Cancer Institute , Vol. 89, No. 19, 1997.

Appendices

Domain appendices

APPENDIX 1

SERACH STRATEGY

SOC domain: compliance, acceptability, satisfaction

MEDLINE

Colorectal neoplasms (MESH term)	OR	(Colorect* OR Colon * OR rect* or anal* or anus* OR intestin* or bowel*)	AND	Test* (All Fiedls)
All terms				OR
Neoplasms, Colorectal		AND		Screening*(All Fields)
Colorectal Neoplasm				
Neoplasm, Colorectal		(carcinoma* OR neoplasm* OR adenocarcinom* OR cancer* OR tumor* OR sarcom* OR polyp* OR adenoma* OR neoplasia)		
Colorectal Tumors				
Colorectal Tumor				
Tumor, Colorectal				
Tumors, Colorectal				
Colorectal Carcinoma				
Carcinoma, Colorectal				
Carcinomas, Colorectal				
Colorectal Carcinomas				

Colorectal Cancer Cancer, Colorectal Cancers, Colorectal Colorectal Cancers								

AND

"Faecal immunochemical test*"	Or	Fit	OR	(immunohistochem* or immunochem* or immunol*) AND (fecal immunochemical test* or faecal immunochemical test* or fecal immunochemistry test* or faecal immunochemistrytest* Or "Screening test*" Or "occult blood test*"	OR	ColoScreen* Or Hema-Screen* or Hemdetect* or Hemoccult* or SENSA* or Hema-Check* or hemoCARE*or Peroheme* or ColoCare* or Lifeguard* or Fecatwin* or HemaW ipe* Or Instaccult* or Monohaem* or Okokit* or Seracult* or Dencoccult* or ColoRectal* or Early detector* Or Fe Cult* or Feca EI A* or Hemo FEC* or Hexagon* or SureScreen* or Hemaprompt* or Hemdetect* or Camco PAK* or Colocheck* or Cecogenics* or Hemates t* or Dencocult* or Fecatest* or Hemofecia* or Quick-CULT* 2 OR "OC-sensor test*" OR "Insure fit" OR "HemeSelect", "FlexSure OBT, and "OC-Sensor Micro FIT*"		

AND

compliance OR adherence OR acceptance OR acceptability OR participation OR preference OR preferences OR invitation OR 'perception OR perceptions OR Non-Adherence OR attitude* OR Satisfaction	OR	Patient compliance MESH term	

Adults, ENGLISH, All fields, Article, e review

EMBASE

Colorectal Carcinoma (EMTREE TERM) OR "Colorectal Carcinoma".exp	OR	(Colorect* OR Colon * OR rect* or anal* or anus* OR intestin* or bowel*) .exp AND (carcinoma* OR neoplasm* OR adenocarcinom* OR cancer* OR tumor* OR sarcom* OR polyp* OR adenoma* OR neoplasia).exp	AND	Test* (Exp) OR Screening*(Exp)	

AND

"Faecal immunochemical test*"	Or	Fit	OR	(immunohistochem* or immunochem* or immunol*).exp AND ((fecal immunochemical test* or faecal immunochemical test* or fecal immunochemistry test* or faecal immunochemistrytest*).exp Or "Screening test*" Or "occult blood test*")	OR	ColoScreen* Or Hema-Screen* or Hemdetect* or Hemoccult* or SENSA* or Hema-Check* or hemoCARE*or Peroheme* or ColoCare* or Lifeguard* or Fecatwin* or HemaW ipe* Or Instaccult* or Monohaem* or Okokit* or Seracult* or Dencoccult* or ColoRectal* or Early detector* Or Fe Cult* or Feca EI A* or Hemo FEC* or Hexagon* or SureScreen* or Hemaprompt* or Hemdetect* or Camco PAK* or Colocheck* or Cecogenics* or Hemates t* or Dencocult* or Fecatest* or Hemofecia* or Quick-CULT* 2 OR "OC-sensor test*" OR "Insure fit" OR "HemeSelect", "FlexSure OBT, and "OC-Sensor Micro FIT*"		

AND

compliance OR adherence OR acceptance OR acceptability OR participation OR preference OR preferences OR invitation OR 'perception OR perceptions OR satisfaction OR Non-Adherence	OR	Patient compliance EMTREE term OR Patient attitude EMTREE

("article" OR "review" OR "short survey") Limits: Humans

Cochrane Library: CDSR, DARE, HTA database, CENTRAL search strategy

Colorectal neoplasms (MESH term) All terms	OR	(Colorect* OR Colon * OR rect* or anal* or anus* OR intestin* or bowel*) ti,ab,kw AND (carcinoma* OR neoplasm* OR adenocarcinom* OR cancer* OR tumor* OR sarcom* OR polyp* OR adenoma* OR neoplasia). ti,ab,kw	AND	Test* ti,ab,kw OR Screening* ti,ab,kw

AND

"Faecal immunochemical test*".ti,ab,kw	Or	Fit	OR	(immunohistochem* or immunochem* or immunol*).ti,ab,kw AND (fecal immunochemical test* or faecal immunochemical test* or fecal immunochemistry test* or faecal immunochemistrytest*).ti,ab,kw Or "Screening test*".ti,ab,kw Or "occult blood test*".ti,ab,kw	OR	(ColoScreen* Or Hema-Screen* or Hemdetect* or Hemoccult* or SENSA* or Hema-Check* or hemoCARE*or Peroheme* or ColoCare* or Lifeguard* or Fecatwin* or HemaW ipe* Or Instaccult* or Monohaem* or Okokit* or Seracult* or Dencoccult* or ColoRectal* or Early detector* Or Fe Cult* or Feca EI A* or Hemo FEC* or Hexagon* or SureScreen* or Hemaprompt* or Hemdetect* or Camco PAK* or Colocheck* or Cecogenics* or Hemates t* or Dencocult* or Fecatest* or Hemofecia* or Quick-CULT* 2 OR "OC-sensor test*" OR "Insure fit" OR "HemeSelect", "FlexSure OBT, and "OC-Sensor Micro FIT*").ti,ab,kw

AND

compliance OR adherence OR acceptance OR acceptability OR participation OR preference OR preferences OR invitation OR 'perception OR perceptions OR Non-Adherence OR Attitude OR attitudes OR satisfaction

("article" OR "review" OR "short survey") Limits: Humans

Other consulted databases (free terms research)

DARE all databases; Agency for Healthcare Research and Quality (AHRQ); Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP-S) , Health Canada; International Network of Agencies for Health Technology Assessment (INAHTA); Medical Services Advisory Committee (MSAC); National Coordinating Centre for Health Technology Assessment (NCCHTA); National Horizon Scanning Centre; National Institute for Health and Clinical Excellence (NICE); NHS Quality Improvement Scotland (NHS QIS); Clinicaltrials.gov, Cancer.gov, Trip Database.

APPENDIX 2

List of included and excluded studies and reasons for exclusions due to the inclusion-exclusion criteria

Reference fit compliance	Target population (adults_19-64 years and elderly _65+ years; male and female. Healthy and/or asymptomatic people),	It is about FIT or/and gFOBT	Measure/deal with outcomes that are related to the social domain (e.g. compliance with one test or the other, capacity to understand information on the two tests, etc.)	Type of study: quantitative studies_experimental or observational AND qualitative studies
1. Akram, S., et al. (2012). "Yield of fecal immunochemical test in detection of colorectal cancer and advanced neoplasia in veteran population at dayton va medical center." Am. J.			NO	

Gastroenterol. 107: S810.				
2. Aschele, C., et al. (2009). "Chemotherapy for operable and advanced colorectal cancer." Cancer Treat Rev 35(6): 509-516.	NO			
3. Bampton, P. A., et al. (2005). "Interval faecal occult blood testing in a colonoscopy based screening programme detects additional pathology." Gut 54(6): 803-806.	NO			
4. Bhattacharya, R., et al. (2010). "Comparison of advanced noninvasive techniques to screen colorectal cancer: Fecal immunochemical test vs. fecal DNA; A cos-effectiveness study." Value Health 13(7): A265.		NO		
5. Birkenfeld, S., et al. (2011). "Factors affecting compliance in faecal occult blood testing: a cluster randomized study of the faecal immunochemical test versus the guaiac faecal occult test." J Med Screen 18(3): 135-141.				
6. Boemo, C., et al. (2012). "Short-term outcomes and cost evaluation of the first two rounds of a colorectal cancer screening programme based on immunochemical faecal occult blood test in a northern italian province." Endoscopy 44(4): 441.		NO		
7. Browne, S., et al. (2011). "Patients' needs following colorectal cancer diagnosis: where does primary care fit in?" Br J Gen Pract 61(592): e692-699.	NO			
8. Byers, T. (2011). "Examining stools for colon cancer prevention: what are we really looking for?" Cancer Prev Res (Phila) 4(10): 1531-1533.				NO
9. Calvet, X., et al. (2002). "Evaluation of Helicobacter pylori diagnostic methods in patients with liver cirrhosis." Aliment Pharmacol Ther 16(7): 1283-1289.	NO			
10. Castiglione, G., et al. (1996). "Immunochemical vs guaiac faecal occult blood tests in a population-based screening programme for colorectal cancer." Br J Cancer 74(1): 141-144.			NO	
11. Cavallaro, L. G., et al. (2011). "Screening for colorectal cancer (CRC) from the first three rounds (2005-2011) in an Italian north-eastern district (ULSS-1) with a high adherence rate: Preliminary results." Dig. Liver Dis. 43: S185-S186.		NO		
12. Cha, J. M., et al. (2011). "Telephone reminder call in addition to mailing notification improved the acceptance rate of colonoscopy in patients with a positive fecal immunochemical test." Dig Dis Sci 56(11): 3137-3142.	NO			
13. Ching, J. Y. L., et al. (2012). "Mailing invitations for colorectal cancer (CRC) screening programme in Hong Kong: A comparison between private and public estates." J. Gastroenterol. Hepatol. 27: 200.		NO		
14. Ching, J. Y. L., et al. (2012). "Compliance with fecal immunochemical tests for colorectal cancer screening: A prospective cohort study." J. Gastroenterol. Hepatol. 27: 197.	The fulltext was not available			
15. Cole, S. R., et al. (2007). "An advance notification letter increases participation in colorectal cancer screening." J Med Screen 14(2): 73-75.		NO		
16. Cole, S. R., et al. (2009). "A faecal immunochemical test for haemoglobin using a single stool sample is effective for detecting significant colorectal neoplasia." J. Gastroenterol. Hepatol. 24: A239.			NO	
17. Cole, S. R., et al. (2003). "A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer." J Med Screen 10(3): 117-122.				
18. Crotta, S., et al. (2012). "High rate of advanced adenoma detection in 4 rounds of colorectal cancer screening with the fecal immunochemical test." Clin Gastroenterol Hepatol 10(6): 633-638.		NO		
19. Crotta, S., et al. (2012). "Interval cancers in a colorectal cancer population screening fit-based: Preliminary result of two rounds." Dig. Liver Dis. 44: S198-S199.	NO			
20. Daly, J. M., et al. (2010). "Mailed fecal-immunochemical test for colon cancer screening." J Community Health 35(3): 235-239.		NO		
21. De Haan, M. C., et al. (2012). "Does CT colonography have a role for population-based colorectal cancer screening?" Eur Radiol 22(7): 1495-1503.		NO		
22. Denis, B., et al. (2007). "Short term outcomes of the first round of a pilot colorectal cancer screening programme with guaiac based faecal occult blood test." Gut 56(11): 1579-1584.		NO		
23. Denters, M., et al. (2010). "Equal advanced neoplasia detection rates in first and second round of an fecal immunochemical test based colorectal cancer screening program." Gastroenterology 138(5): S186.			NO	
24. Denters, M., et al. (2010). "Participation rate in a second round of fecal immunochemical test based screening decreases due to low response rates among previous non-responders and first-time invitees." Gastroenterology 138(5): S186.	NO			

25. Denters, M. J., et al. (2012). "A feces collection paper does not enhance participation in a fecal immunochemical test-based colorectal cancer screening program: Randomized clinical trial." Eur.J. Cancer Prev.		NO		
26. Denters, M. J., et al. (2013). "Involvement of previous non-participants cannot fully compensate for lower participation in a second round of FIT-screening." Cancer Epidemiol.		NO		
27. Desoubeaux, N., et al. (1997). "[Mass screening of colorectal cancer by general practitioners in France: what is the real target population?]." Gastroenterol Clin Biol 21(10): 760-763.	NO			
28. Ealey, J., et al. (2011). "Patients' perspectives on immunochemical fecal occult blood test (I-FOBT or FIT): Not your father's FOBT." Cancer Epidemiol. Biomarkers Prev. 20(10).				
29. Eisinger, F., et al. (2011). "Cancer survivors: familial risk perception and management advice given to their relatives." Fam Cancer 10(1): 147-155.	NO			
30. Federici, A., et al. (2005). "The immunochemical faecal occult blood test leads to higher compliance than the guaiac for colorectal cancer screening programmes: a cluster randomized controlled trial." J Med Screen 12(2): 83-88.				
31. Fenocchi, E., et al. (2006). "Screening for colorectal cancer in Uruguay with an immunochemical faecal occult blood test." Eur J Cancer Prev 15(5): 384-390.		NO		
32. Fraser, C. G., et al. (2007). "Evaluation of a card collection-based faecal immunochemical test in screening for colorectal cancer using a two-tier reflex apprTan, Woach." Gut 56(10): 1415-1418.			NO	
33. Graser, A., et al. (2009). "Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population." Gut 58(2): 241-248.			NO	
34. Grazzini, G., et al. (2000). "Colorectal cancer screening by fecal occult blood testing: results of a population-based experience." Tumori 86(5): 384-388.			NO	
35. Greenwald, B. (2005). "A comparison of three stool tests for colorectal cancer screening." Medsurg Nurs 14(5): 292-299; quiz 300.				NO
36. Hall, M. J., et al. (2011). "Effects of a decision support intervention on decisional conflict associated with microsatellite instability testing." Cancer Epidemiol Biomarkers Prev 20(2): 249-254.		NO		
37. Harden, E., et al. (2011). "Exploring perceptions of colorectal cancer and fecal immunochemical testing among African Americans in a North Carolina community." Prev Chronic Dis 8(6): A134.	no			
38. Hassan, C., et al. (2011). "Cost effectiveness and projected national impact of colorectal cancer screening in France." Endoscopy 43(9): 780-793.			NO	
39. Hassan, C., et al. (2012). "Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test." Aliment Pharmacol Ther 36(10): 929-940.				
40. Hawley, S. T., et al. (2008). "Preferences for colorectal cancer screening among racially/ethnically diverse primary care patients." Med Care 46(9 Suppl 1): S10-16.				
41. Heitman, S. J., et al. (2010). "Colorectal cancer screening for average-risk North Americans: an economic evaluation." PLoS Med 7(11): e1000370.			NO	
42. Hillyer, G. C., et al. (2011). "Feasibility and efficacy of pairing fecal immunochemical testing with mammography for increasing colorectal cancer screening among uninsured Latinas in northern Manhattan." Prev Med 53(3): 194-198.	NO			
43. Hoffman, R. M., et al. (2010). "Colorectal cancer screening adherence is higher with fecal immunochemical tests than guaiac-based fecal occult blood tests: a randomized, controlled trial." Prev Med 50(5-6): 297-299.	NO			
44. Hol, L., et al. (2010). "Screening for colorectal cancer: comparison of perceived test burden of guaiac-based faecal occult blood test, faecal immunochemical test and flexible sigmoidoscopy." Eur J Cancer 46(11): 2059-2066.				
45. Hol, L., et al. (2012). "Uptake of faecal immunochemical test screening among nonparticipants in a flexible sigmoidoscopy screening programme." Int J Cancer 130(9): 2096-2102.	NO			
46. Hol, L., et al. (2010). "Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy." Gut 59(1): 62-68.				
47. Hol, L., et al. (2009). "Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels." Br J Cancer 100(7): 1103-			NO	

1110.				
48. Honda, K. (2004). "A model of perceived risk for colorectal cancer among Japanese Americans." J Cancer Educ 19(4): 251-257.		NO		
49. Hou, W. K. (2010). "Intrapersonal and interpersonal dimensions of cancer perception: a confirmatory factor analysis of the cancer experience and efficacy scale (CEES)." Support Care Cancer 18(5): 561-571.		NO		
50. Hughes, K., et al. (2005). "Guaiac versus immunochemical tests: faecal occult blood test screening for colorectal cancer in a rural community." Aust N Z J Public Health 29(4): 358-364.				
51. Kapidzic, A., et al. (2012). "Quality of life in participants of a CRC screening program." Br J Cancer 107(8): 1295-1301.		NO		
52. Kemeny, M. M. (2004). "Surgery in older patients." Semin Oncol 31(2): 175-184.		NO		
53. Kempe, K. L., et al. (2012). "Automated phone and mail population outreach to promote colorectal cancer screening." Am J Manag Care 18(7): 370-378.			NO	
54. Khalid-de Bakker, C., et al. (2011). "Participation in colorectal cancer screening trials after first-time invitation: a systematic review." Endoscopy 43(12): 1059-1086.		NO		
55. Klaver, Y. L., et al. (2012). "Outcomes of elderly patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal cancer peritoneal carcinomatosis." J Surg Oncol 105(2): 113-118.	NO			
56. Kluhsman, B. C., et al. (2012). "A pilot study for using fecal immunochemical testing to increase colorectal cancer screening in Appalachia, 2008-2009." Prev Chronic Dis 9: E77.		NO		
57. Ko, C. W., et al. (2003). "Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests." Am J Med 115(2): 111-114.	NO			
58. Labianca, R. and B. Merelli (2010). "Screening and diagnosis for colorectal cancer: present and future." Tumori 96(6): 889-901.				NO
59. Ladabaum, U., et al. (2011). "Screening for colorectal cancer with a blood test: Projected effectiveness and cost-effectiveness of a novel plasma methylated septin-9 DNA (mSEPT9) assay." Gastroenterology 140(5): S50-S51.				NO
60. Laiyemo, A., et al. (2012). "DC screen for life program: Taking colon cancer screening to the uninsured." Am. J. Gastroenterol. 107: S569-S570.			NO	
61. Lam, T. Y. T., et al. (2011). "Three-year follow up on a colorectal cancer screening program in Hong Kong: A prospective cohort study." J. Gastroenterol. Hepatol. 26: 6-7.		NO		
62. Lane, J. M., et al. (2010). "Can quantitative immunochemical fecal occult blood tests be used in single sample format without compromising colorectal neoplasia yield?" Gastroenterology 138(5): S184.			NO	
63. Launoy, G. (2009). "[Improvement in screening for colorectal cancer associated with the use of immunochemical faecal occult blood test]." Pathol Biol (Paris) 57(6): 488-492.				NO
64. Lee, V., et al. (2006). "Meaning-making and psychological adjustment to cancer: development of an intervention and pilot results." Oncol Nurs Forum 33(2): 291-302.		NO		
65. Levi, Z., et al. (2011). "A higher detection rate for colorectal cancer and advanced adenomatous polyp for screening with immunochemical fecal occult blood test than guaiac fecal occult blood test, despite lower compliance rate. A prospective, controlled, feasibility study." Int J Cancer 128(10): 2415-244.				
66. Levy, B. T., et al. (2012). "Mailed fecal immunochemical tests plus educational materials to improve colon cancer screening rates in Iowa Research Network (IRENE) practices." J Am Board Fam Med 25(1): 73-82.			NO	
67. Li, C. M., et al. (2007). "Factors associated with referral compliance of abnormal immunochemical faecal occult blood test." J Med Screen 14(4): 186-190.	NO			
68. Manne, S., et al. (2003). "Understanding intention to undergo colonoscopy among intermediate-risk siblings of colorectal cancer patients: a test of a mediational model." Prev Med 36(1): 71-84.		NO		
69. Mantyh, C. R., et al. (2001). "Coloplasty in low colorectal anastomosis: manometric and functional comparison with straight and colonic J-pouch anastomosis." Dis Colon Rectum 44(1): 37-42.		NO		
70. Masya, L. M., et al. (2009). "Preferences for outcomes of treatment for rectal cancer: patient and clinician utilities and their application in an interactive computer-based decision aid." Dis Colon Rectum 52(12): 1994-2002.		NO		

71. McQueen, A., et al. (2008). "Construct validity and invariance of four factors associated with colorectal cancer screening across gender, race, and prior screening." Cancer Epidemiol Biomarkers Prev 17(9): 2231-2237.		NO		
72. Nadel, M. R., et al. (2010). "Fecal occult blood testing beliefs and practices of U.S. primary care physicians: serious deviations from evidence-based recommendations." J Gen Intern Med 25(8): 833-839.			NO	
73. Osborne, J. M., et al. (2012). "Patterns of participation over multiple rounds of faecal immunochemical test-based screening for colorectal cancer." J. Gastroenterol. Hepatol. 27: 27.		NO	NO	
74. Park, D. I., et al. (2010). "Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening." Am J Gastroenterol 105(9): 2017-2025.	NO			
75. Park, M. J., et al. (2011). "Trends in the National Cancer Screening Program for colorectal cancer in the Republic of Korea, 2004-2009." Asian Pac J Cancer Prev 12(12): 3489-3493.		NO		
76. Potter, M. B., et al. (2010). "Comparative effectiveness of two pharmacy-based colorectal cancer screening interventions during an annual influenza vaccination campaign." J Am Pharm Assoc (2003) 50(2): 181-187.	NO			
77. Quintero, E., et al. (2012). "Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening." N Engl J Med 366(8): 697-706.		NO		
78. Rabeneck, L., et al. (2012). "Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening." Can J Gastroenterol 26(3): 131-147.				
79. Rao, R. S., et al. (2004). "Understanding the factors underlying disparities in cancer screening rates using the Peters-Belson approach: results from the 1998 National Health Interview Survey." Med Care 42(8): 789-800.			NO	
80. Ritvo, P., et al. (2008). "Factorial validity and invariance of a survey measuring psychosocial correlates of colorectal cancer screening in Ontario, Canada--a replication study." Cancer Epidemiol Biomarkers Prev 17(11): 3279-3283.		NO		
81. Roslani, A. C., et al. (2012). "Screening for colorectal neoplasias with fecal occult blood tests: false-positive impact of non-dietary restriction." Asian Pac J Cancer Prev 13(1): 237-241.			NO	
82. Rozen, P. et al. (2000). "Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study." Cancer 89(1): 46-52.		NO		
83. Rustagi, T. and V. R. Konjeti (2012). "Survey of primary care residents to assess awareness of updated 2008 ACG guidelines for colorectal cancer screening." Am. J. Gastroenterol. 107: S809.				NO
84. Sastre, J., et al. (2011). "First-line single-agent cetuximab in elderly patients with metastatic colorectal cancer. A phase II clinical and molecular study of the Spanish group for digestive tumor therapy (TTD)." Crit Rev Oncol Hematol 77(1): 78-84.		NO		
85. Schiff, L., et al. (2009). "Development of serum tests for colorectal cancer screening." Value Health 12(7): A257.			NO	
86. Segnan, N., et al. (2007). "Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening." Gastroenterology 132(7): 2304-2312.		NO		
87. Senore, C., et al. (2010). "The added value of immunochemical FOBT following a negative screening sigmoidoscopy." Gastroenterology 138(5): S186-S187.	NO			
88. Senore, C., et al. (2012). "Offering people a choice for colorectal cancer screening." Gut.	NO			
89. Senore, C., et al. (2011). "Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting." J Med Screen 18(3): 128-134.		NO		
90. Senore, C., et al. (2009). "Comparing diagnostic yield and interval cancer rates of different strategies of colorectal cancer screening." Gastroenterology 136(5): A53.			NO	
91. Sharaf, R. N. and U. Ladabaum (2013). "Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies." Am J Gastroenterol 108(1): 120-132.			NO	
92. Shuhaibar, M., et al. (2011). "A comparative study of faecal occult blood kits in a colorectal cancer screening program in a cohort of healthy construction workers." Ir J Med Sci 180(1): 103-108.	NO			
93. Simonds, V. W., et al. (2011). "Cancer screening among Native Americans in California." Ethn Dis 21(2): 202-209.		NO		
94. SR, C., et al. "An advance notification letter increases participation in colorectal cancer screening." Journal of medical screening.		NO		

95. SR, C., et al. "A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer." Journal of medical screening.				
96. Stare, J., et al. (2005). "Goodness of fit of relative survival models." Stat Med 24(24): 3911-3925.		NO		
97. Stegeman, I., et al. (2012). "Implementation of population screening for colorectal cancer by repeated Fecal Immunochemical Test (FIT): Third round." BMC Gastroenterol. 12.	NO			
98. Sule, A. Z., et al. (2007). "One stage procedure in the management of acute sigmoid volvulus without colonic lavage." Surgeon 5(5): 268-270.		NO		
99. Sung, J. J., et al. (2011). "Three years follow-up on a colorectal cancer screening program: A prospective cohort of 4,961 asymptomatic subjects." Gastroenterology 140(5): S182-S183.		NO		
100. Svensson, E., et al. (2006). "Frailty modelling of colorectal cancer incidence in Norway: indications that individual heterogeneity in risk is related to birth cohort." Eur J Epidemiol 21(8): 587-593.		NO		
101.Tan, W. S., et al. (2012). "Opportunistic screening for colorectal neoplasia in singapore using an immunochemical faecal occult blood test (FIT) by the Singapore Cancer Society." Colorectal Dis. 14: 3.		NO		
102.Terhaar sive Droste, J. S., et al. (2011). "Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers." Cancer Epidemiol Biomarkers Prev 20(2): 272-280.			NO	
103.Tiro, J. A., et al. (2005). "Factorial validity and invariance of a survey measuring psychosocial correlates of colorectal cancer screening among African Americans and Caucasians." Cancer Epidemiol Biomarkers Prev 14(12): 2855-2861.		NO		
104.Van Dam, L., et al. (2010). "Comparing participants and non-participants of a randomized colorectal cancer screening program using guaiac-based and immunochemical fecal occult blood test and flexible sigmoidoscopy." Gastroenterology 138(5): S191.		NO		
105.Van Dam, L., et al. (2010). "Experiences of general practitioners regarding their role in the referral process for colonoscopy after a positive colorectal cancer screening test." Gastroenterology 138(5): S191.	NO			
106.VanDam, L., et al. (2010). "Comparison of participants and non-participants in a flexible sigmoidoscopy screening program, with an alternative invitation for fecal immunochemical testing." Gastroenterology 138(5): S351.		NO		
107.Van Roon, A. H., et al. (2011). "Attendance and diagnostic yield of repeated fecal immunochemical test screening with intervals of 1, 2, or 3 years: A comparative population-based colorectal cancer screening trial." Gastroenterology 140(5): S405.		NO		
108.Van Roon, A. H., et al. (2010). "Fecal immunochemical test (FIT) characteristics by sample return time in a population-based colorectal cancer screening trial." Gastroenterology 138(5): S133.			NO	
109.Van Roon, A. H., et al. (2010). "Attendance and diagnostic yield of one versus two-sample fecal immunochemical test (FIT) screening; a comparative population-based colorectal cancer trial." Gastroenterology 138(5): S134.			NO	
110.Van Roon, A. H. C., et al. (2013). "Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening." Gut 62(3): 409-415.			NO	
111.Van Roosbroeck, S., et al. (2012). "Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies." Cancer Epidemiol 36(5): e317-324.		NO		
112. Van Rossum, L. G., et al. (2009). "Cutoff value determines the performance of a semi-quantitative immunochemical faecal occult blood test in a colorectal cancer screening programme." Br J Cancer 101(8): 1274-1281.			NO	
113. Van Rossum, L. G., et al. (2008). "Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population." Gastroenterology 135(1): 82-90.			NO	
114. Van Turenhout, S. T., et al. (2012). "Anticipating implementation of colorectal cancer screening in The Netherlands: a nation wide survey on endoscopic supply and demand." BMC Cancer 12: 46.			NO	
115. Vanness, D. J., et al. (2011). "Comparative economic evaluation of data from the ACRIN National CT Colonography Trial with three cancer intervention and surveillance modeling network microsimulations." Radiology 261(2): 487-498.		NO		
116. Vart, G., et al. (2012). "Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis." Prev Med 55(2): 87-92.				

117.Watts, B. G., et al. (2003). "Intention to be screened over time for colorectal cancer in male automotive workers." Cancer Epidemiol Biomarkers Prev 12(4): 339-349.	NO			
118.Weiss, J. M. and P. R. Pfau (2012). "New era for stool screening tests: Fecal immunochemical tests, DNA, and beyond." Curr. Colorectal Cancer Rep. 8(1): 1-5.				NO
119.Williams, J. A., et al. (1987). "Evaluation of an immunochemical test for faecal occult blood in screening for colorectal neoplasia in a high risk group." Aust N Z J Surg 57(12): 951-957.	NO			
120.Wilschut, J., et al. (2010). "Quantitative immunochemical fecal occult blood screening under a colonoscopy constraint: A Higher cut-off level, a smaller age range or a longer screening interval? A cost-effectiveness analysis." Gastroenterology 138(5): S183.			NO	
121.Wilschut, J., et al. (2010). "Should we offer individuals two samples of a fecal immunochemical test for colorectal cancer screening instead of one? A cost-effectiveness analyis." Gastroenterology 138(5): S183-S184.			NO	
122.Wong, C. K., et al. (2011). "Efficacy of a single day fecal immunochemical occult blood testing (FIT) collection strategy for screening relevant colorectal neoplasias." Gastroenterology 140(5): S410.			NO	
123.Wong, C. K. W., et al. (2012). "The sensitivity and specificity of guaiac and immunochemical fecal occult blood tests for the detection of advanced colonic adenomas and cancer." Int. J. Colorectal Dis. 27(12): 1657-1664.			NO	
124. Wong, M. C., et al. (2012). "Changes in the choice of colorectal cancer screening tests in primary care settings from 7,845 prospectively collected surveys." Cancer Causes Control 23(9): 1541-1548.		NO		
126. Wong, M. C. S., et al. (2010). "A comparison of the acceptance of immunochemical faecal occult blood test and colonoscopy in colorectal cancer screening: A prospective study among Chinese." Aliment. Pharmacol. Ther. 32(1): 74-82.		NO		
127.Young, C. W., et al. (1988). "Phase I trial and clinical pharmacological evaluation of hexamethylene bisacetamide administration by ten-day continuous intravenous infusion at twenty-eight-day intervals." Cancer Res 48(24 Pt 1): 7304-7309.		NO		
128.Young, G. P. (2009). "Population-based screening for colorectal cancer: Australian research and implementation." J Gastroenterol Hepatol 24 Suppl 3: S33-42.				NO
129.Young, G. P. (2012). "New Developments in Screening for Colorectal Cancer: Report on the World Endoscopy Organization Workshop Chicago, May 2011." Pract. Gastroenterol. 36(12): 32-36.				NO
130.Young, G. P. and S. Cole (2007). "New stool screening tests for colorectal cancer." Digestion 76(1): 26-33.				NO
131.Young, G. P. and S. R. Cole (2009). "Which fecal occult blood test is best to screen for colorectal cancer?" Nat. Clin. Pract. Gastroenterol. Hepatol. 6(3): 140-141.				NO
132.Young, G. P., et al. (2003). "Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin." J Med Screen 10(3): 123-128.		NO		
133.Zajac, I. T., et al. (2010). "Endorsement by the primary care practitioner consistently improves participation in screening for colorectal cancer: a longitudinal analysis." J Med Screen 17(1): 19-24.		NO		

APPENDIX 3

published	2011	2003	2005	2012	2008	2010	2010	2005	2010	2012
period study conducted	unclear	April-August 2001	June 2002	studies from 1999-2012	not found	November 2006 to May 2008	between November 2006 and November 2007	The initial mail-out was conducted in November 2000.	2008	2000-2011
country(ies) of study	Israel	Australia	Italy, Lazio region	Italy	USA	NL	NL	Australien, Queensland	Israel	Australia, Italy, Netherlands, USA, Israel
n of studies included (systematic review)	primary study	primary study	primary study	14 in the meta-analysis, 7 double with our search results (Segnan, Ferderici, van Rossum 2008, Hoffmann, Hol 2010 (RCT comparing…), Levi, Quintero 2012	primary study	primary study	primary study	primary study	primary study	7 (6 are also included in our search)
sponsoring	Eiken Japan provided the OC-MICROTM instrument, reagents and partial financial support for administration.	Hemoccult SENSA and FlexSure OBT cards were purchased from Beckman Coulter Inc. (Palo Alto CA, USA). Enterix Inc. (Portland ME, USA) provided InSure test kits. Grants from Bushell Foundation and Enterix Inc. provided part support for salaries (SC, BC).	n.a.	partially funded by the Italy Ministry of Health, through a project coordinated by the Agenzia Nazionale per i Servizi Sanitari and conducted by Laziosanità: 'Strumenti e metodi per il governo dei processi di innovazione tecnologica, clinica ed organizzativa nel SSN – Un sistema integrato di ricerca', sub-project 'Analysis of the impact of professional involvement in evidence generation for the HTA process' grant no. I85J07000080001.	unclear	This trial was funded by the Dutch Cancer Society (EMCR 2006-3673), and the Dutch Ministry of Health, Health Care Prevention Program–Implementation (ZonMw 2006-5877).	This trial was funded by the Dutch Cancer Society (EMCR 2006-3673), the Dutch Ministry of Health, Health Care Prevention Program–Implementation (ZonMw 2006-5877), Olympus Medical Systems Europe GmbH, Hamburg, Germany and Eiken Chemical Co., Tokyo, Japan.	This research was funded by Queensland Health. In addition, funding was subsidised by Enterix (Inc), which made the !nform FOBT kit and its analysis available at a highly discounted rate, and the pathology laboratory at Townsville General Hospital, which provided analysis of Hemoccult-II kits at a greatly reduced fee.	Eiken Japan provided the OC-MICROTM instrument, reagents and partial financial support for administration.	This research was funded via studentship provided by The Guildford Tumour Screening (G.U.T.S) charity for part fulfilment of the degree PhD Health Psychology at the University of Surrey
Quantitative-Experimental	Quantitative-Experimental/ RCT	Quantitative-Experimental/ RCT	Quantitative-Experimental/ RCT	meta-analysis	Quantitative-Observational	Quantitative-Experimental/ RCT	Quantitative-Experimental/ RCT	Quantitative-Experimental/ RCT	Quantitative-Experimental/ RCT	systematic review
Trial registration number (for RCTs only)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Methods	target population and the primary area clinics were clustered according to socioeconomic status (SES). into three SES classes (high, medium, low) using software based on postal code and estimated income. Clinics were then randomly allocated into either the FIT or gFOBT arm.	randomly selected from the electoral roll of the Australian Electoral Commission	13 selected hospitals to accurately represent gastroenterology units and geographic areas. All GPs (more than 100 patients in the target population (age 50–74) included in the survey	Relevant publications were identified by MEDLINE/EMBASE and other databases for the period 1999–2012. A previous systematic review was used for the period before 1966–1999. RCTs and controlled studies including a direct comparison of the uptake rates among different options for CRC screening were included.	Purposive sampling from waiting areas of 3 community health centres. Patients aged 50-80 recruited. They were asked to rate 8 hypothetical CRC screening tests scenarios	A representative sample of the Dutch population (aged 50–74 years) was randomised to be invited for gFOBT, FIT and FS screening. participants were asked to complete a questionnaire in the waiting area of the endoscopy unit	From a representative sample of the Dutch population aged 50–74 years, a random sample of 15 011 individuals was taken by computer generated algorithm and 1:1:1 randomised	The two groups were randomly allocated to kit type by flipping a coin. Patients from the largest and smallest practices received the immunochemical kit, and patients from the other two practices received the guaiac test..	Nine medium-sized primary care clinics (1,000–2,000 patients) were included, three clinics from each SES.	search in Pubmed and Cochrane Db, includion of RCTs comparing FIT versus gFOBT, exclusion of studies comparing with invasive methods,
Outcomes measured	Primary outcomes 1) To compare the 'kit compliance' 2) To compare the compliance for 'kit return' 3) To compare the overall compliance for test uptake Secondary outcome	Primary outcomes 1) Participation rate Secondary outcome 1) demographic variables' impact on participation	Primary outcomes 1) percentage of compliance	Primary outcomes 1) Adherence 2) detection rates for advanced neoplasia and cancer	Primary outcomes 1) screening preferences 2) variation in crc among racially ethnically diverse primary care patients	Primary outcomes 1) To assess differences in perceived burden and willingness to return for a second screening	Primary outcomes 1) participation rate to each of the three screening strategies	Primary outcomes 1) screening participation in a rural community, comparing guaiac and immunochemical tests	Primary outcomes 1) to compare FIT with G-FOBT in screening 2) to assess the feasibility of this approach in the urban population in	Primary outcomes 1) to compare participation rates of gFOBT and FIT Secondary outome

	1) to assess the effect of the sociodemographic factors on the compliance for test uptake.					round among participants			Israel, with special relation to different socioeconomic classes	2 to assess which characteristics of the test acted as barriers or facilitators to participation
participants	Eligible participants aged 50–74 years were linked to the nine selected primary care clinics. Patients who had an established CRC or inflammatory bowel disease were excluded.	A pool of 4000 potential invitees	CRC screening target population (i.e. people aged 50–74) is 1.5 million	Population sample	75 participants per racial/ethnic group	In total 402/481 (84%) gFOBT and 530/659 (80%) FIT screenees returned their questionnaire	Population sample	A rural Queensland community was selected, with a population of approximately 15,000 people (approximately 4,200 were aged 50 years or older)	A total of 12,539 patients were included in the study: 4,657 patients of Group A had FIT and 7,880 patients of Group B had G-FOBT.	The cohorts invited ranged from 1818 (Cole 2003) to 20623 (van Rossum 2008).
n of participants	16132 [10668 (gFOBT) + 5464 (FIT)]	1818 (3 groups of each 606)	n =7320	197910; Five studies compared g-FOBT with FIT, including 59 729 randomised subjects	220	852	15011	3358; Of the 3,861 individuals contacted by the study, 503 (13.0%) received both immunochemical and guaiac kits.	12,539 (4,657 FIT; 7,880 G-FOBT)	the cohorts invited ranged from 1818 (Cole 2003) to 20623 (van Rossum 2008).
age range	60-74	50-69	50-74	50-74 (4x), 50-75 (4x); 55-64 (3x); 50-54/65-69 (1x); 50-80 (1x); 50-69 (1x)	50-80 (mean 59)	50–74	50-74	50-74	mean age FIT: 60.4, mean age FOBT 61.3	50+
gender proportion m to f	43,1% male; 56,9% female	49,5% male, 50,5% female (own calculation of table 1)	Guaiac 46.9% men FIT 45.8% men	male 49.5%; female 50.5% (own calculation of all studies included in the meta analysis)	not specified. Analysis was controlled by age and gender for all groups	45.3% male (FOBT), 50.6% male (FIT), 50.7% (FS)	participation OR for Women 1.1 (0.9 to 1.4) (FOBT) 1.3 (1.1 to 1.4)(FIT) 0.9 (0.8 to 1.0)(FS)	51.2% female	45.4% male for FIT, 42.6% male for FOBT	n.a.
health status	screening population	screening population	screening population	screening population	screening population	screening population	screening population	screening population	screening population	screening population
ethnic minority	10,8% immigrants	Exposure of this population to screening was low by US standards and prior participation in screening had been less than 20%.	no	n.a.	74 white, 60 Africans, 78 Hispanic	5% non Cuacasian	n.a.	no	n.a.	n.a.
specific population group (i.e. economic situation, uninsured, speicif workers,…)	34% high SES, 36,6% medium SES, 29,4% low SES		no	n.a.	racically and ethnically diverse	no	n.a.	no	SES controlled	n.a.
Setting (e.g. population screening program – rounds - opportunistic screening etc.)	primary care clinic registrees, setting population-based like	Typical urban setting that is relatively naïve to the value and practice of screening	population screening	population screening	population screening	population screening	population screening	population screening	population screening	population based program setting
intervention	FIT	FIT	FIT	FIT/gFOBT/endoscopy	all possible screening tests	FIT	FIT	FIT	FIT	FIT
comparator	gFOBT	gFOBT	gFOBT	FIT/gFOBT/endoscopy	using white people as referrence for the regression model	FOBT, FS	FOBT, FS	FOBT, FS	FOBT	gFOBT

APPENDIX 4 Quality Assessment of selected primary studies - QUORUM – 2

			5. Birkenfeld, S., et al. (2011).	17. Cole, S. R., et al. (2003).	30. Federici, A., et al. (2005).	40. Hawley, S. T., et al. (2008).	44. Hol, L., et al. (2010).	46. Hol, L., et al. (2010). 59(1): 62-68.	50. Hughes, K., et al. (2005).	65. Levi, Z., et al. (2011).	116. Vart, G., et al. (2012).
	Internal validity	Select: + , - , ? or NR "Not relevant or of minor relevance in this study"									
		Add free text to explain									
Selection	Was the sequence generation adequate?	+ - ? NR	+	+	+	NR	?	+	+	+	75%+
	Was allocation concealment adequate?	+ - ? NR	NR	NR	NR	NR	NR	+	+	+	60%+
	Was a consecutive or random sample of patients enrolled? (applies to non randomized studies)	+ - ? NR	NR	NR	NR	+					
	Did the study avoid inappropriate exclusions?	+ - ? NR	+	+	+	+	NR	+	+	+	nr
	Were the baseline characteristics similar? (applies to non randomized studies)	+ - ? NR	+	+	+	+	+	+	+	+	nr
	Could the selection of patients have introduced bias?	YES NO	NO	NO	no	no	NO	NO	NO	+	75%-
Conduct	Were participants and personnel blinded?	+ - ? NR	-	-	-	-	NR	+	-	nr	nr
	Were the co-interventions identical?	+ - ? NR	+	-	-	NR	+	+	+	+	nr
	Was the number of withdrawals or uncompleted measurements appropriately low?	+ - ? NR	+	+	+	+	+	+	+	+	nr
	Could the conduct of the intervention have introduced bias?	YES NO	NO	YES	no	NR	no	no	yes (by the information given to the test)	yes (by the information given to the test)	nr
Interpretation	Were outcome assessors blinded?	+ - ? NR	-	-	-	NR	NR	+	+	nr	nr
	Could the interpretation of the intervention have introduced bias?	YES NO	NO	NO	NO	NR	NO	no	no	no	nr
Analysis and reporting	Was data analyzed appropriately?	+ - ? NR	+	+	+	+	+	+	+	+	nr
	Was incomplete outcome data addressed?	+ - ? NR	+	+	+	+	+	+	+	+	nr
	Was the study free from selective reporting?	+ - ? NR	?	+	+	+	+	+	+	+	nr
Other	Was the study funding independent from manufacturer?	+ - ? NR	-	-	+	+	+	-	?	-	nr
	Free of other bias? Which?	+ - ? NR		+	+	+	+	+	+	+	nr

	External validity										
	Relevant patient group	+ - ?	+	+	+	+	+	+	+	+	+
	Relevant intervention	+ - ?	+	+	+	+	+	+	+	+	+
	Relevant comparator	+ - ?	+	+	+	+	+	+	+	+	+
	Relevant endpoint measures	+ - ?	+	+	+	+	+	+	+	+	+

APPENDIX 5

Quality Assessment of selected systematic reviews - AMSTAR (http://amstar.ca/Amstar_Checklist.php)

	Hassan et al., 2012	Vart et al. 2012
For each question, select: • **Yes** • **No** • **Can't answer** • **Not applicable**		
1. Was the sequence generation adequate?	NA	NA
1. Was there duplicate study selection and data extraction?	Yes	Yes
1. Was a comprehensive literature search performed?	Yes	Yes
1. Was the status of the publication used as an inclusion criterion?	Yes	No
1. Was a list of studies (included and excluded) provided?	Yes (in the on line version of the article)	No
1. Were the characteristics of the included studies provided?	Yes	Yes
1. Was the scientific quality of the included studies assessed and documented?	Yes	Yes
1. Was the scientific quality of the included studies assessed used appropriately in formulating conclusions?	Yes	No
1. Were the methods used to combine the findings of studies appropriate?	Yes	Yes
1. Was the likelihood of publication bias assessed?	No	No
1. Was the conflict of interest included?	Yes	Yes
	9/11 (minimum 6 score)	6/11 (minimum 6 score)

Legal aspects

Authors: Ingrid Wilbacher

Summary

	Rights	**Duties/responsibilities**
Patient	Sufficient information and informed consent {86, 87, 92}	Participation/compliance
	right of access to (best) health care {12,13,14}	Risk reduction
	"freedom in participation" {16, 87}	Allow data use for adequate follow up and fluent follow up in case of positive test result
	Data protection {21}	Pay tax or health insurance contributions
	Access without discrimination {25-31,71}	
	Good quality care (state of the art) {12,13,14}	
	Search for healthcare abroad in case of unequalities due to regionalism {32}	
Provider	Right to "physical harm" in case of treatment and with the implicit understanding and consent of the patient. {15}	Information {92}
	Right to charge	Data protection/ adequate use {21,22}
		Provide state of the art quality
Payer	Decision of the contents (oft he screening program) based on HTA {32, 77}	responsibility of providing public health issues and the organization of the delivery {64,65,81}
	Collect contributions (like social insurance or tax)	Provide quality at least according to appropriate market authorization (procurement)
		Contract providers (national law)
		provide follow up treatment in case of positive result (at least abroad; {76}
Others	Industry: healthcare marketing takes place and provides an own journal{91}	Industry: quality of the test; market authorisation
	EU: consumer protection issues	EU: Provide transparent market authorization processes
		Reduced advertisement in health care {national status){88,89,90}
		Appropriate protection of minors and incompetent persons {71,72,73}

Introduction

The legal aspects focus on the legal basics for crc screening, special requirements and specific groups in legislation.

Methodology

Frame

A modified collection scope is used in this domain.

Technology	Fecal Immunochemical Test (FIT) for colorectal cancer screening **Description** FITs use an antibody (immunoglobulin) specific to human globin, the protein component of haemoglobin, to detect fecal occult blood. Immunochemical tests have improved test characteristics compared to conventional guaiac-based tests for fecal occult blood. FIT should not be subject to interference from dietary blood and it is more specific to bleeding from the distal gastrointestinal tract. They could be analytically and clinically more sensitive and specific, Their measurement can be automated and the user can adjust the concentration at which a positive result is reported. A wide range of qualitative and quantitative tests is presently available, with varying levels of sensitivity and specificity (like Hem-SP/MagStream H, Fujirebio Inc. Japan ; OC-Sensor, Eiken Chemical Co., Tokyo, Japan; FOB Gold, Medinostics Products Supplier; Sentinel Diagnostics SpA, Milan, Italy).
Intended use of the technology	Screening **CRC screening with faecal inmunochemical test (FIT)** for detection of occult blood in the stool associated with colorectal lesions (adenomas and CRC). The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Early detection and treatment of colorectal lesions before they become symptomatic has the potential to improve control of the disease, reducing morbidity and mortality associated to CRC. Early treatment of invasive lesions can be generally less detrimental for quality of life. The endoscopic removal of pre-malignant lesions also reduces the incidence of CRC by stopping the progression to cancer. Colorectal cancers and adenomatous polyps bleed has providing fecal blood haemoglobin as the biomarker of choice for current screening programmes. Stool samples could be periodically taken and analyzed for the presence of occult blood, as an early sign of colorectal lesions (adenoma or CRC). **Target condition** Adenomas, as non-malignant precursor lesions of ColoRectal Cancer (CRC). **Target condition description** CRC is the third most common in incidence and the fourth most common cause of cancer death worldwide. CRC is particularly suitable for screening. The disease is believed to develop in a vast majority of cases from non-malignant precursor lesions called adenomas. Adenomas can occur anywhere in the colorectum after a series of mutations that cause neoplasia of the epithelium. At some time , the adenoma may invade the submucosa and become malignant. Initially, this malignant cancer is not diagnosed and does not give symptoms (preclinical phase). It can progress from localised (stage I) to metastasised (stage IV) cancer, until it causes symptoms and is diagnosed. Only 5–6% of the population actually develop CRC. The average duration of the development of an adenoma to CRC is estimated to be at least 10 years. This long latent phase provides a window of opportunity for early detection of the disease. **Target population** *Target population sex*: Any. *Target population age*: adults and elderly. *Target population group*: Healthy and/or asymptomatic people. **Target population description** **Adults, average risk of CRC, aged 50 years or over.** The best age range for offering gFOBT or FIT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years .The age range for a national screening programme should at least include people aged 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. Only the FOBT for men and women aged 50–74 years has been recommended todate by the EU (Council Recommendation and the European guidelines for quality assurance in CRC screening and diagnosis). Members of families with hereditary syndromes, previous diagnosis of CRC or pre-malignant lesions should follow specific surveillance protocols and are not included in the target population
Comparison	CRC screening with Guaiac –based fecal occult blood test (gFOBT) **Description** CRC screening with Guaiac–based fecal occult blood test (gFOBT) The guaiac-based FOBT is still a commonly used method for detecting blood in faeces. To detect hemoglobin the test uses guaiac gum and its efficacy as a colorectal cancer screening test has been analyzed in several randomised controlled trials. The test detects the haem component of haemoglobin, which is identical across human and animal species and is chemically robust and only partially degraded during its passage through the gastrointestinal tract. gFOBTs cannot distinguish between human blood and blood residues from the diet. Many guaiac-based tests are currently on the market (like Coloscreen, Helena Laboratories,Texas,USA; Hema-screen Immunostics Inc.; Hemoccult, Beckman Coulter Inc.; Hemoccult SENSA, Beckman Coulter Inc.; MonoHaem, Chemicon Europe Ltd; Hema-Check, Siemens PLC; HemaWipe, Medtek Diagnostics LLC) The use of the test is considered under conditions of population based colorectal cancer screening, in the context of organised cancer screening programmes as recommended by the EU. Population-based programmes have been rolled out nationwide in several European countries. Many member states haveestablished nationwide non-population-based programmes. Some states are planning or piloting a nationwide population-based programme. These have adopted only FOBT, some only FIT, some a mix between FOBT and endoscopy, or only colonoscopy.
Outcomes	**CUR and TEC** • Health problems (target condition) • Epidemiology • Burden of disease • Target population • Current management of the condition • Features of the technology • Life-Cycle • Regulatory status • Utilization • Investments and tools required to use the technology • Training and information needed to use the technology **SAF** • Colonoscopy probability of perforation • Colonoscopy with polypectomy probability of perforation • Colonoscopy probability of death following perforation • Probability of bleeding following colonoscopy • Psychological harms from false-negatives and false-positives (and generally from participating in screening program) **EFF** • Test (FIT and gFOBT) sensitivity for adenomas • Test (FIT and gFOBT) sensitivity for cancer • Test (FIT and gFOBT) specificity for adenomas

- Test (FIT and gFOBT) specificity for cancer
- Adenoma incidence (detection rates)
- Rectal cancer incidence (detection rates)
- Colon cancer incidence (detection rates)
- CRC incidence (detection rates)
- Stage distribution of detected cancers
- Rectal cancer specific mortality
- CRC specific mortality
- Overall mortality
- Life years saved

ECO:

- Model/template for national pilots to assess the costs and benefits of the two alternative technologies FIT and gFOBT and also no-programmed-screening
- Systematic literature search of available models and/or economic evaluation for screening colorectal cancer with FIT and gFOBT and no screening programme
- Resource Utilization: Publicly funded health care payer costs (screening tests, further examinations e.g. labor, colonoscopy and treatments and administration and organisation costs of screening programme) for FIT and gFOBT (in cooperation with ORG)
- Cost per Case detected (average, marginal, incremental) = intermediate outcome – optional, not decided yet (relevant for deciding how often a test should be carried out and what are the incremental costs for a “new” detected case
- Indirect Costs: not for the Core modell (should be decided later on)
- Test accuracy: from SAF
- Cost effectiveness analysis: HRQoL measures (both generic and context specific) (EFF and SAF for help, own Lit.research), ICER

ORG:

- Responsiveness of target population to invitation
- Invitation-reminder system
- Competence of human resources – health professionals
- Investments needed (material,equipment)
- Costs of using both tests (FIT, gFOBT)
- Timeliness of results and future phases
- Use of tools for process monitoring (completed check lists)
- Model for Budget Impact Analysis from perspective of the payer

SOC

- Compliance with the tests (FIT, gFOBT)
- Anxiety and any psychological effects of using one test or another
- Information, counseling, communication (quality of) for the use of tests
- Satisfaction
- Quality of life
- Equity of access

LEG

- Information as baseline for an informed consent
- Harms or inequities that can be taken to court

More information

If the PICO question is extended to other "modern" tests, especially including genetic analysis, we should ask whether there is a focus on detecting people at special risk rather than detecting crc in people with average risk.

The legal domain will definitely focus on terms of equity by defining average risk groups limited by certain age.

The general legal view for the network-use will focus on transborder healthcare (according to the directive which is to be implemented by 25th Oct 2013[1]. This includes the question whether it is the right of a person to get an (organized) screening or not and if yes, is this covered by the cross border healthcare directive?

[1] Directive 2011/24 of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare. Commission of the European Communities (Articles 1 - 22). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
I0002	Autonomy of the patient	Is the voluntary participation of patients guaranteed properly?	yes	Is the voluntary participation of patients guaranteed properly?
I0034	Autonomy of the patient	Who is allowed to give consent for minors and incompetent persons?	yes	Who is allowed to give consent for minors and incompetent persons?
I0036	Autonomy of the patient	Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?	yes	Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?
I0008	Privacy of the patient	Do laws/ binding rules require informing relatives about the results?	yes	Do laws/ binding rules require informing relatives about the results?
I0009	Privacy of the patient	Do laws/ binding rules require appropriate measures for securing patient data?	yes	Do laws/ binding rules require appropriate measures for securing patient data?
I0011	Equality in health care	Do laws/ binding rules require appropriate processes or resources to guarantee equal access to the technology?	yes	Do laws/ binding rules require appropriate processes or resources to guarantee equal access to FIT?
I0012	Equality in health care	Is the technology subsidized by the society?	yes	Is FIT subsidized by the society?
I0035	Equality in health care	Do laws/ binding rules require appropriate preventive or treatment measures available for all?	yes	Do laws/ binding rules require appropriate preventive or treatment measures available for all?
I0015	Authorisation and safety	Has the technology national/EU level authorisation (marketing authorisation, registration, certification of safety, monitoring, qualification control, quality control)?	yes	Has the technology marketing authorisation?
I0019	Ownership and liability	Does the technology infringe some intellectual property right?	no	The crc test does not have to be licensed for use - this is intended with the purchase.

Methodology description

Deviations from the project scope:

More information:

If the PICO question is extended to other "modern" tests, especially including genetic analysis, we should ask whether there is a focus on detecting people at special risk rather than detecting crc in people with average risk.

The legal domain will definitely focus on terms of equity by defining average risk groups limited by certain age.

The general legal view for the network-use will focus on transborder healthcare (according to the directive which is to be implemented by 25th Oct 2013{1}. This includes the question whether it is the right of a person to get an (organized) screening or not and if yes, is this covered by the cross border healthcare directive?

Information sources

Scientific research

Google search 22.03.2013 *legals aspects for colorectal cancer screening (1 result)*

Pubmed search on 22.03.2013 for "legislation and jurisprudence" [Subheading] AND "Jurisprudence"[Mesh] and colorectal cancer screening 14 results)

Pubmed search on 22.05.2013 for "cancer screening participation" (38 results)

Pubmed search for *incompetent persons* (2316 items)

Scan of the JA2/WP4 general search for crc, thematic elements "fit safety", "fit nuovo", "fit compliance" for elements of legal aspects

Inclusion of literature:

- Legal relevance
- Legal citation
- Discussion of legal aspects
- Main focus on EU relevant studies

Exclusion of literature:

- Studies from other continents than Europe
- Ethal discussion instead of legal discussion
- No legal relevance for crc screening (like organ donation)
- Genetic testing/ genetic aspects

Market authorization

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm?start_search=C (15.5.2013)

http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm

legal background

EU and international law

http://europa.eu/about-eu/institutions-bodies/court-justice/index_de.htm for *Patientendaten, Datenschutz*

court decisions

EU court

http://eur-lex.europa.eu/

http://curia.europa.eu/juris/recherche.jsf?language=de – limitation to health sector, last 5 years – no results (3.5.2013)

http://conventions.coe.int/Treaty/EN/Treaties/Html/005.htm

Quality assessment tools or criteria

The literature research (medical sources) serves for basic aspects and discussion, it usually does not include legal rules. Therefore the evidence levels of the literature results and the quality of the literature are not assessed in this domain.

Peer Review was done by Gottfreid Endel, Hans Seyfried

Analysis and synthesis

Interpretation of the legal text/ papers/ court decisions according to the HTA questions.

Result cards

Autonomy of the patient

Result card for LEG1: "Is the voluntary participation of patients guaranteed properly?"

View full card

LEG1: Is the voluntary participation of patients guaranteed properly?

Result

Literature research

Usually it seems to be standard to assume that people want to participate in screening programmes, although the participation rate does not proof this assumption. In the literature search for the legal domain a critical discussion about the legal mandate for implementing a prevention register for hereditary coloncancer was found. *A legally mandated cancer prevention and treatment tool for hereditary cancers, however, would mean that patients who have chosen not to participate in the programme would be called for check-ups, as well.*{2} Although it addresses only the hereditary crc, the aspects are also interesting for general crc screening and invitation systems, especially in terms of refused screening participation. A repeated call to participate could be interpreted as an unwanted pressure.

Recent European studies report an average of 45% screening participation for FOBT (iFOBT, gFOBT): 19% in Croatia {3}; 30% in France {5}; 42,1% {6}, 52% {4} and between 61% and 64,7% {7} in the Netherlands; 60,6% in the UK {8}; 64,3% in Spain (Basque) {9}; 34,2% in Spain (Canaries) {10}, 49,7% in Italy {11}.

Legislation

Several legislations secure the right of access to (best) health care {12,13,14}, but less about refusal or forced participation. Usually the law takes the view that a patient wants' to have health services available.

Bodily harm is legally forbidden, except for physicians and related occupations in case of treatment and with the implicit understanding and consent of the patient. {15} Therefore it is more or less the non-refusal or the explicit consensus of the patient joining a (nationwide) screening program.

According to article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms {16}, Article 8, *Everyone has the right to respect for his private and family life, his home and his correspondence.* and *There shall be no interference by a public authority with the exercise of this right except such* […] *for the protection of health or morals*, […].

Court decisions

No international EUGH case law was found for diagnostic matters and voluntary participation. (search done in http://curia.europa.eu/juris/recherche.jsf?language=de – limitation to health sector, last 5 years – no results (3.5.2013)

The patient's right for non-treatment is discussed controversially (Several legal rules against euthanasia {17}, legislation about genetic testing {18}) and more or less just in the view of death.

Comment

Conclusion

- **Several legislations secure the right of access to (best) health care {12,1314}, but less about refusal or forced participation. Usually the law takes the view that a patient wants' to have health services available.**

- **The invitation to participate in a screening program can be interpreted as "freedom in participation", if it is free of pressure or consequences, and if an objective and understandable information is provided. According to article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms {16}, Article 8, *Everyone has the right to respect for his private and family life, his home and his correspondence.* and *There shall be no interference by a public authority with the exercise of this right except such* […] *for the protection of health or morals*, […].**

- **Usually it seems to be standard to assume that people want to participate in screening programmes, but this should be discussed critically if it comes to a *legally mandated cancer prevention and treatment tool for (hereditary) cancers.* Bodily harm is legally forbidden, except for physicians and related occupations in case of treatment and with the implicit understanding and consent of the patient. {15} Therefore it is more or less the non-refusal or the explicit consensus of the patient joining a (nationwide) screening program.**

- **Different screening participation rates could be a sign for different information levels about the screening test and possible consequences**

- **No international EUGH case law was found for diagnostic matters. (search done in http://curia.europa.eu/juris/recherche.jsf?language=de – limitation to health sector, last 5 years – no results (3.5.2013)**

- **The patient's right for non-treatment is discussed controversially (Several legal rules against euthanasia {17}, legislation about genetic testing {18}) and more or less just in the view of death.**

As long as there is no legal mandate for cancer prevention and treatment (register) and no other forced screening participation which limits or exceeds the objective information the voluntary participation should be guaranteed.

Importance: Important

Transferability: Completely

Result card for LEG7: "Who is allowed to give consent for minors and incompetent persons?"

View full card

LEG7: Who is allowed to give consent for minors and incompetent persons?

Result

Literature

If the patient is incompetent and the surrogate decision makers or families have reached an impasse with the clinician then some simple preliminary steps may be taken, including seeking a second opinion but it may require seeking clarification with the Supreme Court of the jurisdiction.{69} This article discusses the aim of dialysis/ no dialysis for incompetent persons. The discussion focuses at a more ethical than legal level.

Legislation

The Charter of Fundamental Rights of the European Union *OJ C 326, 26.10.2012, p. 391–407* {70} contents the basic human rights in the European Union, which – of course – are also relevant for persons with disability or for minors.

- The basic right for health care of good quality includes everybody, even minors or disabled persons {71}

- The decision about minors is legally regulated to be provided by an authorized personal guardian {71,72,73}

- No clear legislation exists about the limits and refusal of healthcare. Court decisions about overcoming the guardian/ confirm the refusal by the guardian aim the best balance of benefit of the patient

- In case of CRC screening it will be affecting the case of positive screening result with the need of invasive examinations and cancer treatment procedure

Comment {optional)

The risk group for CRC screening includes persons aged about 50+. It does not exclude people of {much) higher age and disability. The risk of mental illness, especially dementia, increases with age, the possibility to have a higher rate of incompetent persons due to a epidemiologically caused higher rate of dementia in this age group who have eventually to be patronized. Approximately 1% of 65-year-olds and more than 50% of 90-year-olds have a dementia disorder.{74}

Who decides about screening and following treatment in case of a positive screening result for patronized persons? {= who takes the stool test and can the decision be done by this person?)

States Parties recognize that persons with disabilities have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability.{71}

There are several court decisions according to treatment of patronized persons. {72}

"...most authorities are of the view that mature minors should be fully informed and be allowed to have a say in health decisions, coaching them with few exceptions. Ultimately, because of the importance of respect for human dignity, autonomy and self determination along with medical disclosure in today's world, it will be recommended that laws in a number of jurisdictions need to be reviewed to reflect the current international trend and amended or replaced as the need might be." {Bello 2010) {73}

The decision about **screening** for CRC in minors is basically not the main problem in this field. According to the same right to healthcare they have the right for equal access also for CRC screening. The severity of the **problem starts with a positive result after screening** {= an existing CRC which has to be treated).

In case of a refusing cancer treatment decision there has to be controlled and secured properly whether the patients' interest is implemented in the best way, and whether there could be interests in benefit for the guardian party {inheritance law, Co-payments), especially if a family member is the guardian and i.e. the potential inheritor.

For the comparison of two stool tests there will be no difference.

Comment

Conclusion

- **The basic right for health care of good quality includes everybody, even minors or disabled persons {71}**

- **The decision about minors is basically regulated to be provided by an authorized personal guardian {71,72,73}, but there has to be taken a more detailed view on this question in the national legislations. It has to be controlled and secured properly whether the patients' interest is implemented in the best way.**

- **No clear legislation exists about the limits and refusal of healthcare. Court decisions about overcoming the guardian/ confirm the refusal by the guardian aim the best balance of benefit of the patient. It has to be controlled and secured properly whether the patients' interest is implemented in the best way.**

- **In case of CRC screening it will be affecting the case of positive screening result with the need of invasive examinations and cancer treatment procedure**

Importance: Critical

Transferability: Not

Result card for LEG9: "Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?"

View full card

LEG9: Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?

Result

Literature research:

Patient information has to be guaranteed properly.

In order to get realistic expectations and to be able to participate voluntarily, the information for the patient should include {82}

- benefits and the risks of the screening procedure
- associated diagnostics and treatments in case of a positive screening result including the benefits and the risks of the procedures
- detection rates
- efficiency and limitations of the treatment
- healthy lifestyles associated with a reduction in the risk of colorectal cancer
- the natural variability in outcome that can be seen
- *possibility of cancer or pre-cancer being missed*
- lack of 100% accuracy in screening tests

Eaden et al. discussed in 2011{83}the difficulties and conflicts about legal issues in terms of screening:

- confidentiality of patients and other human rights issues
- inexact science in relation to, e.g., faecal occult blood testing for colorectal cancer
- false positive and false negative tests for HIV
- inadequate quality controls in breast cancer screening programmes

and stated the following needs:

- The public need to be made aware of what the screening programmes really offer, balanced against the expectations they may have.
- There needs to be a clearer understanding of the nature of the contractual and other legal rights of patients/consumers as against providers.
- A positive screening test may carry adverse consequences as well as benefits. {e.g. rejection for life insurance policies, job prospects
- The method of informing patients in relation to screening and screening failure has already been considered by the courts.
- Realistic information about both screening and treatment efficiency needs to be offered to patients so that they can have a real understanding of what can and cannot be achieved by current science.
- The development of understanding of the human genome makes the need for clearer legislation in this more urgent.

The study of Hudson et al. 2012 {84} reported that *94% of asked persons overestimated the effect of bowel cancer screening, a lower level of education was associated with higher estimates of minimum acceptable benefit for all interventions*.

A study {85} from 2006 in Massachusetts/USA reports about claims for delayed or missing diagnoses {retrospective insurance data): Table 4

Legal regulation:

- There are clear regulations about patient information: According to the Charter of Fundamental Rights of the European Union {86} the regulations about Human Dignity, Right to Life, Right to the Integrity of the Person, Prohibition of Torture and Inhuman or Degrading Treatment or Punishment, Respect for Private and Family Life, Protection of Personal Data lead to following patients' rights:

The right for self-determination

The right for sufficient information and informed consent {an refusal by the patient, even refusal of the information)

The right for treatment/ medical help

The right for discharge from hospital {except after executive admission)

The right for secrecy of the physician {except infection risk)

The right for access to the medical records

The right for equity

- There is no clear right about refusal by the patient, but for patient autonomy, and freedom of choice {87}
- There are regulations about advertisement in health care {national status) {88,89,90}, but a structured healthcare marketing also takes place and even provides an own journal{91}

Court decisions:

It was decided not to take single court decisions concerning harm due to lack of information/ informed consent, but to refer instead to a summary study about such decisions from Germany:

Result: In 2006 7,201 suspected incidents of malpractice were claimed to the German *Schlichtungsstelle,* which is a kind of pre-court decision process. Out of these 7,201 cases 2,571 {35,7%) included the lack of information. In primary care the most claims were about diagnostics.{92}

Comment

Conclusion

- **The need for information for the patient about benefits, harms and realistic expectations is known and legally regulated**
- **there is uncertainty about how to proof the correct understanding of the given information**
- **There appears to be a minor impact of research about patients refusal and reasons behind and no clear right about refusal by the patient, but for patient autonomy, and freedom of choice**
- **There is a clear need for concluding processes and information about it in case of a positive screening test {correct interpretation, following tests, proceeding to therapy)**
- **The different regulations about usual screening for not-at-risk persons and the special regulation for genetic tests need clarification for how to combine or switch the legal conformity if a non-at-risk person is suspected for genetic reasons**
- **If suspected incidents of malpractice are claimed 35% are reported {German study) to have lack of information included**

Importance: Critical

Transferability: Completely

Privacy of the patient

Result card for LEG2: "Do laws/ binding rules require informing relatives about the results?"

View full card

LEG2: Do laws/ binding rules require informing relatives about the results?

Method

This question was defined as not relevant for the decision between FIT or FOBT

Frame

This question was defined as not relevant for the decision between FIT or FOBT

Result

This question was defined as not relevant for the decision between FIT or FOBT

Comment

This question was defined as not relevant for the decision between FIT or FOBT

Importance: Unspecified

Transferability: Unspecified

Result card for LEG3: "Do laws/ binding rules require appropriate measures for securing patient data?"

View full card

LEG3: Do laws/ binding rules require appropriate measures for securing patient data?

Method

no different method

Result

Literature

No results for the literature search discussing aspects of securing patient data.

There were some aspects found in literature for improving screening results, one is that *The effectiveness of these screening programs is affected by the level of participation in consecutive screening rounds* {19}. This means that not just data protection in an adequate manner (see legislation) but also an adequate data networking-management is necessary especially for preventive measurements that do not necessarily take place at the same health care provider. Another aspect is the situation of double diagnosis as 5.6% to 13.7% *of participants self-reported they were 'overscreeners' (i.e. participated despite being up to date having done another test or recent colonoscopy)* {20}

Legislation

- There are clear regulations in data protection on EU level {21} which are adapted accordingly in the members states

- There could be indication for harm due to failed data protection (including social stigmatization, occupational or financial harm to the patient in case of a positive test and started cancer career) data protection is to be addressed to have higher relevance

- by 22 December 2011 the European Commission adopted a Decision establishing an eHealth Network, as foreseen by the Directive (2011/24/EU) on Patients' Rights in Cross-border Healthcare. For the first time, EU legislation includes provisions on eHealth with clear objectives to find modern, innovative solutions for providing better and safer healthcare for all Europeans. {22}

- *The European Commission launched two initiatives (*2 July 2008; IP/08/1075] *to improve the safety and quality of care to people who require medical assistance while travelling or living abroad: a Recommendation on cross-border interoperability of electronic health record (EHR) systems and the Smart Open Services (SOS) project. The Recommendation aims to provide Member States with basic principles and guidelines for ensuring that doctors can gain access to vital information on patients that they are trying to treat, wherever such information may be located in Europe. The SOS project, co-funded by the European Commission, is supported by 12 Member States and their industry players, to demonstrate the benefits of such interoperability. It will enable health professionals to access specific medical data such as current medications of patients from other EU countries. In an emergency, sharing of medical information could save many patients' lives.* {23}

Comment

Data networks and data communication between different diagnostic and treatment providers have to secure and protect data sources according to legal data protection regulations.

There is existing data protection regulation on international level{21}, which is already adapted and integrated in all of the countries in EU, Norway, Switzerland.{22}

Theoretically, in case if no data security takes place, what were the consequences of unprotected data for the patient?

- Harm in dignity: propably yes. A possible cancer diagnosis and the consequences of embarrassing procedures or consequences (like colostomy) could cause social inacceptance

- Social harm, if hereditary and non-hereditary aspects are not transported accordingly, this could cause serious conflicts in the near social environment of the patient

- Harm as decreased chances on market: Jobmarket - propably not for Persons aged 65+. Privat (health) insurance market - (higher contributions, refusal of contract) propably not in the age above 65

- Potential of misuse from the provider according to civil law (like purchased life annuity)

Theoretically, in case of too much data security or incompetent (no availability of prevention/ screening results for other provider) use of documented data, what are the consequences for the patient?

- Positive results or suspicions are not available for other health care provider with could mean double examinations for the patient and/or missed information (i.e. overseen positive cancer result)

- missed advantages of provider-networking

Conclusion

- **There are clear regulations in data protection on EU level {21}**

- **There is ongoing focus on the uptake of e-Health for providing better and safer healthcare due to the network use of information (data) {22} without a clear regulation now**

- **a valid data protection is of benefit for the patient (i.e. private insurance contract) and a good data-network flow (with appropriate data security) benefits the patient with fluent outgoing healthcare**

Importance: Important

Transferability: Completely

Equality in health care

Result card for LEG4: "Do laws/ binding rules require appropriate processes or resources to guarantee equal access to FIT?"

View full card

LEG4: Do laws/ binding rules require appropriate processes or resources to guarantee equal access to FIT?

Method

no deviation from method

Result

The recommended crc screening age for average risk persons varies, but the lowest age covered by screening programs is 45-50 years.

In the absence of additional evidence, the age range for a screening programme with iFOBT can be based on the limited evidence for the optimal age range in gFOBT trials (EU Guidelines 2010). According the EU Guidelines 2010, the best age range for offering gFOBT screening has not been investigated in trials. Circumstantial evidence suggests that mortality reduction from gFOBT is similar in different age ranges between 45 and 80 years (Level of the evidence IV). The age range for a national screening programme should at least include 60 to 64 years in which CRC incidence and mortality are high and life-expectancy is still considerable. From there the age range could be expanded to include younger and older individuals, taking into account the balance between risk and benefit and the available resources (Level of the evidence VI - B). (see Domain Health Problem and Current Use of the Technology referring to the EU Guidelines 2010)

Legislation

Convention for the Protection of Human Rights and Fundamental Freedoms {24}, Article **14 – Prohibition of discrimination:** The enjoyment of the rights and freedoms set forth in this Convention shall be secured without discrimination on any ground such as sex, race, colour, language, religion, political or other opinion, national or social origin, association with a national minority, property, birth or other status. {24}

- Everybody has the basic right to health care at the state of the art ("best care"). This can be adapted for screening as well

- There are no exclusions/ special protection declarations for gender equality, prisoners, disabled, regional equalities {25,26,27,28,29,30,31}

- The level of quality is included into the right of good care, but there is a need of legal regulation about a minimum defined quality level to provide equal preconditions for everyone

- If the equal right for access to health care (screening) affects two persons in contrary (like in the screening of one person and a possibly affected other) an ethical debate is necessary

- Unequilities due to regionalism (national supply) should be solved by the directive about cross-border healthcare [{32} which theoretically allows health-tourism as well in special conditions, but especially for (CRC-) screening by FIT or FOBT (not expensive and not highly specialized) this should not be the case: in an organized screening program the tests are sent to the inhabitants. It could only be relevant if a test is bought cross-border and reimbursed by the health insurance of the home country, if the test is not available in the country (neither due to the screening program nor at the free market).

- Limited access to Fit or gFOBT in screening programs for special (age) groups are based on the balance between evidence of best detection rates, economic calculations for the screening progam costs and reduction of possible disadvantages due to screening. A defined exclusion for people outside the groups for the screening program is not according to the law ({24}, Article 14 – Prohibition of discrimination)

Comment

There are several regulations on EU- and international level for securing equal access to health care in Europe.{25,26,27,28,29,30,31} It implements that, apart from the screening program (for asymptomatic persons in a risk group), usual care (extended examination) for all other persons who present with suspicious symptoms is provided.

Special problems on CRC screening by Fit versus FOBT:

Gender selection

Is it, according to the legal rules of equal access, appropriate to define risk groups for only one gender group? (i.e. men aged 64+). This can be accepted if there is a clear medical defined unequal risk in one gender group (for crc male persons) compared to the other (for crc female persons).

States Parties {32} shall take all appropriate measures to eliminate discrimination against women in the field of health care.{33}

Prisoners

According to the Council of Europe Committee of Ministers Recommendation (2006)2 of the Committee of Ministers to member states on the European Prison Rules, Part III {34} Healthmedical services in prison shall be organized in close relation with the general health administration of the community or nation. (40.1) Prisoners shall have access to the health services available in the country without discrimination on the ground of their legal situation (40.3).

Does that mean screening is included? Yes.

And if screening is included in this interpretation, is a voluntary participation guaranteed? Do they (prisoners) have any choice? This should be the case (legally). Due to the fact that a stool test does not cause pain, or touch dignity, there should not be any problem. This is different for the (additional or extended) screening by invasive diagnostic methods (like flexible sigmoidoscopy or colposcopy), which could cause pain and influence the feelings of dignity and embarrassment. The patients' rights of prisoners are protected separately.{35}

Regionalism

Stool tests can be provided at home, but what about the consequences in case of a positive result? Can it be secured that people living far from the next cancer care center are not discriminated in any way (transport costs, waiting time)?

What about equality of services among EU citizens? Health for EU citizens working part time in another than their home country and emergency health care during holidays is clearly regulated {36}. As a continuing part of the coordination of the systems of social security in the EU {37} there is now an existing guideline of the EU for patients' rights of cross boarder healthcare {38} which has to be implemented on national levels by October 25th 2013.

Higher age

A selected population for CRC screening could be persons aged 45 or 50 and more. Can it be secured that among this age group no selection for the younger and against the older takes place? Can it be legally secured that there is no discrimination in age (medically) argued by the severity of treatment risks (too old for colonoscopy or surgical treatment, already in nursing home care,...).

The limits of healthcare should be implemented in a balance between the right of access and the patients' right for human dignity, right to life, right to the integrity of the person, prohibition of torture and inhuman or degrading treatment or punishment; and respect for private and family Life. {39}

Especially in the field of e-health *It is essential to discuss, among others, aspects relating to safety and confidentiality; professional accountability; technical standards relating to digital recording, storage, and transmission of clinical data; copyright; authorization from professional regulatory bodies; and licensing for the remote practice of medicine.* (Rezende 2010) {40}

Responsibility:

Legal issues can be solved easily when responsibilities of parties concerned have been established and documented. Loeber 2008 {41}

Conclusion

- **Everybody has the basic right to health care at the state of the art ("best care"). This can be adapted for screening as well**

- **There are no exclusions/ special protection declarations for gender equality, prisoners, disabled, regional equalities {25,26,27,28,29,30,31}**

- **The level of quality is included into the right of good care, but there is a need of legal regulation about a minimum defined quality level to provide equal preconditions for everyone**

- **If the equal right for access to health care (screening) affects two persons in contrary (like in the screening of one person and a possibly affected other) an ethical debate is necessary**

- **Unequilities due to regionalism (national supply) should be solved by the directive about cross-border healthcare [{32} which theoretically allows health-tourism as well in special conditions, but especially for (CRC-) screening by FIT or FOBT (not expensive and not highly specialized) this should not be the case: in an organized screening program the tests are sent to the inhabitants. It could only be relevant if a test is bought cross-border and reimbursed by the health insurance of the home country, if the test is not available in the country (neither due to the screening program nor at the free market).**

- **Limited access to Fit or gFOBT in screening programs for special (age) groups are based on the balance between evidence of best detection rates, economic calculations for the screening progam costs and reduction of possible disadvantages due to screening. A defined exclusion for people outside the groups for the screening program is not according to the law ({24}, Article 14 – Prohibition of discrimination)**

Importance: Important

Transferability: Partially

Result card for LEG5: "Is FIT subsidized by the society?"

View full card

LEG5: Is FIT subsidized by the society?

Method

no deviation

Result

Literature

What affects the participation in screening? Table 1

Legislation

Structure and resources have to be provided appropriately. Union action, which shall complement national policies, shall be directed towards improving public health, preventing physical and mental health. The Union and the Member States shall foster cooperation with third countries and competent international organizations in the sphere of public health. {63} Member States shall be responsible for the organization and the delivery of healthcare. Member States shall facilitate development and functioning of a network connecting the national authorities responsible for health technology assessment. {64}

The Council Resolution of 20 December 1995 on the integration of health protection requirements in Community policies [65] *REAFFIRMS that, in order to ensure a high level of health protection for the citizens of the European Union, the goals to be achieved, mainly by preventive measures, including health promotion, are extending life expectancy and reducing the incidence of premature death, increasing the number of years free of illness, reducing or limiting the negative consequences of illnes and handicaps, promoting healthy life styles and a healthy physical and social environment, and improving the quality of life in general;*

Comment

Conclusion

- there is a clear view and regulation at EU level for the responsibility of providing public health issues and the organization of the delivery of healthcare.

- the implementation of the croosborder healthcare directive has to be fulfilled by October 2013 by the member states

- due to the fact that European countries have public healthcare systems the question of subsidization {amount) is a matter of HTA recommendations

- factors influencing screening participation on crc screening are gender, age, kind of invitation, risk communication, attitudes, social status, region of living, and kind of insurance coverage

Importance: Optional

Transferability: Partially

Result card for LEG8: "Do laws/ binding rules require appropriate preventive or treatment measures available for all?"

View full card

LEG8: Do laws/ binding rules require appropriate preventive or treatment measures available for all?

Method

Legislation – adapt the regulations found for screening from JA1, add crc specialities if possible

Result

- **The test and/or treatment availability (colonoscopy after FIT or gFOBT, surgical treatment of detected crc, advanced therapy, etc.) should not threaten the European health care systems**

- **The basic right to health care at the state of the art and the declarations for gender equality, prisoners, disabled, regional equalities can be interpreted as the expanded right for appropriate equal preventive examinations. In terms of screening this is fulfilled if the screening criteria {high accuracy, acceptable, cost-effective) are reached.{75}**

- **In case of CRC a positive result requires a complex treatment strategy which is able to serve the epidemiological burden. The reimbursement by the national health system for necessary abroad treatment is court-decided by a case and recently regulated by the cross-border healthcare directive.{76}**

Comment

The EU considers that early detection procedures and techniques should be researched more thoroughly before being widely applied in order to guarantee that their use and application is safe and evidence-based; therefore, it is necessary that this research leads to unambiguous and evidence-based recommendations and guidelines; {77} But in further context, the opinion of the EU can be interpreted for defining clear and transparent goals of the screening measurement which should be communicated in public.

A study about longterm care reports that *most variability in advance care planning decisions was the result of differences among community-based long-term care providers {64%) rather than consumers' situational features.* The authors *highlight the need for consistent educational programs regarding the role of the ... provider*. {Baughman 2011){78}

The court decision {79} about abroad treatment states several conditions for the reimbursement by the national health system.

Structure and resources have to be provided appropriately. Union action, which shall complement national policies, shall be directed towards improving public health, preventing physical and mental health. The Union and the Member States shall foster cooperation with third countries and competent international organizations in the sphere of public health.{80} Member States shall be responsible for the organization and the delivery of healthcare. Member States shall facilitate development and functioning of a network connecting the national authorities responsible for health technology assessment.{81}

Importance: Important

Transferability: Partially

Authorisation and safety

Result card for LEG10: "Has the technology marketing authorisation?"

View full card

LEG10: Has the technology marketing authorisation?

Method

A study (one result of the literature research as described in overall method section) was taken for an overview of used fecal occult blood tests as screening tools for CRC in European countries {66}. According to the directive 98/79/EC, Art 2 {93} for in vitro diagnostic medical devices and their accessories each member state has to *take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied and properly installed, maintained and used in accordance with their intended purpose. This involves the obligation of Member States to monitor the security and quality of these devices.* Due to the fact that EUDAMED {68} is not publically available and does not provide a complete content of registered devices, and that for this paper not every single national registration could be evaluated, the search for market authorization level was done in FDA {67} as a surrogate.

Result

In European countries the following tests were used for CRC screening: Hemoccult, Hemoccult II, RPHA immudia, Alpha Wasserman, Alpha Wasserman Sentinel, FlexSure OBT, and Hema Screen. {Table 2)

The FDA {Food and Drug Administration, U.S.) provides 60 registered fecal occult blood test in a public database (Table 3), by registration number 864655021 and product classification code KHE22. The tests *RPHA immudia, Alpha Wasserman, Alpha Wasserman Sentinel,* and *FlexSure OBT* were not found there. Whether and how they are registered in Europe could not be detected by the search as done.

Comment

- **There are several fecal occult blood tests registered by the FDA. European registration situation was not found for public access by the search.**

- **The tests used for CRC screening in European countries as provided by the study of Benson et al. 2007 [3] were not all found in the FDA registration database.**

- **The market authorization has to be checked for the tests *RPHA immudia, Alpha Wasserman, Alpha Wasserman Sentinel,* and *FlexSure OBT.***

Importance: Important

Transferability: Completely

Discussion

LEG1: Is the voluntary participation of patients guaranteed properly?

As long as there is no legal mandate for cancer prevention and treatment (register) and no other kind of forced screening participation which limits or exceeds the objective information the voluntary participation should be guaranteed.

LEG3: Do laws/ binding rules require appropriate measures for securing patient data?

There are clear regulations in data protection on EU level {21} and there is also an ongoing focus on the uptake of e-Health for providing better and safer healthcare due to the network use of information (data) without a clear regulation now.

LEG4: Do laws/ binding rules require appropriate processes or resources to guarantee equal access to FIT?

Limited access to Fit or gFOBT in screening programs for special (age) groups are based on the balance between evidence of best detection rates, economic calculations for the screening progam costs and reduction of possible disadvantages due to screening. A defined exclusion for people outside the groups for the screening program is not according to the law.

LEG5: Is FIT subsidized by the society?

There is a clear view and regulation at EU level for the responsibility of providing public health issues and the organization of the delivery of healthcare.Due to the fact that European countries have public healthcare systems the question of subsidization {amount) is a matter of HTA recommendations. Factors influencing screening participation on crc screening are gender, age, kind of invitation, risk communication, attitudes, social status, region of living, and kind of insurance coverage.

LEG6: Has FIT national/EU level authorisation {marketing authorisation, registration, certification of safety, monitoring, qualification control, quality control)?

There are several fecal occult blood tests registered by the FDA. European registration situation was not found for public access by the search.The market authorization has to be checked for the tests *RPHA immudia, Alpha Wasserman, Alpha Wasserman Sentinel,* and *FlexSure OBT* if used.

LEG7: Who is allowed to give consent for minors and incompetent persons?

The decision about minors is legally regulated to be provided by an authorized personal guardian. No clear legislation exists about the limits and refusal of healthcare. Court decisions about overcoming the guardian/ confirm the refusal by the guardian aim the best balance of benefit of the patient. In case of CRC screening it will affect the case of a positive screening result with the need of invasive examinations and cancer treatment procedure. This question should not be taken without the focus in the national legislation(s).

LEG8: Do laws/ binding rules require appropriate preventive or treatment measures available for all?

The test and/or treatment availability (colonoscopy after FIT or gFOBT, surgical treatment of detected crc, advanced therapy, etc.) should not threaten the European health care systems. In case of CRC a positive result requires a complex treatment strategy which is able to serve the epidemiological burden. The reimbursement by the national health system for necessary abroad treatment is court-decided by a case and recently regulated by the cross-border healthcare directive.

LEG9: Do laws/ binding rules require appropriate counseling and information to be given to the user or patient?

The need for information for the patient about benefits, harms and realistic expectations is known and legally regulated and the crucial element in an informed consent screening, including information about processes in case of a positive screening test {correct interpretation, following tests, proceeding to therapy).

Legal uncertainties occur in terms of responsibility for failed screening-expectations. Who is responsible for what kind of information, how should the informed consent be documented? Who is responsible to organize further processes in terms of a positive screeing result?

A degree of freedom seems to be for patients and their responsibility among offered screening. Do patients have to participate in a compliant way? (What, if not?) Does participation in a screeing program mean to agree in follow-up examinations/treatments?

For FIT and FOBT no transparent market authorization overview among the EU was found. There seems to be a need for consumer protection in terms of healthcare devices and advertisement for special products or services in order to guarantee the freedom of participation based on unbiased information.

References

[1] Directive 2011/24 of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare. Commission of the European Communities {Articles 1 - 22). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

[2] A. Tupsela {2006) European Journal of Cancer Care 15, 257-266. When legal worlds collide: from research to treatment in hereditary cancer prevention

[3] Katicic M, Antoljak N, Kujundzic M, Stamenic V, Skoko Poljak D, Kramaric D, Stimac D, Strnad Pesikan M, Samija M, Ebling Z. Results of National Colorectal Cancer Screening Program in Croatia {2007-2011). World J Gastroenterol. 2012 Aug 28;18{32):4300-7. doi: 10.3748/wjg.v18.i32.4300.

[4] Denters MJ, Deutekom M, Bossuyt PM, Fockens P, Dekker E. A feces collection paper does not enhance participation in a fecal immunochemical test-based colorectal cancer screening program: randomized clinical trial. Eur J Cancer Prev. 2012 Nov 18.

[5] Le Breton J, Journy N, Attali C, Le Corvoisier P, Brixi Z, Bastuji-Garin S, Chevreul K. Improving participation in colorectal cancer screening: targets for action. Prev Med. 2012 Nov;55{5):488-92. doi: 10.1016/j.ypmed.2012.08.004. Epub 2012 Aug 21.

[6] Van Roosbroeck S, Hoeck S, Van Hal G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiol. 2012 Oct;36{5):e317-24. doi: 10.1016/j.canep.2012.04.003. Epub 2012 May 5.

[7] van Roon AH, Goede SL, van Ballegooijen M, van Vuuren AJ, Looman CW, Biermann K, Reijerink JC, Mannetje H', van der Togt AC, Habbema JD, van Leerdam ME, Kuipers EJ. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. Gut. 2013

Mar;62{3):409-15. doi: 10.1136/gutjnl-2011-301583. Epub 2012 Mar 2.

[8] Libby G, Brewster DH, McClements PL, Carey FA, Black RJ, Birrell J, Fraser CG, Steele RJ. The impact of population-based faecal occult blood test screening on colorectal cancer mortality: a matched cohort study. Br J Cancer. 2012 Jul 10;107{2):255-9. doi: 10.1038/bjc.2012.277. Epub 2012 Jun 26.

[9] Portillo I, Idigoras I, Ojembarrena E, Arana E, Luis Hurtado J, Basurko R, Tapia M, Luz Pena M. [Lesions detected in a colorectal cancer screening program in the Basque Country: first round {2009-2011)]. Gastroenterol Hepatol. 2013 May;36{5):301-8. doi: 10.1016/j.gastrohep.2013.02.004. Epub 2013 Apr 22.

[10] Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, Andreu M, Carballo F, Morillas JD, Hernandez C, Jover R, Montalvo I, Arenas J, Laredo E, Hernandez V, Iglesias F, Cid E, Zubizarreta R, Sala T, Ponce M, Andres M, Teruel G, Peris A, Roncales. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med. 2012 Feb 23;366{8):697-706. doi: 10.1056/NEJMoa1108895.

[11] Parente F, Boemo C, Ardizzoia A, Costa M, Carzaniga P, Ilardo A, Moretti R, Cremaschini M, Parente EM, Pirola ME. Outcomes and cost evaluation of the first two rounds of a colorectal cancer screening program based on immunochemical fecal occult blood test in northern Italy. Endoscopy. 2013 Jan;45{1):27-34. doi: 10.1055/s-0032-1325800. Epub 2012 Dec 19.

[12] International Covenant on Economic, Social and Cultural Rights {1966); Article 12; http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx {2.5.2013)

[13] European Code of Social Security {Revised); Article 8 + Article 10; http://conventions.coe.int/treaty/en/Treaties/Html/139.htm {2.5.2013)

[14] A Declaration on the Promotion of Patients' Rights in Europe, WHO 1994; http://www.who.int/genomics/public/eu_declaration1994.pdf {2.5.2013)

[15] criminal law on national level;i.e. A: §§ 83–88 StGB {http://www.ris.bka.gv.at/Dokument.wxe?Abfrage=Bundesnormen&Dokumentnummer=NOR40124586) {2.5.2013); D: § 223-§ 231, § 340 StGB {http://dejure.org/gesetze/StGB/223.html) {2.5.2013); Pl: Dz.U. 1997 nr 88 poz. 553 - Kodeks karny {http://isap.sejm.gov.pl/DetailsServlet?id=WDU19970880553) {2.5.2013);

[16] http://conventions.coe.int/Treaty/EN/Treaties/Html/005.htm {14.5.2013)

[17] German Court, Bundesgerichtshof 2 StR 454/09) 25th June 2010; http://hudoc.echr.coe.int/sites/eng/pages/search.aspx?i=001-113680#{"itemid":["001-113680"]} {2.5.20139

Wet toetsing levensbeëindiging op verzoek en hulp bij zelfdoding http://www.st-ab.nl/wetten/0829_Wet_toetsing_levensbeeindiging_op_verzoek_en_hulp_bij_zelfdoding.htm {2.5.2013)

PROPOSITION DE LOI relative à l'euthanasie volontaire; http://www.senat.fr/leg/ppl10-031.html {2.5.2013)

La loi belge relative à l'euthanasie; http://www.ginsburgh.net/textes/Fin_che_si_compia.pdf {2.5.2013)

L'euthanasie et l'assistance au suicide | Loi du 16 mars 2009. Sommaire. Sommaire. Préface. 6. Questions/réponses sur la loi sur l'euthanasie. 9 et l' assistance; http://www.legilux.public.lu/leg/a/archives/2009/0046/a046.pdf {2.5.2013)

[18] Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes; Articles 1 - 22 and Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes; Articles 1 - 24; http://conventions.coe.int/treaty/en/treaties/html/203.htm {2.5.2013)

[19] Denters, M., et al. {2010). "Participation rate in a second round of fecal immunochemical test based screening decreases due to low response rates among previous non-responders and first-time invitees." Gastroenterology 138{5): S186.

[20] Osborne, J. M., et al. {2012). "Patterns of participation over multiple rounds of faecal immunochemical test-based screening for colorectal cancer." J. Gastroenterol. Hepatol. 27: 27.

[21] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:NOT {10.7.2013)

[22] http://europa.eu/rapid/press-release_IP-11-1589_en.htm {15.7.2013)

[23] http://europa.eu/rapid/press-release_IP-08-1075_en.htm

[24] http://conventions.coe.int/Treaty/EN/Treaties/Html/005.htm {14.5.2013)

[25] International Convention on the Elimination of all forms of Racial Discrimination; Article 5. http://www.ohchr.org/EN/ProfessionalInterest/Pages/CERD.aspx {15.7.2013)

[26] International Convention on the Protection of the Rights of All Migrant Workers and Members of their Families {1990), Art. 28; http://www.un.org/documents/ga/res/45/a45r158.htm {15.7.2013)

[27] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine; Oviedo, 1997, European Treaty Series - No. 164; http://conventions.coe.int/Treaty/en/Treaties/html/164.htm {15.7.2013)

[28] Charter of Fundamental Rights of the European Union {2007/C 303/01), Article 35; http://eur-lex.europa.eu/en/treaties/dat/32007X1214/htm/C2007303EN.01000101.htm {15.7.2013)

[29] Council Regulations {EC) No 1408/71of 14 June on the application of social security schemes to employed persons, to self-employed persons and to members of their families moving within the Community; especially Article 22A.; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1971R1408:20060428:en:PDF {15.7.2013)

[30] A Declaration on the Promotion of Patients' Rights in Europe, WHO 1994; http://www.who.int/genomics/public/eu_declaration1994.pdf {15.7.2013)

[31] World Medical Association Statement on Access to Health Care. Adopted by the 40th World medical Assembly Vienna, Austria, September 1988 and revised by the WMA General Assembly, Pilanesberg, South Africa, October 2006. http://www.wma.net/en/30publications/20journal/pdf/wmj16.pdf {15.7.2013)

[32] DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF {15.7.2013)

[32] States Parties are countries which have adhered to the World Heritage Convention. http://whc.unesco.org/en/statesparties {15.7.20123)

[33] Convention on the Elimination of all Forms of Discrimination against Women; Article 12; http://www.childinfo.org/files/childmarriage_cedaw.pdf {15.7.2013)

[34]Recommendation Rec{2006)2 of the Committee of Ministers to member states on the European Prison Rules1 https://wcd.coe.int/ViewDoc.jsp?id=955747 {15.7.2013)

[35] Recommendation No. R{98) 71 of the Committee of Ministers to Member States concerning the ethical and organisational aspects of health care in prison; https://wcd.coe.int/com.instranet.InstraServlet?command=com.instranet.CmdBlobGet&InstranetImage=530914&SecMode=1&DocId=463258&Usage=2 {15.7.2013)

[36] Council Regulations {EC) No 1408/71of 14 June on the application of social security schemes to employed persons, to self-employed persons and to members of their families moving within the Community; especially Art. 22A; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1971R1408:20060428:en:PDF {15.7.2013)

[37] Regulations {EEC) No 1408/71 from 14th June 1971; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1971R1408:20070102:EN:PDF {15.7.2013)

No 547/72 from 21st March 1972; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1997:176:0001:0016:en:PDF

No 883/2004, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:166:0001:0123:en:PDF

No 988/2009; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32009R0988:en:NOT {all 15.7.2013)

[38] DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF {15.7.2013)

[39] Charter of Fundamental Rights of the European Union {2007/C 303/01); Articles 1 - 4; 7,8; http://eur-lex.europa.eu/en/treaties/dat/32007X1214/htm/C2007303EN.01000101.htm {15.7.2013)

[40] Rezende EJ ; Melo Mdo C ; Tavares EC ; Santos Ade F ; Souza C. [Ethics and eHealth: reflections for a safe practice]. Rev Panam Salud Publica. 2010 Jul;28{1):58-65.

[41] Loeber JG. Legal issues in neonatal screening. Ann Acad Med Singapore. 2008 Dec;37{12 Suppl):92-2.

[42] Van Roosbroeck S, Hoeck S, Van Hal G. Population-based screening for colorectal cancer using an immunochemical faecal occult blood test: a comparison of two invitation strategies. Cancer Epidemiol. 2012 Oct;36{5):e317-24. doi: 10.1016/j.canep.2012.04.003. Epub 2012 May 5.

[43] Poncet F, Delafosse P, Seigneurin A, Exbrayat C, Colonna M. Determinants of participation in organized colorectal cancer screening in Isere {France). Clin Res Hepatol Gastroenterol. 2013 Apr;37{2):193-9. doi: 10.1016/j.clinre.2012.04.011. Epub 2012 Jun 14.

[44] Le Breton J, Journy N, Attali C, Le Corvoisier P, Brixi Z, Bastuji-Garin S, Chevreul K. Improving participation in colorectal cancer screening: targets for action. Prev Med. 2012 Nov;55{5):488-92. doi: 10.1016/j.ypmed.2012.08.004. Epub 2012 Aug 21.

[45] Portillo I, Idigoras I, Ojembarrena E, Arana-Arri E, Zubero MB, Pijoan JI, Lopez Urrutia A, Marques ML. [Main results of the colorectal cancer screening program in the Basque Country {Spain).]. Gac Sanit. 2013 Feb 14. pii: S0213-9111{13)00005-8. doi: 10.1016/j.gaceta.2012.12.013.

[46] Denters MJ, Deutekom M, Bossuyt PM, van Rijn AF, Fockens P, Dekker E. Involvement of previous non-participants cannot fully compensate for lower participation in a second round of FIT-screening. Cancer Epidemiol. 2013 Jun;37{3):330-5. doi: 10.1016/j.canep.2013.01.007. Epub 2013 Feb 9.

[47] Fon Sing M, Leuraud K, Duport N. Characteristics of French people using organised colorectal cancer screening. Analysis of the 2010 French Health, Healthcare and Insurance Survey. Prev Med. 2013 Mar 27. pii: S0091-7435{13)00077-7. doi: 10.1016/j.ypmed.2013.03.008.

[48] Vitek P, Kajzrlikova IM, Bures J, Chalupa J. [Inadequate screening and low awareness about risk factors among first-degree relatives of colorectal cancer patients]. Vnitr Lek. 2011 Dec;57{12):1057-61.

[49] Ait Ouakrim D, Lockett T, Boussioutas A, Keogh L, Flander LB, Hopper JL, Jenkins MA. Screening participation predictors for people at familial risk of colorectal cancer: a systematic review. Am J Prev Med. 2013 May;44{5):496-506. doi: 10.1016/j.amepre.2013.01.022.

[50] de Wijkerslooth TR, de Haan MC, Stoop EM, Bossuyt PM, Thomeer M, Essink-Bot ML, van Leerdam ME, Fockens P, Kuipers EJ, Stoker J, Dekker E. Burden of colonoscopy compared to non-cathartic CT-colonography in a colorectal cancer screening programme: randomised controlled trial. Gut. 2012 Nov;61{11):1552-9. Epub 2011 Dec 23.

[51] van Dam L, Korfage IJ, Kuipers EJ, Hol L, van Roon AH, Reijerink JC, van Ballegooijen M, van Leerdam ME. What influences the decision to participate in colorectal cancer screening with faecal occult blood testing and sigmoidoscopy?. Eur J Cancer. 2013 Apr 6. pii: S0959-8049{13)00193-7. doi: 10.1016/j.ejca.2013.03.007.

[52] Brenner H, Stock C, Hoffmeister M. [Colorectal cancer screening]. Ther Umsch. 2013 Apr;70{4):231-5; discussion 236. doi: 10.1024/0040-5930/a000394.

[53] de Wijkerslooth TR, de Haan MC, Stoop EM, Bossuyt PM, Thomeer M, van Leerdam ME, Essink-Bot ML, Fockens P, Kuipers EJ, Stoker J, Dekker E. Reasons for participation and nonparticipation in colorectal cancer screening: a randomized trial of colonoscopy and CT colonography. Am J Gastroenterol. 2012 Dec;107{12):1777-83. doi: 10.1038/ajg.2012.140.

[54] de Haan MC, de Wijkerslooth TR, Stoop E, Bossuyt P, Fockens P, Thomeer M, Kuipers EJ, Essink-Bot ML, van Leerdam ME, Dekker E, Stoker J. Informed decision-making in colorectal cancer screening using colonoscopy or CT-colonography. Patient Educ Couns. 2013 Jun;91{3):318-25. doi: 10.1016/j.pec.2013.01.004. Epub 2013 Feb 8.

[55] Mila N, Garcia M, Binefa G, Borras JM, Espinas JA, Moreno V. [Adherence to a population-based colorectal cancer screening program in Catalonia {Spain), 2000-2008]. Gac Sanit. 2012 May-Jun;26{3):217-22. doi: 10.1016/j.gaceta.2011.10.020. Epub 2012 Feb 22.

[56] van Dam L, de Wijkerslooth TR, de Haan MC, Stoop EM, Bossuyt PM, Fockens P, Thomeer M, Kuipers EJ, van Leerdam ME, van Ballegooijen M, Stoker J, Dekker E, Steyerberg EW. Time requirements and health effects of participation in colorectal cancer screening with colonoscopy or computed tomography colonography in a randomized controlled trial. Endoscopy. 2013 Mar;45{3):182-8. doi: 10.1055/s-0032-1326080. Epub 2013 Feb 27.

[57] Pontone S. Colorectal cancer screening behavior and willingness. World J Gastroenterol. 2012 Jun 14;18{22):2885-6. doi: 10.3748/wjg.v18.i22.2885.

[58] Ramos M, Taltavull M, Pineiro P, Nieto R, Llagostera M. [Attitudes of primary health care users to a colorectal cancer screening program.]. Gac Sanit. 2012 Dec 29. pii: S0213-9111{12)00328-7. doi: 10.1016/j.gaceta.2012.11.007.

[59] Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Prev Med. 2012 Aug;55{2):87-92. doi: 10.1016/j.ypmed.2012.05.006. Epub 2012 May 23.

[60] Wong AD, Kirby J, Guyatt GH, Moayyedi P, Vora P, You JJ. Randomized controlled trial comparing telephone and mail follow-up for recruitment of participants into a clinical trial of colorectal cancer screening. Trials. 2013 Feb 11;14:40. doi: 10.1186/1745-6215-14-40.

[61] Ferroni E, Camilloni L, Jimenez B, Furnari G, Borgia P, Guasticchi G, Giorgi Rossi P. How to increase uptake in oncologic screening: a systematic review of studies comparing population-based screening programs and spontaneous access. Prev Med. 2012 Dec;55{6):587-96. doi: 10.1016/j.ypmed.2012.10.007. Epub 2012 Oct 11.

[62] Camilloni L, Ferroni E, Cendales BJ, Pezzarossi A, Furnari G, Borgia P, Guasticchi G, Rossi PG. Methods to increase participation in organised screening programs: a systematic review. BMC Public Health. 2013 May 13;13{1):464.

[63] Consolidated versions of the Treaty on European Union and the Treaty on the Functioning of the European Union Official Journal C 115 , 09/05/2008 P. 0001 - 0388; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0001:01:en:HTML

[64] Directive 2011/24 of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare. Commission of the European Communities {Articles 1 - 22). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF

[65] Council Resolution of 20 December 1995 on the integration of health protection requirements in Community policies OJ C 350, 30.12.1995, p. 2–3; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995Y1230{02):EN:NOT {16.7.2013)

[66] Victoria S. Benson, Julietta Patnick, Anna K. Davies, Marion R. Nadel, Robert A. Smith and Wendy S. Atkin on behalf of the International Colorectal Cancer Screening Network. Colorectal cancer screening: A comparison of 35 initiatives in 17 countries. Int. J. Cancer: 122, 1357–1367 {2008) ' 2007 Wiley-Liss, Inc.

[67] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm?start_search=C {15.5.2013)

[68] http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/index_en.htm {15.5.2013)

[69] Stewart C, Brennan F. Legal issues concerning withholding and withdrawal of dialysis. Nephrology {Carlton). 2013 Apr 16. doi: 10.1111/nep.12086. [Epub ahead of print]

[70] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12012P/TXT:EN:NOT {16.7.2013)

[71] Convetion on the Rights of Perosns with Disabilities; Article 25 {Health); http://www.un.org/disabilities/convention/conventionfull.shtml {16.7.2013)

[72] Dissertation Mag. jur. Birgit Stranz. *Die rechtliche Stellung minderjähriger Patienten im Wandel der Zeit unter besonderer Berücksichtigung der Einwilligung in medizinische Behandlungen {20./21. Jh.).* http://othes.univie.ac.at/13759/1/2010-06-27_0001014.pdf {16.7.2013)

[73] Bello BA. Dignity and informed consent in the treatment of mature minors. J Int Bioethique. 2010 Dec;21{4):103-22, 164-5.

[74] Dementia – Etiology and Epidemiology: A systematic Review. Vol 1 June 2008. The Swedish Council on Technology Assessment in Health Care. Available at: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol1.pdf {16.7.2013)

[75] Charter of Fundamental Rights of the European Union {2007/C 303/01); Article 34 {Social Security & Assistance) + Article 35 {Health Care) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2007:303:0001:0016:EN:PDF {16.7.2013)

[76] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF {16.7.2013)

[77] P7_TA{2010)0152 Commission communication on Action against Cancer: European Partnership European Parliament resolution of 6 May 2010 on the Commission communication on Action Against Cancer: European Partnership {2009/2103{INI)); I 39

http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2010-0121&language=EN [4] P7_TA{2010)0152 (16.7.2013)

[78] Baughman KR ; Ludwick RE ; Merolla DM ; Palmisano BR ; Hazelett S ; Winchell J ; Hewit M. Professional Judgments About Advance Care Planning with Community-Dwelling Consumers. J Pain Symptom Manage. 2011 Jul 13.

[79] Judgment of the Court {Grand Chamber) of 16 May 2006. The Queen, on the application of Yvonne Watts v Bedford Primary Care Trust and Secretary of State for Health. Reference for a preliminary ruling: Court of Appeal {England & Wales) {Civil Division) - United Kingdom. Social security - National health system funded by the State - Medical expenses incurred in another Member State - Articles 48 EC to 50 EC and 152{5) EC - Article 22 of Regulation {EEC) No 1408/71. Case C-372/04. http://eur-lex.europa.eu/Notice.do?val=426362:cs&lang=de&list=432665:cs,439339:cs,427772:cs,426362:cs,420145:cs,418803:cs,418258:cs,401136:cs,417775:cs,401132:cs,&pos=4&page=6&nbl=64& (16.7.2013)

[80] Consolidated versions of the Treaty on European Union and the Treaty on the Functioning of the European Union Official Journal C 115 , 09/05/2008 P. 0001 - 0388; http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:115:0001:01:en:HTML (16.7.2013)

[81] Directive 2011/24 of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare. Commission of the European Communities {Articles 1 - 22). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF (16.7.2013)

[82] Suitability and feasibility of a colorectal cancer screening program in Québec; Executive summary and conclusions of the report of the scientific committee established by the Institut national de santé publique du Québec; available at: *http://www.inspq.qc.ca. {30.4.2013)*

[83] Eaden J, Mayberry MK, Sherr A, Mayberry JF. Screening: the legal view. *Public Health* {2001) 115, 218-221. PMID: 11429719

[84] Hudson B, Zarifeh A, Young L, Wells JE. Patients' expectations of screening and preventive treatments. Ann Fam Med. 2012 Nov-Dec;10{6):495-502. doi: 10.1370/afm.1407.

[85] Gandhi TK, Kachalia A, Thomas EJ, Puopolo AL, Yoon C, Brennan TA, Studdert DM.. Missed and delayed diagnoses in the ambulatory setting: a study of closed malpractice claims. Ann Intern Med. 2006 Oct 3;145{7):488-96.

[86] Charter of Fundamental Rights of the European Union {2007/C 303/01); Articles 1 - 4; 7,8 http://eur-lex.europa.eu/en/treaties/dat/32007X1214/htm/C2007303EN.01000101.htm {2.5.2013)

[87] WMA Declaration of Lisbon on the Rights of the Patient, Adopted by the 34th World Medical Assembly, Lisbon, Portugal, September/October 1981 and amended by the 47th WMA General Assembly, Bali, Indonesia, September 1995 and editorially revised by the 171st WMA Council Session, Santiago, Chile, October 2005; http://www.wma.net/en/30publications/10policies/l4/ {2.5.2013)

[88] §§27, 28, 29 Berufsordnung {Satzung) of the Germans Physicians, Musterberufsordnung der Ärzte {MBO), Heilmittelwerbegesetz {HWG), Gesetz gegen den unlauteren Wettbewerb {UWG) http://www.aeksh.de/aerzte/arzt_und_recht/rechtsgrundlagen/berufsordnung/berufsordnung_satzung.html {2.5.2013);

http://www.gesetze-im-internet.de/bundesrecht/heilmwerbg/gesamt.pdf {2.5.2013); http://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10002665 {2.5.2013)

[89] §53 ÄrzteG 1998, BGBl. I 169/1998, Austria; http://www.ris.bka.gv.at/Dokument.wxe?Abfrage=Bundesnormen&Dokumentnummer=NOR30004852

[90] VfGH RdM 1997/32, Austria: V56/00 ua

http://www.ris.bka.gv.at/Dokument.wxe?Abfrage=Gesamtabfrage&Dokumentnummer=JFT_09988999_00V00056_00&ResultFunctionToken=2af216b9-0402-441c-9fd2-9e9429477464&SearchInAsylGH=&SearchInBegut=&SearchInBgblAlt=&SearchInBgblAuth=&SearchInBgblPdf=&SearchInBks=&SearchInBundesnormen=&Search {27.09.2011)

[91] www.doctorix.eu

[92] http://dx.doi.org/10.1016/j.zefq.2008.09.010; available at: http://www.sciencedirect.com/science/article/pii/S1865921708002493 {3.7.2013)

[93] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0079:en:NOT (07.10.2013)

Appendices

Table 1

influences on higher participation	influences on lower participation
female gender {42,43}	male gender {44,45,46}
awareness of risk {48,49}	younger age groups {44,46, 47,43}
participation by mail {42}	social deprivation {44}
recommendation from clinicians {49}	urban people {42}
social influence {49}	expected versus experienced burden {50,51}
inviting eligible individuals {52}	unpleasureness of the examination {53}
attitudes {54,55,51}	not having 100% coverage for medical fees for a long-term disease {47},
expected value {53}	having consulted a medical specialist in the last 12months {47}
living in a pilot district for CRC screening {47}	not smoking {47}
having a private additional insurance {47}	Anxiety, pain, and quality of life {56,51}
health insurance plan {43}	lack of abdominal complaints {51}
high eductaional level {57}	
Physicians contribution {57}	
opportunity for early diagnosis {58, 51}	
acquiring certainty about CRC presence {51}	
individuals offered faecal immunochemical tests {59}	
follow-up by telephone {60,62}	
invitation letter {61,62}	
scheduled appointment {62}	

Table 2

Country	**Brand name of test**
Czech Republic	Hemoccult
Denmark	Hemoccult II

France	Hemoccult
Italy	RPHA immudia
	Alpha Wasserman
	Hemoccult SENSA II
	Alpha Wasserman, Sentinel
	FlexSure OBT
Poland	Hema Screen
Spain	Hema Screen
	Hemoccult
Switzerland	Hemoccult
United Kingdom	Hema Screen

Table 3

Test System Name	Document Number	Analyte Name	Analyte Specialty	Complexity	Effective Date	Device Classification Name	510{K) Number	Model	Device Name	Applicant				Contact	Re Nu
hema screen ER	K102664	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K102664	HSER-50, HSER-100	HEMA SCREEN ER	IMMUNOSTICS, INC.	3505 sunset ave.	ocean, NJ 07712		richard m peoples	8,(
Henry Schein OneStep+ iFOBT	K060463	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K060463		HEMA SCREEN SPECIFIC IFOBT	IMMUNOSTICS, INC.	3505 sunset ave.	ocean, NJ 07712		jeffrey fleishman	8,(
Healthcare Provider Direct OneStep Fecal Occult Blood {FOB) Screen Card Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	07/22/2008	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
HEMOCARE	K840527	Fecal Occult Blood	General Chemistry	WAIVED	02/23/2004	reagent, occult blood20	K840527		COLOTRAK OCCULT BLOOD TEST	BREIT LABORATORIES, INC.					8,(
HELENA LABORATORIES COLOSCREEN-ES	K003359	Fecal Occult Blood	General Chemistry	WAIVED	12/13/2000	reagent, occult blood20	K003359		COLOSCREEN-ES	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
BTNX Inc. Rapid Response Fecal Immunochemical Test {FIT)	K100031	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K100031	440-10	IND ONE STEP FECAL OCCULT BLOOD TEST MODEL 440-10	IND DIAGNOSTIC INC.	1629 fosters way	delta, bc,		jason peng	8,(
BTNX Inc. Rapid Response Immunological Fecal Occult Blood Test {IFOBT)	K061065	Fecal Occult Blood	General Chemistry	WAIVED	07/22/2008	reagent, occult blood20	K061065		FECAL OCCULT BLOOD CARD TEST, MODEL F735-A, FECAL OCCULT BLOOD CARD KIT, MODEL F735-25	TECO DIAGNOSTICS	1268 north lakeview ave.	anaheim, CA 92807		jian vaeches	8,(
BECKMAN COULTER HEMOCCULT ICT	K080812	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K080812		HEMOCCULT ICT	BECKMAN COULTER, INC.	200 south kraemer blvd. w-110	po box 8000	brea, CA 92822	sylvia zorich	8,(
BTNX Inc. Clarity Fecal Occult Blood {FOB) Self Test	K070660	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K070660		INSTANT-VIEW FECAL OCCULT BLOOD {FOB) RAPID TEST	ALFA SCIENTIFIC DESIGNS, INC.	13200 gregg st.	poway, CA 92064		majid pajouh	8,(

BTNX Inc. Know Fecal Occult Blood {FOB) Self Test	K070660	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K070660		INSTANT-VIEW FECAL OCCULT BLOOD {FOB) RAPID TEST	ALFA SCIENTIFIC DESIGNS, INC.	13200 gregg st.	poway, CA 92064		majid pajouh	8,(
BTNX Inc. Rapid Response Fecal Occult Blood {FOB) Self Test	K070660	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K070660		INSTANT-VIEW FECAL OCCULT BLOOD {FOB) RAPID TEST	ALFA SCIENTIFIC DESIGNS, INC.	13200 gregg st.	poway, CA 92064		majid pajouh	8,(
BECKMAN COULTER HEMOCCULT ICT	K961062	Fecal Occult Blood	General Chemistry	WAIVED	06/28/2004	reagent, occult blood20	K961062		FLEXSURE OBT	SMITHKLINE DIAGNOSTICS, INC.	606 elmwood ave.	court iii	sharon hill, PA 19079 1031	marshall c mccarty	8,(
BECKMAN COULTER HEMOCCULT ICT	K961062	Fecal Occult Blood	General Chemistry	WAIVED	05/26/2004	reagent, occult blood20	K961062		FLEXSURE OBT	SMITHKLINE DIAGNOSTICS, INC.	606 elmwood ave.	court iii	sharon hill, PA 19079 1031	marshall c mccarty	8,(
BECKMAN COULTER PRIMARY CARE DIAGNOSTICS HEMOCCULT SENSA	K880499	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K880499		HEMOCCULT SENSITIVE TEST	SMITH KLINE DIAGNOSTICS, INC.	225 baypointe pkwy.	san jose, CA 95134 1622		ronald schoengold	8,(
BERGEN BRUNSWIG TEST FOR FECAL OCCULT BLOOD	K911075	Fecal Occult Blood	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
Centralcheck iFOBT Complete Fecal Occult Blood Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	11/16/2010	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
Care Diagnostic Clarity IFOB Test	K052598	Fecal Occult Blood	General Chemistry	WAIVED	01/26/2010	reagent, occult blood20	K052598		IMMOCARE	CARE DIAGNOSTIC, INC.	1741 wiard street	klamath falls, OR 97603		araceli fancher-ferreira	8,(
CLIAwaived, Inc. Rapid Fecal Occult Blood Test	K061065	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K061065		FECAL OCCULT BLOOD CARD TEST, MODEL F735-A, FECAL OCCULT BLOOD CARD KIT, MODEL F735-25	TECO DIAGNOSTICS	1268 north lakeview ave.	anaheim, CA 92807		jian vaeches	8,(
Care Fecal Occult Blood Test	K051806	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K051806		CARE FECAL OCCULT BLOOD TEST, MODEL KT313	EPITOPE DIAGNOSTICS, INC.	7955 dunbrook rd., suite b	san diego, CA 92126		ping gao	8,(
Clarity Hemosure One-Step Immunological Fecal Occult Blood Test	K041202	Fecal Occult Blood	General Chemistry	WAIVED	03/30/2005	reagent, occult blood20	K041202		HEMOSURE ONE-STEP FECAL OCCULT BLOOD TEST	W.H.P.M., INC.	163 cabot st.	beverly, MA 01915		fran white	8,(
Clearview Ultra FOB Test	K041297	Fecal Occult Blood	General Chemistry	WAIVED	08/18/2004	reagent, occult blood20	K041297		POLYMEDCO OC LIGHT FOBT TEST	POLYMEDCO, INC.	510 furnace dock rd.	cortlandt manor, NY 10567		helen landicho	8,(
CHASMA SCIENTIFIC, INC., CHASMA-CULT {TRI-SLIDE AND SINGLE SLIDE STOOL}	K761232	Fecal Occult Blood	General Chemistry	WAIVED	06/28/2004	reagent, occult blood20	K761232		QUICK CULT SLIDE TEST FECAL OCCULT BLOOD	LABORATORY DIAGNOSTICS CO., INC.					8,(
CHASMA SCIENTIFIC, INC., CHASMA-CULT {QUICK CULT SLIDE}	K761232	Fecal Occult Blood	General Chemistry	WAIVED	06/28/2004	reagent, occult blood20	K761232		QUICK CULT SLIDE TEST FECAL OCCULT BLOOD	LABORATORY DIAGNOSTICS CO., INC.					8,(
CHEMICON MONOHAEM	K901064	Fecal Occult Blood	General Chemistry	WAIVED	05/15/2003	reagent, occult blood20	K901064		MONOHAEM {FECAL OCCULT BLOOD TEST)	SILENUS LABORATORIES PROPRIETARY LTD.	wilmington, DE 19897			william a best	8,(
CIDA COLOCHECK	K911075	Fecal Occult	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh	p.o. box 752	beaumont, TX 77704	pat franks	8,(

		Blood									dr.				
DE HEALTHCARE PRODUCTS DETECT~OCCULT SLIDE TEST FOR FECAL OCCULT BLOOD	K902360	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K902360		HEMA-SCREEN	IMMUNOSTICS CO., INC.	3505 sunset ave.	ocean, NJ 07712		kenneth kupits	8,(
DIAGNOSTICA, INC. EASE-A-CULT SENSITIVE	K002756	Fecal Occult Blood	General Chemistry	WAIVED	02/21/2001	reagent, occult blood20	K002756		EASE-A-CULT	DIAGNOSTICA, INC.	p.o. box 4341	crofton, MD 21114		yolanda smith	8,(
ENTERIX INSURE II FECAL IMMUNOCHEMICAL TEST	K060930	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K060930		INSURE II	ENTERIX INC.	236 fernwood ave.	edison, NJ 08837		edwin diaz	8,(
ENTERIX INSURE FECAL IMMUNOCHEMICAL TEST	K002457	Fecal Occult Blood	General Chemistry	WAIVED	10/16/2003	reagent, occult blood20	K002457		!NSURE FECAL OCCULT BLOOD TEST	ENTERIX INC.	348 us route one	falmouth,, ME 04105		robert c bruce	8,(
ENTERIX !NSURE FECAL OCCULT BLOOD TEST	K002457	Fecal Occult Blood	General Chemistry	WAIVED	01/31/2001	reagent, occult blood20	K002457		!NSURE FECAL OCCULT BLOOD TEST	ENTERIX INC.	348 us route one	falmouth,, ME 04105		robert c bruce	8,(
Forsure One Step Fecal Occult Blood {FOB) Screen Card Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	05/16/2007	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
FISHER HEALTHCARE SURE-VUE FECAL OCCULT BLOOD	K911075	Fecal Occult Blood	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
Germaine Laboratories Compliance Gold iFOB {immunological fecal occult blood)Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
GERMAINE LABORATORIES AimStep Immunological Fecal Occult Blood Test {iFOBT)	K063693	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
Immunostics, Inc., hema-screen STAT	K905782	Fecal Occult Blood	General Chemistry	WAIVED	05/20/2010	reagent, occult blood20	K905782		FHT {FECAL HEME TEST)	AERSCHER, INC.	527 fey rd.	chestertown, MD 21620		robert schreiber	8,(
Inverness Medical Clearview iFOBT Complete Fecal Occult Blood Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
Inverness Medical Clearview iFOBT Complete Fecal Occult Blood Test	K063693	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
Innovacon FOB Flipcard Fecal Occult Blood Test	K063673	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063673		INNOVACON FLIPCARD FECAL OCCULT BLOOD TEST DEVICE	INNOVACON, INC.	4106 sorrento valley blvd.	san diego, CA 92121		edward tung	8,(
InSure Quik Fecal Immunochemical Test {F.I.T.)	K060930	Fecal Occult Blood	General Chemistry	WAIVED	01/26/2007	reagent, occult blood20	K060930		INSURE II	ENTERIX INC.	236 fernwood ave.	edison, NJ 08837		edwin diaz	8,(
Immunostics, Inc., hema-screen SPECIFIC Immunochemical Fecal Occult Blood Test	K060463	Fecal Occult Blood	General Chemistry	WAIVED	06/15/2006	reagent, occult blood20	K060463		HEMA SCREEN SPECIFIC IFOBT	IMMUNOSTICS, INC.	3505 sunset ave.	ocean, NJ 07712		jeffrey fleishman	8,(
immoCARE Fecal Occult Blood Test	K052598	Fecal Occult Blood	General Chemistry	WAIVED	03/22/2006	reagent, occult blood20	K052598		IMMOCARE	CARE DIAGNOSTIC, INC.	1741 wiard street	klamath falls, OR 97603		araceli fancher-ferreira	8,(

Jant Pharmacal Accutest Dual Sample Immunological Fecal Occult Blood {iFOB) Test	K073431	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K073431		FORSURE IFOB DUEL SAMPLE FECAL OCCULT BLOOD TEST DEVICE {FOR PROFESSIONAL AND HOME USE); {FOR PROFESSIONAL); {FOR HOME T	TIANJIN NEW BAY BIORESEARCH CO., LTD.	3108 avenida olmeda	carlsbad, CA 92009		armando torrescano	8,(
Jant Pharmacal Accutest Immunological Fecal Occult Blood Test {iFOBT)	K063693	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K063693		FORSURE ONE STEP FECAL OCCULT BLOOD {FOB) SCREEN CARD TEST	NEW BAY BIORESEARCH CO. LTD.	3108 avenida olmeda	carlsbad, CA 92009		rodrigo berlie	8,(
Medline iFOB One-Step Immunological Fecal Occult Blood Test	K100031	Fecal Occult Blood	General Chemistry	WAIVED	04/19/2012	reagent, occult blood20	K100031	440-10	IND ONE STEP FECAL OCCULT BLOOD TEST MODEL 440-10	IND DIAGNOSTIC INC.	1629 fosters way	delta, bc,		jason peng	8,(
MEDTEK DIAGNOSTICS INSTACCULT	K002930	Fecal Occult Blood	General Chemistry	WAIVED	01/30/2001	reagent, occult blood20	K002930		INSTACCULT	MEDTEK DIAGNOSTICS, LLC.	po box 14125	research triangle park, NC 27709 4125		liane f gosset	8,(
OSOM® iFOB Test OSOM® iFOBT Control Kit	K121397	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K121397	PN 150, PN151, PN152, PN153	OSOM IFOB 25 TEST AND PATIENT COLLECTION KIT OSOM IFOB CONTROL KIT OSOM IFOB 50 TEST KIT	SEKISUI DIAGNOSTICS, LLC	6659 top gun st	san diego, CA 92121		mark stavro	8,(
Orient Gene Biotech - One Step Rapid FOB	K110309	Fecal Occult Blood	General Chemistry	WAIVED	09/20/2011	reagent, occult blood20	K110309		FOB ONE STEP RAPID TEST	ORIENT GENE BIOTECH	150 cherry lane rd	east stroudsburg, PA 18301		gary lehnus	8,(
OC-Light iFOB Test	K041297	Fecal Occult Blood	General Chemistry	WAIVED	03/24/2011	reagent, occult blood20	K041297		POLYMEDCO OC LIGHT FOBT TEST	POLYMEDCO, INC.	510 furnace dock rd.	cortlandt manor, NY 10567		helen landicho	8,(
OcculTech Fecal Occult Blood Rapid Test	K060953	Fecal Occult Blood	General Chemistry	WAIVED	09/22/2006	reagent, occult blood20	K060953		OCCULTECH FECAL OCCULT BLOOD RAPID TEST	YD DIAGNOSTICS CORP.	4304 evergreen lane	suite 101	annandale, VA 22003	dusic kwak	8,(
PSS CONSULT Diagnostic Occult Blood Test	K911075	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
PSS CONSULT diagnostics Occult Blood Test-ES	K003359	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K003359		COLOSCREEN-ES	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
POLYMEDCO POLY STAT OC-LIGHT FOB TEST	K041297	Fecal Occult Blood	General Chemistry	WAIVED	08/18/2004	reagent, occult blood20	K041297		POLYMEDCO OC LIGHT FOBT TEST	POLYMEDCO, INC.	510 furnace dock rd.	cortlandt manor, NY 10567		helen landicho	8,(
PSS SELECT OCCULT BLOOD TEST	K911075	Fecal Occult Blood	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
QuickVue iFOB Test {Immunochemical Fecal Occult Blood) {Cassette)	K021423	Fecal Occult Blood	General Chemistry	WAIVED	#######	reagent, occult blood20	K021423		INSTANT-VIEW FECAL OCCULT BLOOD RAPID TEST	ALFA SCIENTIFIC DESIGNS, INC.	12330 stowe dr.	poway, CA 92064		naishu wang	8,(
REDWOOD BIOTECH FECAL OCCULT BLOOD TEST	K902360	Fecal Occult Blood	General Chemistry	WAIVED	09/25/2003	reagent, occult blood20	K902360		HEMA-SCREEN	IMMUNOSTICS CO., INC.	3505 sunset ave.	ocean, NJ 07712		kenneth kupits	8,(
Status iFOBT	K100817	Fecal Occult Blood	General Chemistry	WAIVED	10/19/2011	reagent, occult blood20	K100817		BIOSIGN IFOBTEST, BIOSIGN FECAL OCCULT BLOOD TEST	PRINCETON BIOMEDITECH CORP.	4242 u.s. rt. 1	monmouth junction, NJ 08852 1905		jemo kang, ph.d.	8,(

Siemens Hematest Reagent Tablets {Pre-amendment device)	X100047	Fecal Occult Blood	General Chemistry	WAIVED	12/17/2010	510{k) Exempt Database	X100047		Hematest Reagent Tablets	Siemens Healthcare Diagnostics Inc.	2 edgewater drive	norwood, MA 02062		sheila smith	8,(
STANBIO HEMA-SCREEN	K911075	Fecal Occult Blood	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
STARLINE COLOSCAN	K911075	Fecal Occult Blood	General Chemistry	WAIVED	09/27/2001	reagent, occult blood20	K911075		COLOSCREEN	HELENA LABORATORIES	1530 lindbergh dr.	p.o. box 752	beaumont, TX 77704	pat franks	8,(
Tianjin New Bay Bioresearch Co., Ltd. ForeSure IFOB Dual-Sample Fecal Occult Blood Screen Card Test	K073431	Fecal Occult Blood	General Chemistry	WAIVED	02/22/2012	reagent, occult blood20	K073431		FORSURE IFOB DUEL SAMPLE FECAL OCCULT BLOOD TEST DEVICE {FOR PROFESSIONAL AND HOME USE); {FOR PROFESSIONAL); {FOR HOME T	TIANJIN NEW BAY BIORESEARCH CO., LTD.	3108 avenida olmeda	carlsbad, CA 92009		armando torrescano	8,(

Table 4

Total number of observed claims	**Detected malpractice**	**Reasons for malpractice**	leading factors that contributed to the errors
307 closed malpractice claims reviewed	181 claims {59%) involved diagnostic errors that harmed patients	failure to order an appropriate diagnostic test {100 of 181 [55%]	failures in judgment {143 of 181 [79%])
	106 of 181 {59%) of these errors were associated with serious harm	failure to create a proper follow-up plan {81 of 181 [45%]	vigilance or memory {106 of 181 [59%])
	55 of 181{30%) resulted in death	failure to obtain an adequate history or perform an adequate physical examination {76 of 181 [42%]	knowledge {86 of 181 [48%])
	For 106 of 181 {59%) of the errors, cancer was the diagnosis involved {breast {44 claims [24%]) and colorectal {13 claims [7%]) cancer)	incorrect interpretation of diagnostic tests {67 of 181 [37%]	patient-related factors {84 of 181 [46%])
			handoffs {36 of 181 [20%])

Collection appendices

Survey for gathering information on technologies Report

Literature Search Strategy

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