Princess máxima center
pediatric oncology

Annual Report
2021

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2021

Board of Directors of the Princess Máxima Center for Pediatric Oncology B.V.

Preface Board of Directors

All the highly complex care and research in the field of pediatric oncology in the Netherlands is concentrated in the Princess Máxima Center for pediatric oncology. Our mission is: to provide a cure for every child with cancer while maintaining an optimal quality of life. We have expanded in recent years to become the largest European center for the treatment of and research into childhood cancer.

The standard care provided by the Princess Máxima Center is reimbursed by healthcare insurance companies. The organization funds its research via other sources. Important contributors to our funding are KiKa (Children Cancer-free Foundation) and a subsidy from the Ministry of Health, Welfare and Sport. Services that fall beyond the standard healthcare insurance cover have been realized in part thanks to the Princess Máxima Center Foundation.

Although the COVID-19 pandemic initially had an impact on fundraising for research projects, this effect was ultimately limited. We see on a daily basis that what we do adds value for our patients and their loved ones. The Princess Máxima Center appointed a renowned external consultancy (SiRM) to determine the value of the treatment and research into pediatric cancer in a socio-economic and macro-economic context. This report concluded that the investment in both the treatment of and research into pediatric cancer is recovered in ample measure in terms of the socio-economic aspect; the costs for a life-year gained amount to € 6,000 - € 8,000. The benefits in health economic terms are six-fold greater than the annual costs.

In addition, the Máxima Center actively contributes to the improvement of the quality of life of both children, parents and caregivers during and after the illness. Working alongside the departments of Hemato-oncology, Solid tumors and Neuro-oncology, the Quality of Life department focuses on reduction of pain and infection, comprehensive psycho-oncological counseling of child and parent and reduction of the late consequences of treatment.

Furthermore, research in the Máxima Center ensures that increasing numbers of children in the Netherlands and abroad can be saved in the future. The research conducted by SiRM demonstrates that – from an international perspective – an increase in at least five extra survivors per year can be attributed to Dutch pediatric oncology research.

All the more reason to forge ahead with our integrated care and research, to pursue resources and leading experts and to continue and expand the collaboration within and beyond the Netherlands.

This report demonstrates that we have once again worked hard on achieving these goals in 2021. Despite the impact of the COVID-19 pandemic on the Máxima Center, the care for our children remained our priority.

This could not have been achieved without the tireless commitment of our nurses, doctors, technicians and all other employees of the Máxima Center. The inspiration and motivation for this among all involved are enormous and make us proud.

We thank everyone for their efforts and are convinced that these will continue unabated in the coming years, so that we can work on expanding the impact of the Princess Máxima Center and achieving our mission.

Prof. dr. Alexander Eggermont, CSO
Drs. Gita Gallé, COO/CFO
Prof. dr. Rob Pieters, CMO

Chair of the Supervisory Board of the Princess Máxima Center for Pediatric Oncology B.V.

Preface Supervisory Board

In the years ahead, the Princess Máxima Center wants to achieve significant progress in the realization of its mission: to provide a cure for every child with cancer while maintaining an optimal quality of life. We want to demonstrate that the integrated approach, in which healthcare and research closely work together, truly provides added value. Children and parents are entitled to expect this from us, as are stakeholders, donors and others.

In 2021, we continued to work hard towards this future, despite the uncertain and sometimes limiting circumstances of the COVID-19 pandemic. Our Board of Directors and staff are fully committed to our aim. The various employee participation bodies also made an important contribution to the growth and development of the Princess Máxima Center. The hard work of many has allowed the organization to take the next step towards achieving their goals.

We thank everyone for their efforts. The Supervisory Board is convinced that these will continue unabated in the coming years, so that we can work on expanding the Princess Máxima Center and achieving our mission. This report describes the tangible steps taken in 2021.

We are fully aware that all these important and positive developments were facilitated by the ongoing support from the many partners of the Princess Máxima Center, such as The Children Cancer-free Foundation (KiKa), Dutch Childhood Cancer Association (VKN), Dutch Childhood Oncology Group (SKION), the Princess Máxima Foundation and its partners and the University Medical Center Utrecht (UMCU) and Wilhelmina Children's Hospital (WKZ). Our thanks are due to all of them.

Ir. Rokus van Iperen

Chair of Scientific Advisory Board
Princess Máxima Center

Preface Scientific Advisory Board

The Princess Máxima Center for Pediatric Oncology continues on its path to becoming one of the world's leading institutions conducting research and translating discoveries into more effective treatment for children with cancer. Progress during the past year has been substantial and impactful.

As chair of the Scientific Advisory Board, I had the opportunity to join prof. dr. Alexander Eggermont and prof. dr. Rob Pieters for the formal ceremony, hosted by Queen Máxima at the Dutch Embassy in Berlin, announcing a new partnership between the Princess Máxima Center and the Hopp Children's Cancer Center Heidelberg (KiTZ), the German Cancer Research Center (DKFZ) and the Heidelberg University Hospital (UKHD) to create new synergies that will accelerate scientific discoveries and treatment advances for childhood cancer. This has created a powerful strategic collaboration by bringing together multiple best-in-class institutions to accelerate progress, and the Máxima Center played a leading role in bringing this to fruition.

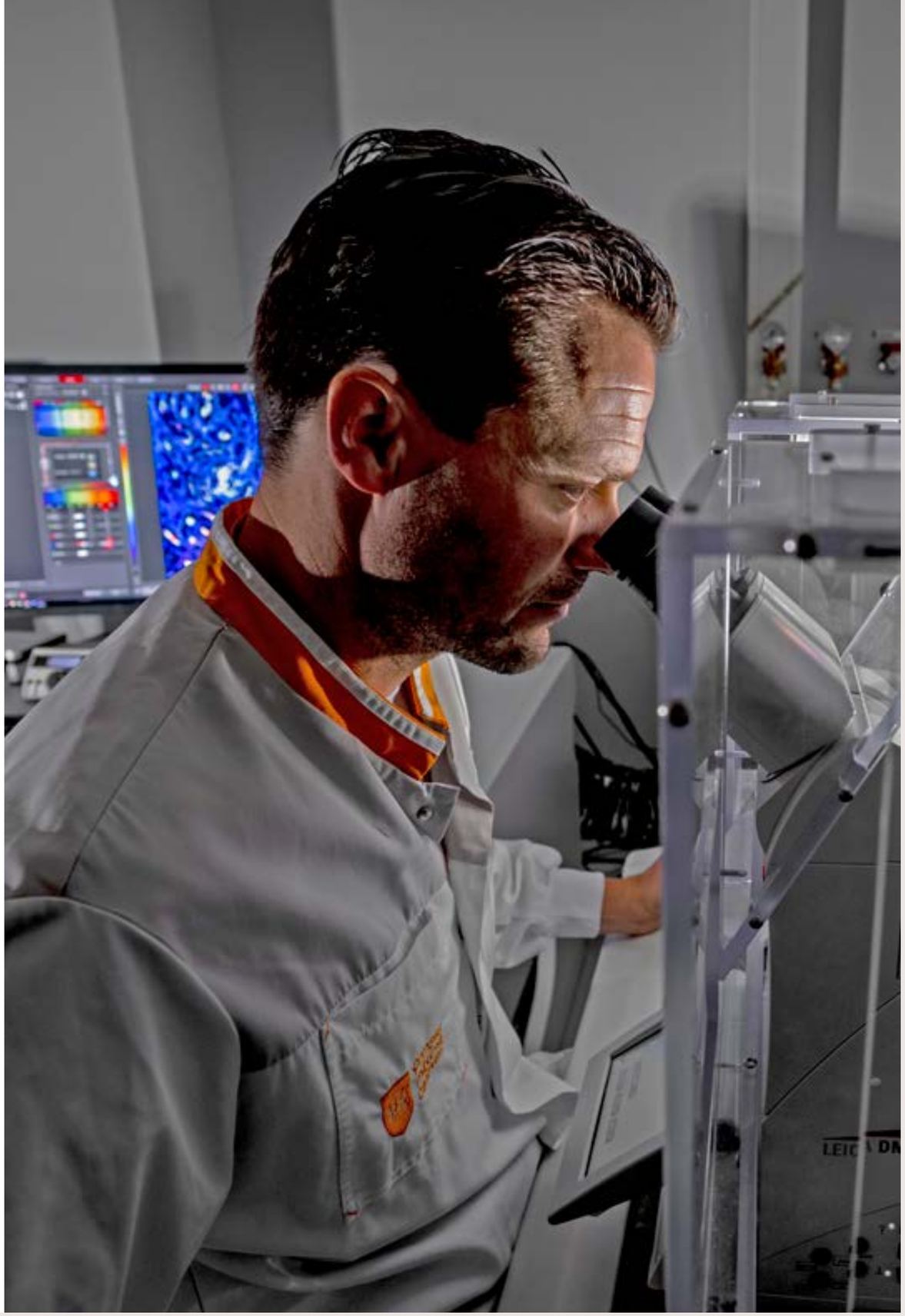
On campus, plans have been finalized to add two new floors to the Máxima research building, expanding it to a seven-floor research facility that will allow the addition of new research programs to expand and deepen the scope of basic and translational research. This includes enhancement of immuno-oncology research and building a Cell Therapy Facility required for CAR-T cell therapy and research.

In November 2021, the Máxima Center underwent an external review of the structure, organization and policies of its research programs, conducted by a distinguished group of investigators from across Europe and US(A). While providing constructive feedback, the committee reported that they were impressed by the high quality of research and the impact that the Máxima Center has had on pediatric cancer in the short period of time since it opened in 2018.

The Scientific Advisory Board, comprising physicians and scientists from Europe and the US, has continued to provide guidance remotely and will convene at the Máxima Center in September for its first on-campus meeting since the pandemic began. The Governing Board of the Máxima Center has also established a Board Committee on Cure and Science, of which I am a member as the SAB chair. This committee ensures that the Governing Board remains fully current on major issues that impact treatment and research programs at the Máxima Center, positioning the Board to respond with alacrity whenever needed to keep the institution at the forefront and moving forward.

As impressive as the first 3,5 years have been, the Máxima Center has built a strong foundation and currently has momentum that will take it to even greater heights in the coming years.

Prof. Dr. William Evans



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General introduction

Princess Máxima Center

The Princess Máxima Center for Pediatric Oncology B.V., hereafter referred to as ‘the Máxima Center’, is the Dutch national center for children with cancer encompassing all the expertise in the field of pediatric oncology. It is a care, research and training center licensed under the Care Institutions (Accreditation) Act (WTZ). The target groups are children with cancer or its preliminary stages, as well as survivors of childhood cancer.

Mission and long-term strategy

The Máxima Center wants to provide a cure for every child with cancer while maintaining an optimal quality of life; that is our mission in a nutshell. We pursue this mission on the basis of two core values: ‘groundbreaking’ and ‘passionate’. Together they form the briefest possible summary of what the Máxima Center stands for: we intend to go further than others have ever gone, with all our hearts. We will achieve this by offering a combination of care and research, supported by parents, caregivers and professionals and with attention to the child and their development. We work with all our partners, with those involved in our cooperative, and with the best people in care, treatment, research and training in the field of pediatric oncology, to substantially improve and innovate the care for children with cancer and their environment. In this way, the Máxima Center aims to make a difference for children with cancer.

Under the heading of Focused & Promising, the Máxima Center has laid out its strategy for the years 2020-2024 to take steps toward the further accomplishment of its mission. Six main objectives have been set. With the further development of the Máxima Comprehensive Childhood Cancer Center (M4C), the Máxima Center aims to be a research hospital where patient care and research form a duality, in combination with the training of professionals. A key focus involves innovative diagnostics and treatment with a focus on reinforcing two areas: immuno-oncology and neuro-oncology. The Máxima Center aims to further improve the quality of life. It aims to realize integrated, state-of-the-art data provision to underpin innovations in research, diagnostics and treatment. An important objective concerns the recruitment, training and retention of top experts in care and research. Lastly, internationalization is an important goal in the context of our mission.

‘To provide a cure for every child with cancer while maintaining an optimal quality of life’

Mission

Structure of the organization

The Máxima Center focuses on the interests of the child and its environment: children with cancer, their parents and caregivers, siblings, family, friends, school and social contacts. In order to always be able to take the child and the environment as a starting point, the Máxima Center aims to be an agile and development-oriented organization with flexible management and minimal overhead. This requires an organizational design in which the problem-solving capacity – competencies of staff, responsibilities, control capacity and information provision – is as close as possible to the child whom it is all about. The organization is based on co-creation and collaboration.

Governance model

The Máxima Center's governance model comprises three bodies: a Board of Directors, a Supervisory Board and a General Meeting of Shareholders. This General Meeting consists of the holders of all ordinary shares, the cooperative consisting of Dutch Childhood Oncology Group (SKION) and Dutch Childhood Cancer Association (VKN), and the holder of the priority share: UMC Utrecht. The responsibilities and powers of the Máxima Center's bodies have been laid down in the articles of association and are further detailed in regulations, in which the following serves as the starting point:

- The Board of Directors is responsible for the strategy and the entire management of the Máxima Center.
- The Supervisory Board supervises the Board of Directors' policy and assists it with advice.
- The General Meeting monitors the Máxima Center's mission.

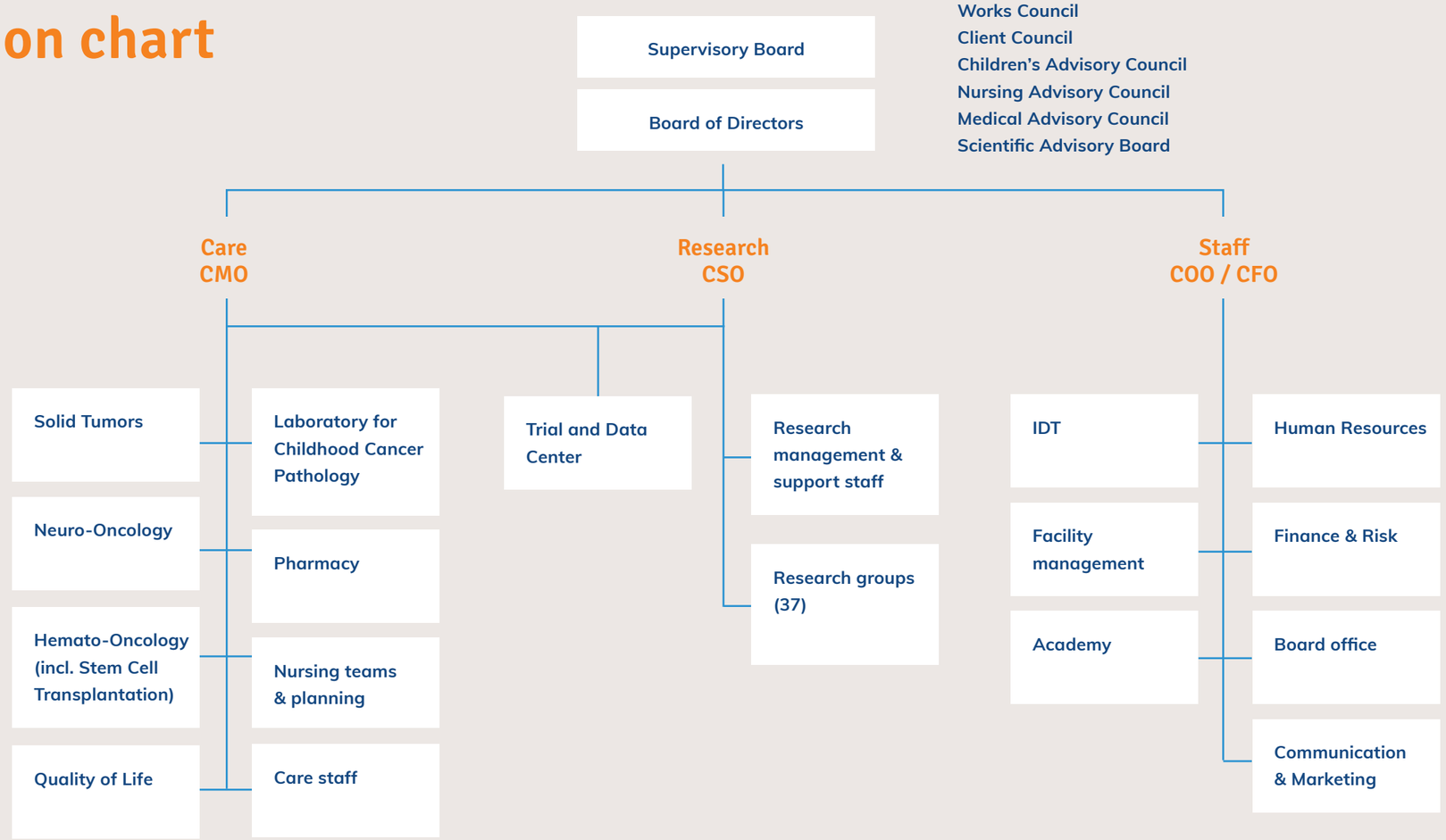
Participation

The Princess Máxima Center has two statutory participation bodies: the Client Council and the Works Council. The Board of Directors regularly consults with these bodies. In addition to the statutory employee participation bodies, the Children's Advisory Council (KAR), the Nursing Advisory Council (VAR) and the Medical Advisory Council (MAR) form part of the Máxima Center's organizational structure. The Board of Directors also requests advice in the field of research from the independent Scientific Advisory Council.

Corporate Social Responsibility

The Máxima Center views the comprehensive approach to childhood cancer as a form of corporate social responsibility (CSR). The set-up and design of a new organization such as the Máxima Center offers excellent opportunities to work better and more sustainably. The Máxima Center facilitates a healthy and healing environment, in which attention is paid to sustainability and the influence of factors such as the building, greenery, nutrition and light on children, parents and staff. Last but not least, the Máxima Center devotes a lot of attention to the position of survivors of childhood cancer in society.

Organization chart

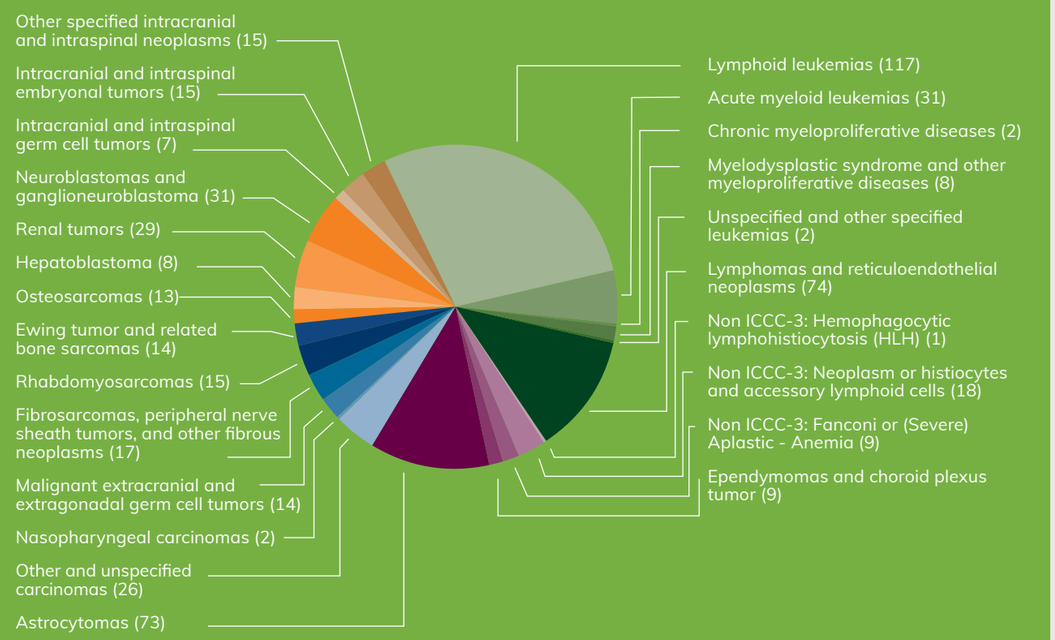


Facts & figures

Patient numbers 2021

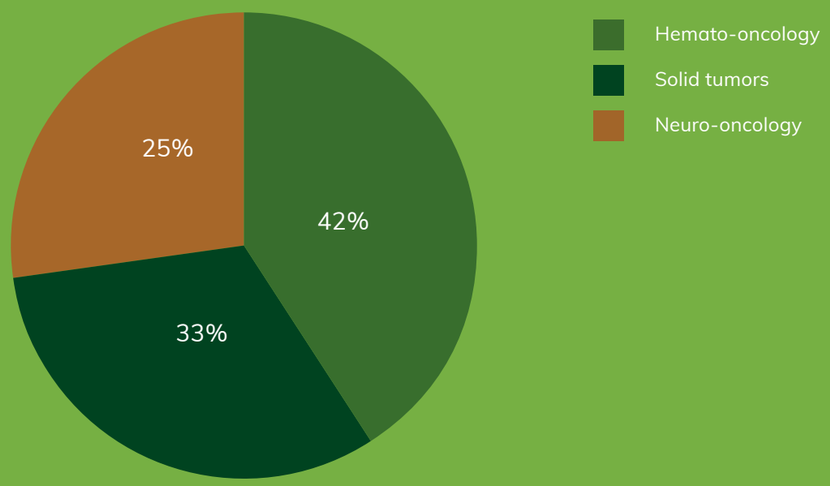
In 2021, a total of 869 patients with a suspected malignant tumor were seen in the Princess Máxima Center, of whom 724 patients were actually diagnosed with malignant tumors (550 new and 174 relapses). The patients had many different types of cancer: 42% percent were treated in Hemato-oncology, 33% percent in Solid tumors and 25% percent in Neuro-oncology. The pie chart in this paragraph shows the patient distribution based on the diagnosis date for all of 2021. More information on 2021 is presented in the following figures and in the Fields of interest chapter.

Spread of new patients in 2021, according to ICCC-3 classification



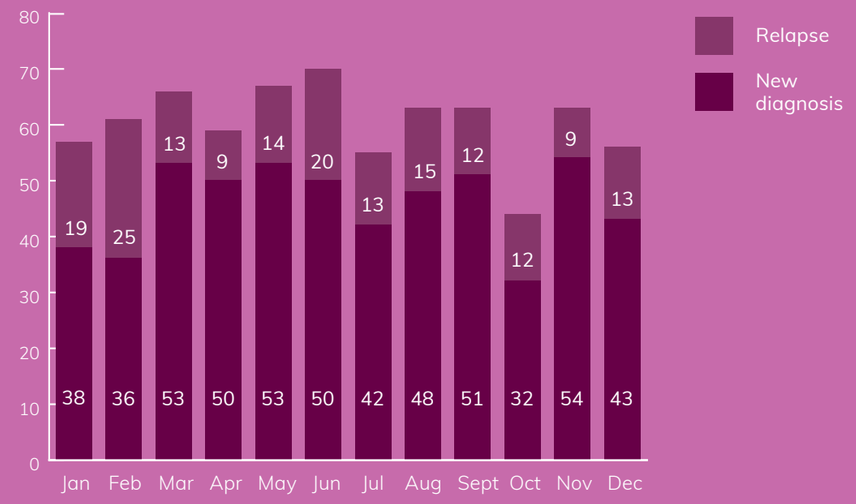
Percentages of diagnosed children in 2021

(per clinical department)



Number of patients with malignant diagnoses in 2021

(per month, based on SKION diagnosis data)

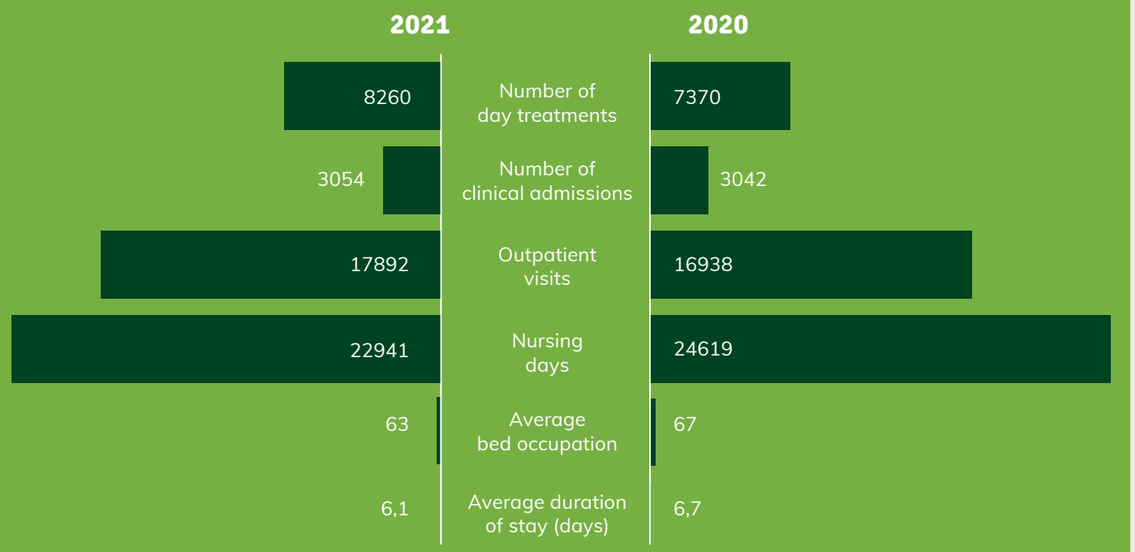


Late effects outpatient clinic

The Princess Máxima Center has a Late effects outpatient clinic for former patients who have been cured of cancer. Here, we focus on investigating, diagnosing and treating late effects of cancer treatment.

Unique Late effects patients	2021	2020
Children	877	870
Adults	1543	1105
Total	**2420**	**1975**

General care figures



Our staff

Growth of our staff	2017	2018	2019	2020	2021
Care	205	703	791	828	837
Research	132	167	313	396	459
Academy	10	20	22	28	26
Staff	75	112	139	146	140
Total	**422**	**1.002**	**1.265**	**1.398**	**1.462**
In FTE	**358**	**861**	**1.094**	**1.203**	**1.237**

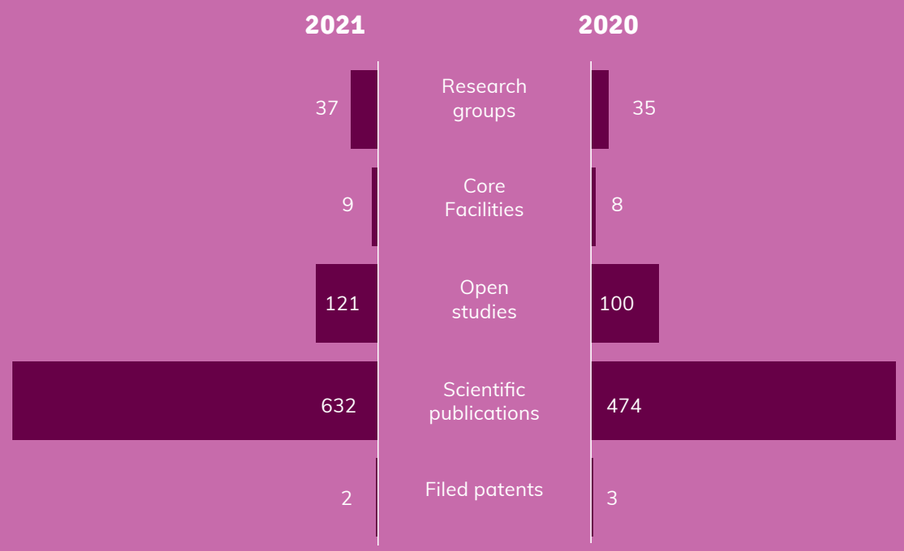
41 different nationalities

5/1 women to men ratio

127 PhD students

25 professors affiliated

Research facts



In the spotlight | vaccination campaign
Jacqueline Zoon, Wim Tissing

‘Vaccination, we did it!’

In the spring of 2021, hospitals were asked to vaccinate their own staff and vulnerable patients against coronavirus. A working group managed to set up a complete vaccination campaign within two weeks.

‘We gave ourselves the task to complete the vaccination campaign within two weeks, to protect our patients and employees as fast as possible. And we did it,’ says pediatric oncologist Wim Tissing. In the spring of 2021, a year after the start of the COVID-19 pandemic, the first vaccines became available in the Netherlands. The government requested hospitals to vaccinate their own staff and vulnerable patients. This meant, depending on the type of vaccine: administering two injections at an interval of one month. A third vaccination followed in the fall.

A huge task

A working group of eight employees organized the vaccination program. This group included Wim Tissing and outpatient clinic team leader Jacqueline Zoon, both also members of the coronavirus coordination team. It was a huge task, the duo explains. Tissing: ‘You need to request and receive the vaccines, involve the hospital pharmacy team to draw up syringes from the vials…’ Zoon adds: ‘Invite everyone for a vaccine, ensure that the vaccinations are recorded in the system of the GGD (Municipal Health Service)… The call team worked during evenings and weekends to contact all parents and caregivers. After all, we didn’t have months to get this done.’

Nose to the grindstone

A suitable location was quickly found: the Auditorium. ‘We had a nice circuit set up there,’ explains Tissing. ‘Reception at the one entrance, the people then walked past registration and received their vaccination and then they spent fifteen to thirty minutes in the foyer for observation.’ We scheduled several vaccination days. A team of fifteen to twenty people were required for each day: the pharmacist and assistants, doctors, doctor’s assistants, IT staff and others. Tissing: ‘The first vaccination day was held on a Saturday, so everyone had to come into work especially for this. Nevertheless we managed to get a team together in no time at all.’ Zoon: ‘Everyone had an attitude of: let’s put our noses to the grindstone.’

Lots of questions

As healthcare professionals and patients were among the first group of people in the Netherlands to receive the vaccine, there were many questions. ‘In particular about side effects,’ says Tissing. Advised by the working group, the communication department handled all these questions. A list of answers to frequently asked questions for parents and children was also published on the website. The vaccination working group did not try to pressurize colleagues in any way, says Tissing. ‘An employer is not allowed to influence employees. We did send out newsletters emphasizing the importance of vaccination.’

Impact

The fact that vaccinated professionals and patients had better protection against COVID-19 did not directly affect healthcare provision. The COVID-19 restrictions, such as specific isolation measures, continued to apply to all, vaccinated or not. But it may have contributed to fewer infections in the Máxima Center, and we did manage to continue all care.’

Social highlight

The employees felt that the vaccination days were a bit of a social highlight, during a period in which they hardly saw each other in person due to the COVID-19 restrictions in place at the time. Zoon: ‘People had to sit in the foyer for a while after the vaccination, for observation. The colleagues enjoyed this: they got to see each other again. I heard from people afterwards that it felt a bit like a team building exercise.’

Jacqueline Zoon is team leader day treatment & outpatient clinic. She was member of the Coordination Team Corona and coordinator of the COVID-19 and Flu vaccination programs.

Prof. dr. Wim Tissing was member of the Coordination Team Corona and the working group vaccination. Tissing is head of the supportive care group, and Principal Investigator of supportive care research. As a pediatric oncologist, Tissing works in the hemato-oncology department.

Staff departments

A business that operates smoothly in all regards is necessary to achieve the grand ambitions of the Máxima Center. This includes financial aspects, IT, human resources, education & training, facilities and a good communication about all these aspects. Good communication between the departments responsible for these aspects is also vital. The staff departments focused on the following issues in 2021.

Leadership

Leadership as a condition for achieving our mission is and will continue to be an important priority in the Máxima strategy. Our ambition demands a lot from our leaders and our leadership. Our leaders are expected to cope with the dynamics and the challenges associated with change, teamwork, complexity and dilemmas. We support them in the development of effective leadership behavior, through our proximity in daily reality.

In 2021, we determined a Máxima vision for leadership and a clear strategy and developed an infrastructure of roles, governance, processes and resources. The Executive Board, together with the Leadership Board, will provide guidance for many small-scale initiatives including programs, courses, masterclasses, peer-to-peer guidance, team development, workshops and coaches.

In 2022, we want to adhere to our strategy and the momentum in leadership and organizational development. Effectively linking leadership to a mission is a multi-annual and emergent process, which remains urgent and relevant via evaluations and discussions, for example in the Leadership Board. The feedback demonstrates that these programs are not only effective for individual participants, but are also meaningful for organizational development and cohesion.

Diversity & inclusivity

Potential talent is present in all echelons of society. In its pursuit of excellence, the Máxima Center aims to create an environment in which this talent can develop to its full potential.
We opted to start smaller initiatives in the various domains of diversity and inclusivity in 2021, each with their own dynamics and potential for expansion.

- **Working group Diversity & Inclusivity:** a group of employees employing a wide range of activities, like workshops, mission statement, videos, to effect a tangible increase in knowledge and awareness in the field of diversity.
- **Máxima International Community (MIC):** a community was created for all international Máxima employees, with the aim of increasing the awareness of the international nature of our organization. The MIC aims to improve language skills and assist with accommodation and intercultural communication.
- **Cultural sensitivity:** The creation of cultural synergy in the communication with patients, parents and caregivers and being more effective at meeting their healthcare needs. Training courses ensure that healthcare professionals become more skilled in actively developing cultural sensitivity.
- **Women in science:** The empowerment of women in research, the creation of

a welcoming environment of gender diversity in which women feel confident and achieving coherence and collaboration that strengthens the research ambitions of the Máxima Center.

The Board of Directors has appointed a coordination group to bring together the various initiatives and to maintain an overview and align them. In addition to 'local' ideas, HR organizes Máxima-wide programs. These are primarily aimed at creating a context, based on a foundation of inclusion. Examples include recruitments, communication, and leadership.

Recruitment, training and retention of employees

Recruitment, training and retention of employees is vital to achieving the mission of the Princess Máxima Center. Being an innovative employer will ensure that the Máxima Center is and continues to be an interesting place to work. In this context, we invest in learning and development opportunities for employees and offer future perspectives. Training is always the first investment made in employees. In 2021, employees of the Princess Máxima Center once again contributed on a large scale to various training and education programs. We also facilitated training and internship positions across healthcare, research and staff. To achieve this, we work closely with the shared care hospitals.

The Talent Program is also relevant to mention here. The ambition is to create a challenging environment to allow talent in pediatric oncology care to develop into internationally authoritative experts and leaders in the field. In 2021, a pediatric oncology research resident, 10 pediatric oncology fellows and a psychologist participated in the Talent Program.

Data-driven healthcare as the next step in IT support

In 2019, the Princess Máxima Center set a goal to take a major leap forward in terms of data provision in clinical healthcare by 2024. One aspect that was specifically mentioned was 'receiving, making available and sharing data with all involved disciplines and partners within and beyond the Máxima Center'. Data sciences play an important role in this. A number of serious steps were undertaken in 2021 to further facilitate this data provision. One important aspect here was the strengthening of the collaboration between the various supporting departments within research, healthcare and staff.

Together we made it possible not only to describe the desired data, which can contribute to data provision in healthcare, but we also took strides towards making this data available within the context of the relevant safety and privacy standards. Approximately 60% of the general data was available by the end of 2021 and a further 10% will become available within a reasonable period of time. A prerequisite to this is the collaboration with the UMC Utrecht, as some of the data is made available by them via their data platforms. This interim step was facilitated in 2021.

The challenge that we have set ourselves for 2022 is to make tumor-specific data available too and to make all available data effectively accessible to our healthcare specialists.

Working at the Máxima Center: hybrid working

In 2021 we developed the vision for working at the Máxima Center after COVID-19. It is a unique opportunity to finetune our way of working and to incorporate the lessons learned whilst working from home during the COVID-19 pandemic. The focal point of our vision is that activities that contribute to our mission 'curing every child with cancer, whilst maintaining optimal quality of life' must be able to take place in our center at all times. Achieving our goals and mission will always determine who works where and when. In many cases, it is vital that we assume that employees will be present in the Máxima Center: for activities such as job familiarization, collaboration and liaising, but more implicit processes such as knowledge transfer and idea development can also benefit from the physical context of the Máxima Center. The building plays a role in this. Hybrid work forms, such as working from home, can be implemented if it helps employees and teams to perform their work properly and the nature of the work allows for this. Working from home has been suggested as an option and

provides a functional addition to our way of working. The option for this work form is neither a right nor an obligation.

Our vision contributes to a potentially more productive working rhythm, to our mobility objectives, to reducing the pressure on office space and makes the Máxima Center an attractive employer. As a result, the focus of the purpose of working in the center shifts more towards meeting others, sharing knowledge, collaborating and socializing.

This vision includes arrangements on working from home, in which we have formalized the agreements about home working and have recorded the rights to compensation and amenities.

In 2022, we will translate the vision of working in the Máxima Center to the layout of the working environment and to an optimum layout and management of the audiovisual resources, in relation to the hybrid work forms.

Sustainability

During the inception of the Princess Máxima Center, the starting points for corporate social responsibility (CSR) were used as important prerequisites and applied – where possible –

during the construction and organization of the center. In the coming years, the Máxima Center aims to undertake efforts in sustainability that contribute to curing patients and improving quality of life. This goes hand in hand with aspiring towards sustainable employability of our own employees and reducing the negative impact on our surroundings and the environment.

Environmental Thermometer Healthcare
In order to visualize all our efforts in terms of sustainable business operation, the Environmental Thermometer Healthcare was completed in 2021. A useful tool for improvement and tangible assessment of the environmental performance and protection. In 2022, we will request an audit by the Environmental Platform Healthcare Sector, with the ambition to achieving a bronze or silver certification.

Green Deal
In addition, preparations were made in 2021 to sign the Green Deal Sustainable Healthcare for a Healthy Future, which can be implemented in 2022. This concerns the contribution that our center can make in improving the environment, such as the reduction of CO^2 emissions and encouraging a circular economy. This also involves the creation of a healthcare environment that encourages healthy behavior from patients, professionals and visitors. And we are also working on reducing medication waste in surface water and groundwater.

Sustainability roadmap
The Dutch government coalition agreement includes agreements with various sectors about making the Netherlands more sustainable. The healthcare sector is eager to join in the process of drafting a sectoral roadmap, which has already been recorded in the Green Deal Healthcare. The roadmap for the Máxima Center used six scenarios to evaluate the available solutions and options to ensure that we meet the targets set for emission reduction of our healthcare real estate in 2030 and 2050. We established and published the roadmap for the Máxima Center in 2021.

Green labs
At the end of last year, we completed the first phase of the LEAF pilot in the Princess Máxima Center, which was coordinated by Green Labs NL. This pilot enables us to reduce our impact on the environment by recycling non-contaminated thermoplastic waste that is produced by the research unit of the Máxima Center. The pilot revealed the large amount of plastic waste that is not contaminated and can therefore easily be recycled.

The brand story of the Princess Máxima Center

The Princess Máxima Center has since the start developed its focus from concentration (patients, professionals and research in one location) to integration: collaboration with all professionals - within and beyond the Máxima Center - aimed at offering new treatments and perspectives to cure and improve the quality of life of children with cancer. With that paradigm shift, the story and promise of the Princess Máxima Center were reformulated in 2021. This was combined with the strategic mission for the coming years, reason to form a brand story. That is why focus in the brand story was shifted from concentration to integration, and why we are working on increasing awareness and consistently conveying innovations that result from internal and external collaborative approaches. The essence of the story forms the starting point for all employees and in all internal and external communication.

New intranet: Join

In 2021, preparations were made for Join, a new social intranet that was launched in early 2022. Join will start automatically when an employee opens an internet browser on their computer. This allows everyone to start their working day with the latest news and access to shared systems that they need for their work.

Join is a platform with information for and by all employees, with useful links and all the options for digital collaboration, fully adapted to the wishes of departments and employees and literally and figuratively in the Máxima style.

In the spotlight | Participation of children and parents

Marjoleine de Lange, Larissa Slotboom, Mildred Klarenbeek

‘Our input improves healthcare’

Participation of children and parents is embedded in the fiber of the Princess Máxima Center. In 2021, they looked into topics such as patient information and participation in research. ‘It’s great to see that we can make real progress together.’

‘Ownership by children, parents, caregivers and professionals is the cornerstone of the institute’, according to Marjoleine de Lange, chair of the Client Council. ‘I’m convinced that the care that we provide at the Máxima Center improves as a result.’ She gives a topical example: the question about which healthcare can take place at home in the future. ‘Healthcare professionals might believe that most parents and children, if possible, would prefer to receive more complex healthcare (like chemotherapy) at home. But this issue requires careful consideration with children and parents to assess if and how this would feel comfortable.’

A lot of participation

Children and parents participate in many different ways. They contribute to the decision-making process through the Client Council, the Children’s Advisory Board (KAR) and the shareholders’ meeting: patient organization Dutch Childhood Cancer Association (VKN) is co-owner of the center. To secure input of children and parents in all hospital policy, a steering committee was established in 2021, in which the Client Council, KAR and VKN work together with professionals. VKN managing director Mildred Klarenbeek explains that they also meet regularly with the Board of Directors. ‘Children and parents have a seat at all tables where policy decisions are made. It’s great to see that we can make real progress together.’

Perspective of the children

Children sometimes have different areas of concern than their parents, according to KAR chair Larissa Slotboom (21). ‘For example, nutrition. It’s easy to say that all food in the center should be healthy. But when you are sick and you have very little appetite, you want to have a say in what you want to eat, just like you have at home. ’The KAR also focuses attention on the shared care centers. Children who live further away from Utrecht can go to these centers between treatments, for example for blood tests or urgent problems. The KAR thinks it could be helpful that friends and family are closer and that travel time can be limited (so you can still attend school or a social event). On the other hand it is important to the KAR that waiting time at emergency departments in hospitals, is reduced as much as possible. Children usually feel very ill because of the treatment and have a dysfunctional immune system, which requires prompt action, preferably by care professionals they know and trust.

Information

The new patient information resources launched by the Princess Máxima Center in 2021 are a great example of a co-creation by children, parents and care professionals. ‘We indicated that the previous line of information could be improved in terms of clarity, tone of voice and look and feel’, explains De Lange. The VKN and medical professionals drafted about 300 leaflets about diseases, treatments and what you can expect as a patient. Klarenbeek: ‘We created an information pack that contains correct information and is clear for the patients.’ Videos will also be produced, for example about an MRI scan. The KAR insisted that these should be animated videos. Larissa Slotboom: ‘ We preferred a cartoon over real children, because it creates the necessary distance, without compromising the message.’

Research

Children and parents also like to be part of the developments within research. ‘We think that it is really great that so much research is taking place, because we really want to see improved outcomes. However, participating in research does ask a lot from children and parents. For instance they are asked to complete lots of questionnaires’, says Klarenbeek. All research involving patient questionnaires is now conducted via one portal, to ensure that patients do not take part in too many trials at the same time. Where possible, the same answers are used for care, quality monitoring and research. For simple questionnaires, the investigators will ask people whether they want to complete the forms in the waiting room. A great solution, according to De Lange. ‘At home, you don’t want to be reminded about the hospital all the time, but in the waiting room you are trying to pass the time anyway.’

Mildred Klarenbeek is director of the Dutch Childhood Cancer Organisation (VKN), the family and survivor association in the Netherlands.

Larissa Slotboom is chair of the Children’s Advisory Board (KAR) at the Princess Máxima Center.

Marjoleine de Lange is chair of the Client Council at the Princess Máxima Center.

2021 Summarized

Overview of major events

January

New Year's Celebration
For the 2021 New Year's Celebration at the Máxima Center, the stage of the Auditorium was transformed into a 'living room' on Tuesday January 5, including a sofa, Christmas trees and 'oliebollen'. Around 400 colleagues were connected to the center via a Zoom connection from home.

The Night Watch in the Princess Máxima Center
A life-sized replica of the Rembrandt painting, The Night Watch, was displayed at the Princess Máxima Center for five weeks. For many children in the center it was their first encounter with one of the world's most famous paintings.

SKION is officially a part of our center
The Dutch Childhood Oncology Group (SKION) was officially transferred to the Princess Máxima Center on January 1. Their activities are now embedded in our center and the employees have also joined our center. SKION will continue to exist as an independent organization and to function as a scientific association for pediatric oncology. Guaranteeing the quality of care in pediatric oncology was and will remain a responsibility of SKION.

February

International Childhood Cancer Day
International Childhood Cancer Day, February 15, was an important day. Due to the corona measures, the Máxima Center, the Foundation, the VKN, the KAR and the Client Council had each invited just a small delegation to mark this year's edition of the awareness day. Some of 'our' children – Sterre, Emma, Luc and Saméo – also attended. We celebrated the success of the new Diary and the launch of the MyMáxima app. Also on the day's program: the Máxima campaign 'The world of Sterre, Yara, Tim and Seven' and the birthday of the new cuddly toy Máxi.

Leontien Kremer appointed as professor of late effects
Prof. dr. Leontien Kremer, pediatrician and Principal Investigator at the Máxima Center, was appointed professor of Late Effects in Pediatric Oncology at the Utrecht University Faculty of Medicine. The chair is unique: it is the first for late effects in pediatric oncology. The position is a major boost for research into reducing health problems linked to treatment for childhood cancers.

March

Hans Clevers wins prestigious prize for contributions to cancer research
In March, prof. dr. Hans Clevers received a prestigious award for his extraordinary achievements in cancer research. Clevers received the Pezcoller-AACR Award for a series of groundbreaking discoveries that led to 'mini-organs', also known as organoids. The cultivation of mini-organs from stem cells has been a crucial step for cancer research: for example, new cancer drugs can now be tested on mini-tumors in the lab.

Purchase of Prodigy for CAR-T treatments
The Prodigy, a machine for making CAR-T cells, was given a celebratory welcome in Utrecht. With this, the Máxima Center took an important step toward offering the CAR-T treatment more quickly and efficiently for children with cancer.

New in memoriam donation platform
The Princess Máxima Center Foundation created a new donation platform, especially for people who want to make a donation or funeral collection after a child has died: the in memoriam platform. For families in our center, but also for other people who would like to raise funds for the Máxima Center around their funeral.

April

Jan Molenaar and Alexander Eggermont appointed as professors
From April 1 the Princess Máxima Center has two new professors: Prof. dr. Jan Molenaar and prof. dr. Alexander Eggermont. Molenaar was appointed professor of Precision Medicine in Pediatric Cancer at the Utrecht University Faculty of Science, and Eggermont was appointed professor of Clinical and Translational Immunotherapy at the Utrecht University Faculty of Medicine.

AFAS Foundation supports Outreach in Kenia
The charity foundation of AFAS Software is supporting the Twinning program in Kenya with an amount of over 4 million euros for the coming five years. AFAS is founding partner of the Outreach program which is led by prof. dr. Gertjan Kaspers, and this commitment means a continuation of the partnership which exists from 2018.

New technology: Single cell sequencing
In childhood cancer, cells have often got stuck in development during pregnancy, causing them to start growing uncontrollably. With single cell sequencing, it is possible to zoom in on individual tumor cells and to map the precursor cells. A number of studies published in the spring used single-cell sequencing to reveal the origins and make-up of neuroblastoma and malignant rhabdoid tumors.

Anne Rios receives L'Oréal Unesco For Women in Science fellowship
In April, dr. Anne Rios received a prestigious L'Oréal-Unesco For Women in Science fellowship. The award enables her to spend time in the NIAS-KNAW Institute, which encourages interdisciplinary collaboration. As part of her fellowship, Rios focuses on the possibility of applying her 3D imaging data in Wilms' tumor to improve diagnostics.

May

Start COVID vaccination program for employees
In May, more than 875 healthcare workers were vaccinated with the Moderna or Janssen vaccine. The 'vaccination street' in the Auditorium was fully booked.

The Waterwork officially opened
With warm words from Gita Gallé, Hanneke de Ridder and our ambassador Bas Smit, the 'Water-work' was officially brought into use on May 17. The Waterwork is a place where our children can play, but it is also meant as a place of remembrance.

June

Kick-off event MIC: Máxima International Community
In the Máxima Center, we have employees from more than 40 different nationalities. Therefore a new initiative was started: the Máxima International Community (MIC). MIC aims to create a community for all our international employees, and awareness within the whole organization of the international nature of our center. On June 16, MIC hosted their Kick-off event.

Online visit by Queen Máxima
Her Majesty Queen Máxima paid an online working visit to our center on June 9 The theme of the visit was the integration of care and research. during her visit, Queen Máxima spoke with our board of directors and several care and research professionals about the latest developments in our center.

Second joint retreat
The second joint retreat for researchers from the Máxima Center and the Hopp Kindertumorzentrum (KiTZ) took place on June 17 and 18 in Heidelberg, Germany. On the eve of an even closer collaboration between the two institutes, the event centered around shared research and infrastructure projects. Some 250 researchers from the Máxima Center and KiTZ logged in on two hot summer days to catch up with each other about the latest developments.

July

Child Health Event
The Wilhelmina Children's Hospital (WKZ) hosted 'The Glass House' on Thursday July 8. That day, all colleagues were able to listen to Child Health Radio presented by radio DJ Giel Beelen, in honor of the collaboration between the Princess Máxima Center and the WKZ. With a live video connection, a varied program full of music, scientific interviews, contests and a roving reporter was enjoyed at home and throughout both organizations.

Josef Vormoor appointed as professor
Prof. dr. Josef Vormoor was appointed professor of Hematological Malignancies in Children at the faculty of medicine of Utrecht University. Vormoor is Clinical Director of the hemato-oncology and stem cell transplant department, and has worked in our center since March 2018.

First operations for brain stem cancer with robotic arm
The robot arm of 'nail polish' Tijn, purchased thanks to the Semmy Foundation, was brought into use in the Princess Máxima Center. The first operations on children with brain stem cancer using the robotic arm were successfully performed in this month. The significance of this robotic arm was celebrated with a memorable and festive gathering in our center.

Twinning agreement between the Máxima Center and KiTZ, Heidelberg
In July, the Princess Máxima Center embarked on a close collaboration with German top centers in Heidelberg in the field of childhood cancer research. With this strategic collaboration, our center and the Hopp Children's Cancer Center Heidelberg (KiTZ), the German Cancer Research Center (DKFZ) and the Heidelberg University Hospital (UKHD) aim to accelerate development towards even better treatment options for children

with cancer. As the namesake of the Princess Máxima Center, Queen Máxima attended the signing of a Memorandum of Understanding between the institutes. With this 'Twinning Program', the Princess Máxima Center joined forces as centers of excellence in the field of pediatric cancer research.

August

Launch of a new nutrition website
There are more myths than facts about healthy eating. Especially concerning the significance of nutrition before, during and after treatment for children with cancer. Therefore the Princess Máxima Center - working with the WCRF (World Cancer Research Fund) - created a new website about nutrition with only facts that are supported by scientific research. The website was launched in August.

MaxiWise a new learning platform
In August, MaxiWise, a digital learning platform for pediatric oncology, went live. Pediatric oncology nurses can learn on the job via this learning platform, whether or not they are in training, and from any work place at any time.

September

Childhood Cancer Awareness Month
The entire month of September, extra awareness is raised for childhood cancer worldwide, and so did the Princess Máxima Center. Via our website and social media we paid extra attention to 'our' children. To mark this month, a video portrait was made about Stef (14), who shared his experience with CAR T-therapy, an innovative treatment for his leukemia.

Upward trend in survival rates for children with cancer
The survival rates of children with cancer in the Netherlands have improved, especially in children whose disease is at an advanced stage. New data from the Dutch Cancer Registry, published at the beginning of September, shows that between 2010 - 2015, 81% of children with cancer survived in the first five years after diagnosis, compared with 72% in the 1990s.

Founding mother Hanneke de Ridder says goodbye
In September, founding mother Hanneke de Ridder bade the Princess Máxima Center farewell. De Ridder was one of the driving forces behind the opening of our center in 2018. She was an indispensable link who time and again managed to connect professionals, patient representatives and many other parties. She started as Director at SKION (Dutch Childhood Oncology Group) in 2005, and held the development-centered care (OGZ) portfolio at the Máxima Center since 2010.

Successful Charity Gala in Carré
On September 23, the Royal Theater Carré was taken over by the Princess Máxima Center. More than 450 guests sat at almost 50 beautifully set tables with a catwalk in the middle. It was a very special evening in which an unprecedentedly high amount was raised: €2.790.118. A royal amount, also thanks to the efforts of our ambassadors, the artists and everyone who made the auction possible.

October

Science Weekend
The Máxima Center took part in this year's Science Weekend ('Weekend van de Wetenschap'). Families with children aged 8-14 came to the center to have a tour of the lab, and to do several experiments and other activities.

Máxima Research Retreat
On October 27 and 28, the Princess Máxima Center organized the Máxima Research Retreat 2021 for all its researchers. The focus of these days was to exchange knowledge and expertise, but also to (re)connect and get to know each other better. The stage was given to inspiring speakers and there were several engaging workshops.

New sports clinic in the Máxima Center
In October, the Esther Vergeer Foundation opened a sports clinic in the Máxima Center where they offer children and parents help in finding a suitable sports club in their neighborhood.

Recruitment campaign starts: #benjijdeverpleegkundigste!
The Princess Máxima Center is looking for new nurses, to provide the best care for children with cancer. Therefore, in October the campaign #benjijdeverpleegkundigste (‘are you the bestest nurse’) was launched. The recruitment campaign is still going strong on Facebook, LinkedIn and Instagram.

Vision for ‘Verpleegkundigste’ in orange booklet
Over the past year, nurses and nursing specialists from all departments worked together on developing a new vision on the nursing professional in 2026. Each nurse specialist received a personal copy in orange booklet. The first three copies of this new vision document were festively handed over to three of our nurses by Rob Pieters (CMO), Hans Merks (pediatric oncologist & MAR chair), and Renske Karens (Team leader & VAR chair).

Inaugural lecture Martha Grootenhuis: ‘Better together?!’
Prof. dr. Martha Grootenhuis was appointed professor of pediatric psycho-oncology at the Faculty of Medicine at Utrecht University. On Tuesday October 12 she delivered her inaugural lecture, ‘Better together?!’, about the psychosocial issues children with cancer and their families often face.

November

Record number of jabs in flu vaccination campaign
On Friday November 5, the last of 840 flu vaccinations was given to an employee of the Máxima Center. A record number of flu jabs were obtained in the four-week flu vaccination campaign #zogeprikt.

Research unit evaluated by external commission
An external committee paid a two-day site visit to the Máxima Center in November to conduct an evaluation of the Research unit. The structure, organization and policies were reviewed along the framework of the Strategic Evaluation Protocol (SEP 2021-2027). The committee shared that they were impressed by the impact of the Máxima Center and the high quality of research. They also commended the enthusiasm and team spirit, and how much has been achieved in a short time since the opening in 2018. The final report follows in the spring 2022.

December

Highest point construction of the new intra-operative MRI operating room
The Princess Máxima Center and the Wilhelmina Children’s Hospital (WKZ) are jointly building an intra-operative MRI operating room. This operating room is being built specifically for the treatment of children with brain tumors and is expected to be commissioned in mid-2022. The construction process is in full swing and reached its highest point on December 2.

Merger of METCs
In December, the medical research ethics committees (METCs) of the Princess Máxima Center, the UMC Utrecht and the Antoni van Leeuwenhoek joined forces to assess human-related research in a qualitative, independent and futureproof manner.

End of the year fundraising efforts
At the end of 2021, a range of fundraising efforts took place, many of them initiated and coordinated by the Foundation. These included ‘Project Glimlach’ by RTL, Mission Radio 538 for the Máxima Center and ‘KiKa korte broeken’.

#benjijdeverpleegkundigste

#are you the bestest nurse?

M4C: Máxima Comprehensive Childhood Cancer Center

The M4C organization

Background and defined goals

To fulfill our Princess Máxima Center mission, the Máxima Comprehensive Childhood Cancer Center initiative started in 2019 with the following four goals:

- integrating research into our day-to-day clinical programs;
- defining the key clinical and translational research challenges;
- connecting researchers and clinical care professionals;
- establishing and investing into new areas of clinical innovation.

These cover the full spectrum of research activities, from basic research, preclinical development, early and late clinical trials, to clinical implementation and quality of life. With its 2020-2024 strategy entitled ‘Focused and Promising’, the Princess Máxima Center aims for innovative diagnostics and treatment related to early clinical phase I and II studies, neuro-oncology and immuno-oncological programs. The M4C structure supports the realization of these aims by setting the priorities in day-to-day practice.

M4C structure and output

The overall M4C structure (Figure 1) actively involves the clinical departments – Hemato-oncology, Neuro-oncology, Solid tumors, and Quality of Life – with the various research groups, including the various Core Facilities and Research Platforms. Specialized disease groups and Themes are initiated under guidance of a clinical and pre-clinical chair position. If required, a Protocol Team is initiated within the disease group for clinical trial preparation purposes. The role and rules related to the M4C disease groups were approved by the Board of Directors and communicated within the organization. All disease groups and themes generated a starting document in which they defined their plans for the coming years. Regular updates are shared on their progress.

Governance and strategic decision making

To optimally facilitate further development of the individual disease groups and themes, the Strategic Research Board (SRB) was installed in the beginning of 2021. The position of the SRB within the Máxima organization is represented in Figure 2. It is composed of the scientific and medical directors, research directorate, the four clinical directors and relevant representatives. The SRB meets every six weeks to set the agenda, making a summary and decisions based on the Strategic Thematic Board (STB) meetings. STB meetings take place every month, attended by the same representatives and other invitees depending on the program. In this manner, communication between the different departments with complementary strategic perspectives is guaranteed resulting in an integrative approach in each decision and process. Starting in 2022, the STB will convene quarterly with all the M4C Disease Groups and Themes chairs, to optimally interact and exchange information.

Targets, talent and evaluation

Besides defining the key clinical and translational challenges, the M4C structure aims to develop a strong international leadership position and an optimal environment to train the next generation of specialized scientists and clinicians, including trialists. This will be based on a SWOT analysis and possible adjustment of the defined goals and deliverables. On an individual basis, the M4C disease group and theme structure is active

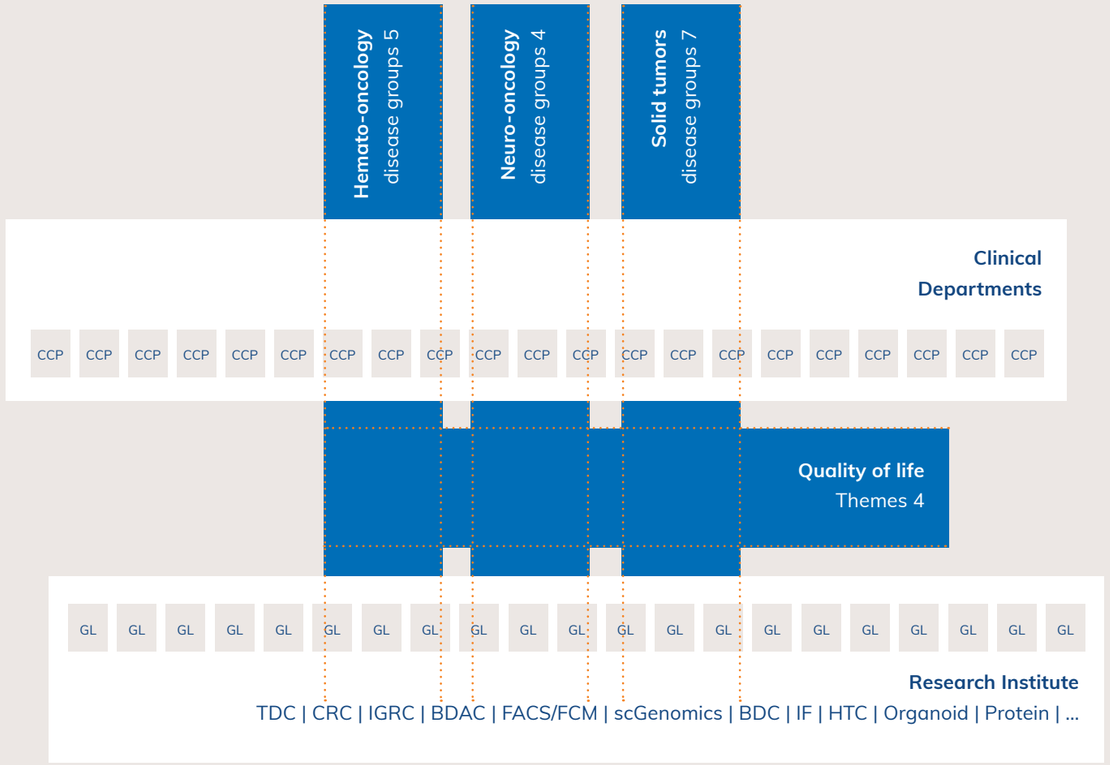


Figure 1: Schematic representation of the M4C structure, showing interactions between the clinical department and Research by the formation of defined disease groups and Themes within the specific pillars of Hemato-oncology, Neuro-oncology, Solid tumors (being vertical in structure), and Quality of Life (horizontal structure). The actual number of disease groups and themes are indicated. (CCP = Clinical Care Professional, GL = Group Leader)

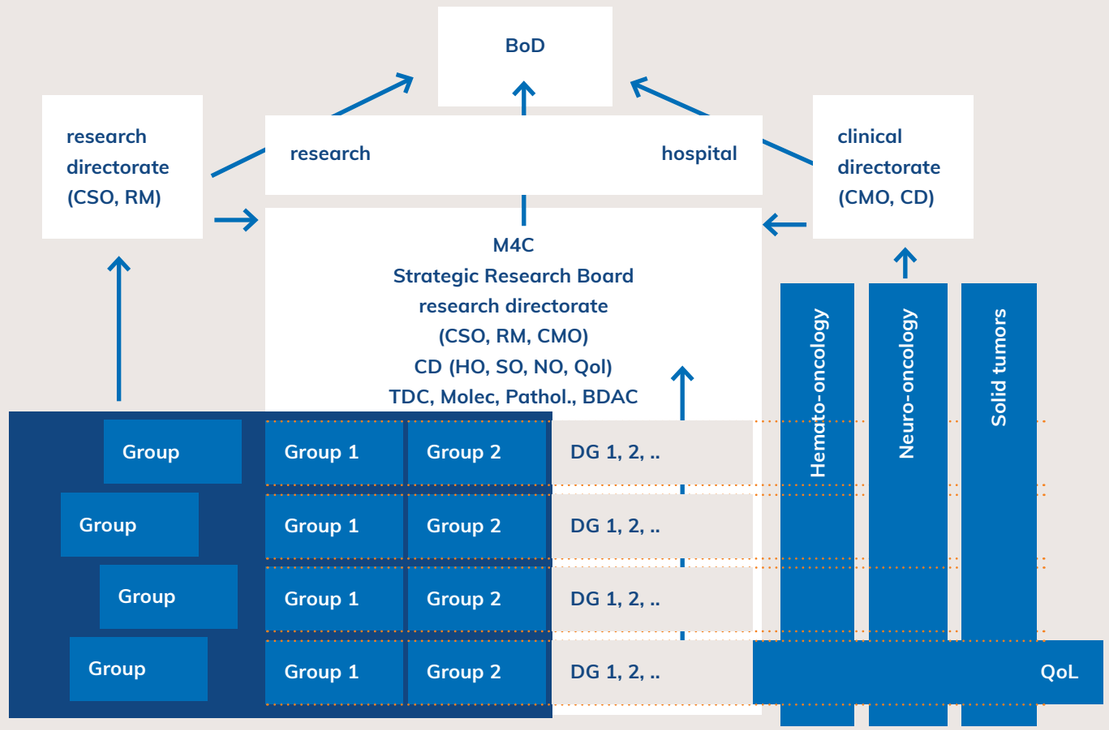


Figure 2: Schematic representation of the position and composition of the Strategic Research Board within the Princess Máxima Center. (BoD = Board of Directors, DG = Disease Group)

in attracting and hiring as well as developing (young) talent - both clinical and research, and in combination - in an optimal environment. To optimally support development and final success, an educational program has been initiated and started by the department of HR in close interaction with research management and clinical directors.

Consistency and homogeneity in job descriptions

A re-evaluation of the existing range of the job descriptions in the Máxima Center has been performed, to facilitate integration between clinical care and research throughout all levels within the organization and to streamline the existing heterogeneous situation. This resulted in a reduced number of possible job roles, each with a clear overview of responsibilities, tasks and expectations. The new structure allows for transparency regarding the input for the so-called Dialogue, a tool to discuss and evaluate progress of individual staff members, as well as in the context of the M4C role they fulfill.

Current status and perspective

In total, four Quality of Life themes and 15 M4C disease groups have been initiated. Disease group and theme members have generated starting documents to indicate their respective discipline and expertise, define their specific clinical and research aims plus the upcoming needs and challenges. The various disease groups and themes will have regular monthly meetings to discuss the further steps in development of their respective research and clinical agenda. An invitation will be sent in 2022 to perform a SWOT analysis for each group. This will be used as active guidance for future decision making. Moreover, the M4C structure will be implemented in a planned update to the website, to improve service to visitors with either a patient or lay-, or a professional background. This will optimally demonstrate our vision of the multidisciplinary work performed at the Máxima Center, and create transparency for all interested parties.

Overview of Themes and Disease Groups

Quality of Life Themes	**Chairs**	**Chairs**
Psychosocial	Laura Beek & Esther van den Bergh	Martha Grootenhuis
Neuropsychology	Femke Aarsen	Marita Partanen
Supportive Care	Marianne van de Wetering	Wim Tissing
Late Effects	Rianne Koopman	Leontien Kremer
Solid Tumors	**Clinical Chair**	**Research Chair**
Neuroblastoma	Max van Noesel	Jan Molenaar
Soft tissue & bone sarcomas	Hans Merks	Claudia Janda
Kidney tumors	Marry van den Heuvel-Eibrink	Jarno Drost
Germ cell tumors	Józef Zsíros	Leendert Looijenga
Liver tumors	Józef Zsíros	Weng Chuan Peng
Rare tumors (thyroid, melanoma, nasopharyngeal carcinoma)	Miranda Dierselhuis	Sheila Terwisscha van Scheltinga
Neuro-Oncology	**Clinical Chair**	**Research Chair**
High grade gliomas	Dannis van Vuurden	Esther Hulleman
Embryonal & Rare CNS tumors	Sabine Plasschaert	Marcel Kool
Craniopharyngiomas & CNS Germ Cell Tumors	Hanneke van Santen	Marc van de Wetering Leendert Looijenga (GCT)
Low grade gliomas	Netteke Schouten - van Meeteren	Mariette Kranendonk
Hemato-Oncology	**Clinical Chair**	**Research Chair**
Acute Lymphoblastic Leukemia	Rob Pieters	Monique den Boer
Myeloid malignancies	Bianca Goemans	Olaf Heidenreich
Lymphoma	Friederike Meyer-Wentrup	Ruben van Boxtel
Bone Marrow Failure/Myelodysplastic Syndromes	Katja Heitink-Pollé	Mirjam Belderbos
Hematopoietic Cell Transplantation and Immunotherapy	Caroline Lindemans	Stefan Nierkens

Fields of interest

Hematato-oncology

Prof. dr. Josef Vormoor, Clinical Director

‘Improving the clinical care of our patients and integrating research and innovation in our daily clinical program has been at the center of all our activities. This has made 2021 another successful year for our multidisciplinary team.’

Hemato-oncology covers the diagnosis and treatment of children and young adults with leukemia, myelodysplastic syndrome, bone marrow failure, lymphoma and histiocytosis. Our state-of-the-art diagnostic facilities include cytology and histology, flow cytometry as well as all current molecular techniques (PCR, RNAseq, WES). The treatment modalities in our portfolio include chemotherapy, cellular therapies such as allogeneic stem cell transplantation and CAR T-cell therapy, targeted therapies with small molecules, immunotherapy with monoclonal antibodies and antibody drug conjugates and occasionally radiotherapy. Our stem cell transplantation unit is a joint program between the Princess Máxima Center and the Wilhelmina Children’s Hospital (WKZ) in which both children with benign (e.g. metabolic disorders) and malignant disorders are treated. In line with the Center’s mission, the department invests in preclinical and clinical research to develop a cure for every child with cancer while maintaining optimal quality of life. Immunotherapy, with antibodies and CAR T-cells, and early phase clinical trials play an important role in improving outcomes, to both reduce toxicity and relapses. State-of-the-art supportive care is important to prevent infections and facilitate best possible quality of life during and after treatment.

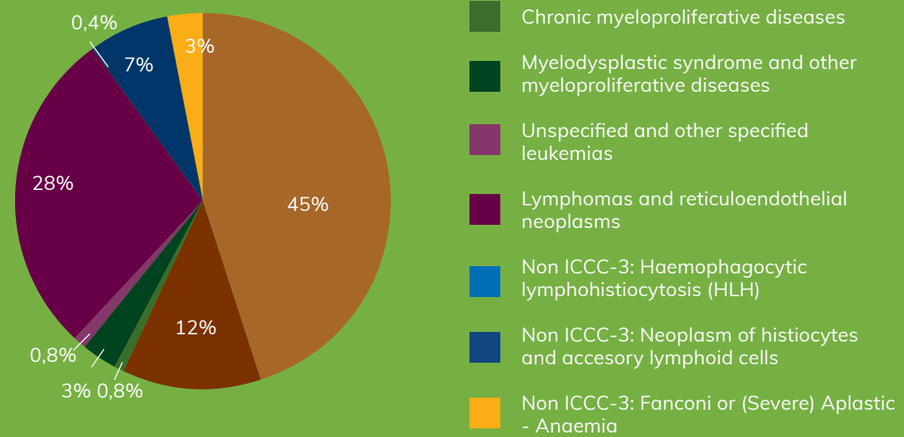
Facts & Figures

The following tables en charts show the hemato-oncology patient numbers in 2021

ICCC-3	Disease	Patient numbers
I.a	Lymphoid leukemias	117
I.b	Acute myeloid leukemias	31
I.c	Chronic myeloproliferative diseases	2
I.d	Myelodysplastic syndrome and other myeloproliferative diseases	8
I.e	Unspecified and other specified leukemias	2
II	Lymphomas and reticuloendothelial neoplasms	74
	Non ICCC-3: Haemophagocytic lymphohistiocytosis (HLH)	1
	Non ICCC-3: Neoplasm of histiocytes and accesory lymphoid cells	18
	Non ICCC-3: Fanconi or (Severe) Aplastic - Anaemia	9
	Total new diagnoses	**262**
	Hematology relapse	41
	Total	**303**

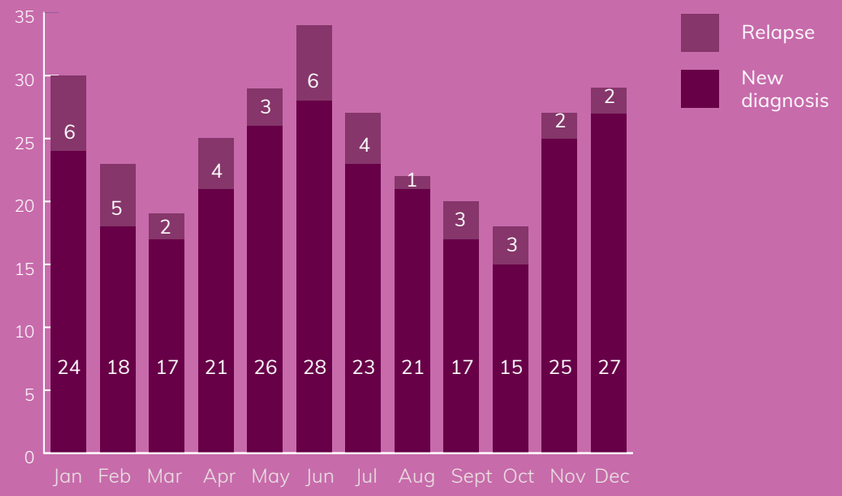
Hemato-oncology patients in 2021

According to ICCC-3 classification



Hemato-oncology patient numbers per month

Based on SKION diagnosis data



Cellular therapy			N
Allogenic Stem cell transplants	8 benign	25 malign	33
Umbilical cord blood unit transplants used			5
CAR T-cell aphareses			8
CAR T-cell therapies			22

Research

Hemato-oncology M4C disease groups

Disease-focused pre-clinical and clinical research and quality of life studies are well-integrated through the M4C groups within our department:

Disease group	Clinical Chair	Research Chair
Acute lymphoblastic leukemia	Rob Pieters	Monique den Boer
Myeloid malignancies	Bianca Goemans	Olaf Heidenreich
Lymphoma	Friederike Meyer-Wentrup	Ruben van Boxtel
Bone Marrow Failure / Myelodysplastic Syndromes	Katja Heitink-Pollé	Mirjam Belderbos
Hematopoietic Cell Therapy and Immunotherapy	Caroline Lindemans	Stefan Nierkens

Examples from our preclinical research portfolio

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for various blood diseases, including high-risk leukemia. With the increasing use of HSCT and improved survival of HSCT recipients, long-term safety of this therapy has become an increasingly important topic. In a recent translational study performed in the Princess Máxima Center, De Kanter, Peci *et al.* have investigated the mutational consequences of HSCT for the transplanted hematopoietic stem cells. Using whole genome sequencing of individual hematopoietic colonies of human HSCT recipients and their donors, the authors demonstrated that the majority of transplanted HSCs did not accumulate additional mutations. This is a reassuring finding, as it confirms the genomic safety of HSCT as a treatment strategy. However, in some patients, the authors identified an excess of somatic mutations, which was caused by treatment with the antiviral drug ganciclovir. Using mutational signature analyses, the authors demonstrated that ganciclovir exposure can induce oncogenic mutations and highlight a potential carcinogenic property of this antiviral compound.

De Kanter JK, Peci F, Bertrums E, Rosendahl Huber A, van Leeuwen A, van Roosmalen MJ, Manders F, Verheul M, Oka R, Brandsma AM, Bierings M, Belderbos M, van Boxtel R. Antiviral treatment causes a unique mutational signature in cancers of transplantation recipients. Cell Stem Cell. 2021 Oct 7;28(10):1726-1739.e6. doi: 10.1016/j.stem.2021.07.012. Epub 2021 Sep 7.

The BCR-ABL1-like subtype of acute lymphoblastic leukemia (ALL) is characterized by fusion genes affecting different tyrosine kinases (together called ABL-class) which is associated with a similarly poor prognosis to BCR-ABL1-positive ALL. We and others have shown that the ABL-class cells are sensitive to tyrosine kinase inhibitors (TKIs). Given the rarity of these patients, an international collaborative study was initiated to determine the clinical characteristics associated with TKI-naïve ABL-class ALL in children. The 5-year event-free survival was 60%. Over 65% of patients had remarkably high minimal residual disease levels after four weeks of induction therapy. These patients often received hematopoietic stem cell transplantation, but the high treatment related mortality jeopardized the outcome, indicating the need for other therapeutic options. This international study sets the reference to establish the effect of TKIs in upfront treatment, like imatinib which is currently given to ABL-class patients in the ALLtogether 1 protocol.

Den Boer ML, Cario G, Moorman AV, Boer JM, de Groot-Kruseman HA, Fiocco M, Escherich G, Imamura T, Yeoh A, Sutton R, Dalla-Pozza L, Kiyokawa N, Schrappe M, Roberts KG, Mullighan CG, Hunger SP, Vora A, Attarbaschi A, Zaliova M, Elitzur S, Cazzaniga G, Biondi A, Loh ML, Pieters R Outcomes of paediatric patients with B-cell acute lymphocytic leukaemia with ABL-class fusion in the pre-tyrosine-kinase inhibitor era: a multicentre, retrospective, cohort study. Ponte di Legno Childhood ALL Working Group.Lancet Haematol. 2021 Jan;8(1):e55-e66. doi: 10.1016/S2352-3026(20)30353-7. Epub 2020 Dec 22.

Clinical research

Infant acute lymphoblastic leukemia (ALL) is rare and a usually aggressive type of leukemia with poor outcome. The leukemic cells frequently carry a specific molecular abnormality, a gene rearrangement involving the lysine methyltransferase 2A gene (KMT2A; formerly known as the mixed lineage leukemia (MLL) gene). We evaluated the value of therapy response in infants with KMT2A-rearranged ALL treated within the Interfant-06 protocol. In this study, lymphoid-style consolidation was compared with myeloid-style consolidation therapy.

This study came to the unexpected conclusion that induction therapy selects patients for subsequent therapy. Infants with a slower therapy response, i.e. a higher load of persisting disease at the end of the initial four-week induction therapy, may benefit from acute myeloid leukemia (AML)-like consolidation, whereas patients with rapid clearance of the leukemic cells, i.e. low or absent minimal persisting disease, may benefit from ALL-like consolidation therapy.
These findings will be used for treatment stratification in the next Interfant protocol.

Stutterheim J, van der Sluis IM, de Lorenzo P, Alten J, Ancliffe P, Attarbaschi A, Brethon B, Biondi A, Campbell M, Cazzaniga G, Escherich G, Ferster A, Kotecha RS, Lausen B, Li CK, Lo Nigro L, Locatelli F, Marschalek R, Meyer C, Schrappe M, Stary J, Vora A, Zuna J, van der Velden VHJ, Szczepanski T, Valsecchi MG, Pieters R.J; Clinical Implications of Minimal Residual Disease Detection in Infants With KMT2A-Rearranged Acute Lymphoblastic Leukemia Treated on the Interfant-06 Protocol. Journal of Clin Oncol. 2021 Feb 20;39(6):652-662. doi: 10.1200/JCO.20.02333. Epub 2021 Jan 6.

The clinical department runs a broad portfolio of clinical trials and quality of life studies. The portfolio is managed through the M4C groups.

Examples of clinical trials that we lead on include:

The SeluDex study is an international phase I/II expansion trial of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated acute lymphoblastic leukemia (ALL). Pediatric patients with multiple relapses of ALL after hematopoietic stem cell transplant (HSCT) and/or CAR T-cell treatment have very few treatment options. These leukemias often carry RAS-pathway mutations, rendering them potentially sensitive to MEK-inhibition. Pre-clinical studies have shown that MEK-inhibition with concurrent glucocorticosteroid treatment have synergistic effects. Physicians from our center have initiated and are the European pediatric coordinators of the SeluDex study. First responses in adult patients have confirmed RAS-pathway mutations as a promising targets and we have now included our first two pediatric patients in this trial.

The Parachute Study (Dutch Trial Register NTR4960) was a single arm Phase II prospective study assessing the safety and effectivity of dosing anti-thymocyte globulin (ATG), a key component of the pediatric transplant conditioning

regimen according to an Utrecht- designed population-based pharmacokinetic model, based on bodyweight, graft source and lymphocyte count. Overexposure to anti-thymocyte globulin leads to poor CD4+ T-cell immune reconstitution, which is associated with inferior overall survival.

Main outcome was a predicted better CD4 immune reconstitution, defined as at least 50 CD4/µl within the first 100 days post HCT, which had to be met in 38 of 54 subjects (70%) for a successful clinical trial and was seen in 80% of subjects in the trial. Individualized dosing of anti-thymocyte globulin led to a significant improvement in early CD4+ immune reconstitution (81% immune reconstitution versus 61% immune reconstitution in historic controls) without increasing graft vs. host disease and graft failure incidence. Post-hoc analysis confirm a clear survival benefit for patients with immune reconstitution post HCT.

Selected publications, highlighting the breadth and impact of our pre-clinical and clinical research:

- Van der Zwet JCG, Buijs-Gladdines JGCAM, Cordo' V, Debets DO, Smits WK, Chen Z, Dylus J, Zaman GJR, Altelaar M, Oshima K, Bornhauser B, Bourquin JP, Cools J, Ferrando AA, Vormoor J, Pieters R, Vormoor B, Meijerink JPP. MAPK-ERK is a central pathway in T-cell acute lymphoblastic leukemia that drives steroid resistance. Leukemia. 2021 Dec;35(12):3394-3405. doi: 10.1038/s41375-021-01291-5. Epub 2021 May 18.

- Versluijs B, De Koning CCH, Lankester AC, Nierkens S, Kollen WJ, Bresters D, Lindemans CA, Boelens JJ, Bierings M. Clofarabine-fludarabine-busulfan in HCT for pediatric leukemia: an effective, low toxicity, TBI-free conditioning regimen. Blood Adv. 2021 Nov 15:bloodadvances.2021005224. doi: 10.1182/bloodadvances.2021005224. Online.

- De Haas V, Pieters R, van der Sluijs-Gelling AJ, Zwaan CM, de Groot-Kruseman HA, Sonneveld E, Stigter RL, van der Velden VHJ. Flowcytometric evaluation of cerebrospinal fluid in childhood ALL identifies CNS involvement better then conventional cytomorphology. Leukemia. 2021 Jun;35(6):1773-1776. doi: 10.1038/s41375-020-01029-9. Epub 2020 Aug 27.

- Goemans BF, Noort S, Blink M, Wang YD, Peters STCJ, van Wouwe JP, Kaspers G, de Haas V, Kollen WJ, van der Velden VHJ, Gruber TA, Zwaan CM. Sensitive GATA1 mutation screening reliably identifies neonates with Down syndrome at risk for myeloid leukemia. Leukemia. 2021 Aug;35(8):2403-2406. doi: 10.1038/s41375-021-01128-1. Epub 2021 Jan 22.

- Brandsma AM, Bertrums EJM, van Roosmalen MJ, Hofman DA, Oka R, Verheul M, Manders F, Ubels J, Belderbos ME, van Boxtel R. Mutation signatures of pediatric acute myeloid leukemia and normal blood progenitors associated with differential patient outcomes. Blood Cancer Discov. 2021 Sep;2(5):484-499.

- RUNX1/RUNX1T1 mediates alternative splicing and reorganises the transcriptional landscape in leukemia. Grinev VV, Barneh F, Ilyushonak IM, Nakjang S, Smink J, van Oort A, Clough R, Seyani M, McNeill H, Reza M, Martinez-Soria N, Assi SA, Ramanouskaya TV, Bonifer C, Heidenreich O. Nat Commun. 2021 Jan 22;12(1):520. doi: 10.1038/s41467-020-20848-z.

Key milestones from Hemato-oncology in 2021

In 2019, CAR T-cells were first introduced into the treatment of children and young people with relapsed acute lymphoblastic leukemia. This new cellular immunotherapy offers a chance of cure for patients who until now were regarded as palliative. In 2020/2021, our CAR T-cell team was consolidated and the first CAR T-cell trials opened for children with high risk newly diagnosed ALL and Burkitt's lymphoma.

Until December 2021, we have performed 45 CAR T-cell infusions in 37 patients establishing ourselves as an internationally recognized clinical CAR T-cell program.

The next step will be to not only use commercially available products but to produce CAR T-cells in an academic setting, targeting novel surface markers for other types of leukemia and with a special focus on solid and brain tumors. We are in the process of establishing an ambitious translational CAR T-cell program to develop innovative academic CAR T-cell trials. We pursue this ambition in close collaboration with our partners at the Utrecht Science Park.

2021 was also an important year for the further development of our clinical team and the empowerment of our professionals. Together with HR we have started a leadership program for our M4C chairs and our clinical team leads. With our new strategic plan for nurses, we are providing opportunities for further professional development within our nurse specialists team (case manager role in our outpatient clinics) and, in 2022, we are introducing our first physician assistant in training on our clinical unit.

Another focus is the continuous improvement of patient care on our wards (family-centered care). We have introduced ward rounds at the bedside to enable good communication with our patients and their parents (patient and parent participation). Supervision schedules have been adjusted to improve continuity of medical care and our supportive care guidelines have been updated. In addition, communication training as well as access to a newly formed ethical committee are now available for all care professionals. Last but not least, a multidisciplinary working group to focus on best care for teenagers and young adults has been initiated.

In the spotlight | M4C disease group Lymphoma

Friederike Meyer-Wentrup and Ruben van Boxtel

Combining clinical and scientific expertise to reduce toxicity

The immune system and the microenvironment of the tumor cell are very promising elements for more effective therapies against cancer. In hemato-oncology most children can be cured by optimized treatment. But the downside is the severe toxicity of these treatments. In tackling this problem, the M4C Disease Group Lymphoma is a key player in the Máxima-strategy towards better overall outcomes for children with cancer.

Originating from Germany, where she was educated as a science-driven pediatrician, Friederike Meyer-Wentrup came over to the Netherlands in 2003 to become a fundamental researcher. Her Dutch still slightly touched by her mother tongue, she passionately attests to her professional mission: improving treatment for children with cancer by interlinking clinical practice with scientific research. Meyer-Wentrup is proud to be one of the pioneering doctors in what would later become the Princess Máxima Center. Her co-chair Ruben van Boxtel is also one of the Máxima-pioneers. He is a biologist who received his PhD at the Hubrecht Institute. He has dedicated his scientific career to research on the genome. His main focus is trying to understand how accumulation of DNA damage can lead to cancer. Within the M4C disease group this can be translated in one key question: what 'drives' lymphoma?

Many unanswered questions

Lymphoma – Hodgkin and Non-Hodgkin – was one of the first types of cancer to be discovered. But many questions about the origin of this illness still remain unanswered. One of the fascinating aspects, Van Boxtel explains, is that the majority of cells in a Hodgkin tumor are nonmalignant. So the question is: how do these normal cells contribute to the survival and growth of the malignant cells? Today, more than 90% of the children survive, Meyer-Wentrup explains, so the tendency could easily be to turn research focuses on other types of cancer for which prognosis is still worse. 'The point is that children with lymphoma pay a high price for their survival. The treatment is very toxic. Short-term side effects – think of severe pain or dangerous infections – are hard to handle, but toxicity can reach far into adulthood. Heart problems can arise, fertility can be reduced and secondary cancers occur more often in adults who have survived.'

Improving treatment outcomes

And this is where the importance of combining care and research becomes inevitable. Van Boxtel: 'Clinical experience shows that although treatments might be successful, they still can be improved a lot in terms of outcomes other than survival. We can only do so by better understanding the biological mechanisms of the cancer itself. Our work on lymphoma will be helpful in other areas of pediatric oncology, or even in oncology as a whole. If survival rates get higher, the problem of dealing with toxicity will become more and more urgent, in all areas of oncology. I think this is really the greatest challenge we face: making successful treatments less toxic, for example by targeting the very mechanisms in every individual cancer cell.' One of the main conditions for this type of innovation is to build a broad set of preclinical and clinical data, combined with a large collection of patient material. Van Boxtel describes the ambitions of the group: becoming an integrated international hub for care and research on lymphoma.

Predicting responses

Meyer-Wentrup fully agrees on this. It surprises her how little focus on biological research there still is in projects on new and improved treatment protocols. 'I think we can be proud to be at the forefront in initiating studies with children using blood and tumor samples to study lymphoma biology. Together with our colleagues in the immunology department of UMC Utrecht we have been able to culture Hodgkin cells. This will help us to better predict responses to treatments, develop targeted therapies and thus reduce toxicity.' In order to support this sort of combined fundamental and clinical research, Van Boxtel is collecting huge amounts of molecular data. 'The more material we have, the better we will be able to stratify patient groups. In the end this will support clinicians in personalizing treatments as precisely as possible.'

Attracting talents worldwide

Both Meyer-Wentrup and Van Boxtel are enthusiastic about the M4C structure, in which doctors and scientists work together very closely and stretch their boundaries. It enables the Máxima Center to derive research questions straight from the clinic and – this is two-way traffic – get research outcomes to the patient much more quickly. Van Boxtel: 'Our ambition to become a central hub that will attract the greatest talents. We want to encourage the best clinicians and researchers from all over the world to come to Utrecht and join our team. In the end it's all about dedicated people who are willing to combine strengths in order to realize a common goal. If we succeed, we will create a new generation of scientific practitioners who will make pediatric oncology really leap forward.'

Dr. Friederike Meyer-Wentrup studied medicine in Germany and came to the Netherlands in 2003 to do research and to continue her career in pediatric oncology. She is driven by the combination of clinical work and basic research. Her goal is to use clinical observations to develop new targets for cancer therapy. If we understand the interaction between the patient's immune cells and the tumor cells, it will be possible to enable the immune system to fight the tumor.

Dr. Ruben van Boxtel is a biologist. His research has been concentrated on studying genome stability in human health and disease. After obtaining his PhD, he studied feedback mechanisms that promote survival of cancer cells upon anti-cancer treatment and genome stability of adult stem cells in organoid cultures. In 2017, Van Boxtel was appointed as a group leader at the Princess Máxima Center.

Solid tumors

Prof. dr. Max van Noesel, Clinical Director

‘In the management of solid tumors in children, we strive to be a strong team which provides cure and care for children and families. In 2021 we developed novel imaging tools for better diagnostics and treatment.’

Solid tumors span a large variety of tumors in children and include organ tumors from kidney, liver, adrenal gland, lungs, testis and ovary and also include soft tissue sarcomas and bone sarcomas. Our diagnostic team includes specialized pathologists, radiologists/nuclear medicine and molecular biologists. The treatment is a collaborative effort of the oncologists, surgeons for abdominal/thoracic tumors, bone and soft tissue, head and neck, radiotherapists, nuclear medicine team and early-drug-development team. The solid tumor team offers treatment according to international standard guidelines, but is also nationally and internationally active to bring frontline, novel treatments to our patients. Many of the medical specialists are active or leading participants of international specialized tumor groups to bring home the best knowledge and treatment. A recent improvement in our diagnostic process is to perform a complete genetic analysis on all tumors. This is an important step in offering personalized drugs in patients with relapsed tumors.

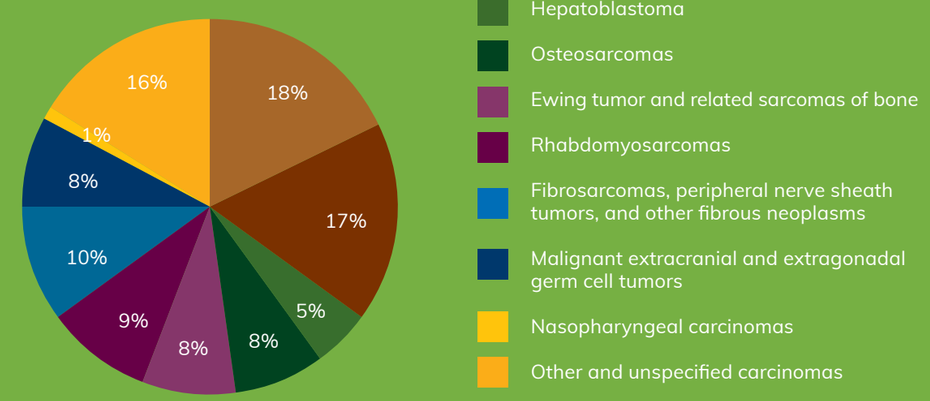
Facts & Figures

The following tables en charts show the solid tumors patient numbers in 2021

ICCC-3	Disease	Patient numbers
IV.a	Neuroblastoma and ganglioneuroblastoma	31
VI	Renal tumors	29
VII.a	Hepatoblastoma	8
VIII.a	Osteosarcomas	13
VIII.c	Ewing tumor and related sarcomas of bone	14
IX.a	Rhabdomyosarcomas	15
IX.b	Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	17
X.b	Malignant extracranial and extragonadal germ cell tumors	14
XI.c	Nasopharyngeal carcinomas	2
XI.f	Other and unspecified carcinomas	26
Total new diagnoses		**169**
Solid tumor relapse		68
Total		**237**

Solid tumors patients in 2021

According to ICCC-3 classification



Autologous stem cell transplantations	N
Aphereses (CD34 + stem cells)	33
Reinfusions (CD34 + stem cells)	44

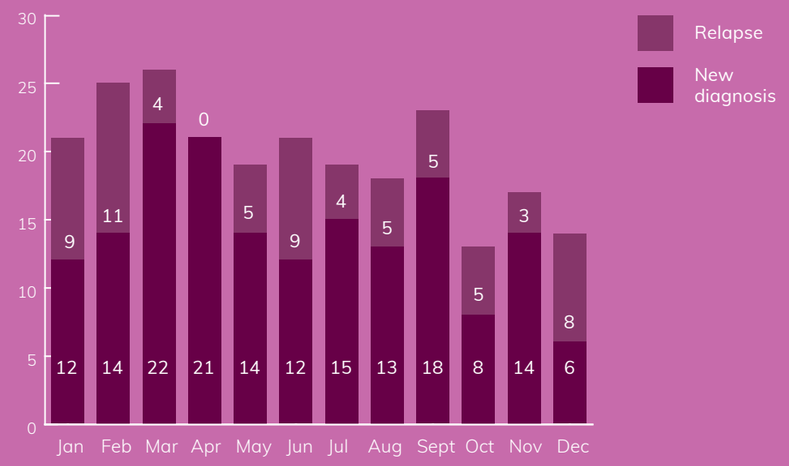
Surgical procedures	N
Kidney tumors	36
Neuroblastoma (resections + biopsies)	58
Lymphoma biopsies	74
Sarcomas (resections + biopsies)	77
Germ cell tumors	10
Melanoma	12
Venous access	698
Other	109

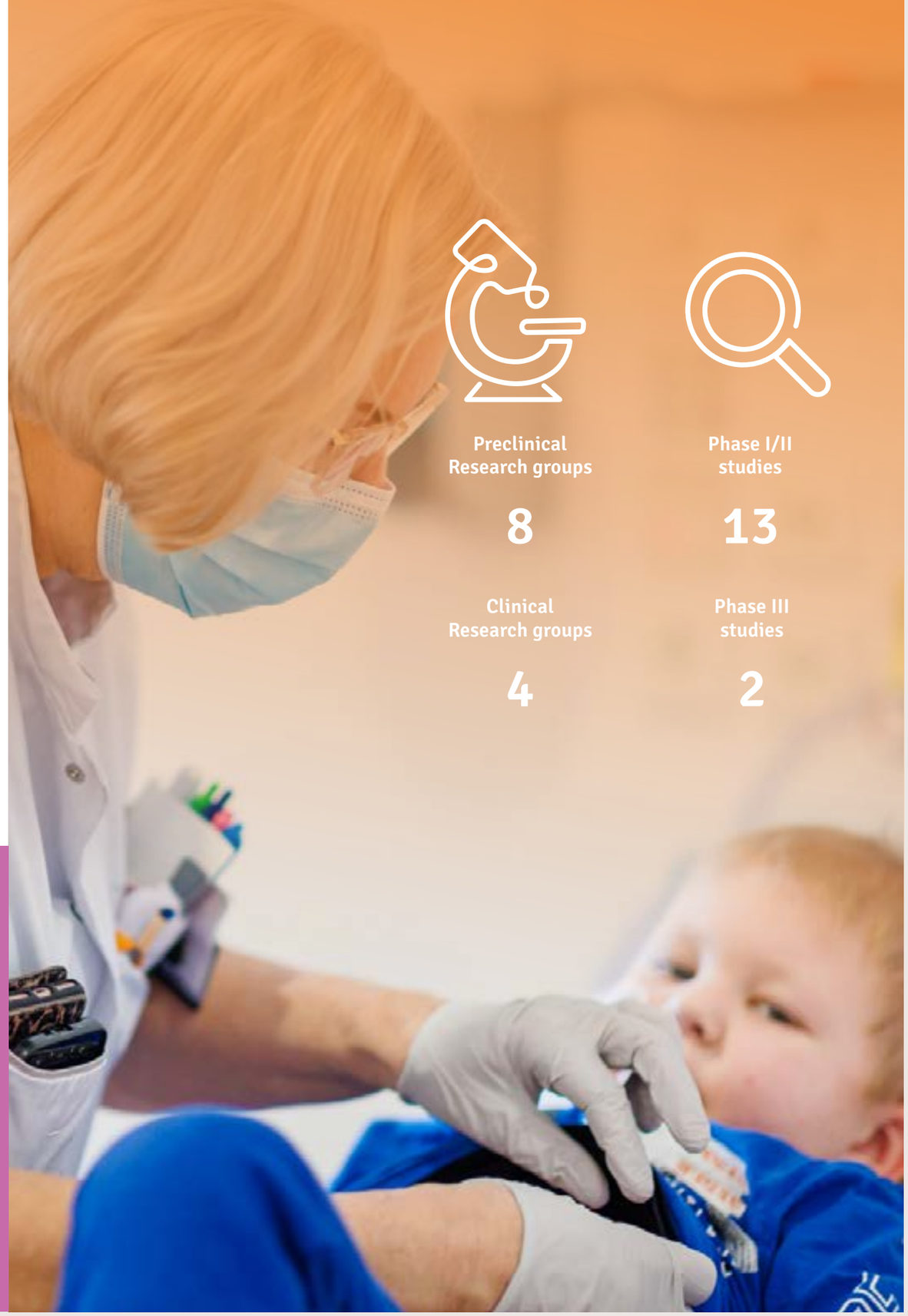
Specialties	N
^{131}I-MIBG therapy*	10
AMORE treatment**	2
Photon therapy	148
Proton therapy***	45

* Innovative treatment using radioactive iodine in children with high-risk refractory or recurrent neuroblastoma
** A specific treatment for rhabdomyosarcoma consisting of Ablative surgery, MOulage brachytherapy and surgical REconstrcuction
*** Innovative form of radiotherapy in collaboration with and performed by the Proton Therapy Center of the UMC Groningen

Solid tumors patient numbers per month

Based on SKION diagnosis data





Research

Solid tumor M4C disease groups

Disease-focused pre-clinical and clinical research and quality of life studies are well-integrated through the M4C groups within our department:

Disease group	Clinical Chair	Research Chair
Neuroblastoma	Max van Noesel	Jan Molenaar
Kidney tumors	Marry van den Heuvel-Eibrink	Jarno Drost
Germ cell tumors	József Zsíros	Leendert Looijenga
Liver tumors	József Zsíros	Weng Chuan Peng
Soft tissue & bone sarcomas	Hans Merks	Claudia Janda
Rare tumors (thyroid, melanoma, nasopharyngeal carcinoma)	Miranda Dierselhuis	Sheila Terwisscha van Scheltinga

Common themes in the research portfolio of solid tumors are: molecular characterization of tumors and personalized medicine, immune environment and immunotherapy, theranostics (therapy & diagnostics) and liquid biopsies.

Theme 1: molecular characterization of tumors and personalized medicine

Cancer is a (epi)genetic disease, also in pediatric solid tumors. For most solid tumors the important and most frequent alterations are well known, but for the individual tumor this can be different. Especially since increasingly many drugs are on the market that target very specific alterations, it is important to understand all the tumor genome alterations of the individual tumor. Understanding in detail for each individual tumor which genetic defects are driving the tumor is essential for the application of novel, targeted drugs. The aim of this research program is to develop better targets for treatment in patients after relapse of disease or in first line treatment.

Van Tilburg CM, Pfaff E, Pajtler KW, Langenberg KPS, Fiesel P, Jones BC, Balasubramanian GP, Stark S, Johann PD, Blattner-Johnson M, Schramm K, Dikow N, Hirsch S, Sutter C, Grund K, von Stackelberg A, Kulozik AE, Lissat A, Borkhardt A, Meisel R, Reinhardt D, Klusmann JH, Fleischhack G, Tippelt S, von Schweinitz D, Schmid I, Kramm CM, von Bueren AO, Calaminus G, Vorwerk P, Graf N, Westermann F, Fischer M, Eggert A, Burkhardt B, Wößmann W, Nathrath M, Hecker-Nolting S, Frühwald MC, Schneider DT, Brecht IB, Ketteler P, Fulda S, Koscielniak E, Meister MT, Scheer M, Hettmer S, Schwab M, Tremmel R, Øra I, Hutter C, Gerber NU, Lohi O, Kazanowska B, Kattamis A, Filippidou M, Goemans B, Zwaan CM, Milde T, Jäger N, Wolf S, Reuss D, Sahm F, von Deimling A, Dirksen U, Freitag A, Witt R, Lichter P, Kopp-Schneider A, Jones DTW, Molenaar JJ, Capper D, Pfister SM, Witt O. The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets. Cancer Discov. 2021 Nov;11(11):2764-2779. doi: 10.1158/2159-8290.CD-21-0094. Epub 2021 Aug 9. PMID: 34373263.

Theme 2: Immune environment and immunotherapy

Immunotherapy works by using and improving the patient's own immune system to attack tumor cells. This is already done by using tumor-specific antibodies to attack tumors, i.e. anti-GD2 based immunotherapy in neuroblastoma. But recent developments have made it possible to genetically engineer tumor-specific T-cells, so-called CAR T, to attack tumors. This is already a success in treating leukemias, but still in early development in solid tumor treatment. Our department works with national and international researchers and clinicians to develop this for future patients.

Wienke J, Dierselhuis MP, Tytgat GAM, Künkele A, Nierkens S, Molenaar JJ. Eur J. The immune landscape of neuroblastoma: Challenges and opportunities for novel therapeutic strategies in pediatric oncology. Cancer. 2021 Feb;144:123-150. doi: 10.1016/j.ejca.2020.11.014. Epub 2020 Dec 18. PMID: 33341446.

Theme 3: Theranostics

In Theranostics, tumor-specific molecules are labeled with radionuclides for imaging in PET scans or nuclear treatment of tumor cells. In recent years, we have developed a novel scan for the diagnosis of neuroblastoma tumors, the so-called M18FBG-PET scan. We have shown improved imaging compared to the standard M123IBG-SPECT scan. This is taken forward for future studies. Nuclear treatment is in development in several international trials using 177Lutetium-dotatate for neuroblastoma and other neuro-endocrine tumors.

Samim A, Tytgat GAM, Bleeker G, Wenker STM, Chatalic KLS, Poot AJ, Tolboom N, van Noesel MM, Lam MGEH, de Keizer B. J. Nuclear Medicine Imaging in Neuroblastoma: Current Status and New Developments. Pers Med. 2021 Apr 4;11(4):270. doi: 10.3390/jpm11040270. PMID: 33916640.

Theme 4: Liquid biopsies

Liquid biopsies enable the diagnosis of cancer in blood or other body fluids such as urine, or cerebral fluid. It is based on the release of proteins and DNA from tumor cells into the bloodstream that can be detected with special techniques. For each tumor, the molecular make-up is unique and this specific profile is used to make a unique diagnostic tool for each tumor. In the blood of the patient these unique alterations can be detected and used in the follow-up of patients at the end of treatment. In neuroblastoma, rhabdomyosarcoma and germ cell tumors we are in different stages of development of liquid biopsies.

Van Zogchel LMJ, Lak NSM, Verhagen OJHM, Tissoudali A, Gussmalla Nuru M, Gelineau NU, Zappeij-Kannengieter L, Javadi A, Zijtregtop EAM, Merks JHM, van den Heuvel-Eibrink M, Schouten-van Meeteren AYN, Stutterheim J, van der Schoot CE, Tytgat GAM. JCO Prec. Oncol. Novel Circulating Hypermethylated RASSF1A ddPCR for Liquid Biopsies in Patients With Pediatric Solid Tumors. Precis Oncol. 2021 Nov 17;5:PO.21.00130. doi: 10.1200/PO.21.00130. eCollection 2021. PMID: 34820594.

Key milestones from Solid Tumors in 2021

Diagnostic Precision Medicine

The clinical implementation of a pediatric cancer precision medicine program is enforced with personalized models. Precision medicine provides genetic and molecular profiles of all tumors and analyzes the possible targeted treatments that can be applied for that tumor. This is possible for each individual patient by performing molecular profiling and organoid culture for all pediatric tumors, with an emphasis on solid tumors. The aim is to identify targets for treatment and to validate those *in vitro*, in organoids.

The FAR-RMS study

FAR-RMS is an international study for the treatment of all rhabdomyosarcoma subgroups. The study aims to: a) test novel drugs in combination with chemotherapy for high risk disease, b) develop drug strategies for relapsed tumor and c) provide standard treatment for low and intermediate risk patients.

The E-SMART study

E-SMART is a multi-arm phase I-II study for the treatment of relapsed patients with solid tumors aimed at different genetic profiles. Each profile contains different targeted drugs or drug combinations. It is an international study involving many centers and countries in Europe.

Fluorescence guided surgery

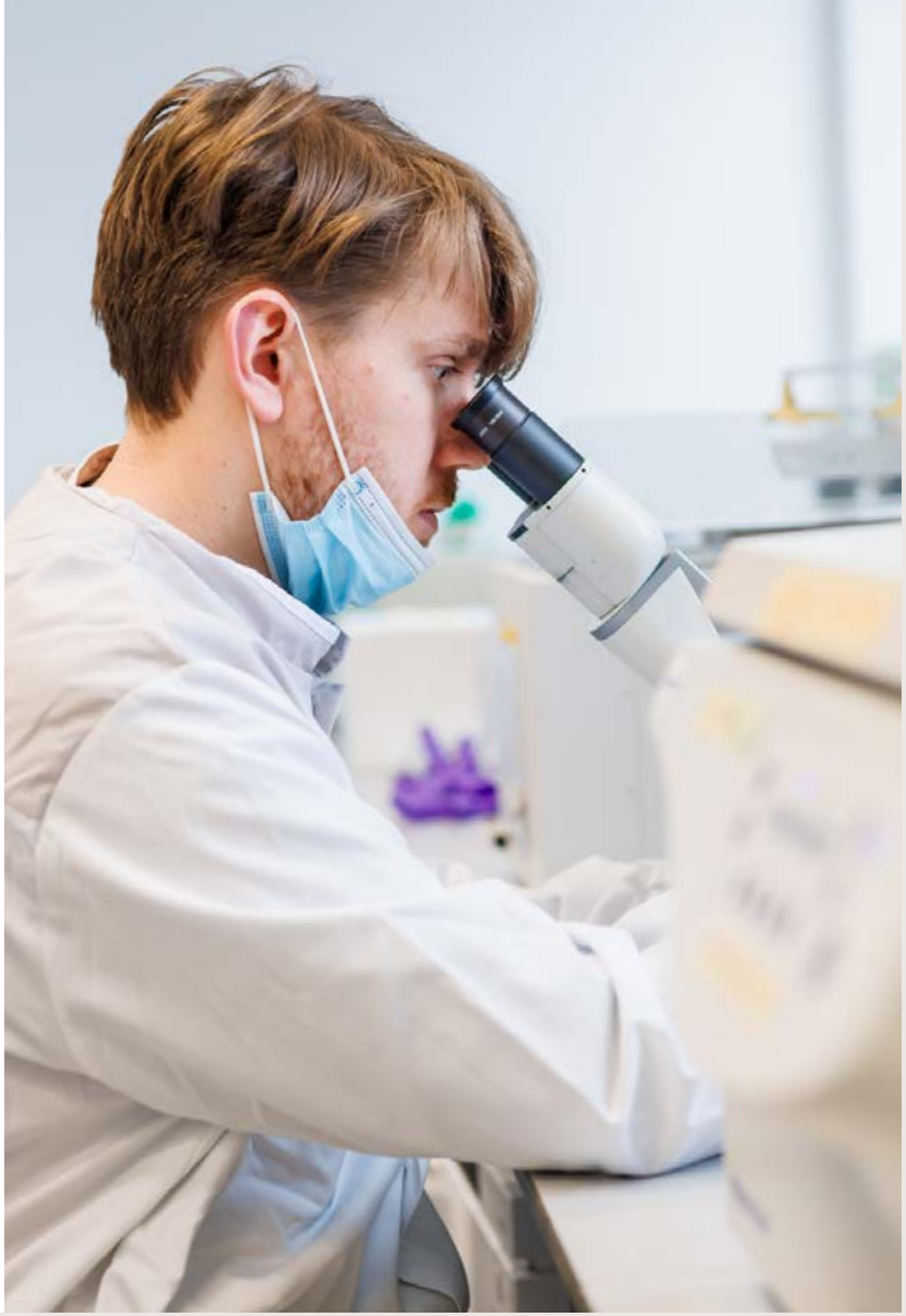
Surgical recognition of tumors is essential in achieving complete resections. The surgical group is developing anti-GD2/dinutuximab fluorescence labeling for intraoperative detection of neuroblastoma using near-infrared fluorescence. The aim of the project is to better recognize tumor areas and improve the surgical resection. The project will start in 2022 with a first phase I study in children with neuroblastoma.

Cell of origin in neuroblastoma uncovered

Neuroblastomas are neural crest developed tumors. The neural crest is an embryonal tissue which gives rise to many different tissues in the human body, including the sympathetic nervous system and adrenal glands. Using novel techniques such as single cell sequencing, the researchers of the Máxima Center together with international partners have uncovered the stage and cell type most likely to be the cell of origin of high risk neuroblastoma tumors. This knowledge will contribute to a better understanding of these tumors, improving classification of patients and will hopefully lead to novel therapeutic approaches.

Future perspective and concluding remarks

The solid tumor team takes pride in the team-work in clinical treatment of patients and the collaboration with researchers. Together, this leads to better care and more clinical studies for the benefit of patients and parents. We will continue to improve our team efforts to improve cure and care. This will be our focus for the years ahead.



Miranda Dierselhuis and Sheila Terwisscha van Scheltinga

Networking for better care around rare tumors

In the Solid Tumors department, the Princess Máxima Center treats children and teenagers with malignant tumors in organs, tissues and the skeleton. The department also treats rare types of childhood cancer. Multidisciplinary collaboration – on a national and even European level – is necessary to improve knowledge on better treatments for these types of cancer. The M4C disease group Rare Tumors takes center stage.

In some way the M4C disease group Rare Tumors is the odd one out: the two co-chairs – Miranda Dierselhuis and Sheila Terwisscha van Scheltinga – are both clinicians. They combine their work as a doctor with scientific activities in a field that still leaves a lot to be discovered. Rare tumors can be so rare that a full year can pass without the emergence of even one single case in a child. This underlines the importance of a close interdisciplinary collaboration on a national and international level. Dierselhuis specialized in pediatrics in Leiden and did a PhD on antigen specific cytotoxic and regulatory immune responses in 2015. After that she became a pediatric oncologist through a fellowship in the Princess Máxima Center. Studies on new drugs have her special interest, also because these novel pharmaceuticals might provide answers to the specific needs of children with rare tumors. Her co-chair Terwisscha is an experienced surgeon, who started her career in adult oncology in 2006. She became a pediatric surgeon in the Sophia Children's Hospital in Rotterdam, before she joined the newly started Máxima Center in 2014.

Adequate post-treatment

The M4C disease group Rare Tumors is relatively new within the Solid Tumors department, Terwisscha says. 'Our group gives host to many different types of cancer that are either rarely seen in children or don't occur in our center very often. A good example is melanoma. This type of skin cancer isn't rare among adults. In children or teenagers it is usually the dermatologist or the adult surgeon who discovers it and starts a treatment. The initial intervention – surgery – can very well be done outside the Máxima, but for adequate post-treatment our expertise is needed. Our center has made agreements on pediatric oncology with all pediatricians in our country, but we don't have these with all other medical specialisms. Part of our mission is therefore to promote that doctors consult us in case of every oncological diagnosis in children.' The scope of the group is broad, and a certain level of sub-specialization became necessary, Dierselhuis says. Melanoma is one of them; the others are nasopharyngeal carcinoma and tumors in endocrine organs, such as the thyroid.'

Quarterly evaluation of patients

In all of these cases the group cooperates with a wide variety of experts in and outside the Máxima Center. Dierselhuis: 'In the example of suspected thyroid carcinoma we take part in multidisciplinary meetings in UMC Utrecht. Suspected cases are usually discovered by our colleagues in the endocrinology department of our neighboring Wilhelmina Children's Hospital (WKZ). Often a tumor turns out to be benign, but in cases of doubt we are consulted.' In order to get a solid diagnosis Terwisscha will operate the child together with one of the UMC Utrecht endocrine surgeons to remove part of the thyroid and send tissue to the pathologists in Princess Máxima Center. Thyroid carcinoma is one of the rare tumors for which treatment is not centralized, Dierselhuis explains. 'In our national collaboration we worked out guidelines and made arrangements with four Dutch centers. Every three months we hold a nationwide multidisciplinary board meeting to evaluate all patients.'

Identifying urgent research topics

So far the group has concentrated on the organizational structures for optimal care. The very rare nature of the tumors urges everyone involved to collaborate intensively. Within the M4C structure research questions almost automatically emerge. Dierselhuis: 'We're in a transition towards more explicitly developing research projects. Our first aim was to get treatment structures right, now we can take a step towards identifying urgent research topics.' Terwisscha fully agrees and suggests one important research theme: 'We will need to build up a solid registry on patient outcomes, in order to both improve follow-up and facilitate analyses that will further improve the quality of treatment of rare tumors. It is one of our ambitions for the next few years to develop a good data system.' Another interesting scientific innovation is research on thyroid organoids.

Improving treatment protocols

To both co-chairs the future is challenging. With regard to thyroid carcinoma things are already settled quite well, they say. But many other rare tumors need good structures in order to optimize collaboration in diagnosis and treatment. Much can be expected from the European EXPeRT group on rare tumors, in which the Máxima Center takes part. Dierselhuis: 'The international guidelines still leave too much room for different interpretations. Our goal is to help improve the protocols, so that all children with rare tumors will receive the best possible treatment.'

Dr. Miranda Dierselhuis is a pediatric oncologist specialized in solid tumors. Her specific focus is on neuroblastoma, immunology within pediatric oncology and studies with new drugs. One of her subspecialties is the treatment of rare tumors such as melanoma and thyroid carcinoma. She is a member of SIOPEN, EXPeRT and ITCC, the Working group melanoma in children and the Working group on development of care pathways and guidelines for children with suspected thyroid carcinoma.

Drs. Sheila Terwisscha van Scheltinga is a pediatric oncology surgeon with specific experience in treating rare tumors. She is chair of the surgical committee of the European Pediatric Soft Tissue Sarcoma Study Group, member of the Working group melanoma in children and the Working group on development of care pathways and guidelines for children with suspected thyroid carcinoma.

Neuro-oncology

Prof. dr. Eelco Hoving, Clinical Director

‘We are excited to explore new opportunities for treating our children with CNS tumors in active collaboration between clinicians and researchers and with promising international partners.’

In 2021 our large pediatric neuro-oncology practice in the Princess Máxima Center was further consolidated. Increasing expertise was fostered in our clinical team among all the various disciplines involved, and together we are driven to create and to provide top clinical care for our patients. At the same time we intend to learn as much as possible from our patients on all levels. Our nursing staff made enormous efforts learning about individual needs of patients and their families while translating this into optimal care. The BrainCARE program was started with the focus on defining when cognitive damage will occur during the clinical course of all new children with brain tumors. Clinical treatment in Phase III studies became available for our medulloblastoma and ependymoma patients, and more patients with recurrent tumors could be treated in Phase I/II trials.

The importance of integration of research with clinical care has become fundamental to create innovative and more effective treatment modalities in order to improve survival with a better quality of life for all our patients. This integration has started to take shape by collaboration between clinicians and researchers in our four comprehensive tumor groups: Glial tumors, with separate High Grade and Low Grade Glial groups, Embryonal tumors and Craniopharyngiomas/Germinomas. In addition, an important external collaboration was started with Heidelberg and we became the first EU member of the Pacific Pediatric Neuro-Oncology Consortium (PNOC). In this PNOC consortium the major American pediatric neuro-oncological centers collaborate to develop and to provide a large portfolio of early phase studies.

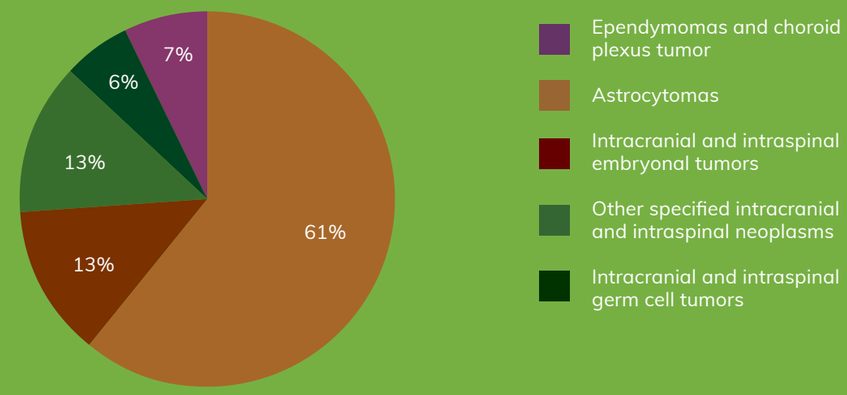
Facts & Figures

The following tables en charts show the neuro-oncology patient numbers in 2021

ICCC-3	Disease	Patient numbers
III.a	**Ependymomas and choroid plexus tumor**	**9**
	Ependymoma	7
	Choroid Plexus Tumor	2
III.b	**Astrocytomas**	**73**
	Diffuse intrinsic pontine glioma	2
	High-grade glioma	21
	Low-grade glioma	50
III.c	**Intracranial and intraspinal embryonal tumors**	**15**
	Atypical teratoid/ rhabdoid tumor	4
	Medulloblastoma	11
III.e	**Other specified intracranial and intraspinal neoplasms**	**15**
	Central nervous system (CNS) tumor, not otherwise specified (NOS)	4
	Craniopharyngioma	11
X.a	**Intracranial and intraspinal germ cell tumors**	**7**
	Total new diagnoses	**119**
	CNS relapse	65
	Total	**184**

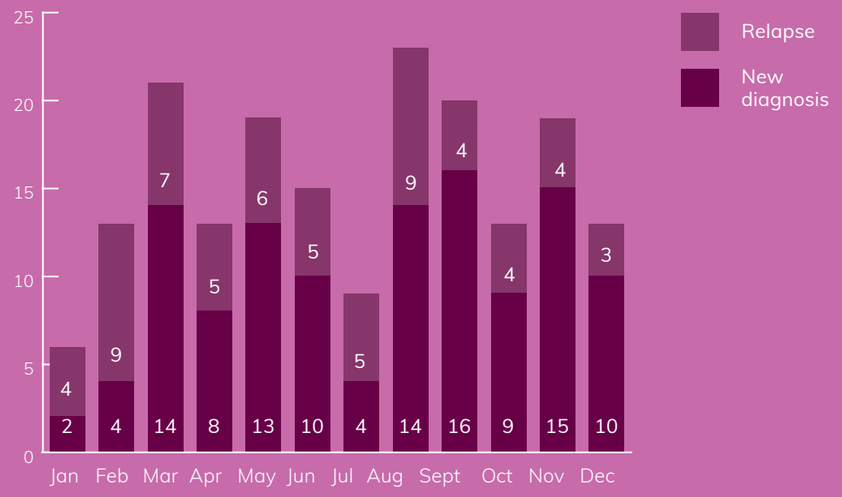
Neuro-oncology patients in 2021

According to ICCC-3 classification



Neuro-oncology patient numbers per month

Based on SKION diagnosis data



Neurosurgical procedures in the Princess Máxima Center	N
Tumor resections	115
Tumor biopsies	50
Total	**165***

* Approximately 80% of all neurosurgical procedures in children with central nervous system (CNS) tumors in the Netherlands

Research

Neuro-oncology M4C disease groups

Disease-focused pre-clinical and clinical research and quality of life studies are well integrated through the M4C groups within our department. Overarching the neuro-oncological M4C disease groups are chaired by Eelco Hoving and Marcel Kool.

Disease group	Clinical Chair	Research Chair
Low grade gliomas	Netteke Schouten–van Meeteren	Mariette Kranendonk
High grade gliomas	Dannis van Vuurden	Esther Hulleman
Embryonal & Rare CNS tumors	Sabine Plasschaert	Marcel Kool
Craniopharyngiomas & CNS Germ Cell Tumors	Hanneke van Santen	Marc van de Wetering (craniopharyngiomas) Leendert Looijenga (Germ Cell Tumors)

Preclinical research in neuro-oncology

Many research teams in the Máxima Center work on pediatric brain tumors. Together they cover different areas of expertise and use state-of-the-art technologies to gain a better understanding of what is driving these tumors, and how they can be targeted better with more specific and personalized treatment strategies that more efficiently kill the tumor cells but are less damaging to the normal developing brain of a child. Patient material (tumor, blood, cerebrospinal fluid) for these studies is routinely collected from all brain tumor patients in the Máxima Center at diagnosis, during treatment, at relapse, or after autopsy. Material is used for diagnostic purposes, disease monitoring, molecular studies, the establishment of preclinical models (organoids, cell lines, xenograft models), and stored in the Biobank for future studies.

Molecular studies on pediatric brain tumors have shown that many genetically and clinically distinct types of pediatric brain tumors exist that would not always have been recognized as distinct by histology alone. An important outcome of these studies is the incorporation of these molecular data and tools in the recent fifth edition of the WHO classification of CNS tumors, published in 2021, and to which several people in the Máxima Center contributed. Current research on pediatric brain tumors focuses on further optimizing diagnostic tools using genomics, advanced imaging, bioinformatics and artificial intelligence (AI) methods. Molecular studies, using multi-omic integrated technologies both at bulk and single cell level, are performed to gain a better understanding of the inter- and intratumor heterogeneity and the tumor microenvironment. In these studies, profiling immune cells within the tumor microenvironment is of specific interest, as major efforts in adults targeting the immune system have shown great clinical promise. A better insight in the tumor microenvironment and how tumor cells communicate with surrounding immune and stromal cells will help to design novel and specific (cellular and/or compound based) immunotherapies for pediatric brain tumors. To test new targets and therapies, including immunotherapies and other targeted therapies, a wide range of molecularly well-characterized preclinical models representing the broad spectrum of pediatric brain tumors is needed. Several efforts are ongoing in the Máxima Center to build a platform of such preclinical models. Here, the focus is on creating a large panel of tumor organoid models either directly from patient material or based on human stem cell protocols used to generate brain region specific tumor organoids. Tumor organoids are used for high-throughput *in vitro* studies, including co-cultures with immune cells, drug and CRISPR screens, or other genetic manipulations to study tumor biology and to find new ways of targeting them.

Important output

- Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021 Aug 2;23(8):1231-1251. doi: 10.1093/neuonc/noab106. PMID: 34185076; PMCID: PMC8328013.

Clinical Research in Neuro-oncology

In 2021, Phase III trials were available for patients with medulloblastoma (PNETV), or with ependymoma (Ependymoma II). A lot of effort went into finishing preparations for the LOGGIC-Core, High Risk Medulloblastoma, and ATRT trials, that will be opened in early 2022.

Concerning Phase I/II trials, the options for patients with relapsed or refractory disease are still limited. 2021 was a year of investment for a better infrastructure for early phase clinical trials for pediatric neuro-oncology, not only for the Netherlands, but also for Europe. Due to the collaboration with PNOC, the Máxima Center will take on a coordinating role for transatlantic trials,

by using the ITCC (BRAIN) network for European implementation. Three large trials are in preparation for implementation in 2022. Currently we have the NivoEnt trial open (sponsor Heidelberg) where we are the top recruiter worldwide. Another important study that was implemented is the Firefly study in which patients with a relapse low grade glioma can be enrolled for a new small molecule drug (sponsor Day01). Although this is not an intervention trial, the data generated can be an important starting point for future immunotherapy trials.

Important output

- Van Schaik J, Hoving EW, Müller HL, van Santen HM. Hypothalamic-Pituitary Outcome after Treatment for Childhood Craniopharyngioma. Front Horm Res. 2021;54:47-57. doi: 10.1159/000515318. Epub 2021 May 7. PMID: 33965963.

- Hill RM, Plasschaert SLA, Timmermann B, Dufour C, Aquilina K, Avula S, Donovan L, Lequin M, Pietsch T, Thomale U, Tippelt S, Wesseling P, Rutkowski S, Clifford SC, Pfister SM, Bailey S, Fleischhack G. Relapsed Medulloblastoma in Pre-Irradiated Patients: Current Practice for Diagnostics and Treatment. Cancers (Basel). 2021 Dec 28;14(1):126. doi: 10.3390/cancers14010126. PMID: 35008290; PMCID: PMC8750207.

- El-Khouly FE, Adil SM, Wiese M, Hulleman E, Hendrikse NH, Kaspers GJL, Kramm CM, Veldhuijzen van Zanten SEM, van Vuurden DG; SIOPE DIPG Network. Complementary and alternative medicine in children with diffuse intrinsic pontine glioma-A SIOPE DIPG Network and Registry study. Pediatr Blood Cancer. 2021 Sep;68(9):e29061. doi: 10.1002/pbc.29061. Epub 2021 May 4. PMID: 33942498.

- Nuijts MA, Stegeman I, Porro GL, Duvekot JC, van Egmond-Ebbeling MB, van der Linden DCP, Hoving EW, Schouten-van Meeteren AYN, Imhof SM. Ophthalmological Evaluation in Children Presenting With a Primary Brain Tumor. J Neuroophthalmol. 2021 Nov 18;42(1):e99–e108. doi: 10.1097/WNO.0000000000001421. Epub ahead of print. PMID: 34812765; PMCID: PMC8834141.

Key milestones from Neuro-oncology in 2021

Main goals

The Neuro-oncology department's major goal in 2021 was to further develop a national practice of excellent clinical neuro-oncological care for children in the Máxima Center. The number of patients has contributed to establishing more neuro-oncological expertise in our medical team and our very dedicated nursing staff. Patients and parents have appreciated their stay in the nursing ward Molen ('Windmill') very much. To keep improving our treatments and outcome, the department aims to treat most new patients in clinical Phase III trials and recurrent tumor patients in Phase I/II trials. This clinical trial portfolio is in progress. To optimally integrate both Neuro-oncology care and research the beforementioned unique setting of the M4C has been developed. Excellent research groups focused on CNS tumors have been established and collaboration between clinicians and researchers will flourish.

New developments

In 2021, a variety of new developments in different fields took place. For example our Neuropsychology program BrainCARE was started to investigate how cognitive impairment arises during treatment and how to offer children appropriate support. In our clinical practice, CNS tumor diagnostics including extensive molecular profiling has created valuable data to feed further progress. For the purposes of multidisciplinary care – an aspect especially important in Neuro-oncology – a great team was built with specialists working in complementary roles to best treat our patients.

The department's pride

In 2021 a lot of progress was achieved in both clinical and research goals, a result of working together in great spirit with the Máxima Center's mission in mind. But we are most proud of our patients, for their faith and expectations concerning the treatments that we offer.

Innovative technologies

In 2021, several innovative technologies were implemented. Firstly, with the money raised by the Semmy Foundation a robotic arm 'de robot van Tijn' was bought that helps operate on children with brain stem tumors. With the robotic arm, surgeons are able to take deep seated brain tumor biopsies and more closely monitor the disease. The new system also offers exciting prospects for research to develop new types of treatments. Secondly, the construction of the intra-operative (IO)-MRI facility started in 2021. In this joint project with the UMC Utrecht, a state-of-the-art operating room is being built in the surgical complex of the Wilhelmina Children's Hospital (WKZ). Thirdly, progress was made in the HIFU project. This project focuses on the treatment of high-grade gliomas by improving drug delivery through Focused Ultrasound (FUS) technology. In 2021, a helmet was purchased that will be incorporated into an MRI scanner. By aiming very precise vibrations at the site of the tumor, the blood-brain barrier will temporarily and locally open, allowing drugs to enter the brain.

Looking forward

In 2022, the intra-operative (IO)-MRI neurosurgical operating suite will become available for the neurosurgical procedures of all children with brain tumors in the Netherlands. This highly innovative operating room offers integration of a semi-robotic microscope, a 3D ultrasound device and the robotic arm for biopsies. The intra-operative MRI will contribute to safer and more radical tumor resections in the brain. We feel very fortunate to be able to use and to further develop these technological innovations. In 2022 we also expect to implement the first studies of the PNOC portfolio in and through the Máxima Center, and we shall explore possible collaborations to stimulate CAR T-technology and studies for neuro-oncology patients.

In conclusion

With neuro-oncology as an area of focus in the Princess Máxima Center's four-year strategic plan, the Neuro-oncology department has unique opportunities to create a basis for both excellent care and research in our center, in order to create better chances of survival with optimal quality of life for all our patients.

In the spotlight | M4C disease group
Craniopharyngiomas & CNS Germ Cell Tumors

Hanneke van Santen and Marc van de Wetering

Joint efforts to improve outcomes of treatment

Craniopharyngioma is a rare tumor in the brain, near the hypothalamus. It is a low-grade tumor with excellent prognosis in terms of overall survival, but survivors may suffer from devastating consequences caused by hypothalamic damage. What can be done to get better outcomes? Scientific innovation in developing organoid models and in unravelling the clinical picture of acquired hypothalamic dysfunction could in future offer new chances for patients and their families. The Princess Máxima Center takes the lead.

Some eight years ago Hanneke van Santen moved her career from Amsterdam to Utrecht to support the Máxima initiative. Her mission: to give endocrinology the place it deserved in the upcoming center for pediatric oncology. She was ahead of the pack, as she calls it, and rightly so. ‘Endocrinology wasn’t really on the minds of many people involved. Whereas endocrinal side effects of both treatments and tumors can be very serious.’ Van Santen remembers a recent case of a mother who said: ‘I’m happy my child is cured from her tumor, but I did not expect that she would become a totally different person.’ This can happen after treatment of a craniopharyngioma, which often leads to an unstoppable urge to eat with (morbid) obesity as a result. Combined with the obsessive-compulsive personality disorders that can occur, the despair of parents becomes very understandable, Van Santen says. Her co-chair Marc van de Wetering, a molecular biologist who has worked with Hans Clevers for more than 30 years now, recognizes the urgency of research on these kinds of problems. His work is dedicated to finding ways to investigate complications of treatments of tumors that are often rare.

Organoids – in vitro tissue constructs that mimic their corresponding in vivo organ – can be an instrument to help answering questions.

Risk of developing comorbidities

Organoids are already rather common in adult oncology research, Van de Wetering explains, but in pediatric oncology there still is a lot of pioneering work to do. ‘Organoids not only enable us to intensely test efficacy and safety of medication, they also provide excellent opportunities for fundamental research on the processes that might lead to cancer.’ To both co-chairs, the added value of the M4C structure has become very clear in the case of craniopharyngioma. In the Netherlands, eight to ten children develop this brain tumor each year. Treatment usually affects the hypothalamus, an important brain region in regulating hormone levels. Van Santen: ‘It’s a complex system that controls a number of processes in the body, like metabolism, day and night rhythm, temperature regulation and pubertal development. These children are at great risk of developing comorbidities leading to premature mortality.’

The close M4C collaboration led to brainstorm sessions with neurosurgeon Eelco Hoving. The ‘eureka moment’ came with the awareness that the affected area consists of epithelial cells, which would make it possible to culture organoids.

Combined research goals

Van de Wetering and co-workers picked up the challenge and succeeded. But their efforts could never have been so successful without the collaboration between lab and clinic, he emphasizes. ‘Ours is a good example of the right balance between care and research. Our close interaction made it possible to generate a disease model that can be intensely scrutinized. Studying patient material is like looking at a snapshot, whereas organoids provide you with a real movie; a moving picture that enables you to follow processes within the cell from onset to end.’ Van Santen underlines the great possibilities of working with these newly developed models. ‘We will also be able to differentiate between subtypes of craniopharyngioma. This is very important, since clinical practice shows that outcomes can result in big differences. And so should therapies, consequently.’

Towards a personalized approach

Van de Wetering agrees on the clear benefits of designing studies within an M4C structure. ‘In the lab our focus can sometimes be too much on fundamental research. Without our M4C I would never be talking with Hanneke and Eelco as intensely as we do now for our research projects. Useful patient oriented lab research can only be designed in close multidisciplinary cooperation with all clinical professionals involved. So yes, I’m very much in favor of this way of working. On the other hand it’s important not to make the M4C into a goal of its own. In the end it is a means toward the real aim of our work: making things better for children and families.’

The work of the Looijenga group on germ cell tumors

The second focus of the M4C group chaired by Hanneke van Santen and Marc van de Wetering are the so-called CNS (‘central nervous system’) germ cell tumors. Research on these tumors is done in collaboration with the research group of Leendert Looijenga. This group is dedicated to investigating the pathogenesis of various types of human germ cell tumors. The aim is to perform optimal (early) diagnosis and treatment, including identification and application of (molecular) biomarkers. This will result in the most effective treatment with limited side effects, both in the short and long term.

Dr. Hanneke van Santen is a pediatric endocrinologist at the Wilhelmina Children’s Hospital and the Princess Máxima Center, as well as clinical scientist in the research program of Child Health, UMC Utrecht and co-Principal Investigator at the Princess Máxima Center. She is specialized in the hormonal consequences of treatments for childhood cancer, in pediatric thyroid cancer and pediatric craniopharyngioma. Her commitment is to improving the endocrine outcome of children with cancer. She is chair of the SIOPe working group for craniopharyngioma.

Dr. Marc van de Wetering is acting group leader of the Clevers Group. Since research on child cancer is complicated by the limited availability of tumor tissue, his focus is on cancer organoids to fill the gap. Currently the organoids are not available for most pediatric cancer types. Van de Wetering and colleagues develop technologies to derive pediatric cancer organoids and use these for fundamental research and drug discovery.

Quality of life

Dr. Wouter Kollen, Clinical Director

‘The combined journey towards our mission connects children, parents and professionals in our tireless efforts to improve quality of life every day.’

The Quality of Life (QoL) department connects six clinical teams and four research groups and enables the positioning of this important theme within the mission statement. It promotes collaboration with the three tumor-specific care departments and the research institute. Quality of Life is also responsible for the organization of shared care and collaboration with the Children’s Advisory Board, Client Council and the Dutch Childhood Cancer Organization (VKN).

All our teams put a lot of effort into the programs this year, which we prioritized with all QoL professionals during our 2020 open space sessions. Three central themes were defined:

- How do we get to know each other better?
- How do we show others what we are capable of?
- How do we improve participation of our patients and families?

We learned a lot about each other with ‘knowledge lunches’, activities like pub quizzes, table tennis competition and two impressive magazines. In the fall, we celebrated our second Quality of Life symposium, organized together with SKION. The festivities around the retirement of Hanneke de Ridder, who played a key role in the development of Quality of Life, represented a highlight during this COVID-19 dominated period.

On Childhood Cancer Awareness Day, we presented a number of accomplishments, for which children, parents and professionals have worked closely together. The VKN-Máxima diary for parents has been reinvented and all available information for families has been revised both in content and design. We presented the ‘Mijn Máxima’ (My Máxima) app, which organizes information and in the future, will function as the portal for all patient information.

Furthermore we continued our efforts to implement the BrainCARE program and to define outcome parameters that we want to use for improvement and benchmarking. Annick Sickinghe inspired us with her impressive documentary ‘LATER’, premiered at the Máxima Center during the Childhood Cancer Awareness Month of September.

The six QoL clinical teams

1. Psycho-oncology

The psycho-oncology department facilitates support for children and parents from the moment of arrival in the Máxima Center after diagnosis. Continuity of care was further supported by systematic screening for family stress and risk factors using the KLIK PROM portal.

To support parents in coping with illness and treatment, the online ‘Op Koers’ program was offered several times. To reduce anxiety and stress, virtual reality (VR) was added to the repertoire of child life specialists. For this purpose, two specific films were developed: preparation for radiotherapy and preparation for an MRI examination. At a multidisciplinary level, contributions were made to the bone tumor clinic, remembrance service, cultural sensitivity, medical ethics, nurse advisory board, medical advisory board and the children’s comfort team in the Utrecht region.

With regard to education, the department contributed to introduction programs for new employees and to the international master course in pediatric oncology. Lessons included medical traumatic stress, talking with children about cancer and developmental psychology. Education was also provided in the Outreach program. The communication learning program has kicked off with positive responses, which is promising for the future.

2. Supportive care

Supportive care is indispensable to reach the mission of the Princess Máxima Center. Over the last three years, since the opening of our center, the supportive care group has been able to further optimize care. The care with respect to nutrition, infectious diseases, catheter care, infections, endocrinology and fertility is now standard of care. The comfort team, founded in 2018, is now involved with over 95% of children in the palliative phase. And, even more importantly, the comfort team is consulted at an increasingly earlier stage of the palliative phase. In 2021, mouth care has been a focus of attention. For this, a nursing program has been started with a new tool to measure oral mucositis. The care of the dentist and the oral hygienist of the Wilhelmina Children’s Hospital (WKZ) has been integrated in standard of care for our patients.

In 2021, we launched a website, where parents and patients get information on nutrition. We provide evidence-based information, and parents can post questions. Moreover, we provide recipes for energy-rich and energy-poor meals. This to optimally facilitate parents for care of their children at home. In 2021, we started integrating care and research by further elaborating the M4C structure. This is a longer process, which will be continued 2022.

3. Sports and Exercise Center

In 2021, the physiotherapists and exercise therapist of the Sports and Exercise Center contributed to the health and quality of life of children with cancer and survivors in several ways. Every day, professionals work together to get children with cancer as active as possible. This helps the children to remain independent and to continue functioning in their daily lives.

In 2021, the department participated in the National Sports Week for the first time. During this week in September, NOC*NSF stimulates schools and (sports) organizations to motivate everyone in the Netherlands to get more exercise. This was of course the ideal opportunity to give extra attention for exercise and sports for children with cancer.

The bone tumor outpatient clinic started at the end of 2021. A multidisciplinary team looks at the consequences of a bone tumor. Questions are answered and data for improving care is collected. Through the ‘KinderOncoNet’ project, a great deal of information has become available about the wants and needs for physical therapy in the home setting of children with cancer. As a result, the first steps have been taken to create a network where healthcare professionals can find each other and share knowledge. This project has since expanded to other fields, such as dietetics, occupational therapy, psychology and social work. With this, we are building a national network that can further improve the quality of life of children with cancer and survivors.

4. Development-oriented care (OGZ)

The central focus in development-oriented care is the development of children and their families. The OGZ staff participates in organization-wide projects and working groups in order to realize the vision of development-oriented care. Alongside this, the various teams also have a specific focus. The educational team, together with children, parents and the children's regular schools, ensure that schooling can continue. The children receive lessons in the classroom, in their own room, or - due to COVID-19- online.

Also in 2021, in cooperation with various partners, we organized daily in-person and online activities for our children and their families, mostly siblings. The activities are offered to different age groups. Examples of our activities include concerts, interactive drawing and music sessions. These activities help our children to relax, provide distraction and stimulate wider development. A group of volunteers help out in standard hospitality tasks and also support families and staff. This varies from crafting with kids while waiting for their appointments to buddy projects to support families from abroad.

5. Quality of care

The Quality of care department has further contributed to improving the quality and safety of care provided. Children and parents find a sympathetic ear in the ombudswomen and the parent-child participation team guarantees structural child/parent involvement in policy. Patient experiences form an increasingly important source for quality improvement. The first Patient Experience Monitor (PEM) questionnaires were sent out with the aim of structurally measuring and evaluating patient experiences.

In 2021, the national instrument to detect clinical decline in children, the Dutch PEWS, was implemented. A dashboard was developed providing insight into the PEWS-scores, 'worry-signs' (an indicator for parent concerns) and the risk category of all children who were hospitalized the previous day. This allows us to better oversee possible critical events. The Princess Máxima Center joined the national program care evaluation and appropriate utilization (ZE&GG), which stimulates the implementation of best practices in hospital care. Nine topics were selected, including nutrition, pain and preventing unnecessary prolonged fasting periods.

The quality system has further evolved by elaborating risk-management policy and the document management system (iMáxima). Furthermore, the Máxima Center built on raising awareness for safety II (learning from work-as-done). The safety culture was stimulated by holding PRISMA/SIRE group meetings, as opposed to holding one-on-one meetings. Lastly, the Princess Máxima Center received the NEN8009 accreditation, thereby fulfilling the standard requirements for a Safety Management System.

6. Late Effects outpatient clinic

The Late Effects outpatient clinic (LATER) is responsible for the care of all survivors of childhood cancer five years after diagnosis. In 2021, over 2,400 patients were seen of whom almost 900 were children under the age of 18 years old. A vision was developed to empower survivors and to optimize organization of the Late Effect care in collaboration with different healthcare partners and stakeholders. As a result, a re-organization was realized to improve workflows and processes and capacity planning was optimized. To better serve the survivors, a specialized psychologist was appointed. We also welcomed one of the VKN-VOX (Survivor Network) employees as a project leader to develop an information platform hosting different subjects that are important for survivors, such as knowledge of the different late effects and lifestyle. Implementation of the KLIK platform was realized and a study on the effect of online lifestyle coaching is nearly finished in close collaboration with the LATER research group. Another collaborative project is the development of an individualized care plan based on an automated guideline tool. Important steps were made to improve the structure of the M4C LATER group. Finally, the international PanCare meeting was organized together with LATER research and was hosted in the Princess Máxima Center.

Research

Quality of Life M4C themes	Clinical Chair	Research Chair
Psychosocial	Laura Beek & Esther van den Bergh	Martha Grootenhuis
Neuropsychology	Femke Aarsen	Marita Partanen
Supportive Care	Marianne van de Wetering	Wim Tissing
Late effects	Rianne Koopman	Leontien Kremer

Psychosocial research

The M4C theme Psychosocial Research distinguishes five programs that are implemented in close collaboration with healthcare professionals from our care department and aligned departments and M4C groups. These five programs are Anxiety and stress; Sleep and fatigue (led by Raphaele van Litsenburg); Communication (led by Sasja Schepers); Psychological consequences of survivors and Development and use of Patient Reported Outcomes (PROMS) in care and research. Among other initiatives, we conducted a study at the outpatient clinic with a social robot using interactive education focusing on sleep hygiene. Using the KLIK PROM database, we could show that the pandemic did not decrease the QoL of the children treated in the Máxima Center over time.

Neuropsychology

The Neuropsychology M4C group focuses on the early identification and intervention of cognitive, social-emotional, or behavioral impairments using a combination of neuropsychological, therapeutic, and neuroimaging measures. In 2021, we opened the NEMO study, which examines methods to improve neuropsychological monitoring across pediatric cancer groups. Our research also covers topics identifying new risk and protective factors, determining biomarkers of outcome, and providing intervention for high-risk groups. These studies will ultimately help to prevent further difficulties and improve quality of life in the long-term for patients with brain tumors, solid tumors, or hematological malignancies.

Supportive care research

In 2021 the Supportive care research program was further elaborated. A new PI was appointed: prof. dr. Louis Bont, to investigate pediatric infectious diseases. In addition to his parttime appointment at the Máxima Center, Bont is Medical Scientific Division Manager of the Children's division of the WKZ. Furthermore, the research programs on nutrition and the program of the physiotherapy department were integrated into the nutrition and motion program. The current programs are:

- Nutrition and motion
- Infections
- Endocrinology
- Nursing studies
- Guideline development
- Nausea and vomiting
- Fertility (together with PI Leendert Looijenga)
- Catheter care (together with PI Marc Wijnen)

The nursing research program has matured in 2021. It is firmly anchored in the nursing department of our center, already improving the quality of all nursing studies, both the smaller (as part of pediatric oncology nurse training) as well as the larger studies (MSc thesis). Over 50 peer-reviewed papers were published.

Late effect (LATER) research

LATER research focuses on how to reduce the late effects of childhood cancer treatment. To achieve this, we follow a four step cycle: 1) clinical research based on gaps in knowledge, 2) systematic reviews, 3) guidelines, and 4) outcome research. The main focus of the group is on late mortality, subsequent tumors, cardiovascular toxicity, burden of disease, fertility, lifestyle, aging, radiation epidemiology, health care burden and evaluation of care.

New projects in 2021 address Innovations for the LATER guideline, PanCareSurPass and PanCareFollowUp, and late pulmonary dysfunction. Other current projects focus on the results of the DCCSS LATER study of more than 6,000 survivors treated in the Netherlands.

In the spotlight | Quality of Life, M4C LATER: late effects in childhood cancer survivors
Rianne Koopman and Leontien Kremer

Constantly improving health and quality of life for childhood cancer survivors

More and more children with cancer are being cured thanks to better treatment and care. There are currently more than 12,000 people in the Netherlands who are 5-year survivor. Research shows that survivors are more likely to have health problems than peers: 70% of all survivors develop one or more serious health issues. These so-called 'late effects' are being evaluated and treated in the LATER outpatient clinic of the Princess Máxima Center.

Rianne Koopman spent the first 12 years of her medical career in the field of vascular medicine. She combined her work on treating patients with science, for example in supervising PhD students. She left her position to become head of the medical department at Sanquin, the Dutch blood bank. 'After 15 years, I wanted to go back to my original vocation. I got the opportunity to join the LATER team at the Princess Máxima Center. It was only a year later that I was asked to become head of the LATER outpatient clinic. A perfect chance to combine management, science and medicine.' Principal investigator Leontien Kremer has worked in children's oncology since her PhD. She started as a pediatrician at the Emma Children's Hospital in Amsterdam and finalized her PhD on cardiotoxicity in childhood cancer survivors in 2001. 'I did my PhD under supervision of Tom Voûte, a well known childhood oncologist. We were some of the first researchers on this topic. I started setting up the LATER registry in which nearly 16,000 survivors are registered. Furthermore, we initiated the development of LATER guidelines and the LATER study.'

Improving cross-fertilization

Koopman and Kremer co-chair M4C LATER on late effects in childhood cancer survivors. Kremer sees the combination of care and research in the Máxima Center as an opportunity. 'In our center we can very effectively link current care for children with knowledge from research on late effects. It's a major challenge to connect the two, in order to make better decisions around the trade-off between chance of survival and the likelihood of late effects. Guidelines are a perfect tool to bridge the gap between care and research.' Soon after Koopman joined the LATER team, the two found each other on a common goal: further improving care and research by collaborating in monitoring treatment outcomes and in research. The overall goal is to increase the quality of childhood cancer care. Koopman: 'Our M4C theme group can be considered a logical follow-up of all the work that has been done so far. In this field, the connection between care and research has always been strong. With our group we can further improve the cross-fertilization between the two.'

Bringing people together

Although cooperation was already common practice within LATER, to really connect care with research remains a challenge, Kremer says. 'The Máxima Center brought childhood oncology in the Netherlands under one roof, but nevertheless the realms of care and research still differ. They have their own organizational structures within our center, so it is necessary to put effort into bringing them together more effectively. Our first aims were to promote collaboration and to connect people from care and research. This is essential to improve the quality of research and to avoid duplication of efforts.' Within specific projects, cooperating closely is already the default, Kremer explains. The real challenge is to do this on a more structural basis. 'Margriet van der Heiden from the Trial and Data Center of the Máxima is also joining M4C LATER. Together we want to streamline the huge amounts of data we already have and still need to produce.'

Real life experience

The current LATER commitment will continue: to create a solid continuum in the care for children who are ill with cancer, through the follow-up to the LATER care based on the best available evidence. In order to do so, researchers and clinicians are working on many specific research questions. To name just one: what will happen – in the long run – to a 10-year old who receives a bone marrow transplant from a 40-year old? Koopman: 'To combine this type of research with questions on the metabolic status of children after transplantation, we brought together the two teams involved.' Scientifically supporting the best possible clinical decisions starts with literally meeting each other in the LATER outpatient clinic, Koopman concludes. 'Making a connection between care and science is much easier if researchers join the LATER professionals for a day every now and then. And also the other way around.' Kremer agrees on the significance of personal experience. 'One of our survivors joined Rianne's team to develop and improve an information website. He also joined our research team as a project leader on involving survivors in the process of guideline development. A perfect way to combine real life experience of survivors in science and care.'

Dr. Rianne Koopman is head of the LATER outpatient clinic. Educated in internal medicine, she started her career as a medical specialist and researcher in vascular medicine. She has a broad experience in scientific research as well as in quality improvement and change management.

Prof. dr. Leontien Kremer is pediatrician and principal investigator at the Princess Máxima Center, where she also leads the LATER research. She is professor of Late Effects in Pediatric Oncology at the Faculty of Medicine of Utrecht University and a professor in Pediatrics at the University of Amsterdam. As a scientist she is specialized in research on the late effects of treatment for childhood cancer. She initiated the Dutch Childhood Cancer Survivor LATER Study (DCCSS), which collected research data on more than 6.000 survivors.

Nursing care

Renske Karens-van Vliet

‘Nurses enjoy the challenge of all the opportunities here’

An ambitious center needs ambitious nurses. Our nurses are essential to provide excellent care for our children and families. How do we energize them, and ensure that the work remains inspiring for them? That is what the ‘Verpleegkundigste’ (‘Bestest nurse’) vision for the Princess Máxima Center is about. Project manager and nurse Renske Karens-van Vliet explains.

Why has the Princess Máxima Center formulated its own vision on the nurse professional?

‘We are an ambitious center and want to provide excellent healthcare and research. With that aim, we need to outline the crucial role that our nurses play in our vision toward the future. Our nurses are like elite athletes. They work with a diverse and international group of patients, so they provide intercultural healthcare and need to be able to switch easily between English and Dutch. They are involved in research, because many children participate in clinical trials. As a leading center for pediatric oncology, we also feel the responsibility to ensure that we always work according to the most up-to-date international standards and continuously improve quality of care and life.’

What was the reason for developing this vision?

In the first three years, we focused on recruiting and training nurses in pediatrics and pediatric oncology. For the next step toward excellent care and research, we need to empower our nurses to further develop themselves and provide added value for the organization. We attract ambitious, passionate nurses and we need to inspire them to be continuously committed to our center’s mission. By facilitating nursing leadership in every sense of the word, we will make the work more challenging, and increase job satisfaction.’

What does the Princess Máxima Center have to offer nurses?

‘We offer the perfect context for personal development, alongside the work at the patient’s bedside, in an inspiring setting. For example, you can conduct nursing research to improve the quality of care and life of the patients. Our ambition is to have a nursing researcher in every department. A number of professionals will complete an academic master program in nursing sciences to achieve this. Our dream for the future is to have a nursing professor of pediatric oncology within our center.

Nursing leadership is key: how can our nurses grow in their role of an equal sparring partner in an interdisciplinary team? We offer all our nurses a program to develop these skills further. You can also develop skills in coaching, teaching, working on improvement cycles or digitalization.’

How do nurses combine all this with daily care tasks?

‘In hospitals you will often see that nurses who are looking for a challenge move into a different position in the staff or management. In the Máxima Center, patient care is the foundation. When nurses and medical professionals take on leadership roles we aim for continuous participation in primary care. To strive for our mission, we continuously improve care and research ‘bottom up’, inspiring professionals to give their best and empowering them to do so.’

Does this vision also help to recruit new nurses?

‘When the vision was completed – in September 2021 – we also launched a new recruitment campaign: Are you the ‘bestest nurse’? This resulted in many responses. Nurses explain that they like the challenge posed by the opportunities in our center. I hear from other hospitals that they are happy when someone even responds to a vacancy. The numbers that we manage to recruit are quite unique.’

Renske Karens-van Vliet is team leader care and chair of the Nursing Advisory Board (VAR). She was chair of the project team policy of nursing care and has an important role in innovation within nursing care.

Supporting departments

Pharmacy

Short interview with dr. Lidwien Hanff, Head of Pharmacy

‘It is very stimulating to contribute to innovative, cutting-edge therapies.’

What have been the pharmacy’s main goals in the past year?

‘An important goal was to integrate pharmacology research and patient care at the Pharmacy. The PI Pharmacology group led by prof. dr. Alwin Huitema, was extended with Postdoc Meta Diekstra and PhD students, contributing to precision medicine by implementing precision dosing of anticancer agents and drugs used in supportive care. The drug laboratory was designed, equipment selected and lab technicians appointed, in order to open in 2022. To further facilitate innovative treatment, the pharmacy obtained a leading role in initiating new Cell Therapy Facilities at the Máxima Center in the upcoming years.’

What new developments have taken place?

‘In 2021 the computerized physician order entry system HIX was improved by introducing a more structured approach in calculating dosages and prescribing continuous IV infusions to increase patient safety. Another IT development made it possible for children or their carers to digitally request refilling for their at-home medication, improving efficiency, reducing waiting times and reducing the risk of miscommunication.’

How does the pharmacy look back on the performance in 2021? And what is the department most proud of?

‘The pharmacy department is constantly focused on improving the quality of pharmaceutical care and the impact on the children and their parents. The policy to offer at-home treatment whenever feasible was expanded with immunotherapy infusion at home instead of in-patient treatment, which greatly contributes to the quality of life for individual children.

Next to the routine drug preparations for children, we were able to provide and safely prepare over 1,500 COVID-19 vaccines and booster injections for all colleagues in the Máxima Center within a very short timeframe.

Financially, for a number of drugs with an off label use in standard pediatric oncology protocols we managed to obtain a reimbursement. These drugs had a value of € 700.000 in 2021.’

Which developments form the basis for 2022?

‘Analyzing current IT issues and selecting opportunities for improvement will give us the focus for the upgrade of the hospital information system (‘HIX standard content’). This will have an large impact on the medication processes in the Máxima Center and the capacity of the pharmacy. The child/parent information on medicine use will be further optimized in collaboration with the Máxima working group on parent information. In-house pharmacogenetic testing will be implemented in collaboration with the pediatric oncology laboratory and chromatographic drug assays will become operational for research purposes. Another development are the new international regulations on performing and reviewing trials, which will have extensive implications for the review of drug protocols by the hospital pharmacists and clinical pharmacologists in the medical research ethics committee.’

Are there other important things to mention?

‘In accordance with our professional standards we conducted a survey among nurses and prescribing doctors. They rated the pharmacy department with a 7.8/10 and provided us with useful tips.’

Facts & figures 2021

Description	2021
Clinical prescriptions reviewed and authorized clinical prescriptions	77.368
IV preparations for individual patients (including chemotherapeutic preparations 47.578)	192.169
Stock medication preparation	111.670
Outpatient prescriptions	41.793
Home-infusions (half of which chemotherapy)	1.470
Open drug trials	44
Named patient drug program	71
Budget medication	€ 18,4M

Laboratory for Childhood Cancer Pathology

Short interview with dr. Bastiaan Tops, Head of Laboratory for Childhood Cancer Pathology

‘The laboratory has always delivered high quality results and now we can demonstrate that.’

What have been the lab’s main goals in the past year?

‘The last year, the laboratory for childhood cancer pathology has focused on its quality management system and getting that accredited by an independent, external partner. Diagnostics were improved by introducing novel tests in the lab. These novel tests include for instance RNA sequencing by which more clinically relevant genetic changes are discovered with one single test. Furthermore, to be in full control of the workflow and diagnostic repertoire, the lab has been actively in-sourcing some tests and techniques, such as immunohistochemistry which is relevant for both clinical diagnosis and research purposes.’

What new developments have taken place?

‘Our lab was the first in the Netherlands to introduce a test to quantify CAR-T cells in patient materials; an important parameter in the CAR-T clinical trial. By quantifying the CAR-T cells in patients, the effectiveness of the treatment can be measured. Furthermore, the lab has been actively working on developing patient-specific follow-up assays for AML and lymphoma patients to monitor treatment over time and for early detection of relapse. Other developments include the production of an informative video for children about the biobank and the lab for childhood cancer pathology.’

How does the lab look back on the performance in 2021? And what is the department most proud of?

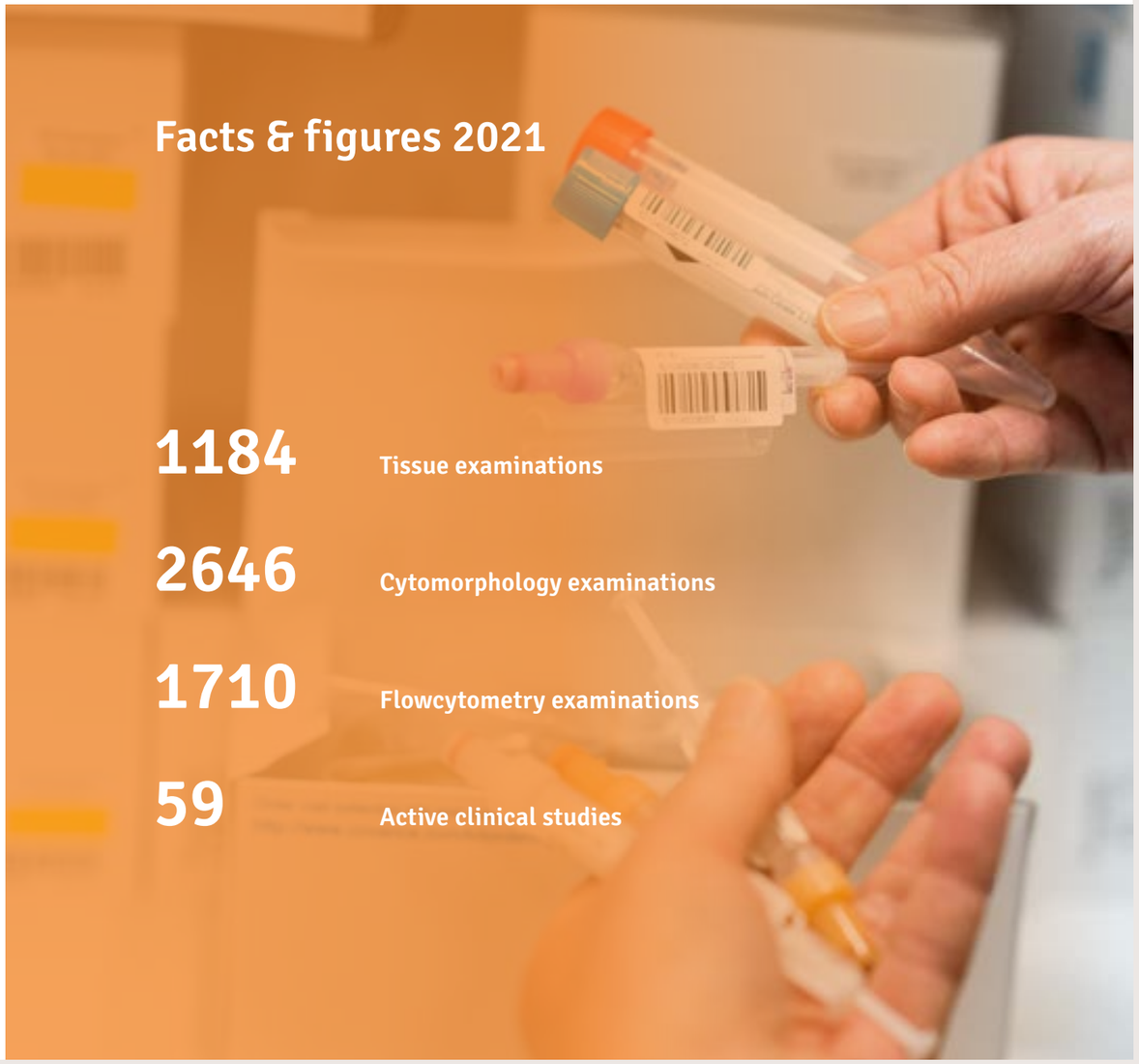
‘The lab had very ambitious goals for 2021, of which most have been achieved despite COVID-19. The most ambitious and overarching goal was to get recognition for the quality and competences according to the ISO15189 standard. This is an international accreditation standard for medical laboratories and the laboratory will officially be accredited in early 2022.’

Which developments form the basis for 2022?

‘We will continue with the implementation of goals that were already ongoing, such as digital pathology and immunohistochemistry. In addition, it will also focus on shortening turnaround times for certain tests, such as RNA sequencing and Whole Exome Sequencing. By shortening the turnaround times by several days, diagnoses are made earlier and treatment may start sooner. Furthermore, we will continue to collaborate with the research department to facilitate the translation of research findings into standard-of-care.’

Are there other important things to mention?

‘In the first few years, the laboratory has focused on getting up-to-speed and improving care for our patients. It will be continuing that work, as well as trying to establish more international collaborations and offering services to external pediatric centers so more children can benefit from the lab’s expertise.’



Trial and Data Center

Short interview with dr. Harm van Tinteren, Scientific head of TDC and prof. dr. Michel Zwaan, Medical Head of TDC

‘Improvements in the TDC help children access the most appropriate clinical trials.’

What have been the TDC’s main goals in the past year?

‘One of the main goals of the TDC in the past year was to build the quality management system for studies. Many procedures already existed, but they did not yet form a comprehensive and logical system. Furthermore, we spent a lot of energy developing a number of international master protocols, and the Máxima-wide data provision in all facets. The latter in close collaboration with the IDT department and the Big Data Core.’

What new developments have taken place?

‘2021 was a productive year for the TDC. The portfolio of studies was expanded with six studies on medicinal products. We put effort into the development of complex master protocols, through collaboration within international consortia (e.g. PEDAL, I-BFM, ITCC). A number of sub-trials will be launched in 2022. 13 phase I/II and 19 phase III investigator-initiated studies are open for patient recruitment and we take part in 21 phase I/II and two phase III company-sponsored clinical trials. 23 non-interventional investigator-initiated studies are open and nine ‘late-effect’-studies. The clinical research committee (CRC) reviewed and approved 39 protocols and grant-applications. Studies based on a pediatric investigational plan (PIP), importantly the inotuzumab ozogamicin phase I/II trial was expanded with a third cohort including 1st relapse ALL VHR patients and in the CRISP-study with critzotinib, the expansion phase of stratum 3 was extended. The brigatinib study, a phase I/II study in ALK-positive ALCL, IMT or other solid tumors in the context of a PIP, was approved by the METC with the Máxima Center as sponsor. We passed a remote audit by Pfizer and were allowed to continue the study with inotuzumab ozogamicin. The TDC grew in number of staff and a pediatrician with extensive experience in early clinical trials was recruited from Spain, Paco Bautista Sirvent. Prior to moving to the Máxima Center, he worked and gained experience in Paris and London before starting a clinical trial office in Madrid.’

How does the TDC look back on the performance in 2021? And what is the department most proud of?

‘At the end of September, the TDC proudly presented its quality management system. The QMS is a comprehensive system including the roles and responsibilities of the TDC, the standard operating procedures (SOPs), a description of the IT-systems used, and the general organization of the TDC. The entire system is defined in a QMS manual that forms the basis. The manual can be found on iMáxima and ManualMaster for respectively the site and sponsor organization. The QMS is set up as a dynamic system that will be evaluated every three years.’

Which developments form the basis for 2022?

‘A new medical research ethics committee (METC) was formed, as a merger of the METCs of NKI-AVL, UMC Utrecht and the Máxima Center. With a well-equipped oncology division, the institutes hope to be prepared for the introduction of the European Clinical Trials Regulation (ECTR) in January 2022. This regulation will change the submission of clinical trials on medicinal products in Europe. An ECTR subcommittee in the TDC has been following all the developments and will be responsible for the submission in the Clinical Trial Information System for new studies, and then transition of ongoing studies in the coming three years.’

Are there other important things to mention?

‘Our department was able to meet remotely through seven webinars and a live team event in September. Hopefully 2022 will allow for more live interaction.’

Facts & figures 2021

~121	Studies
34	Phase I/II studies
52	Phase III studies
24	QoL studies
39	Studies approved by the Clinical Research Committee

Research

Research

Prof. dr. Leendert Looijenga,
***ad interim* Managing Director Research**

‘The 2021 SEP report proved exeptional dedicated research structure, with great potential for the near future to reach our mission.’

Scientific research is essential for understanding childhood cancer, developing new treatments, and gaining insight into the maintenance of an optimal quality of life. Research in the Máxima Center comprises a broad variety of topics, indications, techniques, and expertise. We strive to share our knowledge among each other and to collaborate with scientists worldwide.

Strategic Evaluation Protocol

On November 3 and 4, a site visit following the Strategic Evaluation Protocol (SEP 2021-2027) took place. The goal of the evaluation was to review the research unit and judge whether the structure, organization and policies are optimal to achieve the strategic goals of the Máxima Center. During this evaluation, an external committee of nine people reviewed the research unit as a whole. In two days the committee interviewed a broad selection of researchers, clinicians and staff to develop an idea of the research quality, viability and societal relevance of the research in the Máxima Center. According to the SEP protocol, these criteria are fed by several crucial structures, such as HR policy, PhD programs, open science and the academic culture, and are therefore specifically evaluated. Beforehand the committee was requested to pay extra attention to the topics ‘collaboration and integration’, ‘talent and excellence programs’ and ‘spotless reputation’, as these three fundaments were defined by the Máxima Center and considered essential to achieve our ambitions.

At the end of two full days, the committee informed us that they were impressed by the impact of the Princess Máxima Center, the high quality of research and the accomplishments that have been reached in a short time. In 2022, the final report will be made available with the complete findings and recommendations from the committee and published on our website.

Research expansion

Appointments

In 2021, the research in the Máxima Center further expanded, resulting in a total number of 37 research groups by the end of the year. Dr. Stefan Nierkens started his research group focusing on stem cell transplantation and immune therapy. He has a partial appointment in the UMC Utrecht. Dr. Henrike Karim-Kos has a dual appointment at both the Netherlands Comprehensive Cancer Organisation (IKNL) and the Máxima Center. Her research focuses on childhood cancer epidemiology and outcomes. Dr. Friederike Meyer-Wentrup was appointed Associate Group leader and focuses on immunotherapy in lymphoma. Prof. dr. Louis Bont has a part-time appointment in the Máxima Center and investigates fungal infection in children with cancer. The Trial and Data Center welcomed dr. Francisco Jose (Paco) Bautista Sirvent.

In February, prof. dr. Leontien Kremer was appointed professor of Late effects in pediatric oncology at the Utrecht University Faculty of Medicine. Prof. dr. Alexander Eggermont was appointed professor of Clinical and Translational immunotherapy at the Utrecht University Faculty of Medicine in April 2021. In the same month, prof. dr. Jan Molenaar was appointed professor of Precision Medicine in pediatric cancer at the Utrecht University Faculty of Science, department Pharmaceutical Sciences. Prof. dr. Vormoor was appointed professor Hematological malignancies in children at the Utrecht University Faculty of Medicine.

Two associate professors from the Máxima Center were appointed at the Utrecht University Faculty of Medicine in 2021: Patrick Kemmeren on Bioinformatics in pediatric oncology, and dr. Lieve Tytgat on Biomarkers in pediatric solid tumors. The inaugural speech of prof. dr. Martha Grootenhuis, delayed due to COVID-19, was held in October 2021, with the title ‘Better Together?!’ on improving quality of life through psycho-oncology.

Capacity

In 2021, plans were made official to build a 6th and 7th floor on the research building to increase the gross floor capacity for additional research infrastructure and scientists. A product requirements document was created for laboratories, office spaces and a cell therapy facility for the production of CAR T-cells, amongst others. Final decision making is planned for Q1 2022. The current planning is that the construction is finished in Q4 2023. In 2021, some modifications on the labs on the 3rd and 4th floor were effected including an increase of cell culture capacity.

Research funding

Research in the Princess Máxima Center is financed by core funding and project funding. The Children Cancer-free Foundation (KiKa) provides a stable core funding of €10 million a year, which serves as the basis for the research groups and core facilities in the Máxima Center. In addition, a contribution of €11 million from the Ministry of Health (BBAZ) was added to the core funding.

The recruitment capacity of our researchers was €20,3 million in project funding for 2021. After a decrease in 2020 due to the COVID-19 pandemic, the project funding is back to the level of 2019 and even slightly higher. The project realization has increased as expected since research projects further advanced. The chart below shows the project funding and realization of the Máxima research groups over the years 2015-2021. Overall, we see an increase in pharma and biotech funded research collaborations.

Villa Joep awarded €1.275.000 to Stefan Nierkens, Jan Molenaar and Sebastiaan van Heesch to study the activation of T-cell immunity against high-risk neuroblastoma.

NWO awarded personal grants to Jarno Drost and Judith Wienke. Jarno Drost was awarded a Vidi grant. This grant is intended for scientists with some years of research experience, and enables them to develop their own innovative line of research. With the prestigious grant, Drost plans to conduct research into the regulation of genes in specific childhood tumors. Wienke received a Veni grant for research into new immunotherapies for neuroblastoma.

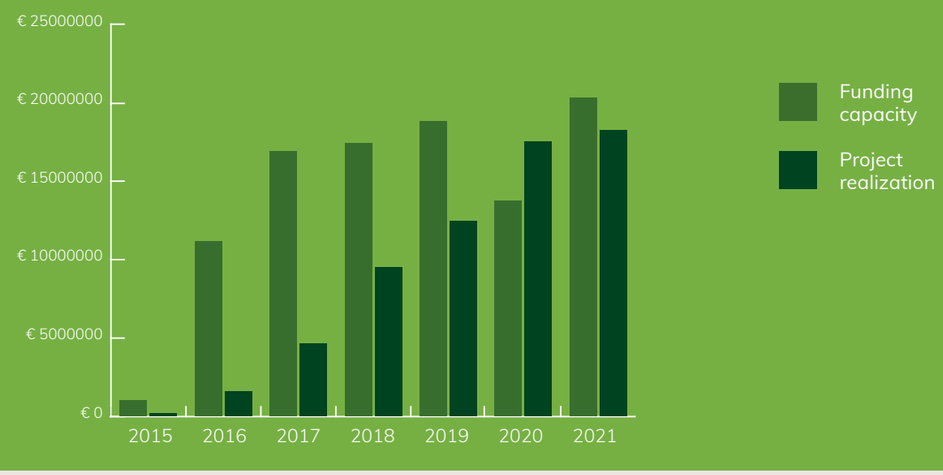
Scientific Integrity

Within the Princess Máxima Center, all employees have the responsibility to maintain scientific integrity. It is expected from each researcher that they adhere to the general principles of professional scientific conduct as described in the Netherlands Code of Conduct for Research Integrity (VSNU 2018). To preserve and assess scientific integrity, the right to complain if employees are suspected of violating integrity is organized via a scientific integrity committee. The Máxima Center is also a member of the National body for scientific integrity (LOWI). In 2021, no complaints were received by the Scientific Integrity Committee.

Scientific Integrity Committee

Member	Function
Jan Hoeijmakers	Chair
Martha Grootenhuis	Member
Florien van Woerden-Poppe	Legal Counsel
Angela Ottenhof	Secretary
Marcel Kool	Confidential counselor
Hans Merks	Confidential counselor

Project funding



Research knowledge exchange

Sharing knowledge is at the essence of science. By sharing findings and expertise, advances in scientific research that may contribute to the mission of the Máxima Center can be accelerated. Researchers in the Máxima Center are therefore encouraged to present their findings in conferences worldwide, meet with international colleagues and participate in our own weekly Máxima Research Meetings and Seminar series. The PhD students and Postdocs of the Máxima Center are invited to present their projects to their peers. Researchers and clinicians are encouraged to attend, to stay informed about the center's ongoing projects and to participate in fruitful discussions after the presentations. In addition, nationally and internationally renowned speakers are regularly invited to present their work during the Máxima Research Seminar series.

In 2021, many of the meetings and seminars had to be held online due to COVID-19. A total of 22 seminars were organized. Nine external speakers, amongst whom seven international speakers and eight internal speakers presented their work. In addition, four M4C disease group presentations took place and the first seminar in the Meet-the-Neighbors series - an initiative to stimulate integration at the Utrecht Science Park by inviting renowned scientists to present and meet with our researchers. The Máxima Center was well-represented at several major international conferences, with for instance twenty presentations at the Annual Meeting of the American Society of Hematology (ASH) and thirty Máxima scientists presenting their work at SIOP 2021.

In October, the annual Máxima Research Retreat was held in the seaside-town of Egmond aan Zee. It was the first social event that could take place in 18 months and was therefore themed 'Let's Re-connect'. Around 400 researchers participated in the wide-ranging program with ample opportunity for networking and knowledge-sharing.

Experimental animal research

To be able to develop better treatments for children with cancer, a crucial step is to understand the cause of each type of cancer. In addition, the development and testing of new drugs that specifically target specific cancer types is very relevant. Experimental animal research plays an essential role in these steps.

Experiments using animals will help us in understanding the cellular and molecular mechanisms that govern normal organ development and to understand how genetic mutations found in patients affect normal organ development resulting in tumor formation. The way tumors grow and develop in the surrounding tissue is also studied in animals. After that first step, new treatments are first tested in *in vitro* experiments using tumor material from patients.

This valuable tumor material often needs to be expanded in mice first as so-called patient-derived xenografts (PDX) to obtain sufficient material for further research. This PDX material is subsequently used to test new drugs *in vitro*. When promising new drugs have been identified, the second step is to translate and validate the efficacy and working mechanisms of the new drugs or drug combinations in animals. In addition, new technologies such as improved surgical removal of tumors or alternative drug delivery therapies are also tested in animals before they can be applied in children. Non-invasive longitudinal visualization of tumor development and therapeutic effects using fluorescent and luminescent markers is implemented in these experiments whenever possible.

In the Netherlands and the rest of the EU, experimental animal research is only allowed when there are no other ways to carry out the research. Furthermore, when using experimental animals for scientific purposes, it needs to be done under the best possible conditions. The Máxima Center is committed to creating an animal facility allowing experimental animal research according to current standards on animal welfare with a strong focus on obtaining in-depth knowledge on tumor biology to aid the development of new treatment modalities. This facility is being built in collaboration with an institute on the Utrecht Science Park and commission is planned in early 2023. Currently, the researchers from the Máxima Center have access to animal research infrastructure through collaboration with several animal facilities and research groups nationwide.

In 2021, the total number of animals used in experiments under the license of the Máxima Center was ~550 mice. More than half of the animals were used to understand tumor formation and growth *in vivo*, a little over one third was used to test new treatments and about 12% was used to expand valuable patient material.

Tumor growth and drug testing in mice

Malignant rhabdoid tumors (MRTs) are a rare and aggressive type of cancer affecting children of very young age. MRTs may arise in any body part, but primarily occur in the kidney or brain and are difficult to treat. Therefore, children with an MRT have a poor prognosis.

In the Máxima Center, the Drost lab studies the biological processes underlying the development of MRTs with the objective to identify new therapies. As a part of this study, the Drost lab develops patient-derived MRT organoids. These organoids are subsequently transplanted into mice, enabling the researchers to mimic the growth and progression of pediatric MRTs. They study which cells are responsible for MRT metastasis formation and therapy resistance, using longitudinal luminescence and fluorescent imaging. New drug targets for MRTs were identified using high throughput drug screenings (provided by the in-house HTS facility) on *in vitro* patient-derived organoids.

Subsequently, existing drugs matching these targets were tested in an *in vivo* MRT xenograft mouse model to study drug availability and pharmacodynamics. By monitoring tumor growth in living animals, the effectiveness of the identified drugs was confirmed. This is an important and required step for translating experimental findings into clinical practice.

Core facilities

Nine core facilities in the Máxima Center aim to share knowledge, bundle expertise and resources in order to maximize the efficacy of the in-house knowhow. In 2021, a new core facility was established; the Protein Facility.

Big Data Core

Biomedical research has rapidly turned into a data intensive research field. Institute-wide coordination concerning data stewardship as well as data and computational infrastructures is pivotal for making optimal use of these types of data for pediatric cancer research and care. The Big Data Core, initiated in May 2020 and led by Patrick Kemmeren, consolidates these activities and provides bioinformatics analyses for the Máxima biobank and the Laboratory for childhood cancer pathology.

As part of the data stewardship activities, the Big Data Core organized six local data stewardship meetings that bring together the local data stewards, updated the research data identifier policy to include radiology images, set up an institutional data management template approved by Dutch Research Council (NWO) and the Netherlands Organisation for Health, Research and Development (ZonMw), co-developed a monthly workshop for research IT & data management and provided general training and support regarding data stewardship.

Regarding data infrastructure, the Big Data Core is responsible for the Central Subject Registry that since December 2020 maintains a catalogue of patients and related information for research purposes. Developments include addition of sequencing availability, structuring of metadata information and preparing for radiology images to be included. Several pilots to support liquid biopsies, digitalization of biobank requests and FAIRification of data through a FAIR data station were initiated in 2021.

The Big Data Core also provides standardized analyses for biobank WGS and RNA-seq samples. In 2021, we also initiated structuring DNA methylation data and quality control. Fifty research shares with sequencing data were made available to 26 different research groups within the Máxima Center. In August 2021, a first cBioPortal release of all Máxima-sequenced cancer genomes was made available for exploratory analyses to all researchers. As part of the diagnostic procedure, we implemented WES and RNA-seq as standard-of-care and offer this service to all patients that are treated at the Princess Máxima Center.

Biobank and Data Access Committee

The primary objective of our central Biobank is to develop a collection of tumor and healthy material, and clinical, genetic and biological data during the patient's diagnostic phase, treatment and long-term follow-up.

Every child and their carers who enter the Princess Máxima Center are therefore asked to contribute to scientific research by giving consent to store biomaterials and data in the Biobank for research purposes.

In 2021, informed consent was retrieved from 616 patients. We see that >95% of the patients participated, a high number that is consistent with previous years. This brings the total number of patients from whom biomaterials and data have been stored in the Biobank since the start of the Máxima to 2350.

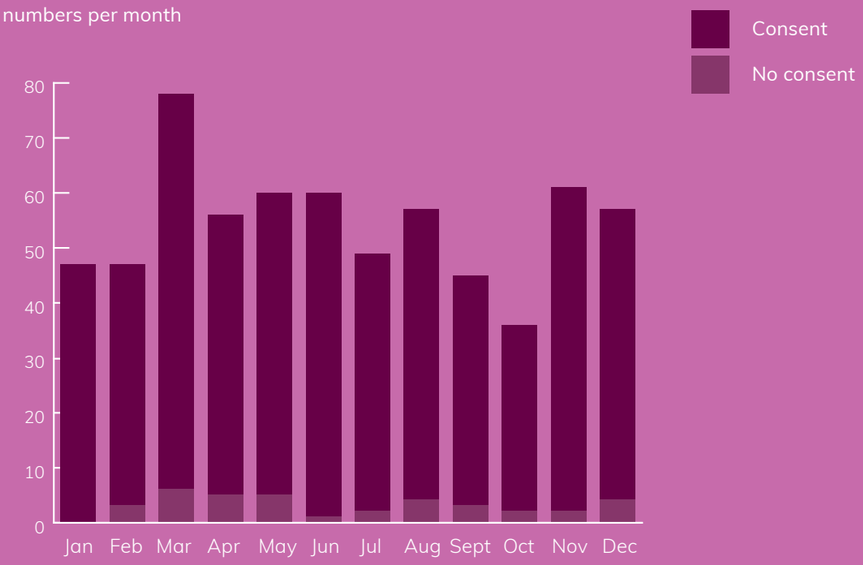
Biobank and Data Access Committee Researchers can submit a request to the Biobank and Data Access Committee (BDAC) to obtain permission regarding the use of these stored samples/ datasets for scientific research purposes. The BDAC meets on a bi-weekly basis to discuss and judge research proposals according to a pre-defined set of criteria, as defined in the Rules of Procedure. A total of about 300 project requests have been approved until now and in 2021 samples and data were released to researchers related to 84 individual research projects.

Biobank and Data Access Committee

Member	Function
Natasha van Eijkelenburg	Pediatric Oncologist (Chair)
Jan Lieverst	Program Manager
Leendert Looijenga	Principal Investigator & Managing Director *ad interim*
Bastiaan Tops	Head of Laboratory for childhood cancer pathology
Eelco Hoving	Clinical Director Neuro-oncology
Marjoleine de Lange	Chair of the Client Council

2021 Consent for Biobank inclusion

patient numbers per month



Optimal usage of the continuously growing Biobank and Data set was facilitated by the launch of the (CRS). This online tool supports the individual researcher to preselect pseudonymized samples and/or data of interest from the Biobank.

The information provided is continuously updated, and currently expanded to also include molecular datasets and radiology information.

We strive to constantly improve the existing infrastructure – from patient to biobank and from biobank to researcher – including optimization of the procedures. In the coming year we will, together with the relevant research groups, embed organoid biobanks as well as the linked (molecular) information within the BDAC structure.

Furthermore, in the beginning of 2022 the BDAC will start a pilot to switch the request and approval procedure to a digital application format, Research Manager. We will also focus on options for coupling systems that contain the requests for release and the registration of issued biomaterials and data.

FACS and Flow cytometry

The Máxima Fluorescence-Activated Cell Sorting (FACS) and Flow cytometry facility offers support to both research and diagnostics. Both the growing interest in single cell genomics technologies as well as expansion of immunotherapy research programs increase demand for these technologies. The Máxima core facility provides training and technical support to effectively use our equipment. Although our high-end FACS machines require the support of a specialized operator, we strive to properly train researchers to do most of their own sorting. Currently, our facility includes three FACS machines and five cytometers. The management, maintenance, training and high-end operation is carried out by a dedicated facility manager, Tomasz Poplonski. At the end of 2021 we obtained a Cytek Aurora, a spectral cytometer for high-end flow cytometry, which allows simultaneous use of 40 colors, including fluorochromes with emission spectra in close proximity to each other. We anticipate that his high-end cytometer will facilitate the development of new diagnostic panels. In addition, we obtained another self-operated sorter, the cytoflex S, to accommodate the increasing demand.

High-Throughput Screening Facility

The High-Throughput Screening Facility is accommodated by the Molenaar group and has been operational since December 2019. It is a state-of-the-art robotic system to facilitate lab automation and perform high-throughput screening work. The system can be used for large scale pipetting, sample preparation, in vitro screens using different types of molecules, and assays with absorbance-, luminescence- or fluorescence-based read-outs. The facility offers support in the translation of research questions into assays suitable for high-throughput screening, sets up new protocols, performs the screens and supports the data analysis.

In 2021, the core facility was primarily used for high-throughput drug screening using our pediatric cancer library of 200 compounds tested at 6-9 concentrations, and their corresponding cell viability assays. A total of 350 screens and assays were performed for >30 researchers from ten different research groups. Cell lines and/or organoids are screened representing almost all major pediatric cancers, including 24 patient-derived organoids within the precision medicine program iTHER. 49% are basic compound screens of cell lines or patient-derived-organoids, 30% of the total amount of screend are combinations of the library with specific drugs, 15% use isogenic systems, 4% screens performed on cell lines that are first made resistant and 0.5% are screens to validate the library and garantuee a good quality.

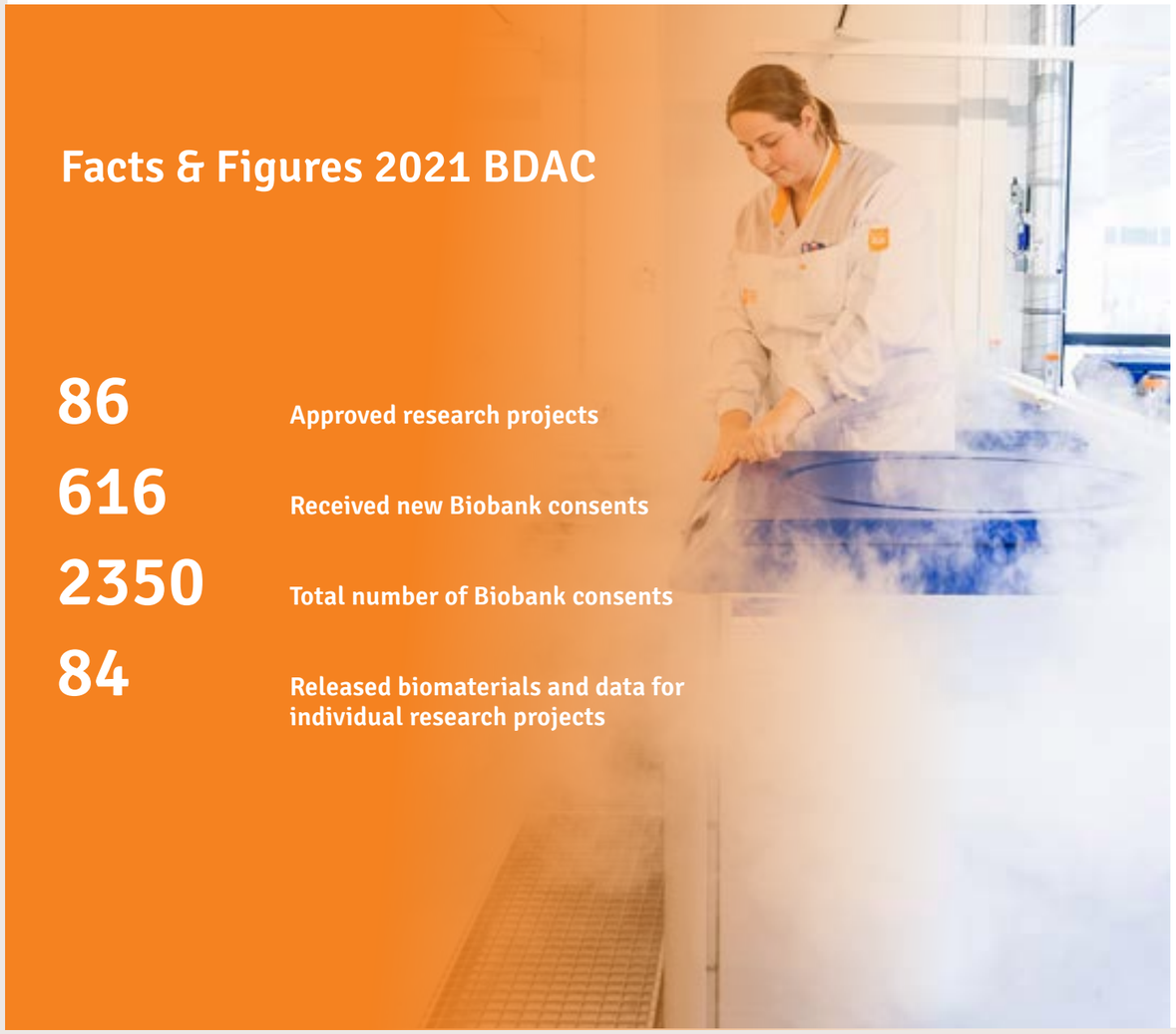
The number of screens increased tremendously compared to 2020 (89 screens), because this year, the system was fully automated. Furthermore, it was upgraded with a UPS system, so it will stay functional during power fluctuations.

We have several external collaborations, e.g. with the University of Utrecht, University hospital Charité (DE), the Institute of Cancer Research (UK), the University of Gent (BE), and several international precision medicine programs that utilize drug screening.

As a highlight, three scientific publications were published based on high-throughput screening data, describing e.g. neddylation as a therapeutic target for malignant rhabdoid tumors (Calandrini, et al., Cell Reports), MERTK as target for desmoplastic small round cell tumor (Bleijs, et *al*., Cancers) and idasanutlin as resensitizing drug for venetoclax-resistant neuroblastoma (Vernooij, et *al*., Molecular Cancer Therapeutics).

Princess Máxima Imaging Center

Since 2017, the Princess Máxima Imaging Center provides imaging related equipment, user training and imaging support. As such, we enable researchers in the Máxima Center to visualize their cells, organoids, or tissues with a variety of different techniques. Current applications range from hematoxylin and eosin (H&E) tissue sections to complex 3D co-cultures of organoids with immune cells labeled with multiple fluorescent dyes. The Imaging Center also supports more clinical research, for instance through the development of novel probes and assays for fluorescence guided surgery. Next to acquiring data, we provide computational infrastructure and expertise. There is active development of advanced image restoration and correction methods. Furthermore, artificial intelligence is increasingly deployed for segmentation and object tracking.



Facts & Figures 2021 BDAC

86 Approved research projects

616 Received new Biobank consents

2350 Total number of Biobank consents

84 Released biomaterials and data for individual research projects

In terms of infrastructure, a new powerful workstation computer was acquired to facilitate image processing and analysis. Furthermore, a new contract was signed with the image visualization and analysis software Bitplane Imaris, which ensures licensed access for Imaging Center users for the next five years. Another notable development was the move of two of our high-end multiphoton/confocal microscopes, a Zeiss LSM880 and Olympus FVMPE-RS, from the Hubrecht building to the Máxima Research wing. The scientific highlight of the year was the development of an 8-color microscopy pipeline combined with deep learning single-cell segmentation for the spatio-phenotypic patterning of cells in healthy and tumor tissues, published in Nature Biotechnology. Another highlight was a collaborative project between the Single Cell Genomics Facility and the Imaging Center, which led to a publication in Developmental Dynamics characterizing LGR6 in kidney development.

The use of the facility continued to expand at a high pace. During the year, 54 new users were trained. The total number of people using the facility grew to 122 users from 29 different groups, an increase of 20% compared to last year. The number of hours booked on our imaging systems also increased to a combined total of 14.907 hours, an 36% increase. We expect this growth to continue along with the growing number of researchers at the Princess Máxima Center.

Organoid Facility

To study pediatric tumors, representative *in vitro* model systems are essential. Patient-derived organoids can provide such model systems. Organoids can be grown with high efficiency from patient material while retaining many characteristics of the tissue from which they were derived.

The organoid facility was founded in 2018 and is headed by Jarno Drost. Since 2020, Yvonne Tiersma is the facility manager. The organoid facility supports organoid-based projects by facilitating quality-tested conditioned media and matrices. Every research group can contact us with their needs regarding their organoid projects. We place bulk orders for the extracellular matrix required for organoid growth, basement membrane extract (BME), allowing for much larger discounts. Each new batch of BME is quality tested by us before it is distributed to the researchers. In addition, we produce and quality test R-spondin and Noggin conditioned media. This quality testing involves testing the activity of the media in reporter assays as well as their ability to support organoid growth. In 2021, eleven different research groups made use of the products facilitated by the organoid facility (one more than in 2020). Projects supported by the facility cover, among others, brain, kidney, and liver malignancies. The facility occasionally gets questions from external researchers for advice about organoid technology and the reagents required for successful culturing of organoids. Moreover, organoid technology was implemented in the institute's individualized medicine program iTHER 2.0, single cell genomics facility, and microscopy & imaging facility, exemplifying the integrative use of organoids within other core facilities of the Princess Máxima Center.

Protein Facility

Recombinant proteins and antibodies have a broad range of applications in basic and translational cancer research and are central to various types of cancer immunotherapy. To facilitate researchers at the Princess Máxima Center to incorporate protein/antibody-related work in their specific research lines, we launched an in-house Protein Facility in 2021. The facility is led by Claudia Janda (group leader) and is supported by Kim van Noort (postdoc) and Fenna van Rijt (technician). We have broad expertise in protein/antibody biochemistry, engineering, and structural biology.
We aim to train researchers on a broad range of experiments, which include:

- Protein/antibody expression and purification.
- Generation of antibodies and antibody fragments (by phage/yeast display library technology and immunization).
- Biophysical characterization of proteins and antibodies
- Structural biology / macromolecular crystallography.

In our first year, we initiated and contributed to various projects, including:

- We collaborate with the researchers and clinicians to discover antibody fragments (nanobodies and scFv) and to engineer chimeric antigen receptors to develop CAR T-cell therapy for pediatric cancers.
- We collaborate with the theranostics research program to isolate nanobodies to develop radiotracers for advanced PET imaging of pediatric tumors and theranostic PET.
- We collaborate with the Clevers lab to develop mimetics of growth factors and extracellular matrix proteins to enhance organoid growth of (pediatric) tumors and healthy (embryonal) tissues.
- We have trained people from various groups to express their proteins of interest in mammalian and/or bacteria cells and purify them for *in vitro* and in vivo/mouse functional studies with a primary focus on developing immunotherapies.

Single Cell Genomics Facility

Single-cell mRNA sequencing (scRNA-seq) enables the study of pediatric tumors one cell at a time. The Single-Cell Genomics Facility makes scRNA-seq technology available to researchers of the Princess Máxima Center and provides services that encompass planning of the experiment, sample and library preparation, in house sequencing, and data analysis. The facility supports two transcriptomics platforms: 10X Genomics and SORT-seq. In 2021 we expanded the repertoire of supported techniques to include 10X Genomics multiomic profiling. This set of approaches allows quantification of open chromatin, cell surface markers, or immune profiling alongside regular gene expression.

In addition, we provide support for the Visium platform for spatial transcriptomics.

In 2021, we undertook more than 13 collaborations and pilot studies with groups of the Máxima Center covering topics from healthy tissue development to solid and hematological malignancies. We also supported five grant applications with proof-of-concept studies, three of which were awarded. We were involved in four collaborations in the Utrecht Science Park. One of these was the Máxima-UMCU-UU immunotherapy initiative, in which we retained a central role.

In terms of infrastructure, 2021 saw the implementation of a custom database where we collect information about all samples, as well as keep track of experimental stages. The data model we use to structure this information was designed for easy integration with the Máxima Biobank and conforms with the foremost public repository for human genomic data (EGA).

Last year the facility contributed to several scientific manuscripts — five of which were accepted for publication — including work on neuroblastoma (Hanemaaijer and Margaritis et al., PNAS; Kildisiute, Kholosy and Young *et al.*, Sci Adv), kidney healthy and tumor development (van Ineveld and Margaritis *et al.*, Dev Dyn; Young et al., Nat Comm), tumor immunology (Dekkers et al., bioRxiv), and leukemia (Candelli and Schneider *et al.*, Leukemia).

Trial and Data Center

The Trial and Data Center (TDC) serves as the medical data center of the institute. It provides the infrastructure for clinical research through biostatistical support, centralized patient data collection and documentation, data processing and coordinated administration of clinical trials. We give an update on the developments in 2021 under Supporting Departments; the Trial and Data Center can be found on page 98.

Single Cell Genomics Facility

Projects 2021	Involved Groups
Normal Tissue Development	Artegiani, Belderbos, Clevers, Janda
Hemato-oncology	Stam, van Boxtel, Zwaan
Neuro-oncology	Clevers, Kool
Solid Tumors	Clevers, Drost, Holstege, Janda, Kemmeren, Molenaar, Peng, Tytgat, Rios, Stunnenberg

Education & Training

Academy

Prof. dr. Gertjan Kaspers, director Academy & Outreach

‘It’s been an exciting year of facilitating a huge number of internships and meetings, with an ever-growing portal filled with our tools for learning and education.’

The best professionals are needed to make the mission of Princess Máxima Center come true. The Academy therefore facilitates the learning process of our colleagues and future professionals. By developing and organizing national and international education and training programs, stimulating learning-on-the-job and the organization of internships.

Developments 2021

Learning-on-the-job
The Academy aims to facilitate professionals in the further development of their professional knowledge and skills, based on their day-to-day learning challenges. Among other projects, in 2021 the Academy implemented the performance support system MaxiWise. With the nursing profession the Academy developed content for the departments of hemato-oncology, solid tumors and neuro-oncology, which nurses can use anytime they need it.

Online and hybrid learning
COVID-19 has been a major catalyst in the development of online and hybrid learning. In 2021, the Academy team further developed the skills and conditions in making online and hybrid lessons as attractive as possible. For example, by facilitating teachers and trainers to professionally record videos and e-clips. The online and hybrid way of organizing training courses and symposia has the advantage of allowing participants to join remotely, which can further contribute to the national and international exchange of knowledge and to learning from each other, all over the world.

More internships
Given the national problems in the labor market, it is important to invest in good internships and training places, for example for (pediatric oncology) nurses, physiotherapists, child life specialists and pharmacy assistants. Despite COVID-19, the Princess Máxima Center welcomed more interns in 2021 than in the previous year. A key factor is the willingness of everyone involved to welcome and supervise the interns and the cooperation with our partner organizations.

National and international knowledge sharing
In 2021, the Academy organized a broad range of national and international symposia and training sessions. For example, different meetings for the research groups, training courses with our shared care partner organizations, an international CAR T-cell symposium, a newly developed hybrid Master Course Pediatric Oncology and – for the first time – a preceptorship meeting ‘Pediatric and Adolescent Acute Lymphoblastic Leukemia’. 34 high potentials from 20 different countries participated in this two-day event.

Developments that form the basis for 2022

In 2021, the foundation was laid for a new curriculum for the training of pediatric oncology nurses. The new curriculum is based on Entrustable Professional Activities (EPAs), and will be more flexible in design. The development takes place in good partnership with College Zorg Opleidingen (CZO) and the UMC Utrecht Academy.

With regard to learning and training, an enormous effort has been made in the last few years. In 2021, a need arose to redefine the vision on learning and development at a strategic level. To this end, a Strategic Educational Board was set up, consisting of representatives of the directors of our departments for care, research and HR as well as the Board of Directors.

Facts & figures 2021
The Academy organized:

Learning & Education

Training sessions (face-to-face and online)	2792
Online e-learning modules completed	4987
Peer-to-peer assessment	1378

Training sessions & symposia

National training sessions	134
International training sessions	1
National symposia	27
International symposia	13

Internships

Total number of interns (+/- 800 internships)	237
Total number of clinical science students	31

Outreach

The Outreach program of Princess Máxima Center consists of four so-called twinning programs, collaborations with hospitals in Yogyakarta, Indonesia, in Eldoret, Kenya, in Pristina, Kosovo and in Blantyre, Malawi. In these long-lasting and formalized twinning programs, we focus on three activities: care, capacity building and research. Better care for children with cancer in these hospitals is being realized by consultations for individual patients, by assuring the availability of up-to-date treatment guidelines for the most relevant types of childhood cancer, and by capacity building. With that, we mean the many educational activities and training programs for healthcare personnel. Research is focused on local issues, such as tools to avoid treatment abandonment, but also on gathering knowledge that could be relevant for children with cancer in the Netherlands, such as on pharmacokinetics of frequently used drugs in relation to ethnicity and malnutrition. All of this with the important financial support of World Child Cancer NL.

In 2021 we prepared three new twinning programs, with hospitals in Bandung, Indonesia, in Moshi, Tanzania and in Nairobi, Kenya. The latter collaboration fits perfectly in our so-called ‘Kenya Program’, which is fully and significantly supported by AFAS Foundation, aiming to have more impact by broadening our activities. In Kenya the twinning programs will thus develop into Pediatric Oncology Health Partnerships, including activities to increase awareness on childhood cancer in the general population and community healthcare workers, to increase the participation in National Health Insurance Fund, to achieve more frequent and earlier referral of children with (suspected) cancer, and to improve social reintegration of childhood cancer survivors.

AFAS FOUNDATION
inspireert beter doen

Collaborations

Shared Care

The Princess Máxima Center works closely together with hospitals in the Netherlands in a network of shared care centers, based on the principle: 'central treatment where necessary, close to home if possible'. This means children can have the less complex parts of their treatment done in their own region.

The Princess Máxima Center and the shared care partners are jointly responsible for treating the patients. However, the diagnosis, direction and ultimate responsibility for the treatment rests with the Princess Máxima Center. The development of the collaboration between the Máxima Center and its shared care partners is assured by the National Shared Care Committee. It is a continuous process of development and optimization to continue to provide excellent care. The year 2021 was about giving further substance to the shared vision for the future, which we will continue to work on in 2022. Due to COVID-19 measures not all initiatives could continue, but results have been achieved as described below.

At the start of the year, 17 hospitals provided shared care. In mutual consultation, two hospitals decided to discontinue their shared care activities, which means that from 2022, 15 hospitals provide shared care.

Implementation new vision

2020 was the year that a new shared care vision was created in collaboration with the shared care centers. In 2021 this vision was implemented in the organization and certain processes were optimized. Actions that have been undertaken include: representatives per care unit were appointed and patient meetings for shared care were set up per care unit. There is uniformity about the chemotherapy treatments that take place in shared care, and last but not least: all departments were actively included in the new vision and importance of shared care. In the implementation of this vision, it is important to be mindful of patient exposure to shared care.

Additional results

We booked several additional noteworthy results in 2021. For example, frequently used documents by shared care have been made public without a login to optimize their use. Furthermore, it is possible for an online introductory meeting to take place between the Princess Máxima Center, shared care and the patient. Finally, healthcare incidents that take place in the collaboration are now structurally exchanged by contact persons per hospital to improve the quality of care.

Facts & figures 2021

National shared care committee met 2 times

1 Number of shared care visits (due to COVID-19)

Shared care day took place 2 times (themes: solid tumors and ALL)

325 Shared care professionals have followed training at the Princess Máxima Center

Newsletter published 2 times

18 Internships took place in the Princess Máxima Center

Shared Care centers

Flevo hospital
Almere

Amsterdam UMC
Amsterdam

Reinier de Graaf hospital / Haga
Delft

Deventer hospital
Deventer

Hospital Gelderse Vallei
Ede

Catharina hospital
Eindhoven

Medisch Spectrum Twente
Enschede

Admiraal de Ruyter hospital
Goes

University Medical Center Groningen
Groningen

Dijklander hospital
Hoorn

Medical Center Leeuwarden
Leeuwarden

Erasmus Medical Center / Sophia Children's hospital
Rotterdam

Jeroen Bosch hospital
's Hertogenbosch

VieCuri
Venlo

Isala Clinics
Zwolle

UMC Utrecht

Collaboration in specialized care and research

The Princess Máxima Center provides highly specialized care for which it collaborates intensively with UMC Utrecht. Specialized pediatricians of UMC Utrecht work with us every day to help cure children with cancer: infectious disease specialists, cardiologists, nephrologists, lung specialists, endocrinologists, intensive care specialists, neurologists, and radiotherapists. These professionals are of great value to the functioning of the Princess Máxima Center, as they give us access to general pediatric knowledge and skills.

The Princess Máxima Center uses the intensive care ward and the operating rooms of the Wilhelmina Children's Hospital (WKZ). We also have close collaborations in the clinical chemical laboratory and the surgical specialties. For example, in 2021 a collaboration was established in the field of onco-orthopedic surgeries. A dedicated department for oncological neurosurgery in children was formed within the Brain Division of the UMC Utrecht. Prof. dr. Eelco Hoving, Clinical Director of Neuro-oncology at the Princess Máxima Center, was appointed head of this new department.

Lab technicians and radiologists from UMC Utrecht Radiodiagnostics work in the radiology department at the Princess Máxima Center. Optimizing the MRI capacity was an important joint topic in 2021. As mentioned in the chapter 'Fields of interest', another important partnership between the Princess Máxima Center and UMC Utrecht is the stem cell transplantation unit located in the Máxima Center. Children with both benign and malignant disorders are treated in this unit. The successful treatment of the first patient with gene therapy was an important milestone in 2021.

The research departments at the Princess Máxima Center and UMC Utrecht also closely work together on several projects. For the focus areas 'Child Health and Cancer' our professionals come together with the UMC Utrecht to improve both research and care.

Last but not least, an agreement was reached with the company Chipsoft to implement new electronic patient file software. This large-scale joint project will be further implemented in the coming years.

Strategic partnership

UMC Utrecht is an important strategic partner of the Princess Máxima Center. Close collaboration with UMC Utrecht offers outstanding possibilities for sharing expertise around pediatric specialisms, which further improves the quality of pediatric oncology and care at the Máxima Center. We can effectively integrate care and research by using the knowledge and quality of the UMC Utrecht. This partnership offers us more opportunities to develop innovative diagnostics and treatment. Significant steps have already been taken in the fields of radiology, nuclear medicine, immunotherapy, pediatric cardiac surgery and radiotherapy to facilitate new analyses and therapies for children in our center. This sets an example and provides a driving force for further innovative diagnostics and treatment in the future.

An illustrative example of our strategic partnership is the intra-operative (IO)-MRI project. In this joint project, a state-of-the-art operating room with integrated MRI is being built in the surgical complex of the Wilhelmina Children's Hospital. Commissioning is expected in the course of 2022.

Joint research projects

The three strategic collaborative research projects between the UMC Utrecht and the Princess Máxima Center that were started in 2020 were continued in 2021. The neuro-oncological project focuses on the treatment of high-grade gliomas by improving drug delivery through Focused Ultrasound (FUS) technology. Progress has been made by the purchase of a helmet that will be incorporated into an MRI scanner. By aiming very precise vibrations at the site of the tumor, the blood-brain barrier will temporarily and locally open, allowing drugs to enter the brain. The collaborative immuno-oncology project focuses on translating the tumor infiltrating immunological landscape into therapeutic concepts. The theranostics project focuses on the integration of treatment and diagnostics by image-driven oncological care. The project has made progress with the preparation for various clinical trials. All three collaborative projects are very successful in recruiting additional project funding.

National and international collaborations

The Utrecht Science Park (USP) is the biggest science park in the Netherlands and the beating heart one of Europe's most competitive regions. In addition to the UMC Utrecht, several institutes at the USP are close collaborators of the Máxima Center. Since the start of our center, our ties with the Hubrecht Institute have been strong, including on joint research projects and shared infrastructure. The Máxima Center also works closely with Utrecht University's Graduate School of Life Sciences in the training and education of PhD students. They participate mostly in the PhD programs Cancer Stem Cells and Developmental Biology (CS&D) and Clinical and Translational Oncology (CTO). Outside of Utrecht, the ties are strong with colleagues at the Antoni van Leeuwenhoek Hospital and the Netherlands Cancer Institute (NKI), particularly in the areas of pharmacology and technology transfer. Moreover, six Principal Investigators are members of the Oncode Institute, which aims to cure cancer by facilitating and funding scientific research.

The medical research ethics committees (METCs) of the Princess Máxima Center/UMC Utrecht and the Antoni van Leeuwenhoek (AvL) have joined forces. The merged METC will be operational from 1 January 2022. The three centers expect to achieve benefits that will enable them to further strengthen their position in the field of research and its assessment. A joint METC also helps to anticipate future legislation and regulations, both at a national and European level.

Internationally, the Princess Máxima Center is involved and often plays a leading role in multiple European consortia and clinical studies. In 2021, the Máxima Center joined the Pediatric Neuro-Oncology Consortium (PNOC) as its first and only European participant.

Hopp Children's Cancer Center (KiTZ)

The Hopp Children's Cancer Center (KiTZ) in Heidelberg, Germany, is a comprehensive cancer center for therapy and research for oncological and hematological diseases of children and adolescents. It is a joint institution of the German Cancer Research Center (DKFZ), the Heidelberg University Hospital (UKHD) and the Heidelberg University (uniHD). In 2021, the KiTZ-Máxima Twinning Program was started, encompassing a structural collaboration between the KiTZ and the Máxima Center to advance research and patient care in all fields of pediatric oncology. In the presence of Queen Máxima, both parties signed a Memorandum of Understanding at the Dutch Embassy in Berlin in July 2021. To promote collaboration between the centers, a starting fund amounting €1.000.000 was established, for which the Princess Máxima Center Foundation and the KiTZ Fundraising Office have raised the resources. Twelve projects, including research projects, infrastructural programs and travel and meeting grants, were selected from a call to receive seed funding. The planned joint research projects and programs were presented during the second joint online retreat in June 2021. In the coming years, much more joint funding will be made available, which will be used to accelerate further collaborations between the two centers, stimulate exchange programs, facilitate running early clinical trials together, and will help to increase our chances to successfully apply for large nationally and internationally competitive grant applications in our respective countries, and in the EU and beyond.

A joint starting fund of €1.000.000 euro allowed the start of new collaborative projects and programs KiTZ/Máxima in 2021.

Title	Category	Contact person	Collaborators
Developing Immunotherapies for Rhabdomyosarcoma	Joint Project	Claudia Janda	Claudia Janda, Ana Banito Michael Meister
Deciphering epigenetic reprogramming in malignant rhabdoid tumors	Joint Project	Jarno Drost	Jarno Drost, Marcel Kool Pascal Johann
Nutritional preconditioning to enhance chemotherapy efficacy and reduce toxicity in pediatric cancers	Joint Project	Wilbert Vermeij	Jan Hoeijmakers, Marcel Kool
Dissection of the role of tumor-TME crosstalk in pediatric brain cancer	Joint Project	Aniello Frederico	Aniello Frederico, Marcel Kool Stefan Nierkens, Jasper van der Lugt, Friso Calkoen
Unraveling the spatial transcriptomic landscape of pediatric gliomas	Joint Project	Henk Stunnenberg	Henk Stunnenberg, Anne Rios David Jones, Felix Sahm
TAI CHI for Pediatric Brain Tumors, Round 1	Joint Project	Pieter Wesseling	Pieter Wesseling, Andreas Sonnen, Felix Sahm, Mortiz Gerstung
Exploring the impact of adult-type cancer predisposition genes and postzygotic mosaicism on pediatric malignancies	Joint Project / Travel & Meeting	Roland Kuiper	Roland Kuiper, Marjolijn Jongmans, Stephanie Smetsers, Kristan Pajtler Natalie Jäger, Steffen Hirsch
KiTZ-Máxima translational platform for pediatric low-grade glioma (pLGG)	Travel & Meeting	Netteke Schouten	Netteke Schouten, Eelco Hoving, Cornelis van Tilburg Olaf Witt, T. Milde
KiTZ-Máxima PDX pipeline	Joint Infrastructure	Marcel Kool	Marcel Kool, Sina Kreth
KITZ-Maxima organoid and iPSC pipeline	Joint Infrastructure	Marcel Kool	Marcel Kool, Lena Kutscher Hans Clevers
Development of a shared liquid biopsy infrastructure	Joint Infrastructure	Kristian Pajtler	Kendra Maaß, Stefan Nierkens, Lieve Tytgat, Bas Tops
KiTZ-Maxima shared infrastructure – data exchange	Joint Infrastructure	Patrick Kemmeren	Patrick Kemmeren, Natalie Jager

Research groups

Research group dr. Benedetta Artegiani

Started in December 2019

Our group focuses on building up novel human organoid culture in conjunction with advanced genome editing approaches to address organ development and dissect mechanisms of tumor initiation, with an emphasis on brain and liver tumors. The aim is to develop faithful and robust models to be used as research platforms both for understanding pathways guiding normal development and alterations occurring in cancer, and possibly for therapeutic read-outs.

Some of our research lines are:

- Our recent research efforts are dedicated to the optimization of robust and long-term lasting brain organoid models from human fetal tissue. Those tissue-derived brain organoids are a self-contained system able: 1) to capture the cellular complexity of the brain regions from which they are derived, 2) to maintain the regional identity over time (>1 year) in culture without the need of specification – as opposed to iPSCs and ESC-derived organoids, 3) to maintain organ functionality to a certain extent and 4) overall to recapitulate the development of the human brain.

- Use of our novel brain organoid models in conjunction with CRISPR-Cas9 to identify genes and signaling pathways involved in the proper growth and cell types specification during brain development.

- Establishment of our tissue-derived brain organoids as an efficient platform to introduce genetic mutations, also in a cell specific manner, occurring in pediatric and adult brain tumors and mechanistic study of their cellular and molecular consequences. Engineered human tumor and mutation models are currently being used to investigate heterogenous cellular population behavior.

- Elucidating pathways that regulate cell fate identity establishment and maintenance in liver, both in context of liver homeostasis and (pediatric) cancer. In this regard, we are interested in understanding the role of BAP1 mutations and how they can cooperate with additional mutations to initiate fibrolamellar carcinoma.

Members of the Artegiani Group

Principal Investigator
Benedetta Artegiani

PhD student
Anna Pagliaro

Research Technician
Simone Massalini

Total no. of Máxima-affiliated publications (2021)	**2**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- Marsee A, Roos FJM, Verstegen MMA; HPB Organoid Consortium, Gehart H, de Koning E, Lemaigre F, Forbes SJ, Peng WC, Huch M, Takebe T, Vallier L, Clevers H, van der Laan LJW, Spee B. (2021) Building consensus on definition and nomenclature of hepatic, pancreatic, and biliary organoids. Cell Stem Cell. 6;28(5):816-832. doi: 10.1016/j.stem.2021.04.005. PMID: 33961769.

- Hendriks D, Artegiani B, Hu H, Chuva de Sousa Lopes S, Clevers H. (2021) Establishment of human fetal hepatocyte organoids and CRISPR-Cas9-based gene knockin and knockout in organoid cultures from human liver. Nat Protoc. ;16(1):182-217. doi: 10.1038/s41596-020-00411-2. Epub 2020 Nov 27. PMID: 33247284.

Grants

Fibrolamellar Cancer Foundation
CRISPR-engineering of human liver organoids to study fibrolamellar carcinoma
€128.658

Patents/licenses

2

Research group dr. Mirjam Belderbos

Started in August 2020

Members of the Belderbos Group

Principal Investigator
Mirjam Belderbos

MD/PhD student
Konradin Müskens

Postdoc
Inge van der Werf

The overall aim of our research is to unravel the mechanisms by which human hematopoietic stem cells (re-)generate blood, and to translate this knowledge into therapies to improve hematopoiesis in children with intrinsic or acquired bone marrow failure, or in children undergoing hematopoietic stem cell transplantation.

Our main topics of research are:

- **Clonal dynamics and functional integrity of hematopoiesis after transplantation**
  Hematopoietic stem cell transplantation (HSCT) is a life-saving therapy for several blood diseases, including high-risk leukaemia. During HSCT, the patient's blood system is replaced by that of a healthy donor. We aim to understand how a relatively small number of stem cells can (re-)generate the entire hematopoietic system, and how transplantation affects the genomic and functional integrity of these cells. Techniques employed include single-cell DNA and RNA sequencing. Furthermore, we recently initiated a clinical study to assess the integrity of hematopoiesis in long-term HSCT survivors.

- **Graft failure after transplantation**
  Graft failure is a rare but life-threatening complication of HSCT, in which the donor stem cells fail to produce sufficient numbers of mature blood cells. The Belderbos group aims to identify the processes underlying HSCT graft failure and, by doing so, identify therapeutic strategies.

- **Myelodysplastic syndromes (MDS) and bone marrow failure**
  Our group also investigates the causes of stem cell dysfunction in pediatric bone marrow failure syndromes, in particular MDS and Fanconi Anemia. Although hematopoietic stem cell failure and cancer predisposition are hallmark features of these syndromes, it is incompletely known when and why this occurs. Using single-cell RNA and DNA sequencing (in collaboration with the van Boxtel group), we aim to define processes that cause stem cell damage in these patients. We envision that this knowledge will contribute to strategies to better predict the occurrence of bone marrow failure/myelodysplasia, allowing for targeted intervention and preventive measures.

Total no. of Máxima-affiliated publications (2021)	**6**
No. of Máxima-affiliated open access publications (2021)	**6**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- De Kanter JK, Peci F, Bertrums E, Rosendahl Huber A, Van Leeuwen A, van Roosmalen MJ, Maders F, Verheul M, Oka R, Brandsma AM, Bierings M, Belderbos M, van Boxtel R. (2021) Antiviral treatment causes a unique mutational signature in cancers of transplantation recipients. Cell Stem Cell. PMID: 34496298.

- Jung JM, Ching W, Baumdick ME, Hofmann-Sieber H, Bosse JB, Koyro T, Möller KJ, Wegner L, Niehrs A, Russu K, Ohms M, Zhang W, Ehrhardt A, Duisters K, Spierings E, Hölzemer A, Körner C, Jansen SA, Peine S, Königs I, Lütgehetemann M, Perez D, Reinshagen K, Lindemans CA, Altfeld M, Belderbos ME, Dobner T, Bunders MJ. (2021)KIR3DS1 directs NK-cell mediated protection against human adenovirus infections. Science Immunology. PMID: 34533978.

- Müskens KF, Lindemans CA, Belderbos ME. (2021) Hematopoietic Dysfunction during graft-versus-host disease: A self-destructive process? Cells. PMID: 34440819.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Sabrina Jacobs, September 2021, University of Groningen, Dissecting diversity: clonal analysis of normal and malignant hematopoiesis using cellular barcodes. Promotor: prof. dr. G. de Haan. Co-promotores: dr. L. Bystrykh, dr. M.E. Belderbos.

Grants

European Hematology Association
Physician Scientist Grant
Peripheral blood or bone marrow stem cells? Population dynamics of blood in human hematopoietic stem cell transplantation recipients
€160.000

Research group prof. dr. Monique den Boer

Started in June 2018

Members of the den Boer Group

Principal Investigator
Monique den Boer
Senior postdoc
Judith Boer
Postdoc
Ilse Dingjan
Cesca van de Ven
Lu Yuan
Project manager
Simone Punt
PhD student
Babette Hoen
Femke Hormann
Uri Ilan
Aleksandra Kordek
Naomi Michels
Inge van Outersterp
Mandy Smeets
Iris van de Sandt
Maike Spoon
Senior technician
Aurélie van Kleef-Boeree
Research technician
Tim Dielen
Jan Orsel
Caitlin Reichert
Bio-informatician
Alex Hoogkamer
Scientific Assistant
Annemarie Heijens

The overall research aim of the Den Boer group is to find new molecular markers that point to more efficacious ways to treat children with B-cell precursor acute lymphoblastic leukemia (BCP-ALL). The program bridges research and clinics, which is illustrated by several inventions that have been implemented in the clinic. A key example is the identification of ABL-class lesions in high-risk BCP-ALL, which has resulted in the implementation of targeted treatment within the first two weeks of diagnosis in the European treatment protocol ALLtogether. Another example is the initiation of the international leukemia target board (iLTB) which prioritizes leukemic lesions at genetic, immunotherapeutic and drug response level, and which is directly linked to the initiation of an European clinical trial I/II initiative for targeted drugs in children with refractory or relapsed leukemia (HEM-iSMART, lead by prof. Michel Zwaan of our center).

Main topics of research are:

- Dissecting genetic lesions with prognostic and/or therapeutic potential.
- Characterizing the functional consequences of genetic lesions in BCP-ALL in in vitro and ex vivo models;
- Studying the ALL-educated bone marrow niche and the interplay with normal immune cells and response to (chemo/immune) therapeutics in ex vivo leukemic niche models;
- Determining which factors (genetics, secretome) of BCP-ALL and ALL-educated niche affect the efficacy of immunotherapeutics given to patients (in collaboration with dr. Stefan Nierkens, dr. Caroline Lindemans , dr. Friso Calkoen);
- Exploring targeted drug and chemotherapeutic drug combinations of interest for clinical implementation.

Total no. of Máxima-affiliated publications (2021)	**10**
No. of Máxima-affiliated open access publications (2021)	**7**
Total no. of external publications (2021)	**4**

Top 3 of Máxima-affiliated publications (2021)

- Den Boer ML, Cario G, Moorman AV, Boer JM, de Groot-Kruseman HA, Fiocco M, Escherich G, Imamura T, Yeoh A, Sutton R, Dalla-Pozza L, Kiyokawa N, Schrappe M, Roberts KG, Mullighan CG, Hunger SP, Vora A, Attarbaschi A, Zaliova M, Elitzur S, Cazzaniga G, Biondi A, Loh ML, Pieters R; Ponte di Legno Childhood ALL Working Group. (2021) Outcomes of paediatric patients with B-cell acute lymphocytic leukaemia with ABL-class fusion in the pre-tyrosine-kinase inhibitor era: a multicentre, retrospective, cohort study. Lancet Haematol. 8(1):e55-e66. PMID: 33357483.

- Michels N, Boer JM, Enshaei A, Sutton R, Heyman M, Ebert S, Fiocco M, de Groot-Kruseman HA, van der Velden VHJ, Barbany G, Escherich G, Vora A, Trahair T, Dalla-Pozza L, Pieters R, zur Stadt U, Schmiegelow K, Moorman AV, Zwaan CM, den Boer ML. (2021) Minimal Residual Disease, Long-Term Outcome, and IKZF1 Deletions in Down Syndrome Acute Lymphoblastic Leukemia in a Matched Cohort Study. Lancet Haematol. 8(10):e700-e710. PMID: 34560013.

- Boer JM, Valsecchi MG, Hormann FM, Antić Ž, Zaliova M, Schwab C, Cazzaniga G, Arfeuille C, Cavé H, Attarbaschi A, Strehl S, Escherich G, Imamura T, Ohki K, Grüber TA, Sutton R, Pastorczak A, Lammens T, Lambert F, Li CK, Carrillo de Santa Pau E, Hoffmann S, Möricke A, Harrison CJ, Den Boer ML, De Lorenzo P, Stam RW, Bergmann AK, Pieters R. (2021) Favorable outcome of NUTM1-rearranged infant and pediatric B cell precursor acute lymphoblastic leukemia in a collaborative international study. Leukemia 35(10):2978-2982. PMID: 34211097.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Sabrina Jacobs, September 2021, University of Groningen, Dissecting diversity: clonal analysis of normal and malignant hematopoiesis using cellular barcodes. Promotor: prof. dr. G. de Haan. Co-promotores: dr. L. Bystrykh, dr. M.E. Belderbos.

Grants

ODAS Foundation
Consortium grant
Identify targets to modulate CAR-T cell functionality using advanced 3D co-culture and imaging technologies: Towards better survival of pediatric BCP-ALL patients
Together with Friso Calkoen, Stefan Nierkens en Rob Pieters
€355.000

Research group dr. Ruben van Boxtel

Started in September 2017

Why do certain individuals develop cancer and others don't? And why do children get cancer? Our vision is that by studying mutations in normal cells, we obtain insight into the etiology of cancer. We think this knowledge is crucial to improve cancer diagnostics and treatment, as well as for developing preventive strategies.

Identifying the rate-limiting steps of cancer initiation in human tissues is challenging as many factors can play a role. The mutations in the genomes of cells can serve as an archive of their life history. We aim to decode these archives in order to pinpoint the initiation of cancer and identify causal processes in human tissues. In our research we focus on two themes:

1. **Tracking the origin of cancer**
   DNA is the largest biomolecule in cells, which unlike other biomolecules is irreplaceable. The processes causing mutations leave characteristic patterns in the DNA, which can serve as a functional readout of mutagenic and/or DNA repair activity. In addition, phylogenetic relationships between different cells of the same individual can be exploited to measure clonal dynamics within tissues. We aim to identify and study the mechanisms underlying characteristic mutation patterns in cancers as well as use mutations to retrospectively trace the cellular origin of cancer.

2. **The etiology of therapy-related malignancies in cancer survivors**
   Most chemotherapeutic drugs act by fatally damaging the DNA or blocking the replication thereof. However, noncancerous cells are also damaged by treatment, which can result in the accumulation of DNA mutations in normal tissues with potentially adverse effects later in life, such as novel malignancies. Our goal is to study the mutational effects of cancer treatment in normal tissues of children in order to develop novel treatment strategies aimed at minimizing or preventing adverse late effects.

Members of the van Boxtel Group

Principal Investigator
Ruben van Boxtel
PhD student
Lucca Derks
Patrick Greve
Karlijn Hasaart
Axel Rosendahl Huber
Jurrian de Kanter
Freek Manders
Flavia Peci
MD PhD Student
Eline Bertrums
Postdoc
Sjors Middelkamp
Joske Ubels
Inge van der Werf
Bioinformatician
Diego Montiel Gonzalez
Mark van Roosmalen
Research Technician
Niels Groenen
Laurianne Trabut
Mark Verheul
Scientific Research Coordinator
Annemarie Rietman

Total no. of Máxima-affiliated publications (2021)	**12**
No. of Máxima-affiliated open access publications (2021)	**12**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- de Kanter JK, Peci F, Bertrums E, Rosendahl Huber A, van Leeuwen A, van Roosmalen MJ, Manders F, Verheul M, Oka R, Brandsma AM, Bierings M, Belderbos ME, van Boxtel R. (2021) Antiviral treatment causes a unique mutational signature in cancers of transplantation recipients. Cell Stem Cell. PMID: 34496298.

- Brandsma AM, Bertrums EJM, van Roosmalen MJ, Hofman DA, Oka R, Verheul M, Manders F, Ubels J, Belderbos ME, van Boxtel R. (2021) Mutation signatures of pediatric acute myeloid leukemia and normal blood progenitors associated with differential patient outcomes. Blood Cancer Discov. PMID: 34642666.

- Hasaart KAL, Bertrums EJM, Manders F, Goemans BF, van Boxtel R. (2021) Increased risk of leukaemia in children with Down syndrome: a somatic evolutionary view. Expert Rev Mol Med. PMID: 33902785.

Patents/Licenses

1

Research group prof. dr. Hans Clevers

Started in 2015

Members of the Clevers Group

Principal Investigator
Hans Clevers

Postdoc
Talya Dayton
Lin Lin
Amanda Andersson Rolf
Karin Sanders
Marc van de Wetering

PhD student
Margit Bleijs
Evelyn Hanemaaijer
Seok-Young Kim
Laurens Verweij

Research technician
Lisanne den Hartigh
Femke Ringnalda

The Clevers group is a pioneer in the field of Wnt signaling, organoid technology and adult stem cells in health and disease. Upon establishing a research group in the Princess Máxima Center, this knowledge and experience was used to initiate a research line aiming to establish organoid technology for pediatric cancers. The Clevers group and others have shown that patient derived organoids retain the characteristics of the tissue of origin and as such can be regarded as patient avatars. This allows the use of organoids to predict drug sensitivity and guide the oncologist to choose the best therapy for the individual patient.

Pediatric cancer research in particular will benefit from the development of organoid models. Given the wide range of pediatric cancer entities, most pediatric cancer types are rare, which severely hampers research. The Clevers group aims to fill this gap by developing organoid technology for pediatric cancers. Clevers envisions that pediatric cancer organoids will accelerate research and, as patient avatars, guide therapy.

Originally focusing on neuroblastoma, medulloblastoma and Ewing sarcoma, the group now has broadened its scope and included rare pediatric cancers which are hardly studied because of their rareness. The team has successfully generated cancer organoids from rare pediatric cancers such as pleuropulmonary blastoma, NUT-midline carcinoma, desmoplastic small round cell tumor, ependymoma, craniopharyngioma and small cell carcinoma of the ovary. This opens new avenues for cancer research into basic (patho-)physiology, drug development and personalized medicine. These cancer organoids will be used in drug discovery projects to identify drugs that may cure these otherwise deadly cancer entities.

Total no. of Máxima-affiliated publications (2021)	**3**
No. of Máxima-affiliated open access publications (2021)	**3**
Total no. of external publications (2021)	**38**

Top 3 of Máxima-affiliated publications (2021)

- Hanemaaijer ES, Margaritis T, Sanders K, Bos FL, Candelli T, Al-Saati H, van Noesel MM, Meyer-Wentrup F, van de Wetering M, Holstege F, Clevers H. (2021). Single-cell atlas of developing murine adrenal gland reveals relation of Schwann cell precursor signature to neuroblastoma phenotype. Proceedings of the National Academy of Sciences of the United States of America, 118(5), e2022350118. https://doi.org/10.1073/pnas.2022350118.

- Busslinger GA, Weusten B, Bogte A, Begthel H, Brosens L, Clevers H. (2021). Human gastrointestinal epithelia of the esophagus, stomach, and duodenum resolved at single-cell resolution. Cell reports, 34(10), 108819. https://doi.org/10.1016/j.celrep.2021.108819.

- Kretzschmar K, Boonekamp KE, Bleijs M, Asra P, Koomen M, Chuva de Sousa Lopes SM, Giovannone B, Clevers H. (2021). Troy/Tnfrsf19 marks epidermal cells that govern interfollicular epidermal renewal and cornification. Stem cell reports, 16(9), 2379–2394. https://doi.org/10.1016/j.stemcr.2021.07.007.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**1**
Total no. of external PhD defenses (2021)	**2**

Máxima/External PhD defenses

Jens Puschhof, March 2021, Hubrecht Institute, Investigations on epithelial biology using organoid differentiation and co-cultures: Building representative models of the snake venom gland and complex tissue interactions in cancer and metabolic diseases. Promotor: prof. dr. J.C. Clevers.

Audrey Sporrij, March 2021, Harvard University & Utrecht University, The Many Faces of Gene Regulation: Extrinsic Control of Cell Fate and Function. Promotores: prof. dr. J.C. Clevers and prof. dr. L.I. Zon.

Lars Custers, October 2021, Princess Máxima Center, Using Organoid Models to Study Malignant Rhabdoid Tumors. Promotor: prof. dr. J.C. Clevers. Co-promotor: dr. J. Drost.

Grants

Daan de Jong Fonds
A Living Biobank of Ependymoma Organoids
€130.000

Stichting Neurofibromatose
€200.000

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Science awards

Pezcoller Foundation
AACR Award
Pezcoller/AACR
Hans Clevers

Honorary Doctorate Catholic University of Leuven, Belgium
Catholic University Leuven, Belgium
Hans Clevers

Research group dr. Jarno Drost

Started in November 2016

Members of the Drost Group

Principal Investigator
Jarno Drost

Co-PI
Ronald de Krijger

PhD student
Lars Custers
Camilla Calandrini
Maroussia Ganpat
Jiayou He
Marjolein Kes
Irene Paassen

Postdoc
Dilara Ayyildiz
Juliane Buhl
Arianna Fumagalli
Francisco Morales-Rodriguez
Frans Schutgens

Research technician
Sofia Doulkeridou
Jolanda Kooiman
Yvonne Tiersma-Gerlach

Kidney cancers represent approximately 7% of childhood cancers, comprised of Wilms tumors, clear cell sarcomas of the kidney (CCSK), malignant rhabdoid tumors (MRT) and renal cell carcinomas (RCC). In addition to the kidney, MRT can also appear in the brain (atypical teratoid rhabdoid tumors (ATRT) and soft tissues. Although survival rates – especially of Wilms tumor patients – increased significantly over the last decades, the harsh chemotherapy regimens result in severe side-effects in survivors. The other renal tumor subtypes generally have a dismal outcome profile, with MRT representing one of the big challenges in childhood cancer with a very poor survival rate. All this creates an urgent need for the development of new therapies.

Many childhood tumors already originate in the developing fetus. They are likely caused by a block in processes driving lineage specification and differentiation. In most cases, the cells from which the tumors originate are only present during short, specific time windows in development. As a consequence, it is challenging to identify the processes initiating and driving tumorigenesis.

The Drost group develops innovative preclinical models, such as organoids and mouse models, of pediatric renal and rhabdoid tumors representative of patient tumors. We exploit these to understand how tumors arise during embryonic development. We combine our pre-clinical models with cutting-edge (single-cell) genomics and transcriptomics, barcode lineage tracing, and high-throughput drug screens to study fundamental processes driving tumorigenesis, with the aim to develop new (immuno-)therapies to treat children with renal and rhabdoid tumors.

Total no. of Máxima-affiliated publications (2021)	**12**
No. of Máxima-affiliated open access publications (2021)	**11**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Custers L, Khabirova E, Coorens THH, Oliver TRW, Calandrini C, Young MD, Vieira Braga FA, Ellis P, Mamanova L, Segers H, Maat A, Kool M, Hoving EW, van den Heuvel-Eibrink MM, Nicholson J, Straathof K, Hook L, de Krijger RR, Trayers C, Allinson K, Behjati S, Drost J. (2021) Somatic mutations and single-cell transcriptomes reveal the root of malignant rhabdoid tumours. Nature Communications. PMID: 33658498.

- Young MD, Mitchell TJ, Custers L, Margaritis T, Morales-Rodriguez F, Kwakwa K, Khabirova E, Kildisiute G, Oliver TRW, de Krijger RR, van den Heuvel-Eibrink MM, Comitani F, Piapi A, Bugallo-Blanco E, Thevanesan C, Burke C, Prigmore E, Ambridge K, Roberts K, Vieira Braga FA, Coorens THH, Del Valle I, Wilbrey-Clark A, Mamanova L, Stewart GD, Gnanapragasam VJ, Rampling D, Sebire N, Coleman N, Hook L, Warren A, Haniffa M, Kool M, Pfister SM, Achermann JC, He X, Barker RA, Shlien A, Bayraktar OA Teichmann S, Holstege FC, Meyer KB, Drost J, Straathof K, Behjati S (2021). Single cell derived mRNA signals across human kidney tumors. Nature Communications. PMID: 34162837.

- Calandrini C, van Hooff SR, Paassen I, Ayyildiz D, Derakhshan S, Dolman MEM, Langenberg KPS, van de Ven M, de Heus C, Liv N, Kool M, de Krijger RR, Tytgat GAM, van den Heuvel-Eibrink MM, Molenaar JJ, Drost J (2021). Organoid-based drug screening reveals neddylation as therapeutic target for malignant rhabdoid tumors. Cell Reports. PMID: 34433038.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**1**
Total no. of external PhD defenses (2021)	**0**

Máxima/External PhD defenses

Lars Custers, October 2021, Princess Máxima Center, Using Organoid Models to Study Malignant Rhabdoid Tumors. Promotor: prof. dr. J.C. Clevers. Co-promotor: dr. J. Drost.

Grants

NWO
VIDI
Untangling the contribution of epigenetic reprogramming to tumorigenesis
€800.000

Stichting Kinderen Kankervrij
KiKa 377
Uncovering metabolic vulnerabilities in childhood kidney cancer
€600.000

Oncode (Technology Development fund)
TechDev grant Oncode
Validation of the MISC-seq technology in pediatric rhabdoid tumors
€35.000

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Awards

Vidi career grant
NWO
Jarno Drost

Tom Voûte young investigator award
KiKa
Lars Custers

Patents/licenses

1

Research group prof. dr. Martha Grootenhuis

Started in September 2015

Members of the Grootenhuis Group

Principal Investigator
Martha Grootenhuis

Fellow
Raphaële van Litsenburg
PhD student
Petra Buursma
Mala Joosten
Kelly Engels - van Bindsbergen
Loes van Erp
Eva Hooft van Huijsduijnen
Annelienke van der Hulst
Jojanneke van Kooten
Eline Kochen
Anne Maas
Shosha Peersmann
Emily Schwartz
Julia Simon
MD/PhD student
Sebastian Bon
Niki Rensen
Postdoc
Marloes van Gorp
Elin Irestorm
Sasja Schepers
Heleen Maurice - Stam
Roel Wouters
Researcher
Gea Huizinga
Support staff
Hinke van der Hoek

Our research focuses on the psychosocial consequences and predictive factors of childhood cancer outcomes for children and their families and the development and implementation of interventions to prevent or reduce these outcomes. Outcomes include medical traumatic stress due to treatment, emotional-behavioral effects such anxiety and depression but also quality of life, fatigue and sleep. We are not only examining these effects during treatment, but also afterwards, until the adult age. How vulnerable children, adolescents and (young) adults, parents and siblings are, depends on several risk and protective factors. These include both socio-demographic, medical, environment, and psychological aspects such as communication, social support, self-esteem and coping. These factors are of the utmost importance as most interventions focus on these potentially modifiable predictors of psychosocial outcomes.

We distinguish five programs that are implemented in close collaboration with healthcare professionals from aligned departments under the umbrella of M4C Psychosocial Oncology:

1. Anxiety/stress: we study anxiety and stress related to several circumstances of disease and treatment (e.g. medical procedures, genetic testing), and we study e-health interventions.
2. Sleep/fatigue: Sleep problems and disturbed circadian rhythms are common and related to increased cancer-related fatigue and lower quality of life, in children and parents. Sleep and the circadian rhythm are therefore important modifiable factors to improve overall well-being. To this end, we will develop a comprehensive approach to sleep and circadian rhythm, including prevention, screening and treatment.
3. Communication: Communication forms the basis of the medical therapeutic relationship. Analyzing communication (mal)practices and studying their effect on psychosocial, quality of life and health outcomes in patients and their families is important to sustain quality of care and find starting points for interventions.
4. Psychological consequences of survivors: studying the relationship between medical late effects, burden of disease and psychosocial late effects of survivors.
5. Patient Reported Outcomes (PROMS) in research and care: continuous process of developing/testing good quality and appropriate questionnaires, and collecting high quality standardized data.

Total no. of Máxima-affiliated publications (2021)	**41**
No. of Máxima-affiliated open access publications (2021)	**31**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- van Erp LME, Maurice-Stam H, Kremer LCM, Tissing WJE, van der Pal HJH, de Vries ACH, van den Heuvel-Eibrink MM, Versluys BAB, Loonen JJ, Bresters D, Louwerens M, van der Heiden-van der Loo M, van den Berg MH, Ronckers CM, van der Kooi ALLF, van Gorp M, van Dulmen-den Broeder E, Grootenhuis MA (2021). Health-related quality of life in Dutch adult survivors of childhood cancer: A nation-wide cohort study. European Journal of Cancer. PMID: 34119924.
- van Muilekom MM, Luijten MAJ, van Oers HA, Terwee CB, van Litsenburg RRL, Roorda LD, Grootenhuis MA, Haverman L. (2021) From statistics to clinics: the visual feedback of PROMIS® CATs. Journal of Patient Reported Outcomes. PMID: 34245390.
- Schepers SA, Schulte FSM, Patel SK, Vannatta K. (2021). Cognitive Impairment and Family Functioning of Survivors of Pediatric Cancer: A Systematic Review. Journal of Clinical Oncology. PMID: 33886349.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**4**

Máxima/External PhD defenses

Lindsey Steur, January 2021, Amsterdam UMC, Sleep in children with acute lymphoblastic leukemia. Promotores: prof. dr. G.J.L. Kaspers, prof. dr. M.A. Grootenhuis. Co-promotor: dr. R.R.L. van Litsenburg.
Merel van der Vlist, September 2021, University of Utrecht, Beyond the diagnosis: A PROactive approach to fatigue, daily life participation, and health-related quality of life in pediatric chronic disease. Promotores: prof. dr. E.M. van de Putte, prof. dr. M.A. Grootenhuis. Co-promotores: Dr. S.L. Nijhof, Dr. G.W. Dalmeijer.
Niki Rensen, November 2021, Amsterdam UMC, Parents of children with cancer, sleep, distress and quality of life. Promotores: prof. dr. G.J.L. Kaspers, prof. dr. M.A. Grootenhuis. Co-promotor: dr. R.R.L. van Litsenburg.
Patrizia D'olivo, June 2021, Delft University of Technology, Designing tactful objects for sensitive settings. Promotores: prof. dr. E. Giaccardi, prof. dr. M.A. Grootenhuis. Co-promotor: Dr. ir. M.C. Rozendaal.

Grants

Stichting Kinderen Kankervrij
KiKa 403
REFLECT: Reactions and Emotions of Families Linked to Exome sequencing in Childhood Cancer
Together with Marry van den Heuvel-Eibrink and Roland Kuiper
€375.355

Stichting Kinderen Kankervrij
KiKa 416
IDENTIFY study. Identifying the course of fatigue and quality of life in childhood cancer: scientific insight and clinical application
€274.123

Science awards

Young Investigator Award
SIOP
Marloes van Gorp

Research group prof. dr. Jan Hoeijmakers

Started in October 2017

Members of the Hoeijmakers Group

Principal Investigator
Jan Hoeijmakers

Senior Postdoc
Wilbert Vermeij

MD PhD student
Chris Oudmaijer

PhD student
Winnie van den Boogaard
Maria Bjork Birkisdóttir
Irene van Dijken
Ivar van Galen
Daphne Komninos
Ziqin Tang

Postdoc
Willianne Vonk

Research technician
Yvonne Rijksen - Kamp
Kimberly Smit

Bioinformatician
Rutger Ozinga

Our team studies genomic instability and its consequences for cancer and aging, two aspects highly relevant for treatment and quality of life of children with cancer. Massive DNA damage, the main cause of genome instability, occurs continuously in every cell and has two main consequences. First, it can lead to mutations and chromosomal aberrations that facilitate carcinogenesis including evolution to malignancy and eventually therapy resistance, hampering an effective cure. Hence, DNA damage is of utmost importance for all aspects of cancer and cancer treatment. Secondly, DNA damage triggers cellular death, senescence, and overall functional decline. Indeed, our group discovered that DNA damage is a main (if not the) driver of aging in mammals. Importantly, in cancer therapy, DNA damage is used to kill tumor cells by most common anti-cancer treatment modalities. Based on the link with aging, we predicted that DNA-damaging chemo- and radiotherapy would accelerate aging. This expectation was confirmed in long-term cancer survivors (e.g. LATER study).

Recently, in mice and cell systems we found that dietary restriction (DR) and short-term fasting (STF) induce a surprisingly powerful, protective 'survival' response, which suppresses growth and prioritizes resilience mechanisms. Importantly, we discovered that DR reduces DNA damage and thereby delays aging. Additionally, DR/STF provide acute protection from ischemia reperfusion injury in surgery, for which we recently initiated several clinical trials in adults and children.

Using our mouse models for human DNA repair syndromes, we intend to obtain full understanding of the intriguing 'survival' response and derive rational-based nutritional and pharmacological strategies that promote healthy aging, postpone dementias and reduce the severe, short- and long-term side-effects of chemo- and radiotherapy and thereby improve quality of life, particularly in children with cancer. Although our approach involves overall health, we pay specific attention to cognitive and other features of neurodegeneration as we found neurofunctioning to benefit disproportionally from DR/STF.

Total no. of Máxima-affiliated publications (2021)	**8**
No. of Máxima-affiliated open access publications (2021)	**6**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Schumacher B, Pothof J, Vijg J, Hoeijmakers JHJ (2021) The central role of DNA damage in the ageing process. Nature;592(7856):695-703. doi: 10.1038/s41586-021-03307-7. PMID: 33911272.

- Birkisdóttir MB, Jaarsma D, Brandt RMC, Barnhoorn S, van Vliet N, Imholz S, van Oostrom CT, Nagarajah B, Portilla Fernández E, Roks AJM, Elgersma Y, van Steeg H, Ferreira JA, Pennings JLA, Hoeijmakers JHJ, Vermeij WP, Dollé MET (2021) Unlike dietary restriction rapamycin fails to extend lifespan and reduce transcription stress in progeroid DNA-repair deficient mice. Aging Cell;20(2):e13302. doi: 10.1111/acel.13302. PMID: 33484480.

- van den Boogaard WMC, van den Heuvel-Eibrink MM, Hoeijmakers JHJ, Vermeij WP (2021) Nutritional Preconditioning in Cancer Treatment in Relation to DNA Damage and Aging. Ann Rev Cancer Biol ;5:161-179 doi: 10.1146/annurev-cancerbio-060820-090737.

Grants

ZonMw
European Joint Program Rare Diseases RD20-113
Transcription stress Counteracted by Nutritional interventions of Exceptional importance for rare DNA Repair disorders (TC-NER)
€1.100.000
consortium project total, of which
€250.000
Máxima affiliated partner

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration
(Chapter Collaborations)

Research group dr. Sebastiaan van Heesch

Started in July 2020

Members of the Van Heesch Group

Principal Investigator
Sebastiaan van Heesch

PhD student
Damon Hofman
Viktor Yurevych

Research Technician
Sem Engels

Bioinformatician
Jip van Dinter

Searching the tumor-specific transcriptome and translatome to find new targets for immunotherapy in pediatric tumors.

Immunotherapy has revolutionized the treatment of cancer in adults, but its application to childhood cancer is still very limited, in part because the right targets for treatment are lacking. As part of the Princess Máxima Center's broader strategy to develop immune therapy options for pediatric cancer patients, the Van Heesch group focuses on the identification of pediatric tumor-specific epitopes that can be targeted with immunotherapy. To find the best targets, we combine genomics (DNA), transcriptomics (RNA) and translatomics (protein synthesis) techniques, which we integrate using computational strategies to monitor gene expression in tumor samples and organoid systems to the greatest possible resolution. Our aim is to discover, prioritize and investigate newly discovered proteins that appear to be unique to (and recurrent within) a certain tumor type, whilst being absent from healthy cells.

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**5**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- Mudge JM, Ruiz-Orera J, Prensner JR, Brunet MA, Gonzalez JM, Magrane M, Martinez T, Schulz JF, Yang YT, Albà MM, Baranov PV, Bazzini A, Bruford E, Martin MJ, Carvunis AR, Chen J, Couso JP, Flicek P, Frankish A, Gerstein M, Hubner N, Ingolia NT, Menschaert G, Ohler U, Roucou X, Saghatelian A, Weissman J, van Heesch S. (2021) A community-driven roadmap to advance research on translated open reading frames detected by Ribo-seq. bioRxiv 2021.06.10.447896. doi: https://doi.org/10.1101/2021.06.10.447896.

- Schneider-Lunitz V, Ruiz-Orera J, Hubner N, van Heesch S. (2021) Multifunctional RNA-binding proteins influence mRNA abundance and translational efficiency of distinct sets of target genes. PLOS Comp Biol.;17(12):e10096582021. PMID 34879078.

- Witte F, Ruiz-orera J, Mattioli CC, Blachut S, Adami E, Schulz F, Schneider-lunitz V, Hummel O, Patone G, Mücke MB, Šilhavý J, Heinig M, Bottolo L, Sanchis D, Vingron M, Chekulaeva M, Pravenec M, Hubner N, van Heesch S. (2021) A trans locus causes a ribosomopathy in hypertrophic hearts that affects mRNA translation in a protein length-dependent fashion. Genome Biol. 22, 191. PMID: 34183069.

Grants

Villa Joep
Immunology consortium
Joining forces to activate T-cell immunity against high risk neuroblastoma
Together with Jan Molenaar and Stefan Nierkens
€1.275.000

Stichting Reggeborgh
Uncovering novel targets for immunotherapy in pediatric tumors
€ 200.000

Research group prof. dr. Olaf Heidenreich

Started in September 2018

Members of the Heidenreich group

Principal Investigator
Olaf Heidenreich

Co-Principal Investigator
Astrid van Halteren
Josef Vormoor

PhD student
Rachel Cameron
Polina Derevianko
Joost Koedijk
Milad Rasouli
Laura Swart

Senior Postdoc
Anja Krippner-Heidenreich

Postdoc
Farnaz Barneh
Kasia Szoltysek

Bioinformatician
Minoo Ashtiani

Research Technician
Anita van Oort-Jansen
David Tuk

The Heidenreich team is interested in the biology of leukemic fusion genes, the investigation of fusion protein-driven transcriptomic and proteomic programs and their translation into novel, more specific and effective treatments.

We are studying the role of the fusion protein RUNX1/ETO in leukemic persistence and drug response. To that end, we inhibited its expression using fusion gene-specific RNA interference followed by global examination of transcriptional and posttranscriptional changes. In collaboration with Vasily Grinev at the Belarusian State University in Minsk we could demonstrate that loss of RUNX1/ETO results in aberrant splicing yielding numerous non-canonical transcripts. In a continuation of this work, we are currently investigating whether these transcripts are recognized by ribosomes (collaboration with Sebastiaan van Heesch) and whether they give rise to novel proteins (collaboration with Matthias Trost, Newcastle University).

We have also established a co-culture platform that enables us to cultivate and expand patient AML cells for several weeks. Importantly, this expansion includes immature cell populations harboring the leukemic stem cells. Based on these results, we are currently evaluating the impact of agents and metabolites on leukemic proliferation, self-renewal, differentiation and the communication between AML and niche cells. Furthermore, we also study drug responses of distinct AML subtypes. In this context, we demonstrated a high sensitivity of AMLs with a NUP98 rearrangement, an AML group with poor clinical outcome, towards a menin inhibitor. These findings supported the inclusion of this patient group into clinical trials that will open next year (collaboration with Michel Zwaan). As a newer development, we also apply this platform to study and visualize the interaction of patient-derived AML cells with cytotoxic T cells (collaboration with Anne Rios and Stefan Nierkens). In parallel we have initiated a project to monitor and document these interactions in AML patients.

We also made substantial progress with the development of a drug delivery platform for therapeutic siRNAs. We established robust protocols for the decoration of lipid nanoparticles with ligands for enhanced cell binding and uptake. This approach has greatly improved the efficacy of fusion gene knockdown in primary AML cells in co-culture and has already yielded promising results in first in vivo studies.

Total no. of Máxima-affiliated publications (2021)	**12**
No. of Máxima-affiliated open access publications (2021)	**3**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Grinev VV, Barneh F, Ilyushonak IM, Nakjang S, Smink J, van Oort A, Clough R, Seyani M, McNeill H, Reza M, Martinez-Soria N, Assi SA, Ramanouskaya TV, Bonifer C, Heidenreich O. (2021) RUNX1/RUNX1T1 mediates alternative splicing and reorganises the transcriptional landscape in leukemia. Nat Commun. PMID: 33483506.
- Swart LE, Heidenreich O. (2021) The RUNX1/RUNX1T1 network: translating insights into therapeutic options. Exp Hematol. PMID: 33217477.
- Koedijk JB, van der Werf I, Calkoen FG, Nierkens S, Kaspers GJL, Zwaan CM, Heidenreich O. (2021) Paving the Way for Immunotherapy in Pediatric Acute Myeloid Leukemia: Current Knowledge and the Way Forward. Cancers. PMID: 34503174.

Grants

Syndax Pharmaceuticals
Preclinical evaluation of SNDX-5613 efficacy in NU
€149.880

Patents/licenses

1

Research group prof. dr. Marry van den Heuvel-Eibrink

Started in January 2015

Grants

Stichting Kinderen Kankervrij
KiKa 403
REFLECT: Reactions and Emotions of Families Linked to Exome sequencing in Childhood Cancer Together with Martha Grootenhuis and Roland Kuiper
€375.355

KWF
KWF 13192
CRADLE II study
€38.750

Private funding
Merging 8000 kidney tumor patients from SIOP-RTSG historical data bases
€50.593

Princess Máxima Center Foundation
Identifying (genetic) determinants of ototoxicity in childhood cancer
€25.000

Princess Máxima Center Foundation
Dexadagen
€30.369

Science awards

SIOP-Young investigator Award
SIOP
M. van der Perk
J. Mul
J. van Atteveld
A. Meijer

EURAPAG Award
A. van der Kooi

Publieksprijs
NVK
J. van Atteveld

Research program, two overlapping research fields:

Renal tumors
Translational Research (biology, epidemiology and toxicity) and outcome determinants research, including diagnostic innovation (radiology/diagnostic discrimination/artificial intelligence and molecular (biomarker/target identification), oncogenetic and renal tumor-genetic susceptibility), connected to basic molecular research(NGS, organoids, and target identification, compound screens), and innovative treatment development(chemo-/immuno-/radiotherapy and surgical), within M4C, with a focus on the adverse prognostic subgroups. The PI is M4C chair renal tumors with dr. Jarno Drost, and international vice-chair of the SIOP-RTSG group and coordinates optimal treatment and research development in over 40 countries on four continents through the SIOP-RTSG-UMBRELLA protocol as coordinator SIOP-RTSG office, now embedded in the TDC at the Princess Máxima Center. She co-chairs with prof. J. Geller, Cincinnati, the transatlantic HARMONICA research initiative of SIOP-RTSG and COG-RTG.

Quality of cure and toxicity
To get insight in the (biological) mechanisms of toxicity and to identify genetic, lifestyle and clinical treatment related risk factors and to design prediction models for treatment related ototoxicity, gonadal function, kidney function and endocrine impairment, to optimize surveillance strategies, and to create and implement successful strategies for prevention and early (during treatment) intervention of treatment related neurocognitive impairment, renal toxicity, ototoxicity, metabolic syndrome, female gonadal fertility (OTC), and bone toxicity, supported by clinical studies and preclinical (mouse) models. To design and prove feasibility of standard surveillance programs for (critical) toxicity for childhood cancer patients. A specific initiative in the group is to identify sequelae in children that are born from mothers that suffer from Cancer in Pregnancy (CIP), by coordinating the national follow-up outpatient CIP clinic for offspring, now established in the Princess Máxima Center, and to unravel the molecular mechanisms of these toxicities.

Prof. dr. Marry van den Heuvel-Eibrink took the lead in successful founding of the International SIOP-RTSG Association in June 2021, as a legal entity, in the Netherlands with support of the Board of the Princess Maxima Center, and dr. Harm van Tinteren, the co-chair TDC, and statistician SIOP-RTSG.

Total no. of Máxima-affiliated publications (2021)	**84**
No. of Máxima-affiliated open access publications (2021)	**1**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- van der Perk MEM, *et al* (2021) Effect of genetic variation in CYP450 on gonadal impairment in a European cohort of female childhood cancer survivors, based on a candidate gene approach: results from the PanCareLIFE study. Cancers (Basel). 13;13(18):4598.

- Graf N, Bergeron C, Brok J, de Camargo B, Chowdhury T, Furtwängler R, Gessler M, Godzinski J, Pritchard-Jones K, Ramirez G, Rübe C, Sandstedt B, Schenk JP, Spreafico F, Sudour-Bonnange H, van Tinteren H, Verschuur A, Vujanic G, van den Heuvel-Eibrink MM. (2021) Fifty years of clinical and research studies for childhood renal tumors within the International Society of Pediatric Oncology (SIOP). Ann of Oncol,];32(11):1327-1331

- Prakriti R, van Peer SE, de Witte MM, Tytgat GAM, Karim-Kos HE, van Grotel M, van de Ven CP, Mavinkurve-Groothuis AMC, Merks JHM, Kuiper RP, Hol JA, Janssens GOR, de Krijger RR, Jongmans MCJ, Drost J, van der Steeg AFW, Littooij AS, Wijnen MHWA, van Tinteren H, van den Heuvel-Eibrink MM. (2021) 517. Characteristics and outcome of children with renal tumors in the Netherlands: the first five-year's experience of national centralization. PLoSOne, in press.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**1**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Annelot Meijer, September 2021, Utrecht University, Childhood related hearing loss and tinnitus, Promotors: prof. dr. M.M. van den Heuvel-Eibrink. Co-promotores: dr. ir. A.E. Hoetink, dr. M. van Grotel.

Selveta van Santen, December 2021, Erasmus University Rotterdam, Body transformation in Life after Tumor: Long term consequences for endocrinology, metabolism, and bone. Promotores: prof. dr. A.J. van der Lelij, prof. dr. M.M. van den Heuvel-Eibrink. Co-promotor: dr. S.J.C.M.M. Neggers.

Members of the van den Heuvel-Eibrink Group

Principal Investigator
Marry van den Heuvel – Eibrink

MD/PhD student
Jenneke van Atteveld
Justine van der Beek
Eline Bertrums
Winnie van den Boogaard
Sebastian Bon
Myrthe Buser
Robin Diepstraten
Alissa Groenendijk
Janna Hol
Annelienke Evangeline Huis in 't veld
van Hulst
Anne-Lotte van der Kooi
Daphne Komninos
Sanne Noort
Joeri Mul
Sophie van Peer
Madeleine van der Perk
Vincent Pluimakers
Paulien Raymakers - Janssen
Demi de Winter

Postdoc
Annelies Bos
Martine van Grotel
Alex Hoetink
Annelot Meijer
Sebastian Neggers

Psychologist, Postdoc
Mathilde van Gerwen

Physiotherapist, postdoc
Annelies Hartman

Bioinformatician
Linda Broer

Radiation therapist, PhD student
Raquel Davilla

PhD student, physiotherapist, epidemiologist
Emma Verwaaijen

Research group prof. dr. Frank Holstege

Started in January 2016

Members of the Holstege Group

Principal Investigator
Frank Holstege

Head single cell genomics facility
Thanasis Margaritis

PhD student
Jeff DeMartino

MD/PhD student
Michael Meister

Postdoc bioinformatician
Tito Candelli
Philip Lijnzaad
Terezinha Souza
Lindy Visser

Lab manager/technician
Mariel Brok

Research Technician
Eduard Bodewes
Ewa Frazer
Marian Groot Koerkamp

Facility scientist
Aleksandra Balwierz

The Holstege group runs two main lines of research in the Máxima Center. The first is a technology-driven focus on studying pediatric tumors using single-cell genomics. This is led by the single-cell genomics facility that is housed within the Holstege group (leader: dr. Thanasis Margaritis) in collaboration with many different research groups.

More details are described in the core facilities section, but highlights include the successful publication of the first projects completely initiated and carried out within the Máxima. One such project is the identification of a subpopulation of cells associated with poor prognosis in infant leukemia, in collaboration with Stam group.

A second line of research focuses on studying pediatric soft-tissue sarcomas using tumor organoid technology (coordinator: Michael Meister, MD). Pediatric soft tissue sarcomas encompass over 20 different types of tumors with generally poor prognosis. These have been less well studied due to a lack of sample numbers, material and cellular models. The first comprehensive set of organoid models have now been established, fully characterized and screened for drug-sensitivities. Publication is pending and requests for use of the models from within and outside our center have already been granted for a wide variety of new lines of research aimed at finding vulnerabilities of these tumors.

Total no. of Máxima-affiliated publications (2021)	**9**
No. of Máxima-affiliated open access publications (2021)	**9**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Candelli T, Schneider P, Garrido Castro P, Jones LA, Bodewes E, Rockx-Brouwer D, Pieters R, Holstege FCP, Margaritis T, Stam RW. (2021) Identification and characterization of relapse-initiating cells in MLL-rearranged infant ALL by single-cell transcriptomics. Leukemia. PMID: 34304246.

- Zelco A, Börjesson V, de Kanter JK, Lebrero-Fernandez C, Lauschke VM, Rocha-Ferreira E, Nilsson G, Nair S, Svedin P, Bemark M, Hagberg H, Mallard C, Holstege FCP, Wang X. (2021) Single-cell atlas reveals meningeal leukocyte heterogeneity in the developing mouse brain. Genes & Development. PMID: 34301765.

- Hanemaaijer ES, Margaritis T, Sanders K, Bos FL, Candelli T, Al-Saati H, van Noesel MM, Meyer-Wentrup FAG, van de Wetering M, Holstege FCP, Clevers H. (2021) Single-cell atlas of developing murine adrenal gland reveals relation of Schwann cell precursor signature to neuroblastoma phenotype. Proc Natl Acad Sci USA. PMID: 33500353.

Research group prof. dr. Alwin Huitema

Started in November 2020

Members of the Huitema Group

Principal Investigator
Alwin Huitema

Co-PI
hospital pharmacist
Lidwien Hanff

Postdoc hospital pharmacist
Meta Diekstra

PhD student
Emma Bernsen
Julia Möhlmann
Eduardo Pennesi

PhD student
hospital pharmacist
Laura Nijstad

MD PhD student
Aniek Uittenboogaard

Research Technician
Albert Dijkhuizen

The overarching research topic of the pharmacology research group is to contribute to precision medicine by implementing precision dosing of anticancer agents and drugs used in supportive care. Ultimately, this should lead to the right dose for each patient.

2021 was the first full year of the pharmacology research group. Several research lines were continued and new research lines have been initiated. Research into precision dosing in infants was continued and extended. The PINOCCHIO study, where the pharmacokinetics (PK) of cytotoxic drugs in infants was studied, was extended to oral anticancer agents. Furthermore, the first cohorts of this study were analyzed and published. In addition to this, the pharmacology group contributed to a study into the PK of peg-asparaginase in infants.

Under supervision of Meta Diekstra, a new research line into pharmacogenetics in pediatric oncology was started. In collaboration with the Kemmeren group, it was explored whether existing WES data can be used to extract pharmacogenetic data to be used in clinical practice.

Another important development for the pharmacology group in 2021 was the preparations to set up a bioanalytical LC-MS/MS laboratory. Measurement of drugs in biological matrices either from clinical and preclinical research is key for our research line. Construction work started in the fourth quarter of 2021 and in the meantime, selection of the LC-MS/MS systems was done. It is anticipated that this laboratory will open in the first quarter of 2022. Preparations for development of the first assays is ongoing to give this laboratory a flying start in 2022.

Total no. of Máxima-affiliated publications (2021)	**6**
No. of Máxima-affiliated open access publications (2021)	**6**
Total no. of external publications (2021)	**50**

Top 3 of Máxima-affiliated publications (2021)

- Nijstad AL, Nierkens S, Lindemans CA, Boelens JJ, Bierings M, Versluys AB, van der Elst KCM, Huitema ADR. (2021) Population pharmacokinetics of clofarabine for allogeneic hematopoietic cell transplantation in pediatric patients. Br J Clin Pharmacol.;87(8):3218-3226.

- Nijstad AL, Barnett S, Lalmohamed A, Berenos IM, Parke E, Carruthers V, Tweddle DA, Kong J, Zwaan CM, Huitema ADR, Veal GJ. (2021) Clinical pharmacology of cytotoxic drugs in neonates and infants: Providing evidence-based dosing guidance. Eur J Cancer.

- Szanto CL, Cornel AM, Tamminga SM, Delemarre EM, de Koning CCH, van den Beemt D, Dunnebach E, Tas ML, Dierselhuis MP, Tytgat L, van Noesel MM, Kraal K, Boelens JJ, Huitema ADR, Nierkens S. (2021) Immune Monitoring during Therapy Reveals Activitory and Regulatory Immune Responses in High-Risk Neuroblastoma. Cancers (Basel).;13(9).

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**1**
Total no. of external PhD defenses (2021)	**0**

Máxima/External PhD defenses

Steffie Groenland, February 2021, Utrecht University/Netherlands Cancer Institute, Optimizing exposure of oral targeted therapies in oncology – towards precision dosing. Promotores: prof. A.D.R. Huitema, prof. J.H. Beijnen. Co-promotor: dr. N. Steeghs.

Research group dr. Esther Hulleman

Started in June 2018

Members of the Hulleman Group

Principal Investigator
Esther Hulleman

PhD student
Aimée du Chatinier
Madelaine van Mackelenbergh
Konstantinos Vazaios

Postdoc
John Bianco
Hans Meel
Dennis Metselaar

Research Technician and lab manager
Piotr Waranecki

Research in the Hulleman group focuses on highly aggressive brain tumors, such as pediatric high-grade glioma, diffuse midline glioma (DMG), ependymoma, and atypical teratoid rhabdoid tumors (ATRT). The Hulleman group performs translational research, which comprises the development of novel treatment modalities, the establishment of primary tumor models, drug screens, liquid biopsies, and the histological and molecular characterization of tumor material for the identification of novel drug targets.

In the past year, the Hulleman group has focused on the blood-brain barrier (BBB) in diffuse midline glioma (DMG) and pediatric high-grade glioma (pHGG). This semi-permeable border of endothelial cells hampers the efficient delivery of most small molecules (≥90%), including frequently used chemotherapy. To better direct treatment choices for pHGG and DMG patients, we have studied the BBB in DMG patient material (El Khouly et al., Free Neuropathology 2021) and compared tumor vasculature of pHGG and DMG animal models (Wei et al., 2021 in collaboration with dr. Timothy Phoenix). Results from these studies indicate that DMG models maintain a more normal vascular architecture and BBB function than pHGG models, although some structural changes are also observed in the BBB of DMG patients, especially at end-stage disease. Since this data confirms that the BBB constitutes an important hurdle in the delivery of chemotherapy in DMG, we continue to investigate compounds that have been shown to cross the BBB for the treatment of diffusely growing brain tumors. For example, we previously reported on the synergy of combination of the BBB-penetrable AXL inhibitor bemcentinib with panobinostat, an inhibitor of histone deacetylases (HDACs).

We now expanded this research line by including other HDAC inhibitors and an alternative drug against AXL, in combination with radiotherapy. Discussions to set up a clinical study based on those results within the Pacific Pediatric Neuro-Oncology Consortium (PNOC) are currently underway.

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**5**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Metselaar DS, Du Chatinier A, Stuiver I, Kaspers GJL, Hulleman E. (2021) Radiosensitization in pediatric high-grade glioma: targets, resistance and developments. Front Oncol. PMID: 33869066.
- Wei X, Meel MH, Breur M, Bugiani M, Hulleman E, Phoenix N. (2021) Defining tumor-associated vascular heterogeneity in pediatric high-grade and diffuse midline gliomas. Acta Neuropathol Comm. PMID: 34425907.
- Karki A, Berlow NE, Kim JA, Hulleman E, Liu Q, Michalek JE, Keller C. (2021) Receptor-driven invasion profiles in diffuse intrinsic pontine glioma. NeuroOncol Adv. PMID: 34013206.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Dennis S. Metselaar, December 2021, Amsterdam University Medical Center, Novel therapeutic strategies in aggressive pediatric brain tumors – navigating the epigenetic landscape. Promotor: prof. G.J.L. Kaspers. Co-promotores: dr. E. Hulleman, dr. M. Bugiani.

Grants

Koppie – Au
Preclinical evaluation of gemcitabine for SHH medulloblastoma
€15.200

Stichting Kinderen Kankervrij
KiKa 389
DNA methylation profiling of pediatric brain tumors using liquid biopsies
€98.000

STOPHersentumoren
A novel therapeutic strategy for the treatment of PF-A ependymoma
€44.500

Research group dr. Claudia Janda

Started in September 2018

Members of the Janda Group

Principal Investigator
Claudia Janda

Postdoc
Kim van Noort

PhD student
Jannet Koelewijn

Research Technician
Lisa Jansen
Fenna van Rijt

Osteosarcoma (OS) is the most malignant bone tumor in children, accounting for around 3% of childhood cancers. It is an aggressive tumor that frequently develops metastases predominantly in the lungs. Current treatment consists of chemotherapy and surgical resection. Unfortunately, children with recurrent and metastatic OS respond poorly and have a have dismal survival chance of 20-30%. The Janda group pursues several research lines to improve our understanding of OS biology and identify new treatment strategies:

- We characterize the tumor (immune) microenvironment of primary tumors and metastases by single-cell RNA sequencing, forming the basis for dissecting tumor heterogeneity, OS evolution and identifying new targets for antibody and cell-based therapies.
- We establish patient-derived OS tumoroids for mechanistic studies and developing targeted therapy.
- We collaborate with various investigators at our center to comprehensively characterize the genomic profiles of primary tumors and metastases to identify characteristic signatures and correlate to drug sensitivities of patient-matched tumoroids.

The Janda group further runs the in-house Protein Facility. We aim to facilitate researchers at our center to incorporate protein/antibody-related work in their research lines. Projects include, but are not limited to:

- We collaborate with the Cell Therapy Facility to develop CAR-T cell therapies.
- We collaborate with the Theranostics Facility to develop radiotracers for PET imaging and theranostic PET.
- We collaborate with the Clevers lab to develop mimetics of growth factors and extracellular matrix proteins to enhance organoid growth.
- We collaborate with the Van Leeuwen lab to prepare recombinant methioninase to investigate its therapeutic efficacy in ALL mouse models.
- We collaborate with the Pieters lab to interrogate the underlying basis of variable immunogenicity of pegylated asparaginase.

Besides, we study the effect of pediatric cancer treatments, particularly dexamethasone, on bone growth and the development of osteonecrosis and osteoporosis using mouse models and primary human samples from childhood cancer survivors.

Total no. of Máxima-affiliated publications (2021)	**1**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- Sonnen KF, Janda CY. (2021) Signalling dynamics in embryonic development. Biochem J. PMID: 34871368.
- Fowler TW, Mitchell TL, Janda CY, Xie L, Tu S, Chen H, Zhang H, Ye J, Ouyang B, Yuan TZ, Lee SJ, Newman M, Tripuraneni N, Rego ES, Mutha D, Dilip A, Vuppalapaty M, Baribault H, Yeh WC, Li Y. (2021) Development of selective biospecific Wnt mimetics for bone loss and repair. Nat Commun. PMID: 34059688.

Grants

Stichting Kinderen Kankervrij
KiKa 384
Toxicity of methotrexate and dexamethasone on developing bone
€119.882

Stichting Kinderen Kankervrij
KiKa 392
Identification and evaluation of markers for immunoPET radiotracers for rhabdomyosarcoma imaging
€125.000

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group dr. Henrike Karim-Kos

Started at November 2021

Members of the Karim-Kos Group

Principal Investigator
Henrike Karim-Kos

PhD student
Raoull Hoogendijk

Postdoc
Maya Schulpen

Our research focuses on analyzing childhood cancer statistics. Looking at these statistics, we aim to expand our knowledge about the incidence of childhood cancer, its spread in the population, possible causes and prognosis. Together, these are known as cancer surveillance. Secondly, we focus on unraveling the causes behind differences in outcomes between children and young adults diagnosed with the same cancer type.

Childhood cancer surveillance
In our cancer surveillance research we mostly use standard surveillance measures: incidence, stage at diagnosis, survival and mortality. These measures are comparable on an international level and are available for the Netherlands since the 1990s. In pediatric oncology, the largest intervention in the Netherlands has been concentration of care in one single center with the ambition to improve the outcome of childhood cancer. It is important to investigate the effect of this centralization on quality of care and 'cure' in the future. Information on the prior situation is fundamental. Therefore, one of the main goals of our research group is to evaluate pediatric cancer care both in the past and the future.

Outcome disparities between children and young adults with cancer
For several cancer types, adolescents and young adults (AYAs, 18-39 years) have a worse prognosis compared to pediatric patients (0-17 years). The exact reasons for the inferior outcomes of AYAs with cancer are, however, still not clear. Notably, in the context of the Netherlands, possible causes have hardly been studied at all. The focus of our research group is to determine factors contributing to the outcome disparities between AYAs and children diagnosed with cancer.

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**5**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Schulpen M, Visser O, Reedijk AMJ, Kremer LCM, Zwaan CM, Eggermont AMM, Coebergh JW, Pieters R, Karim-Kos HE. (2021) Significant improvement in survival of advanced stage childhood and adolescent cancer in the Netherlands since the 1990s. Eur J Cancer. PMID:34492587.

- Schulpen M, Goemans BF, Kaspers GJL, Raaijmakers MHGP, Zwaan CM, Karim-Kos HE. (2021) Increased survival disparities among children and adolescents & young adults with acute myeloid leukemia: a Dutch population-based study. Int J Cancer. PMID: 34913161.

- Lebbink CA, van den Broek MFM, Kwast ABG, Derikx JPM, Dierselhuis MP, Kruijff S, Links TP, van Trotsenburg ASP, Valk GD, Vriens MR, Verrijn Stuart AA, van Santen HM, Karim-Kos HE. (2021) Opposite incidence trends for differentiated and medullary thyroid cancer in young Dutch patients over a 30-year time span. Cancers. PMID: 34680253.

Research group dr. Patrick Kemmeren

Started in January 2016

Members of the Kemmeren Group

Principal Investigator
Patrick Kemmeren

Co-Principal Investigator
Jayne Hehir-Kwa

Senior postdoc
Hinri Kerstens

Postdoc
Josephine Daub

PhD student
Ianthe van Belzen

Bioinformatician
Shashi Badloe
Alex Janse
John Baker-Hernandez
Richard Gremmen
Sam de Vos

Data steward research
Jet Zoon

Research Technician
Kim Verhagen

The Kemmeren group is a computational biology group that uses a combination of bioinformatics and systems biology to understand pediatric cancer. We have developed a unique combination of expertise in bioinformatics, gene expression profiling and molecular-genetic interactions. Since joining the Princess Máxima Center, the group has developed several research lines including driving bioinformatics research for precision oncology and diagnostics, investigating mechanisms of genetic interactions in pediatric cancer and improving structural variation detection in pediatric cancer.

Through collaborations with St. Jude and DKFZ, we have been able to generate a map of genetic interactions within pediatric cancer, providing the most comprehensive map completed so far. Follow-up experiments and analyses investigating potential underlying mechanisms have been initiated in collaboration with other research groups. Integration of WGS and RNA-seq data show that we can provide systematic genomic support for clinically relevant gene-fusion events and rescue detection of lowly expressed gene-fusions.

Within the Princess Máxima Center, we host the Big Data Core facility and coordinate several institute-wide activities centered around the use of big data for research and diagnostic purposes. These include the bioinformatics expertise core, translational bioinformatics, biobank bioinformatics, research data integration platform and data stewardship coordination. In collaboration with the diagnostic lab, we have developed and implemented a WES and RNA-seq based precision oncology platform that is now operating as standard-of-care, resulting in direct patient benefit. As part of the Máxima biobank and genome program (WGS, RNA-seq, DNA methylation), we develop and provide bioinformatics analyses for pediatric cancer genomes as a crucial resource for pediatric cancer research.

Through our involvement in both basic research projects as well as in translational projects, we are committed to improving our understanding of pediatric cancer biology, while at the same time also directly benefiting patient care by implementing computational analyses in routine diagnostics.

Total no. of Máxima-affiliated publications (2021)	**2**
No. of Máxima-affiliated open access publications (2021)	**2**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- van Belzen IAEM, Schönhuth A, Kemmeren P, Hehir-Kwa JY. (2021) Structural variant detection in cancer genomes: computational challenges and perspectives for precision oncology. NPJ Precis Oncol. PMID:33654267.

- Daub JT, Amini S, Kersjes DJE, Ma X, Jäger N, Zhang J, Pfister SM, Holstege FCP, Kemmeren P. (2021) A systematic analysis of genetic interactions and their underlying biology in childhood cancer. Commun Biol. PMID:34615983.

Grants

Adessium Foundation
Biobank 2.0: International collaboration in the cloud
€600.000

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group dr. Marcel Kool

Started in September 2019

Members of the Kool Group

Principal Investigator
Marcel Kool

PhD student
Zelda Odé
Mieke Roosen

Research Technician
Joris Maas
Phylicia Stathi

Senior researcher
Jens Bunt

Our research group studies the genomics and epigenomics of pediatric brain tumors and how to translate findings from these studies into novel therapies. More effective and less toxic therapies are urgently needed. For many types of childhood brain tumors, the survival is still very poor, and survivors suffer from serious long-term side effects caused by their intensive therapies. To develop new therapies, we need better understanding of tumor development and biology as well as molecularly well-characterized preclinical models that represent the broad intra and inter-tumor heterogeneity.

We work in close collaboration with the other research group that Marcel Kool leads at the Hopp Children's Cancer Center (KiTZ) in Heidelberg, Germany. Both groups are part of these same research program and focus on different aspects of ependymomas and embryonal brain tumors, including medulloblastomas, ATRTs, embryonal tumors with multilayered rosettes (ETMR), and some other more rare embryonal tumor types. Combining the complementary expertise, data and other knowledge from both groups and both centers helps to accelerate our research.

Our group in Heidelberg works on the genomic and epigenomic analyses of primary tumors and how to translate (epi)genomic findings to the clinic using patient-derived xenograft (PDX) mouse models. Our group in Utrecht is modeling these tumors in vitro using organoid technology to better understand tumor development and behavior and to perform preclinical experiments. Pediatric brain tumors originate during brain development, which can be recapitulated in vitro using stem cell derived human brain organoids. To mimic tumor initiating mutations in these organoids, DNA plasmids are introduced via electroporation into the cells to knockout tumor suppressor genes or overexpress oncogenes or combinations thereof that drive tumor formation. In addition, we also grow tumor-derived organoids from PDX and primary tumors to expand the number of in vitro preclinical models for drug testing.

Total no. of Máxima-affiliated publications (2021)	**34**
No. of Máxima-affiliated open access publications (2021)	**27**
Total no. of external publications (2021)	**9**

Top 3 of Máxima-affiliated publications (2021)

- von Hoff K, Haberler C, Schmitt-Hoffner F, Schepke E, de Rojas T, Jacobs S, Zapotocky M, Sumerauer D, Perek-Polnik M, Dufour C, van Vuurden D, Slavc I, Gojo J, Pickles JC, Gerber NU, Massimino M, Gil-da-Costa MJ, Garami M, Kumirova E, Sehested A, Scheie D, Cruz O, Moreno L, Cho J, Zeller B, Bovenschen N, Grotzer M, Alderete D, Snuderl M, Zheludkova O, Golanov A, Okonechnikov K, Mynarek M, Juhnke BO, Rutkowski S, Schüller U, Pizer B, von Zezschwitz B, Kwiecien R, Wechsung M, Konietschke F, Hwang EI, Sturm D, Pfister SM, von Deimling A, Rushing EJ, Ryzhova M, Hauser P, Łastowska M, Wesseling P, Giangaspero F, Hawkins C, Figarella-Branger D, Eberhart C, Burger P, Gessi M, Korshunov A, Jacques TS, Capper D, Pietsch T, Kool M. (2021) Therapeutic implications of improved molecular diagnostics for rare CNS embryonal tumor entities: results of an international, retrospective study. Neuro-Oncology. PMID: 34077956.

- Schmitt-Hoffner F, van Rijn S, Toprak UH, Mauermann M, Rosemann F, Heit-Mondrzyk A, Hübner JM, Camgöz A, Hartlieb S, Pfister SM, Henrich KO, Westermann F, Kool M. (2021) FOXR2 Stabilizes MYCN Protein and Identifies Non-MYCN-Amplified Neuroblastoma Patients With Unfavorable Outcome. Journal of Clinical Oncology. PMID: 34110923.

- Korshunov A, Okonechnikov K, Stichel D, Ryzhova M, Schrimpf D, Sahm F, Sievers P, Absalyamova O, Zheludkova O, Golanov A, Jones DTW, Pfister SM, von Deimling A, Kool M. (2021) Integrated molecular analysis of adult sonic hedgehog (SHH)-activated medulloblastomas reveals two clinically relevant tumor subsets with VEGFA as potent prognostic indicator. Neuro-Oncology. PMID: 33589929.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Anke Heit-Mondrzyk, July 2021, German Cancer Research Center (DKFZ), Identification of two novel isoforms of putative ependymoma driving genes by alternative splicing analyses. Promotor: prof. dr. Benedikt Brors. Co-promotores: dr. M. Kool, prof. dr. S.M. Pfister, prof. dr. M. Frye, prof. dr. S. Wölfl.

Grants

Stichting Kinderen Kankervrij
KiKa 410
Genetically Modified Cerebellar Organoids as Models for Sonic Hedgehog Medulloblastoma
€504.893

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group prof. dr. Leontien Kremer

Started in February 2017

Grants

ZonMW
Innovaties voor de LATER richtlijn follow-up kinderkanker: ontwikkeling en implementatie
ZonMW 80-93900-98-952
€317.362

ODAS
Risk of late pulmonary dysfunction in Dutch survivors of childhood cancer – a population based study (Versluys, A.B.)
ODAS 2018-1
€87.000

Netherlands Comprehensive Cancer Organisation (IKNL)
Revisie richtlijn 'Palliatieve zorg voor kinderen'
Palliatieve zorg IKNL
Projectnummer: P0642
€59.556

Survivorship LATER research
The Kremer group focuses on quantification of the role of cancer treatment and other risk factors on long-term health and quality of life, as these are impacted even many years after treatment.
The LATER research is unique in the world. Research topics that the Kremer group addresses are late mortality, burden of disease, subsequent tumors, cardiovascular toxicity, fertility, lifestyle, aging, frailty, fatigue, psychosocial health, radiation epidemiology, healthcare burden and evaluation of care. In the Dutch Childhood Cancer Survivor Studies (DCCSS1&2), 12,000 5-year childhood cancer survivors treated between 1963 and 2014 were identified. Over 6,000 survivors participated in the DCCSS1: data was collected on cancer diagnosis, treatment, lifestyle, psychosocial functioning and health outcomes via questionnaires and linkages to health registries. In the DCCSS2, 2,400 survivors visited the LATER outpatient clinic for additional data collection.

Internationally, we participated as a partner in the European PanCareSurFup and PanCareLIFE projects. Leontien Kremer leads the PanCareFollowUp study to improve people-centered care for childhood cancer survivors and will participate in the new PanCareSurPass project on the implementation of the digital Survivorship Passport. The Kremer Group also collaborates with St. Jude and the Childhood Cancer Survivor Study, United States.

Systematic reviews, guidelines and outcomes of care
Systematic reviews give a transparent insight into available scientific evidence, provide a starting point for new clinical research and form the basis for clinical practice guidelines, which are essential for the translation of evidence into daily practice. Based in the Máxima Center, the editorial team of Cochrane Childhood Cancer is responsible for the support, editorial process and publication of systematic reviews on childhood cancer in the Cochrane Library (IF 9.289).
The Kremer group furthermore provides evidence-based methodology for developing guidelines within pediatric oncology. We have a leading role within the International Guideline Harmonization Group. Moreover, the Kremer group is developing outcome indicators to measure the quality of care.

Total no. of Máxima-affiliated publications (2021)	**61**
No. of Máxima-affiliated open access publications (2021)	**28**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, Quinn GP, van Dulmen-den Broeder E, Byrne J, Haupt R, Wallace WH, van den Heuvel-Eibrink MM, Anazodo A, Anderson RA, Barnbrock A, Beck JD, Bos AME, Demeestere I, Denzer C, Di Iorgi N, Hoefgen HR, Kebudi R, Lambalk C, Langer T, Meacham LR, Rodriguez-Wallberg K, Stern C, Stutz-Grunder E, van Dorp W, Veening M, Veldkamp S, van der Meulen E, Constine LS, Kenney LB, van de Wetering MD, Kremer LCM†, Levine J†, Tissing WJE†; PanCareLIFE Consortium. (2021). Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. PMID: 33539753.

- Van Kalsbeek RJ, van der Pal HJH, Kremer LCM, Bardi E, Brown MC, Effeney R, Winther JF, Follin C, den Hartogh J, Haupt R, Hjorth L, Kepak T, Kepakova K, Levitt G, Loonen JJ, Mangelschots M, Muraca M, Renard M, Sabic H, Schneider CU, Uyttebroeck A, Skinner R, Mulder RL. (2021) European PanCareFollowUp Recommendations for surveillance of late effects of childhood, adolescent, and young adult cancer. Eur J Cancer. PMID: 34333209.

- Bowers DC, Verbruggen LC, Kremer LCM, Hudson MM, Skinner R, Constine LS, Sabin ND, Bhangoo R, Haupt R, Hawkins MM, Jenkinson H, Khan RB, Klimo P Jr, Pretorius P, Ng A, Reulen RC, Ronckers CM, Sadighi Z, Scheinemann K, Schouten-van Meeteren N, Sugden E, Teepen JC, Ullrich NJ, Walter A, Wallace WH, Oeffinger KC, Armstrong GT, van der Pal HJH, Mulder RL. (2021) Surveillance for subsequent neoplasms of the CNS for childhood, adolescent, and young adult cancer survivors: a systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. PMID: 33845037.

Members of the Kremer Group

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Inge Niehoff
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Judith de Bont
Dorine Bresters
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Erna Michiels
Heleen van der Pal
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Research group dr. Roland Kuiper

Started in November 2016

Members of the Kuiper Group

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Cédric van der Ham
Sophie Peer

Postdoc
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Research Technician
Reno Bladergroen

Bioinformatician
Stefan Lelieveld
Freerk van Dijk

In approximately 7-10% of the children with cancer, hereditary factors have played an important role. Still, many genetic causes for childhood cancer predisposition are unknown or incompletely understood. Recognition of childhood cancer predisposition syndromes (CPS) is of high clinical significance, as it may require modifications in treatment, cancer surveillance for early detection of second primary malignancies, and information of cancer risks and cancer surveillance for family members. Our group studies the genetics of childhood cancer from a molecular (Kuiper, PI) to a clinical (Jongmans, co-PI) perspective.

We investigate individual cases with high suspicion for a CPS based on e.g. the type of cancer, additional phenotypic characteristics, multiple primary tumors or affected family members. These studies may initiate research on novel CPS genes, but may also lead to the discovery of aberrations in known genes that have escaped detection in routine analysis. An example is a recently discovered germline retrotransposon insertion in SMARCB1 in two siblings with atypical teratoid rhabdoid tumors that was undetectable with short-read sequencing and standard copy number analysis.

We have developed and implemented analysis pipelines to detect germline mutations in ~140 childhood cancer predisposition genes (pediatric-cancer-predisposition-genepanel.nl) followed by comprehensive genotype-phenotype analyses. We completed a study in a national cohort of 126 Wilms tumor patients (WES-KidTS study, collaboration with PI Van den Heuvel-Eibrink), which revealed an underlying (epi)genetic predisposing factor in 33% of cases. Currently, we focus on the identification of tumor characteristics that hallmark CPS, including mutational, epigenetic and expression-based signatures. These studies will reveal important clues of childhood cancer development in the context of germline CPS gene mutations and may help to further improve CPS diagnosis.

We have initiated studies aimed to improve care for children with CPSs. We have played a leading role in developing European Wilms tumor surveillance protocols and, in collaboration with Prof. J. de Vries, RadboudUMC, we explore the possibility of developing dendritic cell vaccines to prevent cancer in children with Constitutional Mismatch Repair Deficiency.

Total no. of Máxima-affiliated publications (2021)	**19**
No. of Máxima-affiliated open access publications (2021)	**18**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- Kuiper RP, Hoogeveen PG, Bladergroen R, van Dijk F, Sonneveld E, van Leeuwen FN, Boer J, Sergeeva I, Feitsma H, den Boer ML, van der Velden VHJ. (2021) Minimal residual disease (MRD) detection in acute lymphoblastic leukaemia based on fusion genes and genomic deletions: towards MRD for all. Br J Haematol. PMID:34337744.

- Sabatella M, Mantere T, Waanders E, Neveling K, Mensenkamp AR, van Dijk F, Hehir-Kwa JY, Derks R, Kwint M, O'Gorman L, Tropa Martins M, Gidding CE, Lequin MH, Küsters B, Wesseling P, Nelen M, Biegel JA, Hoischen A, Jongmans MC, Kuiper RP. (2021) Optical genome mapping identifies a germline retrotransposon insertion in SMARCB1 in two siblings with atypical teratoid rhabdoid tumors. J Pathol. PMID:34231212.

- Hol JA, Jewell R, Chowdhury T, Duncan C, Nakata K, Oue T, Gauthier-Villars M, Littooij AS, Kaneko Y, Graf N, Bourdeaut F, van den Heuvel-Eibrink MM, Pritchard-Jones K, Maher ER, Kratz CP, Jongmans MCJ. (2021) Wilms tumour surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group. Eur J Cancer. PMID:34134020.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**2**

Máxima/External PhD defenses

Illja Diets, September 2021, Radboud University, Genetic Childhood cancer predisposition: Towards better detection and understanding. Promotor: prof. dr. N. Hoogerbrugge. Co-Promotores: dr. M.C. Jongmans, dr. R.P. Kuiper.

Judith Grolleman, November 2021, Radboud University, Identifying and characterizing hereditary polyposis and colorectal cancer. Promotores: prof. dr. N. Hoogerbrugge, prof. dr. M.J.L. Ligtenberg. Co-Promotores: dr. R.M. de Voer, dr. R.P. Kuiper.

Grants

Stichting Kinderen Kankervrij
KiKa 403
REFLECT: Reactions and Emotions of Families Linked to Exome sequencing in Childhood Cancer
Together with Martha Grootenhuis and Marry van den Heuvel-Eibrink
€375.355

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group dr. Frank van Leeuwen

Started in May 2018

Members of the van Leeuwen Group

Principal Investigator
Frank van Leeuwen

Senior Postdoc
Laurens van der Meer

Postdoc
Shuiyan Wu

PhD student
Willem Cox
Gawin Stoll
Trisha Tee
Britt Vervoort
Miriam Butler

Research Technician / Lab manager
Dorette van Ingen-Schenau

Research Technician
Lieneke Jongeneel

Operator Flow Cytometry and Cell Sorting facility
Tomasz Poplonski

Acute lymphoblastic leukemia is the most common cancer in children. Although cure rates are approaching 90%, therapy resistance and associated relapses remain a significant clinical problem. In addition, many leukemia survivors suffer from long term side effects due to the genotoxic agents used to treat ALL. Therefore, our efforts are aimed at developing more effective and less toxic therapies for ALL. We focus on so called 'high risk' ALL subtypes, as these are more likely to become unresponsive to treatment.

Our group combines in vitro with in vivo experimental approaches using CRISPR/Cas9 to model high-risk genomic abnormalities and study the cell biological consequences of these genetic perturbations on leukemia growth and drug responsiveness both in vitro and in mouse models. For this purpose, we use ALL cell line models, primary leukemic cells and patient-derived xenografts. In addition, we combine CRISPR/Cas9-based reverse genetic screens with drug synergy screens to study mechanisms of acquired drug resistance, and to identify signaling intermediates that can be selectively targeted to overcome therapy resistance. Our attention is primarily directed at improving therapies targeting leukemia metabolism (glucocorticoids, asparaginase, antimetabolites) as well as identifying novel metabolic interventions.

Specific projects:

- Improving therapy response by targeting methionine metabolism in MLL-rearranged leukemia
- Improving asparaginase therapy by targeting the amino acid response pathway
- Defining metabolic vulnerabilities in TP53 deleted ALL
- Improving antimetabolite therapies in IKZF1 deleted leukemia

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**5**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Butler M, van der Meer LT, van Leeuwen FN. (2021) Amino Acid Depletion Therapies: Starving Cancer Cells to Death. Trends Endocrinol Metab. PMID: 33795176.
- Butler M, van Ingen Schenau DS, Yu J, Jenni S, Dobay MP, Hagelaar R, Vervoort BMT, Tee TM, Hoff FW, Meijerink JP, Kornblau SM, Bornhauser B, Bourquin JP, Kuiper RP, van der Meer LT, van Leeuwen FN. (2021) BTK inhibition sensitizes acute lymphoblastic leukemia to asparaginase by suppressing the amino acid response pathway. Blood. PMID: 34280258.
- Antić Ž, Yu J, Van Reijmersdal SV, Van Dijk A, Dekker L, Segerink WH, Sonneveld E, Fiocco M, Pieters R, Hoogerbrugge PM, Van Leeuwen FN, Van Kessel AG, Waanders E, Kuiper RP. (2021) Multiclonal complexity of pediatric acute lymphoblastic leukemia and the prognostic relevance of subclonal mutations. Haematologica. PMID: 33147938.

Grants

Prinses Máxima Centrum Foundation
Genetically engineered PDX models of acute leukemia
€10.000

Research group prof. dr. Leendert Looijenga

Started in October 2018

Members of the Looijenga Group

Principal Investigator
Leendert Looijenga

Research technician
Ad Gillis

Postdoc
Thomas Eleveld

PhD student
Sruthi Sriram
Dennis Timmerman
Caroline Husker
Joaquin Montilla Rojo

Our research focusses on germ cells, both in the context of (preservation of) fertility as well as derailed development leading to neoplasms. These so-called germ cell tumors (GCTs) can be either benign or malignant, which requires personalized treatment of every patient from the moment of the process of primary diagnosis through to (long term) follow-up.

Fertility preservation is a relevant topic because of the survival of the majority of patients with the current treatment protocols, although it might negatively affect natural germ cell maturation. Therefore, an integrated protocol for prepubertal boys has been developed to store testicular tissue for future auto-transplantation and to perform experimental investigations for possible in vitro spermatogonial stem cell propagation.

In collaboration with the UMCU, an NFU-Center of Expertise for testicular and mediastinal GCTs has been established and approved for 5 years by the Ministry of Health, Welfare and Sport. Within this collaboration, expertise will be shared within the Netherlands and Europe regarding clinical and science of this rare type of cancer.

Optimal diagnosis and follow-up of patients with GCTs is a prerequisite to prevent both under and overtreatment of the individual patients. Therefore, a dual-target liquid biopsy profile is under development, including a specific microRNA (miR371a-3p) and a hypermethylated fragment of RASSF1A. The results are highly promising, with a high sensitivity and specificity.

Novel insights have been generated regarding the underlying mechanism of intrinsic malignant potential as well as (linked) treatment resistance of GCTs, predominantly related to anatomical localization (testicular versus mediastinal) and involvement of the P53 pathway. This offers further experimental approaches to investigate possible ways of interference, resulting in more effective treatment options, with fewer (long term) side effects, resulting in a better chance of the individual patient to be cured with an optimal quality of life.

Total no. of Máxima-affiliated publications (2021)	**18**
No. of Máxima-affiliated open access publications (2021)	**14**
Total no. of external publications (2021)	**10**

Top 3 of Máxima-affiliated publications (2021)

- Lobo J, Leão R, Gillis AJM, van den Berg A, Anson-Cartwright L, Atenafu EG, Kuhathaas K, Chung P, Hansen A, Bedard PL, Jewett MAS, Warde P, O'Malley M, Sweet J, Looijenga LHJ, Hamilton RJ. (2021) Utility of Serum miR-371a-3p in Predicting Relapse on Surveillance in Patients with Clinical Stage I Testicular Germ Cell Cancer. Eur Urol Oncol.; 4: 483-491.

- Lobo J, Van Zogchel LMJ, Nuru MG, Gillis AJM. Van der Schoot CE, Tytgat GAM, Looijenga LHJ. (2021) Combining hypermethylated RASSF1A detection using ddPCR with miR-371a-3p testing: an improved panel of liquid biopsy biomarkers for testicular germ cell tumor patients. Cancers; 13(20): 5228.

- Timmerman DM, Eleveld TF, Gillis AJM, Friedrichs CC, Hillenius S, Remmers TL, Sriram S, Looijenga LHJ. (2021) The Role of TP53 in Cisplatin Resistance in Mediastinal and Testicular Germ Cell Tumors. Int J Mol Sci. 29;22(21):11774. doi: 10.3390/ijms222111774.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Suzuki Lucia, September 2021, Erasmus MC, To BE or not to BE. Promotores: Prof. dr. L.H.J. Looijenga, Prof. dr. F. van Kemenade. Co-promotor: Dr. K. Biermann.

Grants

European Commission
diaRNAgnosis: A novel platform for the direct profiling of circulating cell-free ribonucleic acids in biofluids.
H2020-MSRA-RISE-2020
€124.200

Patents/licenses

1

Research group dr. Jules Meijerink

Started in September 2016

Our group investigates intrinsic and extrinsic pathogenic mechanisms that underlie T-cell malignancies in children. In this research line, our focus is on T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL), that both represent diseases of disrupted thymocyte development.

The generated knowledge aims to develop novel therapeutic strategies for these diseases specifically, but is focused on broader applicability of findings towards other diseases in children and adults. Our research is focused on:

- Deciphering pathogenic mechanisms and targeted therapy
- Mechanisms of IL7 signal transduction mutations and steroid resistance
- Stromal safe haven niches in therapy resistance, disease dissemination, and relapse
- Mechanisms of oncogenic enhancer regulation.

Members of the Meijerink Group

Principal Investigator
Jules Meijerink

PhD student
Valentina Cordo
Emma Kroeze
Vera Poort
Jordy van der Zwet

Postdoc
Mariska Meijer

Research Technician
Jessica Buijs - Gladdines
Rico Hagelaar
Laurianne Trabut

Total no. of Máxima-affiliated publications (2021)	**9**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- van der Zwet JCG, Buijs-Gladdines JGCAM, Cordo' V, Debets DO, Smits WK, Chen Z, Dylus J, Zaman GJR, Altelaar M, Oshima K, Bornhauser B, Bourquin JP, Cools J, Ferrando AA, Vormoor J, Pieters R, Vormoor B, Meijerink JPP. MAPK-ERK is a central pathway in T-cell acute lymphoblastic leukemia that drives steroid resistance. Leukemia. 2021 Dec;35(12):3394-3405. doi: 10.1038/s41375-021-01291-5. Epub 2021 May 18. PMID: 34007050.

- van der Zwet JCG, Smits W, Buijs-Gladdines JGCAM, Pieters R, Meijerink JPP. Recurrent NR3C1 Aberrations at First Diagnosis Relate to Steroid Resistance in Pediatric T-Cell Acute Lymphoblastic Leukemia Patients. Hemasphere. 2020 Dec 21;5(1):e513. doi: 10.1097/HS9.0000000000000513. PMID: 33364552; PMCID: PMC7755520.

- Meijerink JPP. BCL11B, the Cerberus of human leukemia. Blood. 2021 Sep 2;138(9):741-743. doi: 10.1182/blood.2021011856. PMID: 34473234.

Grants

Stichting Kinderen Kankervrij
KiKa 393
Mutational spectrum of pediatric T-cell lymphoblastic lymphoma to identify targets for therapeutic intervention
€109.303

Research group dr. Hans Merks

Started in May 2019

Members of the Merks Group

Principal Investigator
Hans Merks

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Lianne Haveman
Reineke Schoot

PhD student
Kiki Blom
Cyrano Chatziantoniou
Marinka Hol
Michele Morfouace
Floor Postema
Leonie Tigelaar
Bas Vaarwerk

PhD student/pediatric oncologist
Rutger Knops

PhD student/ fellow pediatric oncology
Roelof van Ewijk

Professor in Radiology
Rick van Rijn

The focus of the Merks group is to answer key clinical questions in pediatric sarcoma staging, treatment, and follow up, with the aim to improve cure and quality of life. As Chair of the European pediatric Soft tissue sarcoma Study Group (EpSSG) and Vice-Chair of the Executive Board of the Euro Ewing Consortium (EEC), Merks' aim is to coordinate, design and implement international prospective clinical trials, including translational research, focused on sarcoma across the pediatric and young adult age range. Research in pediatric sarcoma is a distinctly multidisciplinary collaboration including a diversity of basic, translational and clinical research partners.

- The Pediatric Sarcoma Imaging Group aims to design and implement innovative imaging studies to identify early prognostic and predictive biomarkers in clinical trials and individual patient care, and to optimize staging. This entails a close collaboration with the PROVIDI lab of Alexander Leemans (Imaging Sciences Institute UMCU), Simone ter Horst, Bart de Keizer, and Arthur Braat (Radiology UMCU) and prof. dr. Rick van Rijn (AUMC).
- Individualized prediction of treatment-induced facial deformities and functional impairments for children with head and neck rhabdomyosarcoma (HN RMS). This international (US, Fr, UK, NL) multicenter, multidisciplinary project aims to develop a decision support model that enables well-informed shared multimodal treatment decision-making based on Adverse Event prediction for individual HN RMS patients.
- Functional outcome and quality of life after local therapy for bone sarcoma in children. This multidisciplinary project aims to describe functional outcome and quality of life in bone sarcoma survivors with the ultimate goal of generating a prediction model for local therapy related adverse effects and functional outcome, which will optimize shared decision-making.
- Recognition of cancer predisposition syndromes (CPS). The aim is to develop strategies to guarantee recognition of established CPS in childhood cancer patients and identify potential new CPS in collaboration with the Kuiper group and Raoul Hennekam.

In collaboration with national and international colleagues, dr. Hans Merks participates in consortia funded by the Hanarth Fund, Cancer Research UK and Fight Kids Cancer.

Total no. of Máxima-affiliated publications (2021)	**23**
No. of Máxima-affiliated open access publications (2021)	**8**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Vaarwerk B, Breunis WB, Haveman LM, de Keizer B, Jehanno N, Borgwardt L, van Rijn RR, van den Berg H, Cohen JF, van Dalen EC, Merks JHM. (2021) Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography (CT) for the detection of bone, lung, and lymph node metastases in rhabdomyosarcoma. Cochrane Database Syst Rev. PMID: 34753195.

- Cameron AL, Elze MC, Casanova M, Geoerger B, Gaze MN, Minard-Colin V, McHugh K, van Rijn RR, Kelsey A, Martelli H, Mandeville H, Bisogno G, Lowis S, Ronghe M, Orbach D, Guizani C, Fürst-Recktenwald S, Chisholm JC, Merks JHM. (2021) European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) and the European Innovative Therapies for Children with Cancer (ITCC) Consortium. The Impact of Radiation Therapy in Children and Adolescents With Metastatic Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. PMID: 34217789.

- van Ewijk R, Vaarwerk B, Breunis WB, Schoot RA, Ter Horst SAJ, van Rijn RR, van der Lee JH, Merks JHM. (2021) The Value of Early Tumor Size Response to Chemotherapy in Pediatric Rhabdomyosarcoma. Cancers. PMID: 33561094.

Grants

BAYER
FaR-RMS: an overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma; funding award for Princess Máxima Center for the central review of DW-MRIs in patients enrolled in the FaR-RMS study
€341.109

Research group dr. Jan Molenaar

Started in January 2016

Grants

Stichting Kinderen Kankervrij
KiKa 404
Towards TIL therapy for neuroblastoma
€124.998

Villa Joep
Immunology consortium
Joining forces to activate T-cell immunity against high risk neuroblastoma Together with Sebastiaan van Heesch and Stefan Nierkens
€1.275.000

Solving Kids' Cancer
Cobimetinib in induction treatment
€31.559

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Science awards

VENI
NWO/ZonMw
Judith Wienke

The Molenaar group is specialized in translational research in pediatric solid tumors with a focus on neuroblastoma. As nine out of ten clinical trials fail, there is a strong need for the development of new targeted interventions that are less toxic and more effective. The Molenaar group aims to identify and validate specific interventions for neuroblastoma and other solid tumors and generate a platform to perform evidence based, targeted compound, combination trials in biomarker positive patients.

For this purpose, the team has developed an experimental pipeline which starts with basic molecular biology research and ends with implementation of new treatment options for pediatric cancer patients. Crucial in this pipeline is the use of high throughput analysis including WES, WGS, RNAseq, scRNAseq and compound screening. The group is studying ATRX, aberrations in the G1 checkpoint including CDKN2A and CDK4/6, The RAS-MAPK pathway, BCL2, MCL1, MDM2, EXH2 and CHK1 as potential interventions. Known targeted compounds are evaluated, but we also develop new compounds using PROTAC technology. In addition, we have started to identify new interventions in the field of immunology, by various advanced techniques including co-culture systems, single cell RNAseq analysis to study the tumor microenvironment, multicolor FACS. Molenaar and his team have established a fully automated compound screening facility in the Princess Máxima Center. Research groups within and outside the Princess Máxima Center are using this facility to identify and validate novel tumor specific biomarker-drug response associations. Finally, to support implementation of targeted therapeutic options, our group has initiated the iTHER precision medicine program for pediatric cancer, which has included over 300 patients and is currently implemented in the standard diagnostic procedures.

With a close (international) collaboration between pediatric oncologists, surgeons, pathologists, researchers, patients and parents, the Molenaar group strives to make a difference for neuroblastoma patients and use this as a blueprint for other pediatric cancer types.

Total no. of Máxima-affiliated publications (2021)	**17**
No. of Máxima-affiliated open access publications (2021)	**14**
Total no. of external publications (2021)	**9**

Top 3 of Máxima-affiliated publications (2021)

- Kildisiute G, Kholosy WM, Young MD, Roberts K, Elmentaite R, van Hooff SR, Pacyna CN, Khabirova E, Piapi A, Thevanesan C, Bugallo-Blanco E, Burke C, Mamanova L, Keller KM, Langenberg-Ververgaert KPS, Lijnzaad P, Margaritis T, Holstege FCP, Tas ML, Wijnen MHWA, van Noesel MM, Del Valle I, Barone G, van der Linden R, Duncan C, Anderson J, Achermann JC, Haniffa M, Teichmann SA, Rampling D, Sebire NJ, He X, de Krijger RR, Barker RA, Meyer KB, Bayraktar O, Straathof K, Molenaar JJ, Behjati S. (2021) Tumor to normal single-cell mRNA comparisons reveal a pan-neuroblastoma cancer cell. Sci Adv. PMID: 33547074.

- van den Boogaard ML, Oka R, Hakkert A, Schild L, Ebus ME, van Gerven MR, Zwijnenburg DA, Molenaar P, Hoyng LL, Dolman MEM, Essing AHW, Koopmans B, Helleday T, Drost J, van Boxtel R, Versteeg R, Koster J, Molenaar JJ. (2021) Defects in 8-oxo-guanine repair pathway cause high frequency of C > A substitutions in neuroblastoma. Proc Natl Acad Sci U S A. PMID: 34479993.

- van Tilburg CM, Pfaff E, Pajtler KW, Langenberg KPS, Fiesel P, Jones BC, Balasubramanian GP, Stark S, Johann PD, Blattner-Johnson M, Schramm K, Dikow N, Hirsch S, Sutter C, Grund K, von Stackelberg A, Kulozik AE, Lissat A, Borkhardt A, Meisel R, Reinhardt D, Klusmann JH, Fleischhack G, Tippelt S, von Schweinitz D, Schmid I, Kramm CM, von Bueren AO, Calaminus G, Vorwerk P, Graf N, Westermann F, Fischer M, Eggert A, Burkhardt B, Wößmann W, Nathrath M, Hecker-Nolting S, Frühwald MC, Schneider DT, Brecht IB, Ketteler P, Fulda S, Koscielniak E, Meister MT, Scheer M, Hettmer S, Schwab M, Tremmel R, Øra I, Hutter C, Gerber NU, Lohi O, Kazanowska B, Kattamis A, Filippidou M, Goemans B, Zwaan CM, Milde T, Jäger N, Wolf S, Reuss D, Sahm F, von Deimling A, Dirksen U, Freitag A, Witt R, Lichter P, Kopp-Schneider A, Jones DTW, Molenaar JJ, Capper D, Pfister SM, Witt O. (2021) The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets. Cancer Discov. PMID: 34373263.

Members of the Molenaar Group

Principal Investigator
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Celina Szanto
Selma Eising
Judith Wienke

Bioinformatician
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Junior researcher
Nora Loze

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Linda Schild
Bianca Koopmans
Femke van den Ham
Kimberley Ober
Vicky Amo-Addae

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Research group dr. Marita Partanen

Started in September 2019

Members of the Partanen Group

Principal Investigator
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PhD student
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Marisa Huisman
Anne Leenders

Research assistant
Mandy Jansen

Data scientist
Bruno de Brito Robalo

Children with cancer may develop neuropsychological impairments after treatment, such as changes in cognition, academics, or social-emotional functioning. Our group focuses on the early identification and early intervention of these impairments using a combination of neuropsychological, therapeutic, and neuroimaging measures. The overall goal is to help prevent further difficulties and improve quality of life for patients and survivors of brain tumors, solid tumors, or hematological malignancies.

- **Neuropsychological monitoring**
  For some children, neuropsychological deficits are shown shortly after diagnosis which could be due to the disease, treatments, or fatigue. Comprehensive neuropsychological testing is not feasible or necessary to conduct with all patients, and thus, brief measures that are sensitive to impairments are needed. One goal of our research is to identify brief screening measures that can be used to monitor functioning across patient groups.

- **Risk and protective factors**
  Another goal is to identify risk and protective factors that are associated with neuropsychological outcome. For example, risk factors may include psychosocial well-being, sleep, anesthesia exposure, or treatment-related complications. Our goal is to identify these factors to help guide assessment and interventions for children who are at risk.

- **Pathophysiology of neuropsychological outcome**
  The pathophysiology of brain damage that leads to neuropsychological impairment is poorly understood. In our group, we use brain magnetic resonance imaging (MRI) as potential biological markers of neuropsychological outcome. Our goal is to investigate whether the extent of changes in brain function or structure precede or worsen neuropsychological deficits, which could then be used as a predictive tool.

- **Early interventions for high-risk groups**
  Some groups are at high risk of developing neuropsychological impairments, e.g. received cranial radiation. Despite this knowledge, there are few evidence-based interventions to prevent or rehabilitate neuropsychological deficits. One of our aims is to develop early intervention strategies for these high-risk groups.

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**1**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Partanen M, Anghelescu DL, Hall L, Schreiber JE, Rossi M, Gajjar A, Jacola LM (2021). Longitudinal associations between exposure to anesthesia and neurocognitive functioning in pediatric medulloblastoma. European Journal of Cancer, 148, 103-111. PMID: 33743477.

- Partanen M, Alberts NM, Conklin HM, Krull KR, Pui CH, Anghelescu DA, Jacola LM (2021). Neuropathic pain and neurocognitive functioning in children treated for acute lymphoblastic leukemia. PAIN, in press. PMID: 34813516.

- Partanen M, Phipps S, Russell K, Anghelescu DL, Wolf J, Conklin HM, Krull KR, Inaba H, Pui CH, Jacola LM (2021). Longitudinal trajectories of neurocognitive functioning in childhood survivors of acute lymphoblastic leukemia. Journal of Pediatric Psychology, 46, 168-178. PMID: 33011782.

Research group dr. Stefan Nierkens

Started in September 2018

Members of the Nierkens Group

Principal Investigator
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PhD student
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Linde Dekker
Joyce Meesters-Ensing
Vania Lo Presti

Clinical Fellow
Alexandre Troullioud Lucas
Alice van Velzen

Research technician
Noël Dautzenberg
Ester Dunnebach

We study strategies to enhance immunity against pediatric cancers. We specifically focus on the function of immune cells over time in children undergoing hematopoietic cell transplantation (HCT) or receiving immunotherapy, such as CAR T-cells.

On HCT: Many complications after HCT are a direct consequence of immune recovery and immune (dys)regulation. Our research provides strategies to increase the efficacy and safety of HCT by optimizing immune recovery and limit immune dysregulation in the reconstituting immune repertoire post-HCT. Our current research programs focus on:

- Defining markers predicting post-HCT immune recovery and function, and clinical outcome using an in-depth immune monitoring program.
- The pathophysiology of graft-versus-host disease using human intestinal organoid coculture models.
- Pharmacokinetic and pharmacodynamic modeling of drugs used in the conditioning and treatment regimen (current focus on steroids, clofarabine) to find optimal exposure levels in each patient to erase residual disease with limited toxicity (collaboration with A. Huitema).

On cell therapy: We study the functional dynamics of cell therapy products in patients and the association with clinical efficacy. In addition, we innovate cell therapy options for cells expressing chimeric antigen receptors (CAR), engineered T cell receptors (TCR), and generated a GMP protocol for the production of dendritic cells as a vaccine against AML. Our current research programs focus on:

- The U-DANCE trial, studying the safety of our dendritic cell vaccine post-HCT in AML patients will start recruiting in 2022.
- Defining parameters influencing the expansion and function of CAR-T cells ex vivo, including fludarabine exposure levels, and dynamic interactions between CAR-T cells, leukemic blasts and MSCs (collaboration with Monique den Boer and Anne Rios).
- Gene modification, using lentiviral vector transduction, in combination with Crispr-Cas technology, to engineer graft-derived T and NK(T) cells (TCR or CAR-T) for optimal efficacy and low toxicity, with particular focus on use in hematological malignancies, neuroblastoma and brain tumors.

Total no. of Máxima-affiliated publications (2021)	**24**
No. of Máxima-affiliated open access publications (2021)	**11**
Total no. of external publications (2021)	**10**

Top 3 of Máxima-affiliated publications (2021)

- de Koning C, Prockop S, van Roessel I, Kernan N, Klein E, Langenhorst J, Szanto C, Belderbos M, Bierings M, Boulad F, Bresters D, Cancio M, Curran K, Kollen W, O'Reilly R, Scaradavou A, Spitzer B, Versluijs B, Huitema A, Lindemans C, Nierkens S*, Boelens JJ*. (2021) CD4+ T-cell reconstitution predicts survival outcomes after acute graft-versus-host-disease: a dual-center validation. Blood. ;137(6):848-855. doi: 10.1182/blood.2020007905. PMID: 33150379; PMCID: PMC7986048.

- Szanto CL, Cornel AM, Tamminga SM, Delemarre EM, de Koning CCH, van den Beemt DAMH, Dunnebach E, Tas ML, Dierselhuis MP, Tytgat LGAM, van Noesel MM, Kraal KCJM, Boelens JJ, Huitema ADR, Nierkens S. (2021) Immune Monitoring during Therapy Reveals Activitory and Regulatory Immune Responses in High-Risk Neuroblastoma. Cancers (Basel).;13(9):2096. doi: 10.3390/cancers13092096. PMID: 33926057; PMCID: PMC8123570.

- Lo Presti V, Cornel AM, Plantinga M, Dünnebach E, Kuball J, Boelens JJ, Nierkens S, van Til NP. (2021) Efficient lentiviral transduction method to gene modify cord blood CD8+ T cells for cancer therapy applications. Mol Ther Methods Clin Dev.;21:357-368. doi: 10.1016/j.omtm.2021.03.015. PMID: 33898633; PMCID: PMC8056177.

Grants

Princess Máxima Center Foundation
Ontwikkeling van effectieve CAR-T cel therapie voor kinderen met een T-cel leukemie of lymphoom
€403.758

ODAS Foundation
Consortium grant
Identify targets to modulate CAR-T cell functionality using advanced 3D co-culture and imaging technologies: Towards better survival of pediatric BCP-ALL patients
Together with Monique den Boer and Anne Rios
€355.000

Villa Joep
Immunology consortium
Joining forces to activate T-cell immunity against high risk neuroblastoma
Together with Sebastiaan van Heesch and Jan Molenaar
€1.275.000

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group dr. Weng Chuan Peng

Started in December 2019

Members of the Peng Group

Principal Investigator
Weng Chuan Peng

PhD student
Thomas Kluiver
Lianne Kraaier
Yuyan Lu

Postdoc
Stephanie Schubert

We are a translational stem cell biology lab with a primary focus on the liver. At the Princess Máxima Center, we study pediatric liver cancer, a rare cancer that affects approximately 1 in a million children. In the Netherlands, fewer than 10 children are diagnosed with liver cancer every year. The most common malignant liver tumors in children and adolescents are hepatoblastoma and hepatocellular carcinoma (HCC, and fibrolamellar HCC). Due to the limited number of patients, these tumors are poorly understood.

We employ multiomic approaches (whole genome sequencing, single cell RNA-seq, spatial transcriptomics, imaging CyTOF) to investigate the molecular mechanism underlying pediatric liver tumors, and to chart tumor expression pattern, tumor microenvironment and immune landscape. In addition, we have ample experience in the culture of organoids derived from liver tissues. We use patient-derived tumor organoids to find new therapeutics (e.g., high-throughput drug screening, evaluating responses to chemotherapy agents), to model immune-tumor interactions, and to discover biomarkers for monitoring disease progression.

In addition, we are interested in organoid biology and regenerative medicine, for instance, using organoids to model various liver diseases and organoid transplantation to treat liver diseases. We have previously demonstrated that long-term cultured murine hepatocyte organoids engrafted efficiently the injured liver of a mouse model with a chronic metabolic liver disease (Peng et al., Cell, 2018). We will continue to work towards expanding high quality human hepatocytes from donor materials for cell transplantation, which may one day address the issue of organ shortage.

At the Princess Máxima Center, we work closely with the clinical team (i.e., pediatric oncologists, pathologists and surgeons) to advance our understanding of liver tumors. Our long-term goal is to find novel treatment modalities for high risk liver tumors, expose fewer children to chemotherapy, and improve the survival of patients without compromising their quality of life.

Total no. of Máxima-affiliated publications (2021)	**2**
No. of Máxima-affiliated open access publications (2021)	**-**
Total no. of external publications (2021)	**-**

Top 3 of Máxima-affiliated publications (2021)

- Peng WC, Kraaier LJ, Kluiver TA. (2021) Hepatocyte organoids and cell transplantation: What the future holds. Exp Mol Med. PMID: 34663941.

- Marsee A, Roos FJM, Verstegen MMA; HPB Organoid Consortium, Gehart H, de Koning E, Lemaigre F, Forbes SJ, Peng WC, Huch M, Takebe T, Vallier L, Clevers H, van der Laan LJW, Spee B. (2021) Building consensus on definition and nomenclature of hepatic, pancreatic, and biliary organoids. Cell Stem Cell.;28(5):816-832. doi: 10.1016/j.stem.2021.04.005. PMID: 33961769.

Research group prof. dr. Rob Pieters

Started in 2014

Members of the Pieters Group

Principal Investigator
Rob Pieters

PhD student
Leiah Brigitha
Linde Dekker

Research assistant
Salena Meivis

Postdoc
Marc Bierings
Valérie de Haas
Melanie Hagleitner
Peter Hoogerbrugge
Inge van der Sluis
Janine Stutterheim

The focus of the Pieters group is to improve outcome of children with acute lymphoblastic leukemia (ALL) by the development of personalized therapies. Data from preclinical, translational and clinical studies on (epi)genetic abnormalities, monitoring early therapy responses by minimal residual disease (MRD), immunotherapeutic and chemotherapeutic developments and from therapeutic drug monitoring are studied and implemented in national and international clinical study protocols.

Specific goals are:

- implementation of immunotherapies including antibody based strategies and cellular therapies in treatment protocols for frontline and relapsed ALL.
- reduction of therapy and thereby improving quality of life for specific patient groups selected by genetic features and MRD.
- improving cure rate by development of more effective and more specific therapies for molecular genetic and immunophenotypic subclasses of ALL.
- more rational and specific use of chemotherapeutic agents.

Total no. of Máxima-affiliated publications (2021)	**52**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**52**

Top 3 of Máxima-affiliated publications (2021)

- Stutterheim J, Van der Sluis IM, de Lorenzo P, Alten J, Ancliffe P, Attarbaschi A, Brethon B, Biondi A, Campbell M, Cazzaniga G, Escherich G, Ferster A, Kotecha RS, Lausen B, Li CK, Lo Nigro L, Locatelli F, Marschalek R, Meyer C, Schrappe M, Stary J, Vora A, Zuna J, van der Velden VHJ, Szczepanski T, Valsecchi MG, Pieters R. (2021) Clinical implications of minimal residual disease detection in infants with KMT2A rearranged acute lymphoblastic leukemia treated on the Interfant-06 protocol. J Clin Oncol:39:652-662.

- den Boer ML, Cario G, Moorman AV, Boer JM, de Groot-Kruseman HA, Fiocco M, Escherich G, Imamura T, Yeoh A, Sutton R., Dalla-Pozza L, Kiyokawa N, Schrappe M, Roberts KG, Mullighan CG, Hunger SP, Vora A, Attarbaschi A, Zaliova M, Elitzur S, Cazzaniga G, Biondi A, Loh ML, Pieters R. (2021) Outcomes of paediatric patients with B-cell acute lympocytic leukaemia with ABL-class fusion in the pre-tyrosine-kinase inhibitor era: a multicentre, retrospective, cohort study. Lancet Haematol: 8: e55-66.

- Reedijk AMJ, Coebergh JWW, de Groot-Kruseman HA, van der Sluis IM, Kremer LC, Karim-Kos HE, Pieters R. (2021) Progress against childhood and adolescent acute lymphoblastic leukemia in the Netherlands, 1990-2015. Leukemia;35: 1001-1011.

Grants

Takeda
Fase I/II studie Ponatinib
€116.000

Piet Poortman Fonds/KWF
PACMAN-Hu19: Pediatric and young adult MAligNancies using a Humanized CD19 recognition domain
€787.365

Research group dr. Anne Rios

Started in March 2017

Members of the Rios Group

Principal Investigator
Anne Rios

PhD student
Emma Bokobza
Ravian van Ineveld
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Heggert Rebel
Mario Barrera Román
Celina Honhoff
Sam de Blank

Lab manager
Hannah Johnson

Computational scientist
Michiel Kleinnijenhuis

Grant Writer
Ellen Wehrens

Next to innovating 3D imaging technology, the Rios group implements Artificial Intelligence (AI) to offer computational solutions for understanding complex 3D imaging data. A deep learning-based (sub-)cellular segmentation pipeline has been developed that together with a new method for 8-color 3D imaging can extract molecular, morphometric and spatial features from millions of cells in intact tissues. This enables omics-like analysis of 3D imaging data, which was exploited to identify new tumor cell subsets in Wilms tumor (Nature Biotech, 2021). This method has been validated for a wide range of tissues from various origins and optimized for imaging of paraffin embedded tissue. Together, this offers a versatile protocol for cancer research with potential for patient diagnosis and treatment stratification (Nature Protocols, in revision).

To further increase the depth of imaging results, multi-omics platforms are being developed to integrate single-cell imaging data with transcriptomics. BEHAV3D analyzes cellular immunotherapy response in a patient-personalized manner in immuno-organoid co-cultures and can thereby identify mechanisms of treatment resistance. Moreover, it links cell behaviour to transcriptomic profiling to unravel the gene signatures associated with functional behaviour that can be exploited to improve tumour targeting (Nature Biotech, in revision).

To develop advanced human tissue models, the Rios group combines organoid technology with bioengineering. This has resulted in a new breast organoid model, exploiting human milk as a non-invasive cell source (The EMBO Journal, in revision). In addition, a new human brain organoid with medulla/pontine-fate has been developed that can be transduced into a Diffuse Midline Glioma (DMG) model that recapitulates timing and location of disease onset, as well as tumor heterogeneity observed in patients.

By advancing 3D imaging technology and human modeling, fundamental knowledge on cancer can be gained, new therapeutic targets identified, and efficacy of cellular therapy predicted in a patient-specific manner.

Total no. of Máxima-affiliated publications (2021)	**4**
No. of Máxima-affiliated open access publications (2021)	**3**
Total no. of external publications (2021)	**1**

Top 3 of Máxima-affiliated publications (2021)

- van Ineveld RL, Kleinnijenhuis M, Alieva M, de Blank S, Barrera Roman M, van Vliet EJ, Martínez Mir C, Johnson HR, Bos FL, Heukers R, Chuva de Sousa Lopes SM, Drost J, Dekkers JF, Wehrens EJ, Rios AC. (2021) Revealing the spatio-phenotypic patterning of cells in healthy and tumor tissues with mLSR-3D and STAPL-3D. Nature Biotechnology. PMID: 33692550.

- Dekkers JF, van Vliet EJ, Sachs N, Rosenbluth JM, Kopper O, Rebel HG, Wehrens EJ, Piani C, Visvader JE, Verissimo CS, Boj SF, Brugge JS, Clevers H, Rios AC. (2021) Long-term culture, genetic manipulation and xenotransplantation of human normal and breast cancer organoids. Nature Protocols. PMID: 33692550.

- Dawson CA, Mueller SN, Lindeman GJ, Rios AC, Visvader JE. (2021) Intravital microscopy of dynamic single-cell behavior in mouse mammary tissue. Nature Protocols. PMID: 33627843.

Grants

KWF
Consortium Grant UMCU
Targeting human cancer with the next generation of engineered immune cells: TEGs
€330.649

ZonMw Veni
Radioresistance of tumors of the brainstem in children: a role for the tumor micro environment?
€250.000

Friesland Campina – sponsored partnership
In vitro system for studying biological and nutritional factors affecting lactation and the function of human milk on intestinal development and physiology
€400.000

Ministry of Health, Welfare and Sport – Dutch Government
LEAF
Pilot study for increasing research laboratory sustainability using LEAF
€24.490

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Science awards

L'Oréal-UNESCO
For Women in Science Award
Anne Rios

Patents/licenses

1

Research group dr. Ronald Stam

Started in September 2016

Although the prognosis for childhood leukemia in general has steadily and progressively been improved over the last decades, there still remain various subtypes of patients that are at high-risk of therapy failure. The 5-year event free survival chances of patients diagnosed with MLL-rearranged acute lymphoblastic and myeloid leukemia, or NUP98 translocated acute myeloid leukemia, to date remain <40%. Hence, current therapeutic regimens clearly are not suitable for these specific patient groups, emphasizing the urgent need for more adequate treatment options for these children.

Using various high-throughput screening approaches, including elaborate drug library screens, combinatorial drug synergy screens, RNA and whole genome sequencing, CRISPR/Cas9 library screens, single-cell RNA sequencing, microarray and protein array analyses, we are continuously searching for novel therapeutic targets and innovative treatment strategies. In 2019, all of these efforts resulted in the identification of multiple innovative treatment rationales and potential therapeutics directed against newly recognized vulnerabilities in high-risk types of leukemia such as MLL-rearranged ALL and AML. With the majority of the in vitro work completed, we have been optimizing refined and comprehensive in vivo mouse models in order to validate the potential of identified therapeutic options, striving to provide sufficient preclinical evidence that allows the application of these newly found treatment opportunities in a clinical setting in the near future. With all the in vivo optimization in place, we will now turn to actually testing various promising treatment strategies in our comprehensive mouse models.

Members of the Stam Group

Principal Investigator
Ronald Stam

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Research Technician
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Total no. of Máxima-affiliated publications (2021)	**9**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Candelli T, Schneider P, Garrido Castro P, Jones LA, Bodewes E, Rockx-Brouwer D, Pieters R, Holstege FCP, Margaritis T, Stam RW. (2021) Identification and characterization of relapse-initiating cells in MLL-rearranged infant ALL by single-cell transcriptomics. Leukemia.;36(1):58-67.

- Kerstjens M, Garrido Castro P, Pinhanços SS, Schneider P, Wander P, Pieters R, Stam RW. (2021) Irinotecan Induces Disease Remission in Xenograft Mouse Models of Pediatric MLL-Rearranged Acute Lymphoblastic Leukemia. Biomedicines.;9(7):711.

- Wander P, Arentsen-Peters STCJM, Pinhanços SS, Koopmans B, Dolman MEM, Ariese R, Bos FL, Castro PG, Jones L, Schneider P, Navarro MG, Molenaar JJ, Rios AC, Zwaan CM, Stam RW. (2021) High-throughput drug screening reveals Pyrvinium pamoate as effective candidate against pediatric MLL-rearranged acute myeloid leukemia. Transl Oncol. ;14(5):101048.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**1**

Máxima/External PhD defenses

Christopher Adrian Jaramillo Mantilla, June 2021, Department of Hematology Amsterdam University Medical Center, Leukemia Treatment - Studies Exploring Bone Mareow Microenvironment, Drug Resistance and Cannabidiol'. Promotores: prof. dr. G.J. Peters, prof. dr. J. Cloos. Co-promotores: dr. G. Janssen, dr. R.W. Stam.

Research group prof. dr. Henk Stunnenberg

Started in March 2019

Members of the Stunnenberg Group

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PhD student
Farid Keramati
Cristian Ruiz Moreno
Zhijun Yu
Yanan Zhai

Visiting PhD student
Mawada Abakar

Senior Postdoc
Peter Brázda
Gitanjali Dharmadhikari

Junior Postdoc
Prashant Singh

Senior Bioinformatician
Wout Megchelenbrink

Research assistant
Brigit te Pas

The overall aim of our group is to generate and integrate single-cell data to identify tumor clonal heterogeneity and spatial organization, to define the tumor micro-environment (TME) and the communication between tumors and the TME. Single-cell and spatial transcriptome approaches allow for the first time to molecularly define tens of thousands of single cells that make up the tumor and infer their specific role in tumor initiation and maintenance.

High-grade brain malignancies
We built a glioblastoma atlas at single-cell resolution in adult patients that compiles different studies and created a curated reference map. Our resource provides an easy-to-use platform for cell annotation and hypothesis generation. Besides, we continue studying the cell heterogeneity and how in high-grade gliomas in children, the tumor is organized into distinct cellular communities to understand and unravel the role of the tumor microenvironment (TME) in cancer behavior and development. Finally, the local signaling environment between cancer cells and TME will be studied in intact tissues using spatial transcriptomics.

HCA|Organoid
This project aims to establish a comprehensive single-cell reference map of human patient-derived organoids and matched primary tissue to generate gene expression and open chromatin profiles from the same cell. With the reference map, we aim to provide a better insight between and understanding of health and disease.

Pediatric and adult AML
Acute Myeloid Leukemia (AML) is an aggressive hematopoietic malignancy with low overall survival; adult and pediatric AML patients suffer from high risk of relapse. To gain insight into the clonal heterogeneity during disease progression, we perform in depth (epi)genome analysis and single-cell RNA sequencing of bone marrow at diagnosis and relapse. In collaboration with the Zwaan and Heidenreich groups, we focus on diagnosis-relapse pairs in childhood AML. These experiments will advance our understanding of clonal evolution and treatment related changes in the composition.

Total no. of Máxima-affiliated publications (2021)	**5**
No. of Máxima-affiliated open access publications (2021)	**4**
Total no. of external publications (2021)	**11**

Top 3 of Máxima-affiliated publications (2021)

- Schmalbrock LK , Dolnik A, Cocciardi S, Sträng E, Theis F, Jahn N, Panina E, Blätte TJ, Herzig J, Skambraks S, Rücker FG, Gaidzik VI, Paschka P, Fiedler W, Salih HR, Wulf G, Schroeder T , Lübbert M, Schlenk RF, Thol F, Heuser M, Larson RA, Ganser A, Stunnenberg HG, Minucci S, Stone RM, Bloomfield CD, Döhner H, Döhner K, Bullinger L (2021) Clonal evolution of acute myeloid leukemia with FLT3-ITD mutation under treatment with midostaurin. Blood. PMID: 33598693.

- Bock C, Boutros M, Camp JG, Clarke L, Clevers H, Knoblich JA, Liberali P, Regev A, Rios AC, Stegle O, Stunnenberg HG, Teichmann SA, Treutlein B, Vries RGJ. (2021) Human Cell Atlas 'Biological Network' Organoids. The Organoid Cell Atlas. Nat Biotechnol. PMID: 33384458.

- Della Torre L, Nebbioso A, Stunnenberg HG, Martens JHA, Carafa V, Altucci L. (2021) The Role of Necroptosis: Biological Relevance and Its Involvement in Cancer. Cancers (Basel) PMID: 33567618.

PhD defenses

Total no. of Máxima-affiliated PhD defenses (2021)	**0**
Total no. of external PhD defenses (2021)	**4**

Grants

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Research group prof. dr. Wim Tissing

Started in June 2018

Members of the Tissing Group

Principal Investigator
Wim Tissing
Co-Principal Investigator
Louis Bont
Hanneke van Santen
PhD student
Coco Beudeker
Ceder van den Bosch
Mirjam van den Brink
Emma den Hartog
Julia Simon
Sruthi Sririam
MD PhD student
Didi Bury
Denise Froon-Torenstra
Chantal Lebbink
Jiska van Schaik
Juliëtte Schmidt
Debbie Stavleu
Marijn Soeteman
Clinician Scientist
Erna Michiels
Evelien de Vos
Marianne van de Wetering
Postdoc
Aeltsje Brinksma
Agnes van den Hoogen
Erik Loeffen

Our group focuses on supportive care in childhood oncology: prevention and management of the adverse effects of childhood cancer and its treatment. The overall goal is to decrease morbidity and mortality due to side effects, and ultimately increase quality of life of children with cancer.

Since this is a very broad field, in 2021 we have added two topics to our research program: nutrition and motion, and infections. The current programs in the Tissing Group are:

- Nutrition and motion, PI Tissing, in collaboration with the Physiotherapy department
- Infections, PI Bont and Tissing, in collaboration with the UMCU Infectious Diseases department. Louis Bont was appointed in 2021 to further expand the studies on infections in childhood cancer patients
- Endocrinology, PI van Santen, in collaboration with the UMCU Endocrinology department
- Nursing studies, PI Tissing, Postdocs Brinksma and Van den Hoogen
- Guideline development, PI Tissing, in collaboration with the Kremer group
- Nausea and vomiting, clinician scientists De Vos and Van de Wetering

Besides collaboration with the UMCU, we collaborate nationally with other universities, and internationally, with organizations such as IPOG, the SIOP supportive care working group, the SIOP nutrition study group for high income countries, and the Umbrella Network on infectious diseases.

Total no. of Máxima-affiliated publications (2021)	**50**
No. of Máxima-affiliated open access publications (2021)	**50**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, Quinn GP, van Dulmen-den Broeder E, Byrne J, Haupt R, Wallace WH, van den Heuvel-Eibrink MM, Anazodo A, Anderson RA, Barnbrock A, Beck JD, Bos AME, Demeestere I, Denzer C, Di Iorgi N, Hoefgen HR, Kebudi R, Lambalk C, Langer T, Meacham LR, Rodriguez-Wallberg K, Stern C, Stutz-Grunder E, van Dorp W, Veening M, Veldkamp S, van der Meulen E, Constine LS, Kenney LB, van de Wetering MD, Kremer LCM, Levine J, Tissing WJE. (2021) Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. PanCareLIFE Consortium.Lancet Oncol. PMID: 33539753.

- Bury D, Wolfs TFW, Ter Heine R, Muilwijk EW, Tissing WJE, Brüggemann RJ. (2021) Pharmacokinetic evaluation of twice-a-week micafungin for prophylaxis of invasive fungal disease in children with acute lymphoblastic leukaemia: a prospective observational cohort study. J Antimicrob Chemother. PMID: 34939125.

- van Schaik J, van Roessel IMAA, Schouten-van Meeteren NAYN, van Iersel L, Clement SC, Boot AM, Claahsen-van der Grinten HL, Fiocco M, Janssens GO, van Vuurden DG, Michiels EM, Han SKS, van Trotsenburg PASP, Vandertop PWP, Kremer LCM, van Santen HM. (2021) High Prevalence of Weight Gain in Childhood Brain Tumor Survivors and Its Association With Hypothalamic-Pituitary Dysfunction. J Clin Oncol. PMID: 33621126.

Grants

Zieke Kinderen Fonds
Microbiota and faecal metabolomics as potential prognostic biomarkers for bloodstream infections in paediatric haematological malignancies
€75.000

Kenniscentrum Kinderpalliatieve Zorg
Kinderpalliatieve zorg in de research
€21.000

SKMS
Richtlijn Ontwikkeling
€68.000

Prinses Máxima Centrum Foundation
Sport en Bewegen
€327.250

Research group dr. Lieve Tytgat

Started in September 2016

Members of the Tytgat Group

Principal Investigator
Lieve Tytgat

PhD student
Caroline Hochheuser
Paula Martinez Sanz
MD PhD student
Astrid van Barneveld
Thomas Blom
Nina Gelineau
Nathalie Lak
Yvette Matser
Atia Samim
Michelle Tas
Lieke van Zogchel
Postdoc
Gitta Bleeker
Zeinab van Gestel-Fadaie
Janine Stutterheim
Ilse Timmerman

Research Technician
Giovanna Terhuizen

Collaborator, external PI
Bart de Keizer
André van Kuilenburg

Driven to bridge the gap between the bedside and basic science, as pediatric oncologist, Lieve Tytgat initiates translational studies. As about 30-50% of patients with solid tumors suffer from recurrent disease with poor outcome, the Tytgat group aims to develop new biomarkers and liquid biopsy/ laboratory tests to predict in which patients the current therapy will not lead to eradication of the disease.

Focusing on the whole patient, we were the first to demonstrate the applicability of neuroblastoma-specific mRNA markers, epigenetic and tumor-specific DNA markers and markers that detect neuroblastoma cells that have undergone epithelial to mesenchymal transition (Eurostars, Neuroblastoma UK). Furthermore, we have detected new urinary markers that identify high-risk patients with good and poor prognosis (Villa Joep). The bone marrow, containing metastases, the microenvironment and crosstalk of tumor and BM cells and effect of high-dose chemotherapy and bone marrow transplantation is being investigated (KiKa 347). Finally, clinically decision marking (nuclear)imaging, 123I-MIBG and new MFBG-scans will be studied (KiKa 421) in collaboration with the theranostics consortium.

As all pediatric solid tumors are rare diseases, we have established international collaborations. Dr. Lieve Tytgat is one of the internationally leading neuroblastoma liquid biopsy researchers, and actively involved in the international SIOPEN: as Executive Board member, member of the translation steering committee, vice-chair long term follow-up committee, founder of the Catecholamine working group and chair of the SIOPEN liquid biopsy committee, in which 'our' cfDNA-marker, hypermethylated RASSF1A, will be tested in more than 800 patients. To accelerate liquid biopsies in other solid tumors, our rhabdomyosarcoma mRNA panel and the combination of mRNA and cfDNA is being investigated. For pediatric renal tumors, we initiated international liquid biopsy studies in the international Umbrella trial (KiKa 397).

Dr. Tytgat was the first Princess Máxima Center PI to be nominated as UMC Associate Professor (Strategic Program Cancer).

Total no. of Máxima-affiliated publications (2021)	**19**
No. of Máxima-affiliated open access publications (2021	**19**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- van Zogchel LMJ, Lak NSM, Verhagen OJHM, Tissoudali A, Gussmalla Nuru M, Gelineau NU, Kannengieter L, Javadi A, Zijtregtop EAM, Merks JHM, van den Heuvel-Eibrink M, Schouten-van Meeteren AYN, Stutterheim J, van der Schoot CE, Tytgat GAM. (2021) Novel Circulating Hypermethylated RASSF1A ddPCR for Liquid Biopsies in Patients With Pediatric Solid Tumors. JCO Precis Oncol. PMID: 34820594.

- Lak NSM, Voormanns TL, Zappeij-Kannegieter L, van Zogchel LMJ, Fiocco M, van Noesel MM, Merks JHM, van der Schoot CE, Tytgat GAM, Stutterheim J. (2021) Improving Risk Stratification for Pediatric Patients with Rhabdomyosarcoma by Molecular Detection of Disseminated Disease. Clin cancer Res. PMID: 34285060.

- Blom T, Meinsma R, di Summa F, van den Akker E, van Kuilenburg ABP, Hansen M, Tytgat GAM. (2021) Thrombocytopenia after meta-iodobenzylguanidine (MIBG) therapy in neuroblastoma patients may be caused by selective MIBG uptake via the serotonin transporter located on megakaryocytes. EJNMMI Res. PMID: 34424429.

Grants

Stichting Kinderen Kankervrij
KiKa 374
The metastatic bone marrow niche in Neuroblastoma: Crosstalk between tumor cells and Mesenchymal Stromal Cells?
€599.646

Villa Joep
Catecholamines and Metabolism – applications for diagnostics, risk assessment, and identification of potential new therapeutic targets in neuroblastoma
€1.189.782

Rijksdienst Voor Ondernemend Nederland
Catalyze Eurostars
MonitoRD – The World's first personalised liquid biopsy test for disease monitoring in pediatric cancers **€150.000**

Stichting Kinderen Kankervrij
KiKa 397
The Circle study: Liquid biopsies in pediatric renal tumors
€593.557

Internal sponsoring is awarded for participation in the Máxima – KiTZ collaboration (Chapter Collaborations)

Science awards

SIOP 2021
Award – Clinical Trials
Yvette Matser

EANM 21
European Nuclear Medicine Congress 2021
Best Abstract, selected as highlight and top-rated presentation
Atia Samim

UU Graduate School of Life Sciences
2nd place Supervisor of the year
Lieve Tytgat

UMC Strategic program Cancer
Associate Professor
Lieve Tytgat

SIOP 2021
MFBG abstract selected as late breaking abstract and Oral Presentation
Atia Samim

SIOP 2021
Oral presentation
Nina Gelineau

ANR2021
Virtual meeting
Oral presentation
Lieke van Zogchel

Research group dr. Dannis van Vuurden

Started in July 2018

Members of the van Vuurden Group

Principal Investigator
Dannis van Vuurden

PhD student
Josh Baugh
Elvin ‘t Hart
Fatma El-Khouly
Raoull Hoogendijk
Milen Kebede
Myrthe Nuijts

Postdoc
Marc Derieppe
Sophie Veldhuijzen van Zanten

Research Technician
Yan Su

Collaborator, external PI
Mario Ries

The blood-brain barrier (BBB) is a major hurdle in the treatment of children with brain tumors. Our group strives for the development of novel treatment strategies for the treatment of pediatric high-grade brain tumors, focused on technologies to cross the BBB, such as focused ultrasound-mediated blood-brain barrier disruption (FUS-BBBD). In a translational research framework, the group is composed of a preclinical and clinical arm closely interacting with one another to foster the application of ‘bench-to-bedside’ approaches.

In the lab, FUS-BBBD research is focused on improving drug (small molecules, monoclonal antibodies) delivery to the brain in models of diffuse midline glioma (DMG). These studies include the delivery of radiosensitizers to enhance therapeutic efficacy of radiotherapy in these models. Drug exposure profiles anticipated with FUS-BBBD and convection-enhanced delivery (CED) are mimicked using microfluidic ‘brain-on-a-chip’ systems in collaboration with UTwente to assess therapeutic index and ultimately optimize treatment planning in patients. Combining FUS-BBBD/CED with novel immunotherapeutic approaches will be investigated to translate the findings into clinical trials. Exploration of targets for immunotherapeutic modulation of the tumor immune micro-environment are part of a collaborative project with the Stunnenberg group.

Furthermore, collaboration with UMCU (dr. Mario Ries) explores FUS-BBBD-enhanced liquid biopsies in high-grade glioma. For clinical FUS-BBBD studies, the Dutch Neuro-FUS Consortium was established, led by Dannis van Vuurden. This is a multicenter collaborative set up around a clinical FUS-BBBD infrastructure acquired by the Princess Máxima Center and UMC Utrecht. Clinical trials using FUS-BBBD-mediated drug delivery are developed in pediatric and adult brain tumors and Alzheimer’s Disease. Furthermore, Dannis van Vuurden leads the SIOPE European Diffuse Intrinsic Pontine Glioma / Diffuse Midline Glioma (DIPG/DMG) Registry from the Máxima Center as well as a nation-wide retrospective study of high-grade pediatric brain tumors in the Netherlands.

Together with the UMCU, we received funding for two projects: The ALBINO (Acoustically-enhanced Liquid Biopsies for Neuro-Oncology) project sponsored by NWO and a project entitled: ‘Drug delivery for the treatment of pediatric brain tumors by FUS-mediated local efflux transporter inhibition’ funded by KiKa.

Total no. of Máxima-affiliated publications (2021)	**8**
No. of Máxima-affiliated open access publications (2021)	**3**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- El-Khouly FE, Veldhuijzen van Zanten SEM, Jansen MHA, Bakker DP, Sanchez Aliaga E, Hendrikse NH, Vandertop WP, van Vuurden DG, Kaspers GJL. (2021) A phase I/II study of bevacizumab, irinotecan and erlotinib in children with progressive diffuse intrinsic pontine glioma. J Neurooncol. PMID: 33963476.

- Baugh JN, Gielen GH, van Vuurden DG, Veldhuijzen van Zanten SEM, Hargrave D, Massimino M, Biassoni V, Morales la Madrid A, Karremann M, Wiese M, Thomale U, Janssens GO, von Bueren AO, Perwein T, Hoving EW, Pietsch T, Andreiuolo F, Kramm CM. (2021) Transitioning to molecular diagnostics in pediatric high-grade glioma: experiences with the 2016 WHO classification of CNS tumors. Neurooncol Adv. PMID: 34595479.

- El-Khouly FE, Adil SM, Wiese M, Hulleman E, Hendrikse NH, Kaspers GJL, Kramm CM, Veldhuijzen van Zanten SEM, van Vuurden DG; SIOPE DIPG Network. (2021) Complementary and alternative medicine in children with diffuse intrinsic pontine glioma-A SIOPE DIPG Network and Registry study. Pediatr Blood Cancer. PMID: 33942498.

Research group prof. dr. Marc Wijnen

Started in October 2014

Members of the Wijnen Group

Principal Investigator/ surgeon
Marc Wijnen

MD PhD student
Guus Bokkerink
Matthijs Fitski
Bernadette Jeremiasse
Lianne Wellens

PhD student
Ceder van den Bosch
Myrthe Buser
Rixt Bruinsma

Surgeon PhD student
Caroline Hulsker
Sheila Terwisscha van Scheltinga

Surgeon
Lideke van der Steeg
Kees van de Ven

Our research is focused on improving our surgical skills, especially using image guided surgery with 3D-imaging and fluorescence guided operations.

The aim of our research is to diminish complications in surgery, including line infections and complications during small and large operating procedures. This is done by measurement and benchmarking of results and interventional studies such as antimicrobial locks in venous access.

Total no. of Máxima-affiliated publications (2021)	**27**
No. of Máxima-affiliated open access publications (2021)	**13**
Total no. of external publications (2021)	**28**

Top 3 of Máxima-affiliated publications (2021)

- Jeremiasse B, van der Steeg AFW, Fiocco M, Hobbelink MGG, Merks JHM, Godzinski J, Shulkin BL, Wijnen MHWA, Terwisscha van Scheltinga CEJ. (2021). Value of the Sentinel Node Procedure in Pediatric Extremity Rhabdomyosarcoma: A Systematic Review and Retrospective Cohort Study. Ann Surg Oncol. PMID: 34057567.

- Wijnen MWH, Davidoff AM. (2021) Minimally Invasive Techniques in Pediatric Surgical Oncology. Surg Oncol Clin N Am. PMID: 33706909.

- Bruinsma RS, Nievelstein RAJ, Littooij AS, Vermeulen MA, van de Ven CP, van Noesel MM, Wijnen MHWA, van der Steeg AFW, de Krijger RR. (2021) Diagnostic accuracy of image-guided core needle biopsy of non-central nervous system tumors in children. Pediatr Blood Cancer. PMID: 34121329.

Grants

Princess Máxima Centrum Foundation
Infuus fiets
€25.000

Research group prof. dr. Michel Zwaan

Started in 2016

The Zwaan group focuses on drug development and early clinical trials. There is a specific interest in translational research into acute myeloid leukemias (AML) and Down syndrome related leukemias. Michel Zwaan also heads the Trial and Data Center (TDC) together with Harm van Tinteren, statistician.

Early phase and other clinical trials
This includes clinical studies of novel agents for children with cancer. The group focuses on therapeutic drug monitoring, bioequivalence of pediatric-friendly formulations, and pediatric pharmacokinetics/dynamics. Zwaan leads several academic phase 1-2 'intent to file' studies (e.g inotuzumab, ozogamicin and bosutinib).

We obtained approval for the brigatinib study for children with inflammatory myofibroblastic tumor (IMT) and anaplastic large cell lymphoma (ALCL), and a vyxeos/clofarabine study for AML. A precision medicine study almost finalized recruitment (iTHER-2). We study population pharmacokinetics of chemotherapeutics, with a prospective trial having opened to study optimal duration of aprepitant therapy. In pediatric AML, major efforts will go to the PEDAL initiative. The Leukemia and Lymphoma Society (LLS) supports this initiative, the first intent to file subtrial (venetoclax) has been submitted to ethics, with the Princess Máxima Center acting as European sponsor and LLS as North-American sponsor with COG.

A new initiative is an international leukemia tumor board, to discuss profiling results and allocate patients to trials. Michel Zwaan was granted co-chairmanship of the ITCC Hematological Malignancies group, with Jan Molenaar as co-chair of the Solid Tumor group. The Princess Máxima Center signed an agreement with the Pacific Neuro-Oncology Consortium to boost early-phase clinical research in pediatric brain tumors. Van der Sluis was invited to present the blinatumomab data at the American Society of Hematology (ASH) best abstract session. Zwaan functioned as ad-interim chair of the Medical Research Ethics Committee in Utrecht as of May 2021. This will provide the Máxima Center with a European leadership position in the field of clinical research.

Acute Myeloid Leukemia (AML)
Pediatric AML is a relatively rare malignancy characterized by significant heterogeneity in genetic aberrations. Despite intensive treatment with chemotherapy and stem cell therapy (SCT), outcome plateaus at ~70% overall survival. The main focus is on elucidating the genetic background and improving the risk group stratification of pediatric AML. Collaboration exists within the Máxima Center and involves e.g. investigating the complexity of treatment response by single cell sequencing, studying the role of the immune environment, targeting fusion genes with novel methods of drug delivery, novel treatment options for NUP-98 rearranged AML (menin inhibitors, a clinical phase 1 study for children is due to open in the Máxima Center as the only pediatric site in Europe), but also clinical research in pediatric AML to develop immunotherapy. These approaches should lead to better treatment outcome for this disease.

Total no. of Máxima-affiliated publications (2021)	**25**
No. of Máxima-affiliated open access publications (2021)	**0**
Total no. of external publications (2021)	**0**

Top 3 of Máxima-affiliated publications (2021)

- Fischer M, Moreno L, Ziegler DS, Marshall LV, Zwaan CM, Irwin MS, Casanova M, Sabado C, Wulff B, Stegert M, Wang L, Hurtado FK, Branle F, Geoerger B, Schulte JH. (2021) Ceritinib in paediatric patients with anaplastic lymphoma kinase-positive malignancies: an open-label, multicentre, phase 1, dose-escalation and dose-expansion study. Lancet Oncol. PMID: 34780709.

- Michels N, Boer JM, Enshaei A, Sutton R, Heyman M, Ebert S, Fiocco M, de Groot-Kruseman HA, van der Velden VHJ, Barbany G, Escherich G, Vora A, Trahair T, Dalla-Pozza L, Pieters R, Zur Stadt U, Schmiegelow K, Moorman AV, Zwaan CM, den Boer ML. (2021) Minimal residual disease, long-term outcome, and IKZF1 deletions in children and adolescents with Down syndrome and acute lymphocytic leukaemia: a matched cohort study. Lancet Haematol. PMID: 34560013.

- Van Tilburg CM, Pfaff E, Pajtler KW, Langenberg KPS, Fiesel P, Jones BC, Balasubramanian GP, Stark S, Johann PD, Blattner-Johnson M, Schramm K, Dikow N, Hirsch S, Sutter C, Grund K, von Stackelberg A, Kulozik AE, Lissat A, Borkhardt A, Meisel R, Reinhardt D, Klusmann JH, Fleischhack G, Tippelt S, von Schweinitz D, Schmid I, Kramm CM, von Bueren AO, Calaminus G, Vorwerk P, Graf N, Westermann F, Fischer M, Eggert A, Burkhardt B, Wößmann W, Nathrath M, Hecker-Nolting S, Frühwald MC, Schneider DT, Brecht IB, Ketteler P, Fulda S, Koscielniak E, Meister MT, Scheer M, Hettmer S, Schwab M, Tremmel R, Øra I, Hutter C, Gerber NU, Lohi O, Kazanowska B, Kattamis A, Filippidou M, Goemans B, Zwaan CM, Milde T, Jäger N, Wolf S, Reuss D, Sahm F, von Deimling A, Dirksen U, Freitag A, Witt R, Lichter P, Kopp-Schneider A, Jones DTW, Molenaar JJ, Capper D, Pfister SM, Witt O. (2021) The Pediatric Precision Oncology INFORM Registry: Clinical Outcome and Benefit for Patients with Very High-Evidence Targets. (2021) Cancer Discov. PMID: 34373263.

Grants

Takeda Development Center Americas Inc
ITCC-098
Brigatinib study
€6.055.576

Minkes Wish
€49.093

Jazz
ITCC-092
Vyxeos-Clofarabine phase 1B
€180.000

EuPAL foundation
€352.240

Daiichi-Sankyo
Quizartinib study
€129.905,85

Science awards

Abstract award
American Society of Hematology
Valeria Ceolin

Members of the Zwaan Group

Principal Investigator
Michel Zwaan

Co-Principal Investigator
Jaap-Jan Boelens

Clinical Trialists
Auke Beishuizen
Miranda Dierselhuis
Natasha van Eijkelenburg
Caroline Lindemans
Maaike Luesink
Jasper van der Lugt
Britta Vormoor-Burger

PhD student
Fabienne Adriaanse
Eline Bertrums
Valeria Ceolin
Joost Koedijk
Laura Nijstad

Clinical Research fellow
Erica Brivio
Sae Ishimaru

PhD
Uri Ilan
Naomi Michels
Sanne Noort
Milad Rasouli
Sebastiaan Sassen
Romy van Weelderen

Members of the TDC staff

PI Early clinical trials / Medical lead TDC
Michel Zwaan

Statistical lead TDC
Harm van Tinteren

Clinical Scientist
Paco Bautista-Sirvent

Contract Manager
Steven Vanhoutvin

Local security officer
Anneke Ammerlaan

Program Manager Clinical Data
Jan Lieverst

Communication Advisor
Astrid Danen-van Oorschot

Quality management
Marlien Beusink
Angela Vlug

Safety officer for studies with genetically modified products
Fraukje Bitter van Asma

Administrative management support
Jeanny Born – van der Velden
Monique Schnater

ITCC coordinator
Anneke Ammerlaan

Statisticians and epidemiologists
Saurabh Chandra
Rana Dandis
Marta Fiocco
Yilin Jiang
Henrike Karim-Kos
Maya Schulpen
Adriana Thano

Team leader Sponsor Office
Karolien Makkink

Trial and project management
Anneke Ammerlaan
Marlous Bakker
Esther de Boer
Maaike Boonstra
Anne Elsinghorst
Thea Godschalk
Debbie Hendrickx
Judith Hoevenaars
Raoull Hoogendijk
Leonie Kastaneer
Marjolein Mijnders
Jaap Mur
Mirjam Nauta
Yvonne Ruchti
Peggy Scholte-van Houtem
Miriam Stumpf
Femke Verwer
Jacqueline Vreijling
Marieke Willemse
Pauline Winkler-Seinstra

Clinical Trial assistant
Gertruud Bakker
Vivian Eekhart
Jet Jansen
Nanda Muijser
Susan Westdijk

Central data management
Yen Dang
Shivani Dontham
Lucienne Grundeken
Margriet van der Heiden-van der Loo
Alexandra Hung
Anke Keizer-Schellekens
Mireille Koenders
Ria Koolma
Pakriti Roy
Nieke de Ruiter
Ingrid Schut
Lennart Teunissen
Ashwini Vijayakumar
Moniek Vos
Nynke Vrolijk-Barkhuijsen
Evelyn Wiesen

Clinical data scientist
Karin Damen-Korbijn
Hester de Groot-Kruseman

Database designer
Annelies Rotte

Team leader Site Office
Edith Schasfoort

Local data management
Lisette Adams
Eveline Adriaans
Manita van Baalen
Liesbeth de Boer
Daniel van Eijden
Gerda de Heus-Colijn
Leanne Koningen
Sandra van der Kroef-de Haas
Laura Kruize
Felice van der Linden
Aslihan Mantici
Anne Nuijens
Chantal van Overbeek
Merian van Overveld
Miquel Quaedvlieg
Saskia Rasser
Monique Schippers
Harm Schoo
Chantal Smit-Rooijakkers
Soroush Sourani
Suzanne Vesters

Project support PEWS
Maartje Marcelis

Research nurse/coordinator
Charlotte van Aart
Martine van Engelen
Margot Geerdink
Corinne Gerhardt
Femke Herber
Anneke Heutinck
Liset Lansaat
Monique Legemaat
Dominique Mangert
Kyra van Schijndel
Jenny Smink
Ilse Stolte
Sandra Verbeek-van Rest

Research assistant
Tamara Buunk
Nurten Deniz
Tamara van Minkelen
Emma van Rooijen
Mariska Timmer

Start-up coordination/Trial support
Abi Aramugam
Bo Heijnen
Leonie Kastaneer
Marjanka van der Kloes
Inge Niehoff
Corinne Stoop

Medical student support
Marije Kuiper
Daphne van Rijn

Appendix

Appendix 1

Clinical Studies Phase I/II

Open Investigator-sponsored studies

Study	Working title	Setting	Role DCOG-ECTC	Unit	Date of opening NL	Status
A Phase I/II study of Bosutinib in pediatric patients with newly diagnosed chronic phase or resistant/intolerant Ph+ Chronic Myeloid Leukemia, study ITCC-054/COG AAML1921	Bosutinib (BCHILD)	International	Erasmus MC sponsor	HO	Approved 13-06-2016 First pt. 25-11-2016	Open
A phase I/II study of Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/ refractory Acute Lymphoblastic Leukemia - Study ITCC-059	Inotuzumab	International	Erasmus MC sponsor	HO	Approved 02-09-2016 First pt. 23-01-2017	Open
A pilot study to test the feasibility, safety and efficacy of the addition of the BiTE antibody Blinatumomab to the Interfant-06 backbone in infants with MLL-rearranged Acute Lymphoblastic Leukemia	Blinatumomab Infant	International	Princess Máxima Center sponsor	HO	Approved 17-10-2017 First pt. 31-07-2018	Inclusion closed
An international phase I/II expansion trial of the MEK inhibitor Selumetinib in combination with dexamethasone for the treatment of relapsed/ refractory RAS-pathway mutated pediatric and adult Acute Lymphoblastic Leukemia (ALL)	Seludex	International	Newcastle	HO	Approved 8-1-2021 First pt. 26-1-2021	Open
A randomised phase IIb trial of BEvACizumab added to Temozolomide ± IrinOtecan for children with refractory/relapsed Neuroblastoma	Beacon	European	CRCTU Birmingham sponsor	SO	Approved 16-02-2015 First pt. 14-10-2015	Inclusion closed
A phase 1B of Crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies - Study ITCC 053	CRISP	European	Erasmus MC sponsor	Precision medicine NO SO HO	Approved 3-11-2016 First pt. 22-05-2018	Open
European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in relapsed/ refractory tumors in children	E-SMART	European	IGR	Precision medicine NO SO HO	Approved 23-2-2018 First pt. 14-5-2018	Open
INFORM2 exploratory multinational phase I/II combination study of Nivolumab and Entinostat in children and adolescents with refractory high-risk malignancies	INFORM 2 NivEnt	European	Heidelberg	Precision medicine NO SO HO	Approved 27-6-2019 First pt. 10-6-2020	Open
An international multicenter phase II randomised trial evaluating and comparing two intensification treatment strategies for metastatic neuroblastoma patients with a poor response to induction chemotherapy A SIOPEN Study	VERITAS	International	IGR sponsor SKION NCC	SO	Approved 27-09-2019 First pt. 20-02-2020	Open
A phase I/II study evaluating the safety and activity of Pegylated recombinant human Arginase (BCT-100) in Relapsed/refractory cancers of Children and young adults	PARC	International	CRCTU Birmingham	SO	Approved 12-5-2020 First pt. 29-6-2020	Open
International multicenter open-label, phase 2 study to treat molecular relapse of pediatric acute myeloid leukemia with Azacitidine	AMoRe2017	European	GPOH sponsor		Approved 06-02-2019 Frist pt. 20-05-2020	Open
Biological Medicine for Diffuse Intrinsic Pontine Glioma (DIPG) Eradication	Biomede	European	IGR sponsor Erasmus MC national co-sponsor	NO	Approved 13-02-2018 First pt. 19-02-2019	Inclusion closed
A Phase Ib study of Vyxeos® (liposomal daunorubicin and cytarabine) in combination with Clofarabine in children with relapsed/refractory AML	VyClo	International	Princess Máxima Center sponsor	HO	Approved 6-11-2020	Open

Clinical Studies Phase III

Open Investigator-sponsored studies

Study	Working title	Setting	Role DCOG-ECTC	Unit	Date of opening NL	Status
optimal Duration of Aprepitant therapy for nausea and Vomiting INduced by ChEmotherapY in children: a double-blind placebo-controlled crossover randomized phase III trial	Davincy	National	Princess Máxima Center	HO SO NO SCT	Approved 21-12-2021	Open
ALLTogether1 - A Treatment study protocol of the ALLTogether Consortium for children and young adults (1-45 years of age) with newly diagnosed acute lymphoblastic leukemia (ALL)	ALLTogether-1	International	Karolinska	HO	Approved 7-7-2020 First pt 14-7-2020	Open
FaR-RMS - An overarching study of Children and adults with Frontline and Relapsed Rhabdomyosarcoma	FaR-RMS	International	CRCTU Birmingham	SO	Approved 26-10-2020 First pt. 10-11-2020	Open
UMBRELLA PROTOCOL SIOP-RTSG 2016 Integrated research and guidelines for standardized diagnostics and therapy for pediatric renal tumors	UMBRELLA	International	Homburg	SO	Approved 25-2-2019 First pt. 7-6-2019	Open
An International Prospective Trial on Medulloblastoma (MB) in Children Older Than 3 to 5 Years With WNT Biological Profile (PNET 5 MB - LR and PNET 5 MB - WNT-HR), Average-risk Biological Profile (PNET 5 MB-SR), Or TP35 Mutation, and Registry For MB Occurring in the Context of Genetic Predisposition	SIOP PNET5	International	Univ. Hamburg	NO	Approved 17-2-2020	Open
International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis	LCH-IV	International	St. Anna Wien	HO	Approved 6-1-2014 First pt. 15-1-2014	Open
International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukemia	Interfant 06	International	SKION	HO	Approved 1-1-2006 First pt. 2-5-2006	Open
Second International Inter-Group Study for Classical Hodgkin's Lymphoma in Children and Adolescents	EuroNet-PHL-C2	International	Univ. Giessen	HO	Approved 9-9-2016 First pt. 20-10-2016	Inclusion closed
NOPHO-DBH AML 2012 Protocol: Research study for treatment of children and adolescents with acute myeloid leukemia 0-18 years	NOPHO DBH AML 2012	International	Vastra Gotaland Regionen	HO	Approved 1-1-2014 First pt. 11-1-2014	Open
An international Clinical Program for the diagnosis and treatment of children, adolescents and young adults with ependymoma	Ependymoma II	International	St. Leon Berard	NO	Approved 6-7-2020 First pt. 13-7-2020	Open
Pediatric Hepatic International Tumor Trial	PHITT	International	CRCTU Birmingham	SO	Approved 18-6-2019 First pt. 30-7-2019	Open
Allogeneic Stem Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukemia	ALL SCTped FORUM	International	St. Anna Wien	HO	Approved 10-9-2014 First pt. 10-10-2016	Open
International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones	EsPhALL2017	International	Univ. Milano Bicocca	HO	Approved 18-7-2018 First pt. 5-11-2018	Open
High-Risk Neuroblastoma Study 2 of SIOP-Europa-Neuroblastoma (SIOPEN)	HR-NBL2/ SIOPEN	International	IGR	SO	Approved 3-3-2021	Open
Teicoplanin as Infection Prophylaxis in Pediatric Acute Myeloid Leukemia (Pro-Teico): An open-label, randomized clinical trial on teicoplanin infection prophylaxis in pediatric patients with acute myeloid leukemia	Pro-Teico	International	Princess Máxima Center	HO	Approved	Open
International cooperative treatment protocol for children and adolescents with lymphoblastic lymphoma	LBL 2018	International	Munster	HO	Approved 21-6-2021	Open
IntReALL SR 2010; International Study for Treatment of Standard Risk Childhood Relapsed ALL 2010; A randomized Phase III Study Conducted by the Resistant Disease Committee of the International BFM Study Group	IntReALL SR 2010	National	Charité - Universitäts-medizin Berlin	HO	Approved 27-10-2016	Inclusion closed
Therapeutic drug monitoring of asparaginase and methotrexate metabolism in childhood acute lymphoblastic leukemia	ALL11	International	Princess Máxima Center	HO	Approved 9-11-2012 First pt 2-4-2012	Inclusion closed

Clinical Studies other

Open Investigator-sponsored studies

Study	Working title	Setting	Role DCOG-ECTC	Unit	Date of opening NL	Status
PINOCCHIO-study: Pharmacokinetics of chemotherapeutic agents in children's oncology (PINOCCHIO)	PINOCCHIO	National	Princess Máxima Center sponsor	SO NO HO	Approved 21-12-2021	Open
A retrospective study on compassionate use of Inotuzumab Ozogamicin in infants and younger children with relapsed or refractory acute lymphoblastic leukemia (ALL)	InO compassionate use	International	Princess Máxima Center sponsor	HO	Approved 1-11-2018 First pt. 1-2-2019	In publi-cation
Near-infrared fluorescence imaging using indocyanine green as an adjunct to improve standard-of-care lymph node procedure in pediatric patients with melanoma or sarcoma of head/neck/trunk or extremities: a feasibility trial	Near Infrared	National	Princess Máxima Center sponsor	SO	Approved 7-7-2020 First pt. 14-7-2020	Open
iTHER 2.0: Clinical implementation of a pediatric cancer precision medicine program, enforced with personalized models	iTHER 2.0	National	Princess Máxima Center sponsor	Precision medicine	Approved 15-4-2020 First pt. 22-4-2020	Open
Non-invasive characterization of pediatric brain tumors using metabolic imaging at high magnetic field	7T MRI MITCH	National	UMC Utrecht	NO	Approved 24-12-2020	Open
Testen van een nieuwe antistof therapie met bloed van kinderen met B-cel Non-Hodgkin lymfoom	NHL-IgA	National	UMC Utrecht	HO	Approved 27-5-2021	Open
Fasting Intervention for children with Unilateral Renal Tumors to reduce Toxicity	FIURTT	National	Princess Máxima Center sponsor	SO	Approved 18-6-2021	Open
Immune monitoring in pediatric brain tumors	MIMIC Brain	National	Princess Máxima Center sponsor	NO	Approved 1-7-2021	Open
Prospective monitoring of immune response following COVID-19 vaccination in children with cancer	VACCinATE	National	Princess Máxima Center sponsor	HO SCT NO SO	Approved 16-7-2021	Open
Gonadal Function and Fertility in Children with Hodgkin Lymphoma Treated According to the EuroNet-PHL-C2 Protocol	EuroNet Fertility	National	VUmc Amsterdam	HO		Inclusion closed
Long-term integrity of hematopoiesis in pediatric stem cell transplantation survivors	Long-term HIT	National	Princess Máxima Center sponsor	SCT	Approved 23-11-2021 First pt 12-1-2022	Open
PK/PD of corticosteroids in graft-versus-host disease after hematopoietic cell transplantation in children	PIKACHU	National	Princess Máxima Center sponsor	SCT	Approved 30-9-2020 First pt. 30-9-2020	Open
International Study for Treatment of High Risk Childhood Relapsed ALL 2010 - A randomized Phase II Study Conducted by the Resistant Disease Committee of the International BFM Study Group	IntReALL HR 2010	International	Charité Berlin		Approved 18-6-2020 First pt. 19-10-2020	Open
Identification of pediatric Hodgkin lymphoma biomarkers and novel therapeutic targets	Hodgkin Biomarker	European	Erasmus MC sponsor	HO	Approved 21-07-2016 First pt. 16-11-2016	Inclusion closed
Skeletal complications of prophylactic Ciproxin in the treatment of pediatric ALL	MRI-study	National	Erasmus MC sponsor	HO	Approved 16-05-2013 First pt. 9-09-2014	Inclusion closed
Single-cell tracing of genomic mutations in human hematopoietic stem cell transplantation recipients	Tracing stem cells	National	Princess Máxima Center sponsor	SCT	Approved 22-05-2019 First pt. 22-10-2019	Open

Clinical Studies Phase I/II

Open Company-sponsored studies

Study	Working title	Unit	Date of 1st site in NL	Status
A Phase II Study of Dasatinib Therapy in Children and Adolescents with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia or with Ph+ Leukemias Resistant or Intolerant to Imatinib	CA180-226	HO	Approved 6-9-2018	Open
CA209-744 -Risk-based, response-adapted, Phase II open-label trial of Nivolumab + Brentuximab Vedotin (N + Bv) for children, adolescents, and young adults with relapsed/ refractory (R/R) CD30 + classic Hodgkin lymphoma (cHL) after failure of first-line therapy, followed by Brentuximab + Bendamustine (Bv + B) for participants with a suboptimal response (CheckMate 744)	CA209-744	HO	Approved 28-8-2017	Inclusion closed
Open-label, Multicenter, Phase 2 Study Evaluating the Efficacy and Safety of Daratumumab in Pediatric and Young Adult Subjects ≥1 and ≤30 Years of Age With Relapsed/Refractory Precursor B-cell or T-cell Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	Daratumumab ALL2005	HO	Approved 21-8-2018	Open
Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies	Durvalumab	HO SO	Approved 17-9-2019	Open
Open-label, Single-arm Trial to Evaluate Antitumor Activity, Safety, and Pharmacokinetics of Isatuximab Used in Combination With Chemotherapy in Pediatric Patients From 28 Days to Less Than 18 Years of Age With Relapsed/-Refractory B or T Acute Lymphoblastic Leukemia or Acute Myeloid Leukemia In First or Second Relapse	Isatuximab	HO	Approved 12-9-2019	Open
Phase 1/2, multi-center, dose-escalating study to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of Quizartinib administered in combination with re-induction chemotherapy, and as a single-agent maintenance therapy, in pediatric relapsed/ refractory AML subjects aged 1 month to < 18 years (and young adults aged up to 21 years) with FLT-3-ITD mutations	Quizartinib	HO	Approved 31-1-2019	Open
Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive relapsed or refractory High Grade Glioma (HGG)	Dabrafenib	NO	Approved 14-2-2018	Open
A phase II trial of tisagenlecleucel in first-line high-risk (HR) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy	CASSIOPEIA	HO	Approved 14-6-2019	Open
A phase II trial of tisagenlecleucel in first-line high-risk (HR) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (B-ALL) who are minimal residual disease (MRD) positive at the end of consolidation (EOC) therapy	BIANCA	HO	Approved 25-6-2019	Inclusion closed
A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE C19 in Pediatric and Adolescent Subjects with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (r/r ALL) (ZUMA-4)	ZUMA-4	HO	Approved 27-9-2017	Open
Phase 1/2 Dose Finding, Safety and Efficacy Study of Ibrutinib in Pediatric Subjects with Chronic Graft Versus Host Disease (cGVHD)	PCYC1146-IM	SCT	Approved 20-11-2019	Inclusion closed
A Phase 1 Study of the Safety and pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients with Relapsed or Refractory Malignancies	M13-833	HO SO	Approved 19-12-2017	Open
A Phase 1/2 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors	LOXO	SO NO	Approved 25-9-2018	Open
An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Pediatric Participants	Ponatinib-INCB 84344-102	HO SO	Approved 22-1-2020	Open
A Multicenter, Open-label, Randomized Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination with Ifosfamide and Etoposide versus Ifosfamide and Etoposide in Children, Adolescents and Young Adults with Relapsed or Refractory Osteosarcoma (OLIE)	OLIE Lenvatinib	SO	Approved 1-12-2020	Open
A Randomized, Open-Label Phase 1b/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor (J1S-MC-JV01)	Ramucirumab JV01	SO	Approved 4-1-2020	Open
A Randomized, Open-Label Phase 2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma	Ramucirumab JV02	SO	Approved 4-1-2020	Open

An Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy (KEYNOTE 667)	Pembrolizumab	HO	Approved 16-3-2021	Open
An Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy (KEYNOTE 667)	Ponatinib-1501 Takeda	HO	Approved 19-4-2021	Open
A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with BRAF-Altered, Recurrent or Progressive Low-Grade Glioma	Firefly D101	NO	Approved 8-11-2021	Open
A PHASE 1/2, OPEN-LABEL, SINGLE ARM, A phase 1 / 2, open-label, single arm, multicohort, multicenter trial to evaluate the safety and efficacy of JCAR017 in pediatric subjects with relapsed/refractory B-ALL and B-HL (Transend Pedall)	JCAR study	HO	Approved 25-8-2020	Open

Clinical Studies Phase III & Other

Open Company-sponsored studies

Study	Working title	Unit	Date of 1st site in NL	Status
A Phase 3 Study of Lenti-D Drug Product After Myeloablative Conditioning Using Busulfan and Fludarabine in Subjects ≤ 17 Years of Age With Cerebral Adrenoleukodystrophy (CALD)	ALD-104	SCT	Approved 24-6-2019	Open
Long Term Follow-up of Patients Exposed to Lentiviral-Based CD19 directed CAR T-CELL Therapy	PAVO	SCT	Approved 8-4-2020	Open

Other Investigator-initiated studies

Other indications (QoL or PK)

Study	Working title	Date of opening Princess Máxima Center	Status
Cancer in Pregnancy (CIP)	CIP	6-6-2018	Open
Clinical validation of a dried blood spot (DBS) method for the analysis of immunosuppressive and antifungal drugs in pediatric patients (Protect)	Protect	1-9-2018	Open
Divergent Low Level Laser Therapy as novel treatment for oral mucositis in pediatric cancer patients (DuLamp)	DuLamp	Unknown	Open
Preserving ovarian function through cryopreservation and informing girls with cancer about infertility due to gonadotoxic treatment	PAREL	19-11-2020	Open
Early detection of acute and early-onset cardiovascular toxicity in children with cancer using a multiparametric approach	EARLY	19-11-2020	Open
Managing Insomnia after Childhood Cancer in Adolescents (Micado-2)	Micado-2	29-8-2018	Open
Visual impairment in children with a brain tumor in the Netherlands: a prospective nationwide study using standard visual testing and optical coherence tomography	KIZZ	Unknown	Open
The THYRO-Dynamics study: Is the dynamics of thyroid hormones during cancer treatment in children adaptive or disruptive? - a prospective evaluation	THYRO-Dynamics	10-1-2020	Open
Resting energy expenditure in children with cancer	ENERGICE	13-2-2020	Open
Improving care for children with a brain tumor. The SuSPeCT study: getting insight into stress, sleep and cognitive functioning	SuSPeCT	6-1-2020	Inclusion closed
Smell and Taste changes in Childhood Cancer Patients (SENSORY-2)	SENSORY-2	5-8-2020	Open
Body composition of patients with neuroblastoma	BODY	Unknown	Open
Empowering parents in pediatric oncology with an online cognitive-behavioral based group intervention: a randomized controlled trial	OpKoersOnline	3-9-2020	Inclusion closed
The efficacy of a lock solution containing taurolidine, citrate and heparin for the prevention of tunneled central line-associated bloodstream infections in pediatric oncology patients, a randomized controlled, mono-center trial	CATERPILLAR	19-10-2020	Open

A prospective study on determinants of ototoxicity during treatment of childhood cancer (the SOUND study)	SOUND	24-12-2020	Open
Reducing Pain in Pediatric Oncology Patients at Home Effectiveness of the KLIK Pijnmonitor App	RELIEF-2	8-1-2021	Open
Longitudinal Monitoring of Neuropsychological Outcomes in Pediatric Oncology	NEMO	11-6-2021	Open
Diagnosis and Management of Febrile Illness using RNA Personalised Molecular Signature Diagnosis	DIAMONDS	3-9-2021	Open
Testicular Biopsies in Young Boys Diagnosed with Cancer To Cryopreserve Future Fertility; Towards a Safe and Feasible Future Autologous Cell Therapy	PRINCE	17-9-2021	Open
Evaluatie van Shared Decision Making bij primaire maligne bottumoren chirurgie rond de knie bij kinderen en jongvolwassenen	SDM bone tumors	19-10-2021	Open
Bereavement care for parents of critically ill children during end-of-life and after death	EMBRACE	6-7-2021	Open
Functional outcome, quality of life and adverse events after local therapy for bone sarcoma in children; a multidisciplinary and standardized approach feeding into optimal follow-up care for the future	FU-poli bone sarcomas	1-11-2021	Open
The contribution of genetic predisposition to pediatric cancer: a study integrating extensive phenotyping and state of the art genotyping	PrediCT	10-9-2020	Open

Late effects studies

Studies with a visit to the Late effects ('LATER') outpatient clinic on Late effects after childhood cancer

Study	Working title	Status Protocol	Date protocol open in NL
LATER A-dataregistratie	LATER A-data registration	Open	1-1-2008
DCCSS LATER 1 study extension: risk and time trends of subsequent tumors after five decades of pediatric cancer treatment	DCCSS LATER 1 extension; SMN	NA	1-1-2019
Registration & medical record study: Health problems after 3D-planned pediatric radiotherapy	Registration & medical record study: RT 3D-planned	NA	1-1-2017
Facilitators and barriers in childhood cancer survivors for adopting healthy lifestyle behaviors: development and evaluation of feasibility of a PanCareFollowUp lifestyle intervention	PCFU substudy: WP 5.5 Lifestyle	Open	1-12-2019
DCCSS LATER 1 substudy: Long-term side effects of upper-body radiotherapy: Evaluation of risk factors and detailed assessment of clinical characteristics to inform pediatric radiotherapy and survivorship care	DCCSS LATER 1 substudy: Long-term side effects of upper-body radiotherapy	Open	1-1-2017
DCCSS LATER 1 study: Colorectal adenoma and cancer after treatment for pediatric cancer - risk, risk factors, and surveillance guidelines	DCCSS LATER 1 substudy: Colon carcinoma and adenoma	Open	1-1-2018
Innovaties voor de LATER richtlijn follow-up kinderkanker: ontwikkeling en implementatie	Máxima Innovatie LATER-richtlijn FU na kinderkanker	Open	1-1-2021
Monitoring QoL in Long-Term Follow-Up Care of Childhood Cancer Survivors: Implementation and Evaluation	KLIK LATER	Open	3-9-2021
International DCCSS LATER study : International Collaborative Studies to improve risk stratification for breast cancer surveillance among female survivors of childhood and adolescent cancer	International DCCSS LATER study: IPD Breast Cancer	NA	1-1-2019

CRC Approved studies

Approved studies Clinical Research Committee Princess Máxima Center

PMC CRC number	Approval for:	Title	Working title	PI
PMC CRC 2021-002	Protocol	EMBRACE	emBRACE-study: Kwalitatief onderzoek naar de ervaringen met verlies en rouw bij ouders van ernstig zieke kinderen en na het overlijden van het kind.	Prof. dr. Grootenhuis
PMC CRC 2021-003	Protocol	TEMOKIDS	A population pharmacokinetic, acceptability and safety study for Kimozo, a pediatric oral suspension of temozolomide.	Dr. Van Eijkelenburg
PMC CRC 2021-006	Grant	Mondzorg Kinderen Kanker	Vooraanvraag: Implementatie richtlijn mondzorg kinderen met kanker	Prof. dr. Tissing
PMC CRC 2021-007	Protocol	KLIK LATER	Monitoren van de kwaliteit van leven bij lange-termijn follow-up zorg bij survivors van kinderkanker met behulp van online, patiënt-gerapporteerde uitkomstmaten via het KLIK PROM portaal	Prof. dr. Grootenhuis/ Prof. dr. Kremer
PMC CRC 2021-008	Protocol	Poli bone sarcomas	Functional outcome, quality of life and adverse events after local therapy for bone sarcoma in children; towards a prediction model for the outcome of local therapy	Dr. Merks
PMC CRC 2021-009	Protocol	DAY101-001	FIREFLY-1: A Phase 2, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of the Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with BRAF-Altered, Recurrent or Progressive Low-Grade Glioma	Dr. Van der Lugt
PMC CRC 2021-010	Protocol	5-ALA	Clinical safety study on 5-Aminolevulinic acid (5-ALA) in children and adolescents with supratentorial brain tumors	Prof. dr. Hoving
PMC CRC 2021-011	Grant	[18F]mFBG PET-CT study	Diagnostic accuracy of [18F]mFBG PET-CT compared to [123I]mIBG scanning – a prospective non-inferiority study	Dr. Tytgat
PMC CRC 2021-012	Protocol	Hem-iSMART	Diagnostic accuracy of [18F]mFBG PET-CT compared to [123I]mIBG scanning – a prospective non-inferiority study	Prof. dr. Zwaan
PMC CRC 2021-014	Protocol	Plasma urine study	International multicenter observational study to determine the diagnostic sensitivity of catecholamine metabolites in urine compared to their diagnostic sensitivity in plasma in children with high risk neuroblastoma	Dr. Tytgat
PMC CRC 2021-016	Grant	Growth curves QoL	Growth curves of quality of life and participation in children after treatment for cancer: clinical application and scientific insight	Prof. dr. Grootenhuis
PMC CRC 2021-017	Grant	Holographic navigation kidney tumors	Holographic navigation for pediatric kidney tumor surgery	Prof. dr. Wijnen
PMC CRC 2021-018	Grant	ACCESS	Providing ACces to targeted treatments for ChildrEn with nrStS (ACCESS)	Prof. dr. Van Noesel
PMC CRC 2021-019	Grant	iBrain	iBrain: a personalized intervention program to improve daily functioning for children with brain tumors	Dr. Partanen
PMC CRC 2021-021	Protocol	ALCL-VBL	International cooperative prospective study for children and adolescents with standard risk ALK-positive anaplastic large cell lymphoma (ALCL) estimating the efficacy of Vinblastine	Dr. Veening
PMC CRC 2021-022	Protocol	Briga-ped	A phase I/II study of Brigatinib in pediatric and young adult patients with ALK+ Anaplastic Large Cell Lymphoma, Inflammatory Myofibroblastic Tumors or other solid tumors	Prof. dr. Zwaan
PMC CRC 2021-029	Protocol	Diagnosis trajectory in pediatric oncology	Analysis of patient-centered communication during the diagnosis trajectory for children with hematological malignancies	Prof. dr. Grootenhuis
PMC CRC 2021-031	Grant	FASTigial study	FASTigial study: Finding anatomical substrates in cerebellar mutism syndrome in children with posterior fossa tumors	Dr. Partanen
PMC CRC 2021-033	Protocol	ATRT01	An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT) including A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy	Dr. Franke
PMC CRC 2021-034	Protocol	SNDX-5613	A Phase 1/2, Open-label, Dose-Escalation and Dose-Expansion Cohort Study of SNDX-5613 in Patients with Relapsed/Refractory Leukemias, Including Those Harboring an MLL/KMT2A Gene Rearrangement or Nucleophosmin 1 (NPM1) Mutation	Prof. dr. Zwaan
PMC CRC 2021-035	Protocol	PanCareSurPass	PanCareSurPass: facilitators and barriers for scaling up use of SurPass v2.0 in three health system scenarios - a survey study	Prof. dr. Kremer
PMC CRC 2021-036	Protocol	Carfilzomib	Phase 1b/2 study of Carfilzomib in combination with induction chemotherapy in children with relapsed or refractory acute lymphoblastic leukemia	Dr. Van der Sluis
PMC CRC 2021-037	Protocol	MIMIC AML	Monitor immune microenvironment and systemic immune effects in pediatric acute myeloid leukemia	Prof. dr. Zwaan
PMC CRC 2021-038	Protocol	IZP	De volgende stap in het kind- en gezinsgerichte individuele zorgplan	Prof. dr. Kremer
PMC CRC 2021-040	Protocol	Ganepos	Gabapentin for the Treatment of Neuropathy in Pediatric Oncology Settings	Dr. Vormoor
PMC CRC 2021-042	Protocol	Robot sleep professor	The robot sleep professor: a pilot study of a social robot providing sleep education in pediatric oncology	Prof. dr. Grootenhuis/ dr. Merks
PMC CRC 2021-043	Protocol	VACCinATE	Prospective monitoring of immune response following COVID-19 vaccination in children with cancer	Prof. dr. Tissing
PMC CRC 2021-044	Grant	Hypo-effect	Medische- en kosten effectiviteit van de behandeling middels een behandelalgoritme over 6 klinische domeinen voor verworven hypothalame obesitas op de kinderleeftijd	Prof. dr. Tissing

PMC CRC 2021-046	Protocol	APAL2020D	Randomized phase 3 trial of fludarabine/cytarabine/ gemtuzumab ozogamicin with or without venetoclax in children with relapsed AML	Dr. Goemans
PMC CRC 2021-047	Protocol	ZN-c3-003	A phase 1/2 dose escalation and dose expansion study of ZN-c3 in combination with Gemcitabine in adult and pediatric subjects with relapsed or refractory osteosarcoma	Dr. Van Eijkelenburg
PMC CRC 2021-048	Protocol	NB2015-LR	Prospective multicenter clinical trial for risk estimation and treatment stratification in low and intermediate risk neuroblastoma patients	Prof. dr. Van Noesel
PMC CRC 2021-049	Protocol	NBL dinutuximab-IRDye800CW	A phase 1-2 first-in-human imaging study of anti-GD2-IRDye800CW in patients with neuroblastoma	Prof. dr. Wijnen
PMC CRC 2021-051	Protocol	DIAMONDS biomarker	Proteomic signatures to diagnose etiology of fever in pediatric cancer patients	Prof. dr. Tissing
PMC CRC 2021-057	Grant	TRINGQS study	Tinnitus and its relation with hearing loss, biomarkers, genetics and quality of life in childhood cancer survivors	Prof. dr. Van den Heuvel
PMC CRC 2021-059	Protocol	Microbiome diversity	Changes in nutritional status and micro-biome diversity in children with cancer	Prof. dr. Tissing
PMC CRC 2021-060	Grant	LATER MetVasA	Metabolic syndrome and vascular damage in relation to accelerated aging in survivors of hematopoietic stem cell transplantation for hematologic malignancy: towards preventive lifestyle interventions	Dr. Bresters/ dr. Pluijm
PMC CRC 2021-065	Grant	INTERACT	INTERcultural heAlth CommunicaTion in pediatric oncology: achieving quality of care for all (The INTERACT study).	Prof. dr. Grootenhuis
PMC CRC 2021-067	Grant	Early toxicity	Early onset toxicity from image-guided highly-conformal radiotherapy to the upper abdomen in children with neuroblastoma and renal tumors.	Dr. Janssens
PMC CRC 2021-072	Grant	Neurotoxic effects	Neurotoxic effects of cancer and treatment on the developing brain	Dr. Partanen

Appendix 2

Princess Máxima Center publications

- Aarsen FK, van Veelen-Vincent MC, Partanen M, Catsman-Berrevoets CE. Perioperative risk factors for long-term intelligence in children with postoperative cerebellar mutism syndrome after medulloblastoma surgery. Pediatr Blood Cancer. 2022 Mar;69(3):e29536. doi: 10.1002/pbc.29536. Epub 2021 Dec 31. PMID: 34971023.

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