Original Article

Defining functional requirements for a patient-centric computerized glaucoma treatment and care ecosystem

Nahum Goldmann[1]^, Simon E. Skalicky[2]^, Robert N. Weinreb[3]^, Ricardo Augusto Paletta Guedes[4]^, Christophe Baudouin[5]^, Xiulan Zhang[6]^, Aukje van Gestel[7], Eytan Z. Blumenthal[8]^, Paul L. Kaufman[9], Robert Rothman[10,11,12], Ana Maria Vasquez[13], Paul Harasymowycz[14]^, Derek S. Welsbie[15]^, Ivan Goldberg[16]^

[1]ARRAY Development, Ottawa, ON, Canada; [2]Department of Surgery Ophthalmology, University of Melbourne, Melbourne, VIC, Australia; [3]Hamilton Glaucoma Center, Viterbi Family Department of Ophthalmology and Shiley Eye Institute, University of California San Diego, La Jolla, CA, USA; [4]Paletta Guedes Eye Institute and Federal University of Juiz de Fora, Juiz de Fora, MG, Brazil; [5]Quinze-Vingts National Ophthalmology Hospital, and Vision Institute, IHU ForeSight, Paris, France; [6]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Ophthalmology and Visual Science, Guangdong Provincial Clinical Research Center for Ocular Diseases, Guangzhou, China; [7]Studio van Gestel, Helmond, the Netherlands; [8]Department of Ophthalmology, Rambam Health Care Campus, and Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel; [9]Department of Ophthalmology & Visual Sciences, School of Medicine & Public Health, University of Wisconsin - Madison, Madison, WI, USA; [10]Glaucoma Consultants of Long Island/OCLI, Bethpage, NY, USA; [11]Ophthalmology, Zucker School of Medicine at Hofstra/Northwell, West Hempstead, NY, USA; [12]InFocus Capital Partners, Jericho, NY, USA; [13]Instituto de Oftalmología y Glaucoma Vásquez, Hospital Metropolitano, Quito, Ecuador; [14]University of Montreal, Bellevue Ophthalmology Clinics and Montreal Glaucoma Institute, Montreal, Canada; [15]Hamilton Glaucoma Center, Viterbi Family Department of Ophthalmology, University of California, San Diego, La Jolla, CA, USA; [16]Discipline of Ophthalmology, The University of Sydney, Glaucoma Unit, Sydney Eye Hospital and Eye Associates, Sydney, NSW, Australia

Contributions: (I) Conception and design: N Goldmann, I Goldberg, SE Skalicky, RN Weinreb; (II) Administrative support: N Goldmann; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Nahum Goldmann. ARRAY Development, Box 815, Fort Erie, Ottawa, ON, L0S 1B0, Canada.
Email: NahumGoldmann@ARRAYdev.com.

Background: Glaucoma is a group of chronic diseases that cause progressive damage to the optic nerve, resulting in irreversible and potentially debilitating visual loss. A unified, comprehensive and quantitative decision-making methodology is necessary to support clinicians and patients when conducting effective computer-aided glaucoma clinical diagnosis, monitoring, treatment and quality of life (QoL) assessment.

Methods: We set out the functional requirements for a patient-centric computerized glaucoma treatment and care ecosystem with a 5- to 20-year time horizon. We evaluate three approaches used for glaucoma diagnosis, treatment and establishment of QoL targets: firstly, the Biomedical Model based on biophysical testing; secondly, conventional QoL assessment approach based on various patient-reported outcome (PRO) questionnaires; and thirdly, Outcomes models to evaluate healthcare based on analysis of Quality Adjusted Life Years (QALYs).

Results: We identify many critical issues related to handling and analysis of glaucoma patient health data (technical, regulatory, security and privacy), as well as those related to the assessment of biological, psychological, and socioeconomic wellbeing, risk management, the ability to live independently, with adaptation to different cultures, languages and local healthcare delivery patterns. We address health planners, glaucoma research bodies and healthtech investors. We propose a blueprint for computerized actions required to improve treatment outcomes and to reduce costs while simultaneously providing individualized

^ ORCID: Nahum Goldmann, 0000-0002-0387-5035; Simon E. Skalicky, 0000-0001-8022-8002; Robert N. Weinreb, 0000-0001-9553-3202; Ricardo Augusto Paletta Guedes, 0000-0002-9451-738X; Christophe Baudouin, 0000-0003-1743-6698; Xiulan Zhang, 0000-0002-9288-0767; Eytan Z. Blumenthal, 0000-0001-6836-0473; Paul Harasymowycz, 0000-0003-2524-7811; Derek S. Welsbie, 0000-0002-3772-9335; Ivan Goldberg, 0000-0001-7180-6202.

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support to millions of glaucoma patients globally.

Conclusions: Such patient-centric methodology must be based on interdisciplinary integration and mutual assistance from these three complementary approaches, as well as on their ongoing simultaneous improvements. To implement an effective healthcare decision support platform globally, all these challenges must be resolved. All this can be achieved in a consistent, cost-effective, high-quality manner.

Keywords: Glaucoma; chronic diseases; computerized treatment and care ecosystem; functional requirements; blueprint for actions

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Introduction

We outline functional requirements for a glaucoma medical treatment and quality of life (QoL) digital healthcare ecosystem using artificial intelligence (AI). Digital business ecosystems are critical platforms to attain sustainable benefits for participants and stakeholders. Management, innovation, knowledge and technology ecosystems are large, complex, closely interconnected global business networks of complementary computerized organizations and consumers, which produce and support specialized products and services.

The principal goal of sustainable healthcare ecosystems is to raise the quality of health outcomes and to solve unmet needs—by improving the efficiency of healthcare services, the effectiveness of resource usage, and patient satisfaction (1-3). An ecosystem's stakeholders jointly create outputs that recognize goals and enhance activities of individual participants, influencing behaviors of partners, competitors and customers. The operational dynamics of ecosystems have strategic implications for practitioners, platform managers, technology architects, policymakers, entrepreneurs and clients (4-10). The concept of ecosystems has been applied productively to digital healthcare (11-17).

An effective glaucoma healthcare ecosystem must follow and support numerous individual patients, each for many years. It should assist health professionals to improve glaucoma diagnosis, to optimize effectiveness of each individual's treatment while reducing possible side effects, and it should facilitate productive lives for patients and their families. Detection and management of comorbidities must be included, all in the framework of optimal use of limited financial resources on a population basis.

The coronavirus disease 2019 (COVID-19) pandemic has highlighted current healthcare structural deficiencies and the need for cost-effective, standardized protocols to manage glaucoma and ocular hypertension. It has increased interest from payers for effective remote monitoring and management.

Glaucoma is a group of chronic diseases that cause progressive damage to the optic nerve, resulting in irreversible and potentially debilitating visual loss. Gradual changes in midperipheral vision often delay patient awareness of disease until significant damage has occurred. While for most patients, visual loss can be slowed or halted, early detection is key to avoid disability. Reduction of intraocular pressure (IOP) is the major modifiable treatment strategy to slow progressive glaucomatous damage. Effective glaucoma management identifies the disease early, with lifelong IOP-lowering and monitoring (18-20).

The Global Burden of Disease Study 2017 (21) identified visual impairment as one of the top three principal causes of years of life lived with disabilities. The World Health Organization (WHO) estimated that worldwide more than 2 billion individuals have some type of visual impairment, at least half of them preventable (22). Because vision is a dominant sense throughout life, visual disability greatly impacts individuals. The socioeconomic effects of direct medical, non-medical and various indirect costs impact employment, QoL and care needs of those visually disabled, their families, caregivers, health systems and society (22-24).

We suggest a 5- to 20-year time horizon to develop and implement a smart glaucoma healthcare ecosystem. To do so, we evaluate three approaches used for glaucoma diagnosis, treatment and establishment of QoL targets—firstly, the Biomedical model based on biophysical testing; secondly, conventional QoL assessment approach based on various patient-reported outcome (PRO) questionnaires; and thirdly, Outcomes models to evaluate healthcare based on analysis of Quality Adjusted Life Years (QALYs). Effective computer-aided glaucoma clinical diagnosis, monitoring,

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treatment and QoL assessment can only be achieved with a unified, comprehensive and quantitative decision-making methodology. Such patient-centric methodology must be based on interdisciplinary integration and mutual assistance from these three complementary approaches, as well as their substantial, simultaneous and ongoing improvements.

We identify many critical issues related to handling and analysis of glaucoma patient health data (technical, regulatory, security and privacy), as well as those related to the assessment of biological, psychological, and socioeconomic wellbeing, risk management, the ability to live independently, with adaptation to cultural and language differences and local healthcare delivery patterns. To implement an effective healthcare decision support platform globally, all these challenges must be resolved.

We address health planners, glaucoma research bodies and healthtech investors. We propose a blueprint for computerized actions required to improve treatment and to support millions of glaucoma patients all over the world, in a consistent, cost-effective, high-quality manner.

The need for a new glaucoma healthcare ecosystem

Conventional glaucoma management is based on IOP-reduction with intermittent monitoring of damage endpoints, such as visual field sensitivities and optic nerve head changes. Treatment and diagnostic methods have become entrenched. New medications and microsurgeries are sometimes less effective, even though they might have increased safety profiles (25-30).

Current treatment strategies often rely on topical IOP-lowering drops, despite demonstrated poor adherence and perseverance, with little likelihood for improvement even with patient education. Such suboptimal treatment strategies compound the challenges posed by the very high proportion of the global glaucoma population undiagnosed both in developed and developing countries. According to the latest data, in North America, 62% of glaucoma cases are undiagnosed, in Europe, 68%, in Asia, 84%, and in Africa, 94%; these patients are not being treated to prevent irreversible blindness (31). This has immediate consequences, as disease progression undermines QoL (32-56).

The novel field of healthcare ecosystems is being built on the boundary of several well-established professional practices, among which the most prominent and sizable are medicine and IT-System Integration (SI). The global healthcare services market size is expected to grow from $6.87 trillion in 2021 to $10.41 trillion in 2026, at a compound annual growth rate (CAGR) of 8–10% (57). Revenue in the IT Services market is projected to grow from $1.1 trillion in 2022 to $1.6 trillion by 2027 with a CAGR of 7% (58), of which AI is among the fastest growing segments that promise to domineer IT services within 10 years, valued at $60 billion in 2021, reaching $422 billion by 2028 with CAGR of 39% (59).

To date, the success rate of mid-size to large IT-SI and AI healthcare projects has been modest for valid objective and subjective reasons, whose analysis lies outside the scope of our paper (60-66). Success rates for IT-SI and AI projects in other large-scale industrial segments, like financial or government, are not better than that of healthcare. According to Standish Group's Annual CHAOS report based on analysis of 50,000 projects globally and supported by many industry sources, 66% of technology projects end in partial or total failure (67,68).

Large software development projects are conceptually risky, with the majority failing to deliver desired outcomes. The main goal of the Functional Requirements Specifications (FRS) is to balance the needs of stakeholders to manage such existential risks. Being on the boundary of several disciplines, patient-centric computerized glaucoma treatment and care ecosystems necessitate effort by all stakeholders to understand the critical challenges to its successful development that lie outside of their comfort knowledge zone. The main challenges in fusing medical and IT-SI/AI approaches while obtaining tangible results are to build mutual trust and understanding between two different professional disciplines, each with its well-established terminology, ontology, classifications and expectations for project outcomes.

As in other industrial sectors, every IT-SI and AI healthcare project usually starts with the development of FRS, to formalize outcome agreements between project stakeholders. Each year a vast number of requirement specifications have been produced by software developers globally. Large SI projects failure is usually due to shortcomings in these critical documents, mostly from a bias in several SIs that dominate this industrial segment, as well as limited input from their clients in FRS creation (69-71).

We hope to start a pre-competitive strategically successful requirement-gathering process that will develop a more formal FRS for an effective, efficient, integrated patient-centric glaucoma healthcare ecosystem. Requirements for an effective software platform are listed in *Table 1*. Addressing these requirements will identify our

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Table 1 Typical input requirements for a sustainable healthcare ecosystem platform (72-77)

Description of services that the software must offer
Demonstration of the platform's added value and economic benefits to its principal stakeholders (critical for evaluation of any ecosystem's sustainability)
Applicable regulatory frameworks (functional, socioeconomic, security, privacy)
Required properties of inputs and outputs
Features, functions and components of the system and its subsystems needed to satisfy its numerous users
Work and data flows
System's behavior in real life, including critical user interfaces
Risk profiles

project's scope, cost and chance of success.

A critical document, FRS quantifies for stakeholders system implementation, delineates the character and accuracy of assumptions and constraints, benefits and sustainability, and outlines how to control risks to enhance deployment and operations. This 'evergreen' (78) document would need to crystallize broad agreement between clients and developers, supported by health innovation, medical and regulatory communities in many countries, on how to implement, continuously to improve and to extend a glaucoma holistic ecosystem. While FRS provides a sound basis for the project, it does not circumscribe how the healthcare ecosystem should be implemented, nor constrain its developers to any specific design or technology.

As this approach requires substantial development outside existing health support and biomedical research structures, with regulatory approvals in many countries, the FRS needs to crystallize broad agreement with support from the health innovation community for a new patient-focused glaucoma diagnosis, treatment and holistic interaction healthcare ecosystem. While innovation is inherently risky, if seen as a large digital platform and an AI methodology-development exercise, it could provide clinicians embracing this new healthcare ecosystem flexibility and freedom to question established dogmas. In the post-COVID-19 healthcare services and socioeconomic environment there would seem to be no viable alternative to such a radical change.

Glaucoma patients' requirements for a computerized healthcare ecosystem

Glaucoma is a group of chronic neurodegenerative diseases, mostly affecting the older population. Most glaucoma patients are above 40 years old (79-81) while prevalence increases considerably after age 60; with the aging population worldwide, it is expected to continue to increase. The glaucomas are the second most common cause of blindness worldwide: in 2020 there were 79.6 million individuals globally with glaucoma, estimated to increase to 111.8 million in 2040, of whom 13% will become bilaterally blind (82).

With medical treatment, the mean time between the appearance of the first visual changes and blindness might be 30–40 years for younger patients (80). However, there is considerable variability, as some individuals worsen in just a few years (83-85). Monitoring and treatment services provided to individuals with glaucoma before they reach advanced stages of this disease are important to prevent irreversible blindness. When the considerable negative impact of blindness on individuals, their families and communities is taken into account, ongoing monitoring and treatment are cost-effective (86), providing they are supported by a potent, consistently efficient healthcare ecosystem.

Recently, there has been an acceleration in the use of telemedicine to deliver healthcare. Remote healthcare services improve access, decrease costs, are convenient for patients (especially those less mobile or living distantly), and also improve patient satisfaction (87). Over 70% of patients preferred virtual visits if given a choice (88). Direct-to-patient (DTP) care delivery is one of the most effective, safest and popular forms of telehealth. It has the potential to provide interactions with patients that are not currently accessing healthcare regularly; it can be successfully implemented in ways that limit costs and improve care. The remote ordering and automated delivery by the DTP drug supply chain allow patients to access medications

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without going to the clinic or pharmacy in person. This is essential to protect patients during epidemics (89). For example, centralized procurement of IOP-lowering drugs can decrease each patient's cost, which improves medication adherence (90-97).

Teleophthalmology might not be suited yet for a detailed examination of vision, intraocular structures and surgery (98), although evolving new technologies are moving in this direction in all medical disciplines. Safadi *et al.* (99) recommend that teleglaucoma should be used to follow up routine cases with instructions about treatment. As contemporary office-based measurements are already insufficient to discover diurnal pressure changes and spikes, as well as to demonstrate effects of medications and adherence, patient-directed self-tonometry could be performed throughout the day, becoming an important part of the delivery of care to glaucoma patients (99). As periodic measurements of central and peripheral vision are critical in glaucoma management, telehealth methods of peripheral and central vision assessment, as well as integrated clinical systems to store, monitor and analyze changes in vision over time, need to be further developed and implemented (100). Although challenging, telehealth methods need to incorporate equivalents to structural tests such as optical coherence tomography (OCT) and disc photos, as well as gonioscopy. Such demanding tests could also be effectively and cost-efficiently accommodated in specialized local glaucoma testing centers.

Introduction of a glaucoma medical treatment and QoL digital ecosystem and wide use of new telehealth practices requires retraining and redeployment of clinical staff for new tasks. It needs creative rethinking on how best to examine patients and to support their ongoing treatment, health and comfort decisions. Testing of IOP and visual field, and examining optic nerve head changes are particularly challenging—without them, it is difficult to assess glaucomatous progression, which drives clinicians to make treatment decisions.

Such a radical and rapid realignment of glaucoma treatment services is impossible to achieve just by improving the status quo, however significantly. It requires pragmatic digitization of the whole glaucoma care process, changes in financing and administration, and necessitates proactive involvement of patients. The AI-based methodological approach described in this article could result in the implementation of an effective, efficient and optimized platform in support of the required fundamental changes that are needed in glaucoma testing, treatment and patient support.

Demand for personalized care

Neurodegenerative processes are multifactorial (environmental and genetic), driven by stressor accumulation and failure of biologic resiliency. They might be sporadic or rapid, appearing as random and unique for each patient.

All neurodegenerative diseases are complex, with significant and increasing impact on patients. Lack of curative therapies notwithstanding (101,102), many glaucoma patients can save their vision with appropriate IOP reduction. Successful glaucoma patients' treatment and support require personalized care with individualized therapeutic targets to safeguard their QoL.

Biomedical testing targets for glaucoma patients must be individualized based on factors like glaucoma type, its course, severity at diagnosis, life expectancy, risks to vision, as well as risks and benefits of various treatment strategies (33,44,81,103,104). For a patient with an incurable condition, long-term treatment priorities and risk profiles are different from those with an acute disease, as the clinician cannot base management just on biomedical testing results. Targets need to account for each individual's essential QoL, socioeconomic situation and personalized visual needs, along with limited societal financial resources and long-term risks.

Overly aggressive treatment targets might lead to overtreatment with more side effects and waste of resources, while insufficient targets risk undertreatment with visual loss. Hence the need for a precise treatment and ongoing support balance for each individual (105). As glaucoma progresses and/or an individual's circumstances change, testing, treatment and QoL targets need to be revised jointly by the clinician with the patient. Flexibility is vital.

Need for AI in glaucoma diagnosis, monitoring and treatment

A personalized glaucoma diagnosis and treatment ecosystem is complex, with many dynamic functions and variables. Effective global implementation is only possible with a powerful computerized AI-based decision-making system that acknowledges glaucoma's chronicity, maximizes the therapeutic ratio (effectiveness versus costs), and focuses on patient QoL rather than the disease alone. Such a healthcare ecosystem will need to adapt to different languages, cultures and healthcare systems. Exponential data accumulation

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and the limits to human cognition make an AI system indispensable (106-108) (see section "*Economic foundations of a glaucoma healthcare ecosystem*").

Only computerization of this ecosystem enables long-term personalized medical treatment and ongoing QoL support. AI systems have high implementation costs, substantial scaling challenges and potentially lower solution accuracy. They overparameterize small datasets and/or produce fragile models that degrade rapidly at the in-field deployment phase. AI algorithms rapidly age in operation and maintenance; they must be constantly updated (109-111).

Cloud computing networks have the processing capacity to handle complex methodological approaches, algorithmic or AI, as long as they are logical, quantifiable and well formalized. They will likely be able to support this immense computational challenge.

Compared with the current human expert-driven approach, effective computerization requires a far more systematic and analytic patient treatment methodology. Clinicians are fallible and inconsistent: medical diagnosis and treatment require simultaneous consideration of multiple interlocking factors, often in a busy clinical environment with numerous stressors. Such complex decisions can be oversimplified, with many aspects of patient care overlooked. A coherent methodological approach to treat chronic glaucoma patients should be able to provide a viable foundation to digitize this complex and interconnected workflow of biomedical testing, patient treatment and QoL assessment. Such a massive algorithmic problem will need new computational and AI approaches.

The need for a coherent workflow-based methodology

To resolve this contradiction, a coherent workflow-based methodology charted with the proactive participation and biomedical guidance of leading glaucoma academic and clinical experts would greatly facilitate development of a patient-centric diagnosis, medical treatment and QoL healthcare ecosystem supported by AI. Such methodology should also be capable of being dynamically updated by computers based on new knowledge, as well as on feedback from clinical experts and patients collected by the smart system itself; all while it functions and continues to evolve. Hopefully, the system would be capable to preserve and build on the experience and legacy of the retiring baby-boomer generation of clinicians and health experts by facilitating their knowledge transfer to younger specialists.

We do not believe that such medical treatment and QoL support system should replace clinicians, as some AI software developers might claim (106,107,112-114). We envision it to support human glaucoma experts, mainly physicians but perhaps also an optometrist or a clinician assistant, especially in developing countries, where there are not enough clinical ophthalmologists. Regrettably, under the current socioeconomic conditions, badly needed glaucoma experts are even less likely to appear soon enough for numerous patients that require qualified help. It is very costly and takes many years to educate a glaucoma specialist (115-117). Regrettably, the training of new glaucoma clinicians is not matching the swift increase in glaucoma patients worldwide; especially in already underserved developing countries (118-122).

Balancing stakeholder needs

In defining a comprehensive AI glaucoma medical treatment and QoL ecosystem, we aim to balance the objectives of the three most important treatment participants and stakeholders—physicians, patients and health services.

Physicians' and other health practitioners' principal goal is an effective diagnosis and less risky course of treatment for patients with various types of glaucomas, at various stages of progression of their chronic disease. An efficient glaucoma healthcare ecosystem must help health practitioners in their step-by-step dealing with very complex sets of various glaucomas, their ever-changing testing and treatments using brand and generic medications, surgeries and implants; and with the exponentially increasing specialized academic and clinical information flow. The healthcare ecosystem should address a significant shortage of clinical glaucoma experts, especially in the developing countries but also in the developed economies; also dealing with the increasing devolution of clinical glaucoma treatment to optometrists, i.e., in Africa, the Caribbean region, Canada. The system should ideally detect visual and ophthalmic comorbidities that develop while the patient is being monitored; be sufficiently sensitive and specific to detect glaucoma at initial assessment and for subsequent glaucoma progression over a long period (30–40 years); and be conveyed intuitively and clearly.

Patients mostly rely on their physicians to guide them in managing their treatment based on very complex and ever-changing biomedical information that even many MDs could not always fully decipher and entirely comprehend.

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Many patients, when informed by their clinician at the outset of their diagnosis on the impact of glaucoma, are frightened about a possible loss of their vision; however, their early motivation to manage daily adherence to IOP self-treatment often allays their concerns. In the absence of a practical ability to control treatment outcomes and of the credible information on likely risks for possible treatment strategies, most patients largely aim to maintain their long-term QoL. QoL is by far the main factor that patients want to address, especially as it typically concerns not just them personally but also their families and other personal contacts and business colleagues. By formulating precise questionnaires based on the unique circumstances of each patient, the integrated patient-centric glaucoma healthcare ecosystem should address the medical and QoL requirements of mostly elderly chronic glaucoma patients, concerns of their families and primary caregivers, while taking into account potential conflicts and side effects of treating other chronic diseases that they might have. Based on the patient's situation, personal choices and likely risk profile, it should be able to generate individualized forecasts of disease progression and provide a trustworthy "second opinion". It could be especially valuable in times of important and stressful decisions, such as consenting to eye surgery.

The Health system's objective is to maintain patients' health and QoL, to prevent visual disability for the individual, with all associated direct and indirect costs for the family and society while also keeping in check expensive treatment options and further expanding costs of long-term chronic treatment.

This paper identifies the principal biomedical, QoL and health status outcome requirements necessary for development of a patient-centric integrated ecosystem.

Key points

(I) We outline functional requirements and principal elements of the underlying methodology for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem as a platform to attain sustainable benefits for glaucoma patients and other stakeholders. We aim to balance the needs of physicians, patients and health services.

(II) With exponential data accumulation and human limitations to make healthcare decisions, the use of AI systems is vital.

(III) To be effective and global, the AI-based approach requires substantial development efforts beyond the capabilities of existing health support and biomedical research structures. For a glaucoma treatment, this would optimize effectiveness with incurred costs, while maintaining focus on the biomedical status of this chronic disease and the patient's QoL.

(IV) To minimize visual deterioration, to support patients holistically and to maximize their QoL, treatment targets need to be individualized. This arises from joint physician-patient development of a personalized management plan. Such a dynamic, multi-faceted challenge needs a digitized AI-based ecosystem.

(V) It is necessary to utilize global cloud-computing processing capacity to handle the multiple complexities of the proposed platform. A coherent methodology would underpin all development and operating processes.

Methods

Approaches to medical treatment, to long-term care and to optimizing QoL for glaucoma patients are fragmented and sporadic worldwide but especially in the developing world. It is further aggravated by the shortage of qualified health and support specialists, along with overworked expert ophthalmologists, reduced funding of health and social support systems, devolution of treatment to optometrists, inconsistencies in medical treatment and substantial increases in patients' misdiagnosis and overtreatment. Implementation of an overarching management structure is increasingly crucial (33,39,45,53,54,56,104,123-129).

Methodological foundation for a new computerized approach

The more glaucoma affects a patient, the more significant impact it has on this patient's QoL and daily functioning (130-135). However, unlike the medical care (that in developed countries is usually covered by public or private insurance), QoL needs of patients in all countries are rarely addressed by their physicians, other health professionals or social workers. Considerable QoL costs encountered by patients are not typically funded by government budgets. While many patients live for 30–40 years with deteriorating vision, often with other chronic diseases, the effect of glaucoma on patients' work, driving, family involvement and their psychological state is neither monitored nor managed.

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A perfunctory reproduction of the existing body of biomedical and QoL knowledge and clinical practice would be insufficient to develop an effective methodological foundation for a new computerized approach that covers the patient's medical treatment and QoL care. However, it would be unproductive to dismiss a large body of objective historical knowledge in research publications and human practice. An effective and powerful methodology for developing a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem should combine both legacy scientific and clinical information with the new knowledge especially formulated and developed for digital applications.

Incorporation of the legacy scientific and clinical information is a critical challenge to develop any medical, financial, or general science AI platform. This problem is exacerbated by the exponentially shrinking half-life of medical knowledge (currently measured in weeks, and soon in days or even hours), with most legacy information becoming rapidly obsolete (136-139). Obsolete knowledge cannot be used to train AI systems, yet valuable older scientific information and clinical 'know-how' must be included. This mammoth task requires development of specialized AI systems that could contain the signal-to-noise ratio of peta-, exa- or even zettabyte knowledge banks within 'reasonable' limits for human comprehension. Such a goal is beyond human abilities or even current supercomputers. Although no such AI systems are being currently commercially developed, the need for them is self-apparent; they will possibly be researched as a part of quantum computing, along with other challenges that future developments of FRS should expose. It reinforces the necessity to plan ahead for complex ecosystem platforms as covered in our article. Because such specialized AI systems have to be built to manage all aspects of innovative knowledge, the principles of their development fall outside of our scope.

Many patients would like to have a rolling 5–10 years forecast of their ability to work, drive a car, their need for personal care and the likelihood of major surgeries. Such a forecast should be based on biomedical testing results, actual data on the patient's adherence to management and other objective and subjective criteria, personal circumstances and priorities. This forecast would also be helpful for clinicians to guide glaucoma management decisions.

Glaucoma patients often have to plan their finances and allocate required resources ahead of their treatments, to sustain their QoL needs. Barring some unforeseen sudden deterioration of a patient's vision, a well-organized computerized medical treatment and QoL support healthcare ecosystem should be able to produce and periodically update personalized mid- and long-term forecasts useful to patients and their health practitioners. To ensure appropriate health and social cost coverage along with necessary treatment and support resources, government budget authorities and private insurers must also accurately estimate such needs.

Currently, this is all but a pipe-dream, as glaucoma patients usually see their ophthalmologists briefly 2–4 times a year; even if a clinician attempts to predict a patient's visual deterioration, there are no resources for them to derive dependable QoL forecasts. As they don't have either time or knowledge on how to tackle patient's QoL issues, it is not routinely addressed. Health systems, social services and insurers do not possess the required reliable treatment and QoL data either.

Therefore, to ensure the effectiveness and efficiency of their treatment and QoL support, smart computerization of the overall system to deal with glaucoma patients is all but inevitable. To be effective and efficient, it must be built on a new and solid methodological foundation that is focused on treating and supporting individual patients over an extended period, rather than just treating the symptoms of this debilitating and incurable disease; which is a far more complex digitization and decision analytic challenge.

Achieving patient-centric computerized glaucoma treatment and support

Guided by clinical, QoL and health system experts, an AI-enabled glaucoma diagnosis and treatment ecosystem could save its participants valuable time and resources, ensuring its viability, caring character and cost-effectiveness. However, in the last several years, there has been observed a huge gap between the AI research and AI implementation, with most media announcements 'being illusory' and only one in ten AI companies achieving actual traction in any meaningful way (112,140-142).

Numerous systematic examinations of the design, reporting standards, risk of bias and claims of various AI medical studies have consistently found under-specification; poor standards of reporting; missing critical data; lack of external validation by testing numerous real-world datasets collected from other institutions that well represent all target demographics and disease states; and lack of transparency that prevents the clinical community

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from determining their reproducibility and deviations from existing reporting standards. Limited availability of code and the use of obscure retrospective datasets with embedded biases or misrepresented data; a small sample size of clinicians to assess AI algorithmic performance; and overhyped, profit-driven, and not always in patients' best interest conclusions of many such reports could result in serious diagnostic or predictive inaccuracy (143-148).

With the help of Moore's law, conventional programming algorithms could be scaled up by the use of faster computer systems and more proficient software languages. For some objective and subjective reasons that are being currently explored, this is not necessarily the case when developing AI platforms (109,110,149). Even though currently the speed of AI computation doubles every three months outpacing Moore's Law (150), some technology observers believe that it is just a short-term fluke; i.e., see (151,152).

In the last 20 years, publications on AI feasibility in healthcare have grown exponentially, reaching 9 thousand academic articles in 2019. However, only a tiny proportion of them has been devoted to actual clinical deployment, with independently verified success stories at the operational/maintenance phase all but lacking (111).

In the multifaceted clinical environment, AI systems, however powerful, could not possibly consider the many subtle and ambiguous but critical situational factors. Nor could they take into account all unwritten social norms and values that humans usually adhere to. This might result in dangerous unintended consequences. Hence, the bottom line is that the key assumption of every buyer of a medical system, which includes AI components, should always be that unless proven otherwise theoretically or experimentally, no AI proof-of-concept model could be safely and timely scaled up and validated for deployment to regulated clinical practice systems.

According to Kelly *et al.* (142), key challenges for the translation of lab AI systems to healthcare practice include those intrinsic to the science of machine learning, logistical difficulties in implementation, and consideration of the barriers to adoption, as well as sociocultural or pathway changes. Thus, Huang *et al.* (112) have attributed the failure of most commercial AI systems in clinical settings to such systems not taking into account the complete diagnosis, as being too complex to process. Instead, their developers usually focus on one or two specific subtasks that their preferred AI engines could competently handle.

Faggella *et al.* (140) notice the lack of explainability of AI medical diagnosis. Kelly *et al.* (142) state that the vast majority of AI studies have been retrospective, i.e., they use historically labeled data to train and test various proof-of-concept algorithms. In contrast, as the retrospective analysis performance is likely to be weakened when encountering real-world data, only the use of prospective studies could address the challenge of successfully translating AI results to clinical practice. Prospective studies, in which patients are typically followed for many years, better represent the clinical paradigm; however, good prospective health studies are decidedly rare and expensive to conduct.

Recognizing these intricate challenges, various guidelines address some of the problems of introducing AI to medical practice—such as preselected retrospective datasets, clean and well-annotated, with small sample sizes and high signal-to-noise ratios. Such constraints are required for a rapid and effective AI model training and validation step that usually looks good in the laboratory as a coveted 'proof-of-concept'. Lab datasets might characterize the disease, but usually poorly represent clinical conditions, administrative matters, the overall state of a patient's health and QoL and possible societal impacts (153). Often they lack adequate reporting and are ambiguous.

To address critically important scalability, SPIRIT-AI and CONSORT-AI, are two comprehensive guidelines recently published by an international multi-stakeholder group to ensure quality of clinical trials for AI health solutions (154,155). Another proposed quality standard, MINIMAR (MINimum Information for Medical AI Reporting), describes the minimum information necessary to understand intended predictions, target populations, hidden biases and the ability to generalize emerging AI technologies (148). Oakden-Rayner and Palmer have proposed the use of summary receiver operating characteristic curve analysis, a technique commonly used in the meta-analysis of diagnostic test accuracy studies, as a methodologically robust method to compare human performance against AI models in medical studies (156).

The US Food and Drug Administration (FDA) is advancing a regulatory framework to develop safe and effective medical devices that take into account the iterative nature of AI learning algorithms. This new regulation (157,158) should allow medical software to improve its performance using real-world AI algorithm learning while ensuring that changes meet the FDA standards for safety and effectiveness throughout the product's lifecycle.

Real-life patient registration and care datasets that cover in-field and operational/maintenance phases are typically patient-centric rather than focused just on the

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disease itself. They are coarse, with a low signal-to-noise ratio for information on a particular disease or sub-diseases that might be useful to AI model processing; they degrade rapidly and must be constantly updated, which might cause misidentification of unrelated processes if their probability scores are higher than for the disease of primary interest. This is yet another argument for the need for explainability of AI medical diagnosis (111).

Currently we don't have a clearly defined gold standard to determine the presence and severity of glaucoma, which undermines the training of AI algorithms (159). Significant improvements in AI performance require substantive advances in diagnostic methodologies, more robust and clinically objective definitions of the disease, and improved methods to extract knowledge from learned results.

Health system databases have been set up for reasons other than training AI algorithms. In addition to managing patient history of diseases, admissions, family situations, insurance coverage and the like, their secondary function has been to help insurers pool epidemiological data, support actuarial predictions and reveal broad socioeconomic and geographical patterns of disease with incurred health costs. These secondary functions often do not work well for critical non-AI applications either. It would be problematic to utilize these existing bulky patient health data sets, with all their errors and biases, for a subtle and complex process of in-field and operational/maintenance phase training AI algorithms (160).

To achieve our goals, we need new comprehensive 'end-to-end' methods to ensure that when collecting new data required to support AI training at in-field and operational/maintenance phases, or when using data from existing data banks, their structural integrity and significance to patient's health and QoL have been preserved. We also require broad development of large data infrastructure to create sustainable change (111,160), as simply adding AI applications to a fragmented system would likely fail. While cost implications are significant, there is no viable alternative.

Health system databases are fragmented among medical clinics, hospitals, health establishments and jurisdictions, severely constraining ability to provide effective services to patients across organizations (160). They are usually poorly defined, structured and maintained, incomplete, inaccurate, with biases and data shifting over time. Health registration datasets might be multilingual, cover a range of ages, socioeconomic statuses, jurisdictional regulatory constraints along with security and privacy characteristics. They are loosely linked to other health, pharmaceutical, imaging, financial, insurance and government data collections, which are invariably siloed. They typically impede subsequent learning processes by even the most powerful AI engines.

Well-thought-out guidelines stipulate peer-reviewed randomized trials as the gold standard to compare effectiveness of AI systems with clinicians and with clinicians supported by AI platforms. SPIRIT-AI and CONSORT-AI require that an AI clinical report should include information on the provenance, quality and representativeness of input data, the format of output data, an indication of how they contribute to decision making, as well as a description of the algorithm (its version, evolution, underlying assumptions, risks of bias, employed human-AI interface and user training requirements).

Quality randomized AI studies are rare. Needed to allow trust in the AI system and to evaluate its usefulness, such trials might also provide evidence that AI engine accuracy does not necessarily represent clinical efficacy; as compared with a clinician, a higher AI system accuracy might not result in better patient outcomes (142,161-164). Better outcomes are of most interest to patients (142); unless they feel they are reasonably serviced by a physician. This situation is different if they were seeking more effective treatment or a second opinion when faced with a critical decision, such as the need for major surgery, or when their access to an alternative top human expert is limited, as is the case for most patients worldwide.

Most current AI/deep learning research systems outperform human experts only in specific sub-tasks, such as in diagnostic imaging, test results (e.g., visual tests), as well as electrodiagnosis (e.g., electrocardiography) (165), or on the initial identification of the disease. Experimental handling of such subtasks under artificially constructed research conditions is then hyped for their 'superpower' in medical applications. The outperformance of a particular AI algorithm in a narrowly defined unauthentic task usually results from much of real-life patient information being omitted by the computerized system developers.

Due to well-known AI scalability challenges (166-170), AI algorithm that only handle subtasks could not be easily scaled up into commercial medical products. We need strong methodological foundations for AI engines used for medical applications based on comprehensive knowledge of practical clinical treatment and patient's QoL rather than solely on the theory of AI computing (112-114,171,172).

Huang *et al.* (112) have identified some of the critical factors necessary to ensure practicability and effectiveness

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of AI medical diagnostic application that could be implemented in the clinical setting, such as:

- Patient's reliance on the medical expert's clinical knowledge.
- Substantial effects of comorbidity.
- Stratification of different therapeutic procedures, as many diseases have various subtypes and stages.
- Implementation of flexible process workflow according to each patient's situation.
- Integration of comprehensive, interrelated and often contradictory knowledge of diverse components that describe unique health, QoL and socioeconomic conditions of every patient.
- The AI application must reflect long-term benefits for patients.

We need large size and well-annotated datasets of medical records required for training deep learning engines for proper diagnosis in clinical conditions (173-177). Park and Kressel (113) have independently derived clinical validation criteria that are mostly based on the AI technology considerations.

A powerful biomedical testing and diagnostic ecosystem must effectively support the input and real-time analysis of dozens of tests and historic data that include thousands of critical parameters:

- Seamlessly fuse various kinds of complex patient assessments (biomedical, QoL, socioeconomic).
- Efficiently extract essential information from the patient's health record.
- Ask the patient for the up-to-date additional and missing information, i.e., by dynamically selecting and administering appropriate new biomedical tests and QoL questionnaires based on the patient's responses.
- Structure critical information for the physician and the patient and communicate the results to them.
- Manage and analyze health system data.
- Relay and archive physician orders and referrals to the patient, other clinicians, nurses, test technicians, optometrists, drug stores and insurance providers.

Most of the above-listed criteria are directly applicable to glaucoma stakeholders and need to be actively integrated into the Functional Requirements for the patient-centric computerized glaucoma treatment and care ecosystem.

Methodological requirements of a digitized clinical system

Commercial AI medical applications that have been developed to extract essential information from patient health records are mostly incapable of clinical implementation, as they overlook some clinical tasks or do not provide tangible benefits for patients. There are numerous technological challenges, like overfitting, when the AI algorithm fits all data points on the training set rather than identifying and predicting the general trend characteristic of the overall process (178,179). As a result, most AI systems fail to obtain approval from the US FDA or China Food and Drug Administration (CFDA), while approved commercial products are not qualified to handle clinical diagnoses, even though governments are eager to use AI to improve their national healthcare (107,112-114,172,173).

New approaches must address complex real-life needs identified by clinicians, glaucoma patients and healthcare administrators, with AI being one of several key enablers of comprehensive and intelligent digital solutions. This goal could be ensured by capturing essential clinical, QoL and health system administrative tasks to guide the lifecycle of the AI-supported system, including adoption and implementation.

AI engines are particular in understanding the substance of a clinical quest. Unlike human experts, they might understand what we said but not what we meant, as they are unable to re-phrase our questions. AI programmers do not build in the required redundancy in the engine query process, on the assumption that human contributors could always mentally visualize and articulate what they already know or wish to achieve. Mostly, this is not the case.

Ongoing treatment and support of a glaucoma patient is quite complex. This necessitates substantial advances in the AI/deep learning approaches. For medical and QoL-supporting implementation, a scientifically sound AI-focused methodology is needed, even if it differs from the current paradigm. Skeptical clinicians would more likely trust an advisory system if it followed a familiar decision tree. An AI engine should be able to elucidate reasons and quantify risks of alternative approaches. The methodology of testing and treatment run by an AI engine must be individualized for each patient.

Building blocks for a digitized healthcare ecosystem

The five critical building blocks of our integrated approach are (*Figure 1*):

- Integrated computer-aided glaucoma support block: achieving integrated, patient-centric, computer-aided glaucoma medical treatment, ongoing QoL

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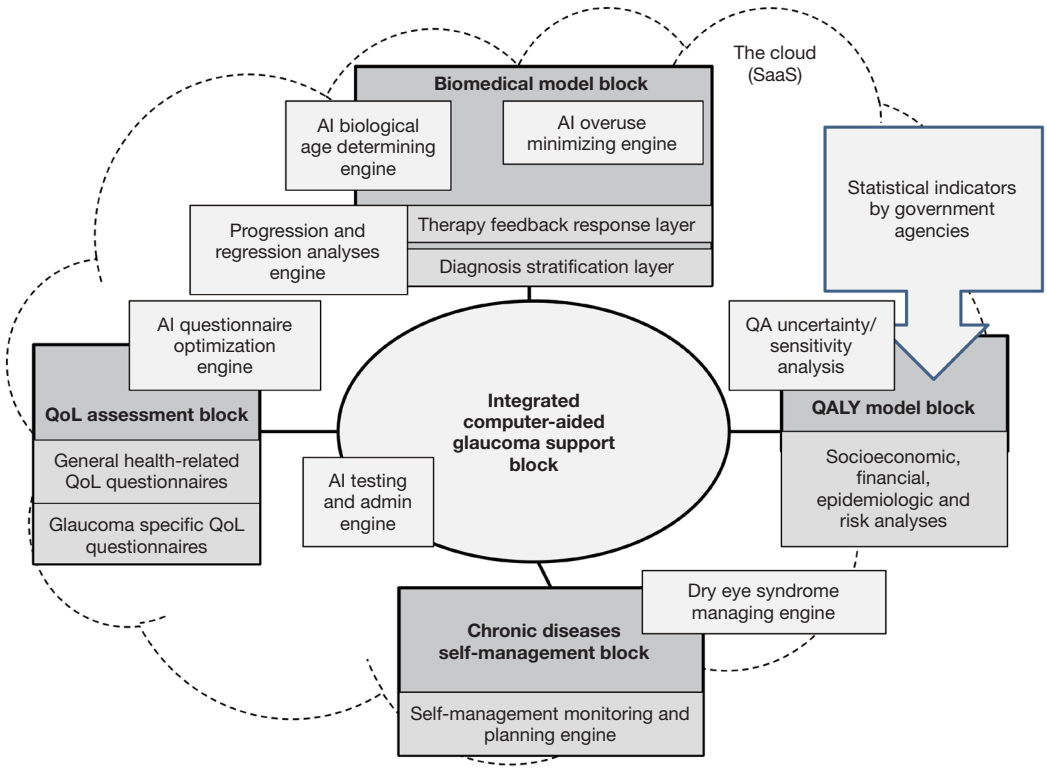

Figure 1 Critical building blocks and enabling commercial and proprietary engines of the integrated approach to define functional requirements and develop an underlying methodology for a patient centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem (see text). AI, artificial intelligence; QA, quality assurance; QALY, quality adjusted life years; QoL, quality of life; SaaS, software as a service.

support, and big data decision-analytic modeling required to optimize health system's resources in the current healthcare services and socioeconomic environment.

- ❖ Biomedical model block: advancing conventional Biomedical Model in support of smart computerization of glaucoma treatment.
- ❖ QoL assessment block: use of interactive QoL assessment questionnaires for glaucoma patients.
- ❖ Healthcare cost-effectiveness block: use of QALY for evaluating efficiency and cost-effectiveness of the healthcare and for administering of social support services for glaucoma patients.
- ❖ Chronic diseases self-management block: supporting chronic patients in addressing glaucoma as a chronic disease; while ascertaining contributions of patient's other chronic diseases.

Recently introduced powerful computer- and AI-based methodologies could support the multifaceted functionality of these building blocks while fusing and balancing numerous complex and often contradictory requirements derived from their interplay and analysis. These building blocks are at various levels of maturity, which depend on the quality of their underlying processes and the numerous applicable constraints—biomedical, socioeconomic, regulatory and technological. Broadly outlined here advancement criteria for these complicated building blocks are necessary to optimize effective integrated computer-aided decisions necessary for glaucoma management.

Selection criteria for an AI engine

Only a very limited number of AI engines assessed for health applications have been found suitable for clinical practice. In the 1970s to 1980s, the development of expert systems was an original principal method of AI implementation in medical diagnostics. Rules for decisions were derived through an explicit representation

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of established knowledge, conventions and relationships articulated by medical experts.

While each particular rule might express coherent reality, a group of integrated expert rules invariably exposes inconsistencies and gaps in the underlying treatment methodology and inadequacy of its knowledge base. More importantly, the initial development and growth of expert systems was 'expert labor intensive' and hence expensive. First-generation expert systems were inflexible and not suited for complex problems; hence their popularity has waned (107,180).

With mass digitization of health information, machine learning algorithms have been developed that attempt to uncover hidden relationships. With more powerful computers, machine learning systems could automatically extract rules or decision trees directly from a large number of example cases, selected and 'data annotated' by experts or by AI systems controlled by experts. Using compute-intensive interactive and iterative data mining and intelligent data analysis techniques, such a system can expose underlying principles or knowledge in the form of prevalent patterns and rules; in particular as disease processes evolve.

Machine learning algorithms can often outperform expert-driven analytical approaches. As they do not require explicit human programming, they are less expert-biased and more cost-effective. However, as such models expose hidden statistical correlations rather than biomedical causations, their decisions might be less apparent to clinicians (181-185).

Some modern machine learning algorithms have effective decision-analytic means to reveal the essence of a patient's syndrome while handling incomplete descriptions, exceptions, uncertain or noisy data and medical errors. They are able to select the appropriate minimum number of diagnostic tests, which speeds up the decision-analytic process and reduces costs. The resulting rules could be hierarchically organized and validated by medical experts for their accuracy and knowledge consistency (186).

Medical knowledge extracted by machine learning systems could be used for biomedical diagnosis, long-term monitoring (especially important when treating chronic diseases), disease forecasting, and patient management. Slow, abrupt or recurrent changes in the patient's chronological data stream could support clinicians, individualizing treatment decisions.

Cloud computing with its ubiquitously available inexpensive data and graphics processing units enables even more sophisticated and compute-intensive types of AI for health diagnosis. Modern AI methods learn inference from the data by using supervised learning from annotated case studies. All patients recorded in such a collection must be represented by a set of biomedical, personal and QoL data, with annotations identifying their glaucoma diagnoses.

Supervised learning algorithms associate various patients' diagnoses with their corresponding annotations, providing more clinically relevant results. After the learning stage, such associations could be recognized in other databases of similar case studies, which the AI algorithm could now annotate accordingly. It could also further refine and improve its own precision and recall when processing additional databases and records (187).

At present, the most powerful form of machine learning involves various neural network models of deep learning, which can uncover levels of features or variables that predict diagnostic outcomes. Hence, they can expose complex nonlinear patterns in large volumes of clinical data. Currently, the most popular deep learning algorithm in medical applications is Convolutional Neural Network (CNN), which could proficiently assist disease diagnosis in health screening programs, where image recognition, analysis and interpretation are central.

However, the reasoning of deep learning algorithms such as CNN is difficult to understand. Interpretability and explainability of algorithm decision-making are essential because all these AI technologies might be capable of augmenting and enhancing human processing, cognition and work, rather than replacing them (107,140,180,188). Without algorithm explainability, clinicians might ignore AI advice, especially if it has implications for their professional liability (140,142,189,190). Explainability of medical diagnosis is also required by various health-related regulatory frameworks—the US Health Insurance Portability and Accountability Act (HIPAA), the FDA, Medical Device Regulation (MDR), General Data Protection Regulation (GDPR) in the European Union, American Medical Association's (AMA) June 2018 Policy on Augmented intelligence in health care. Clinicians have to minimize threats of medical malpractice lawsuits, even if these systems could deliver better diagnoses statistically than doctors themselves (140,190).

The reliability and transparency of medical diagnosis could be substantially improved by multistrategy learning, which enhances the power and flexibility of AI solutions. Theoretically, it is possible to integrate and combine into a single computer model the outputs of several AI learning

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strategies, each using a different method to derive a medical diagnosis (186,191-196). However, combined models for medical diagnostics that could use poorly structured and segmentized in-field health databases are currently scant, aside from a few proof-of-concept studies that have rarely been successful (111).

More likely to improve accuracy and performance of AI health engines are continual learning (CL) or adaptive/incremental learning models that operate with ongoing retraining. These types of AI engines gradually increase output accuracy and minimize test numbers, by constantly learning and adapting as new information arrives. The AI engine could select a new algorithm to improve performance under the new conditions. One key complexity in this approach is that each candidate algorithm must have been trained and validated for the changing data set. The entire process must be tightly monitored and well managed (197).

Medical diagnosis requires a credible representation of the complex, interconnected workflow of biomedical testing, patient treatment and QoL assessment. An increasingly deep understanding of biomedical data underpins the search for critical signals in the high-level noise generated by vast heterogeneous data (179). After initial training with historical data at the validation step, workflow representation could be combined and constantly augmented by the use of deep learning algorithms. Continued data flow facilitates further development and improvement of the system.

Compared with conventional machine learning methods, this approach could improve interpretability of medical treatment, the trust of clinicians in AI-generated recommendations, and the confidence of funding agencies. By removing marginal fictitious associations that might cause monumental prediction failures, this approach might be more constructive. Although such an approach would increase the complexity of AI engine development, recent research suggests it could be viable for application in medical diagnosis (198-201).

With the extensive R&D effort, it should be possible to define and implement a potent global health data infrastructure. A researched and well-defined powerful infrastructure could also ensure a proper structuring of patient data.

By their applications, AI platforms split into two major categories. The first category analyzes structured data, such as images and test results, by clustering patients' traits or inferring the probability of disease outcomes. The second category uses natural language processing (NLP) methods, which 'mine' disease-relevant keywords from unstructured clinical notes and academic sources to enrich medical data. Keywords are examined and validated for their effects on the classification of normal and abnormal cases. The resulting structured output can be analyzed by the first category engines to support clinical decision making—by enriching initially structured data (165). Both categories could be quite useful for supporting glaucoma diagnosis and treatment.

Figure 2 illustrates the historic evolution of AI engine types suitable for medical diagnostic applications.

Panch *et al.* have defined health data infrastructure as the hardware and software necessary to securely aggregate, store, process and transmit healthcare data. In the 21st-century health data infrastructure is a strategic necessity, typically underwritten by governments in expanding a nation's essential wealth (160). Substantial infrastructure costs of AI healthcare solutions require large investments to develop and support operation of a patient-centric diagnosis, medical treatment and QoL ecosystem. Mid-size healthcare delivery organizations would be unable to underwrite and implement such multifaceted intelligent systems. In the current socioeconomic environment, only a limited number of very large, globally dominating high-tech corporations are able to rapidly establish comprehensive and powerful standardized solutions that would make obsolete and redundant similar systems of their smaller competitors.

Key points

(I) A smart computerized system to manage glaucoma patients holistically and over a long period must be built on a new and solid methodological foundation that is AI-supported. We outline broad criteria necessary to optimize the efficacy of the resulting integrated computer-aided decision-making system.

(II) Conventional in-field and operational/maintenance AI algorithm training is unable to use existing health data sets of chronic patients owing to inbuilt biases and errors. To be effective, we need to start anew. Further development of such a novel system could improve current AI-learning algorithms, enabling them to meet our needs better.

(III) A well-defined infrastructure could guide the proper structuring of each patient's data and ensure granular analysis of selected patients' segments. A computerized medical treatment and QoL support ecosystem should support the multifaceted functionality of the

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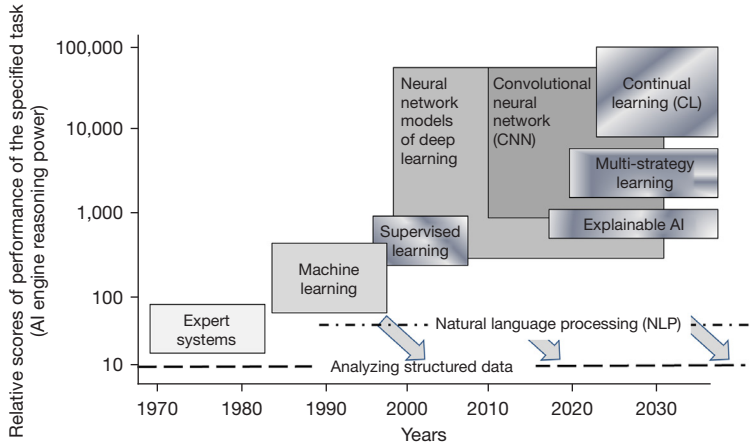

Figure 2 Historic evolution of prime AI engine types suitable for medical diagnostic applications. The dotted lines represent relative scores of AI engine performance required to run a specified task. Gray arrows represent initial introductions of corresponding AI engine research prototypes into clinical practice. AI, artificial intelligence.

five critical building blocks of our defined integrated approach. It should also produce and periodically update personalized mid- to long-term forecasts useful to glaucoma patients, their health practitioners, government budget authorities and private insurers.

(IV) Implementation of such a system must be scientifically sound, especially if it differs radically from current prevailing AI technology approaches. AI-run testing and treatment methodologies must be individualized for each patient, including their stage of the disease. Although no current proof-of-concept AI training algorithms can meet these complex challenges, with extensive R&D we should be able to define and later implement a potent global health data infrastructure.

(V) We identify many interdependent issues (including health/analytical, ability to live independently, psychological, risk, technical, regulatory, security and privacy) necessary to resolve to create an effective healthcare decision support platform on a large scale and outline selection criteria for an AI engine. We also establish AI engine types likely suitable for medical diagnostic applications. Large investments are needed to develop a relevant AI healthcare solution.

(VI) The key assumption of every buyer of a medical system, which includes AI components, should always be that, unless proven otherwise theoretically or experimentally, no AI proof-of-concept model could be safely and timely scaled up and validated for deployment to the regulated clinical practice systems.

(VII) *Figure 1*. "Critical building blocks and enabling commercial and proprietary engines…" presents a condensed block diagram of the integrated approach to define functional requirements for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem.

Results

Glaucoma as a chronic disease

In the 1990s health treatment paradigms shifted from acute to chronic care. This has substantial implications for the definition of functional requirements and for the development of underlying methodologies for a patient-centric computerized glaucoma diagnosis, medical treatment and the QoL ecosystem.

Characteristics of chronic diseases

Slowly progressing and often 'silent' chronic diseases in concert with problems of older age have become leading causes of morbidity and mortality, responsible for the largest share of global healthcare expenditures (13,179,202-207). In the USA in 2019, 90% of the nation's 3.3 trillion dollars in annual healthcare expenditures were for management of chronic diseases and mental health conditions; in the European Union, 70% to 80% of all healthcare costs are for people with chronic conditions (179,208-210).

Modern medicine has addressed acute diseases, cured

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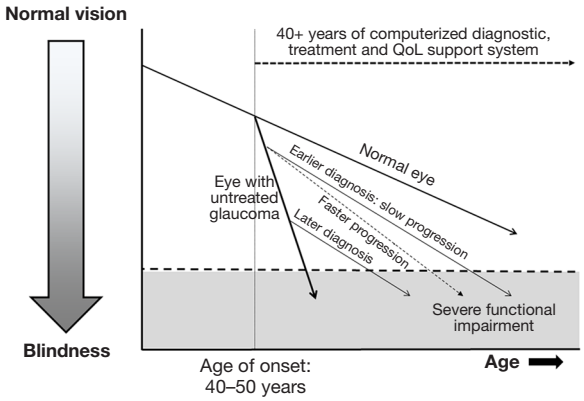

Figure 3 Effect of patient's engagement with healthcare on long-term glaucomatous progression. QoL, quality of life.

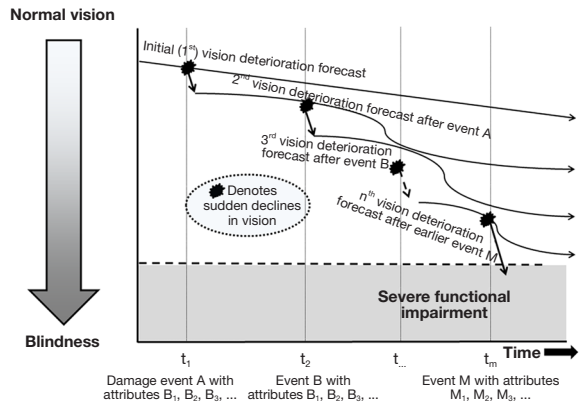

Figure 4 Effect of sudden events that lead to the rapid degradation of glaucoma patient's vision. At times it might take as many as 8–12 jumps to reach functional impairment. The time-scale on this 'sudden events' chart is shorter than that on the 'gradually aging' chart in *Figure 3*.

within a short time, with patients' involvement mostly passive and reactive to their treatment directed by physicians. From the healthcare system's cost point of view, acute cure needs to be achieved in minimal time and cost, especially including any hospital stay (211-214). Such a quick-fix approach is usually feasible and desired by patients, clinicians and health authorities (215,216).

Conversely, managing a chronic disease lasts for years, with recovery unlikely and deterioration probable; while the increasing global life expectancy poses rising challenges (13,208). Health deterioration ranges from slow to sudden, with no quick fixes.

Biological systems are non-linear (217-219). Driven by stressors and failed resilience, a neurodegenerative process might change rapidly, appearing as random and unique for each patient (202,220,221). Hence, chronic disease treatment requires individualized care for each person's unique biology, and addressing underlying causes rather than just symptoms (179).

This is especially so for glaucomas, neurodegenerative diseases akin to Alzheimer's and Parkinson's. Glaucoma pathogenesis is complex and multifactorial, with genetic, IOP, vascular, neurodegenerative processes and perhaps chronic inflammation all contributing (222-235). Long-term rate of glaucoma progression are influenced by a patient's engagement with healthcare, as earlier diagnosis and more aggressive treatment reduce the rate of progression (*Figure 3*).

Any effective healthcare ecosystem needs quantitative digital modeling of chronic disease progression for each type of glaucoma, as this would enable individual patient forecasts (104,236,237). For example, van Gestel *et al.* (45,238) have developed a model of glaucomatous disease progression based on decreases in the visual field's linear mean deviation. The Discrete Event Simulation (DES) technique that they use calculates a slope of the mean deviation's decline, which depends on the patient's risk of rapid deterioration and the IOP value. This technique can be used to analyze and forecast the deterioration of glaucomatous processes (*Figure 3*).

Based on a random draw from the distribution of the annual loss of mean deviation in untreated patients, the van Gestel *et al.* model forecasts the time to blindness if the patient is not treated. With treatment, IOP lowering might reduce the deterioration and extend the time to blindness. If patients stop taking their medication, their IOP increases, which leads to a decline in the mean deviation.

Glaucoma progression is not consistent over the long term as suggested in *Figure 3*. Often patients experience stable disease for long periods with bouts of sudden deterioration (*Figure 4*). Compared with more gradual vision deterioration (*Figure 3*), such rapid degradation falls are unpredictable and more difficult to treat, as they require complex treatment strategies. The causes for such falls are multifactorial, often relating to co-morbid ocular or systemic health issues, as well as psychosocial influences, i.e., stressful events or periods of missed drops. A recent cross-sectional study of 239 participants from four clinics in Australia with suspected or established primary open-angle glaucoma suggests genetic causes for IOP spikes (239). For some types of glaucomas, like exfoliation with its strong genetic pre-disposition, sudden disease progression is more

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common.

Meaningful rates of the visual field change vary, depending on many internal or external events (*Figure 4*). Optic disc changes, inadequate IOP control, advanced field damage, exfoliation, increased age and morbidity in the fellow eye have different relative weights when driving glaucomatous progression. To determine this rate for each type of glaucoma and for every patient, a minimum number of visual field examinations per year are required. Examinations number, type [i.e., standard automated perimetry (SAP) or other perimetric techniques], the strategy that estimates visual thresholds, and quality (which mostly depends on eye test technicians being well trained and motivated) might all be determined using statistical modeling techniques (86,240-244).

A powerful modeling technique such as the one developed by van Gestel *et al.* (45,238) can be extended to cover sudden 'jumpy' changes characteristic of rapid disease progression for some glaucoma patients. DES models are somewhat more intricate and analytically demanding, compared with more conventional computation and AI models previously used to describe long-term glaucomatous progression. Hence DES models might better characterize effective multi-step treatment strategies for both types of glaucomatous progression presented in *Figures 3*,*4*.

In DES models, time progression is event-based, with the model jumping from one event to the next. An event in this context is anything that happens at a discrete moment in time—a model can encompass various types of events. Examples are life events, treatment decisions, the occurrence of comorbidities, changes in the patient's behavior, environmental exposure or sudden glaucomatous deterioration. Each event that could lead to the debilitating damage of the patient's visual nerve might necessitate complete reevaluation of disease forecast and treatment. The resulting new order of disease phases might differ from that produced by the previous forecast. We address in more detail the computational challenges inherent to DES models in section "*QALY decision analytic modeling in an academic environment*" below.

Challenges to treating the patient not the disease

The nature of patient-centric monitoring and support for chronic diseases differs from that for acute disease. Many acute diseases are managed in hospitals, while chronic patients are treated for years in community clinics, often with multidisciplinary inputs from various allied health professionals complementing clinical experts.

Acute disease treatment is driven by biomedical testing. For chronic diseases there are additional challenges, like the need for more effective, individualized glaucoma treatments that proactively address life-long patient objectives, maximize QoL, minimize costs and counterbalance long-term risks, such as overtreatment and overmedication. This is especially important for older glaucoma patients, who often suffer from physical and psychological problems caused by several chronic diseases. To slow down health deterioration and to manage the treatment risk, each chronic patient needs 'holistic' care, not separate treatment for each condition. This is not what usually happens today.

In developed countries, medical treatment costs are underwritten by taxpayers or by private insurers, with patients increasingly paying a larger percentage of their care themselves (13). Medical personnel are not compensated to provide an all-embracing holistic service to tackle multiple comorbidities, to navigate the challenges imposed on everyday life and to reconcile sometimes contradictory daily needs (179). Increasingly, telemedicine might become a billable service for all health systems. This might improve accessibility with reduced costs. Qualified services delivered by telemedicine might be especially important to developing countries (245-247).

Chronic diseases typically affect all aspects of a patient's life, often requiring multiple forms of health monitoring, self-testing and drug self-administration, use of mobile apps, health support and implantable devices, resolving mobility and transport issues, with ramifications for family, finances, housing, education, employment and retail activities (204). Holistic treatment of a patient with multiple chronic comorbidities is a principal strategy to slow health deterioration, to manage risks of conflicting treatments and to achieve each patient's unique QoL objectives (202,204,248). Changes in the number of chronic disorders by age group in the UK population (248) are quite revealing (*Figure 5*). The age-related character of glaucoma (*Figure 6*) correlates with the presence of other chronic disorders that a patient might experience. In countries with less advanced health treatment and social support systems than in the UK, the increase in the number of chronic disorders might be greater for earlier age groups, with the percentage of afflicted patients even higher.

Chronic patients' treatment and risk management are complicated, as each clinician treats a specific disease without taking into account any others. Glaucoma patients often take systemic medications for other chronic conditions, such as statins, calcium channel blockers or

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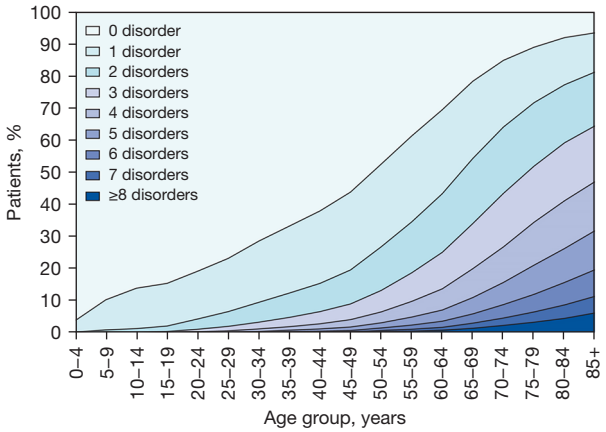

Figure 5 Number of chronic disorders by age-group in the UK population (248).

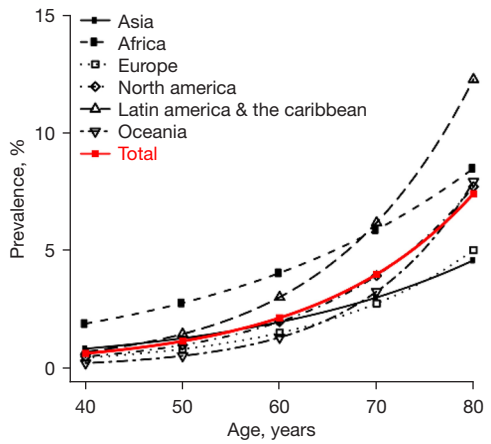

Figure 6 Age-specific prevalence of POAG by world regions and in total (79). POAG, primary open-angle glaucoma.

diuretics, which might increase glaucoma risk (52). Applied simultaneously, various medications and surgeries might damage vital organs and might impair mobility or cause psychological problems. For instance, falls and risk of falling are of concern in elderly patients with multiple comorbidities and simultaneous use of numerous drugs; glaucomatous visual loss increases such risk (249-252).

Thus, in the UK, according to Oliver *et al.* (204): "*Older people with multiple conditions are likely to be on multiple medications: around 20 per cent of people over 70 are taking at least five medications and 16 per cent are taking 10 or more. While some of this will be appropriate, concern has been expressed that older people are too often being 'medicalised' […] and over-treated with medication whose risks outweigh the benefits. Not only does ageing lead to altered pharmacodynamics and kinetics, and increasing difficulties with concordance, but also to considerable drug-drug and drug-disease interaction. For example, a range of medicines can precipitate acute delirium in frail older people.*"

Clinicians need to prescribe with full consideration of interactions between drugs, ageing and disease, and the older person's ability to adhere to medication regimes, as well as prioritising the person's own goals for treatment.

In some clinical studies, over 90% of participants had one or more chronic conditions in addition to the one being studied (248,253), such as the Medical Outcomes Study (MOS) that recruited patients who with one of six chronic disease states (253-255). "*The NHS [The National Health Service in the UK] has designed hospital medical specialties around single organ diseases. Primary care consultations and payment systems do not lend themselves to treating patients with multiple and complex conditions.*" (204). Similarly, MD training narrow-focuses on singular specializations. According to Sagner *et al.* (202), "*Minimal interactions among specialists and limited information to the general practitioner and patient lead to a fragmented health approach, non-concerted and sometimes ineffective interventions, a scattered follow-up and a suboptimal cost-effectiveness ratio.*"

The average glaucoma patient has three other chronic diseases for which they take 4–5 additional medications. A 50-year-old person in a developed country with a first-rate health system, who is newly diagnosed with primary open-angle glaucoma (POAG) and treated chronically to reduce IOP, has a 20% probability of a second chronic disease rising over the years to more than 80%. The probability of having simultaneously six chronic diseases at the end of this life-long journey increases to more than 20% (256)! For numerous elderly people who do not follow prescribed treatment or who have limited access to state-of-the-art healthcare, the above percentages will be even less favorable.

For a particular glaucoma patient, additional factors might raise these probabilities further. Side effects of long-term treatments might result in more complications, affecting other organs and functions. Impaired mobility accelerates health decline.

Worldwide public health service financial constraints illustrate the need to balance treatments of the several chronic illnesses, to reduce side effects and to guide patients who seek better QoL. Practicing ophthalmologists usually don't have time to service general medical needs, other chronic conditions, side effects and QoL issues. There is a

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shortage of glaucoma clinicians to meet needs globally; but especially in developing countries. To support glaucoma patients and experts, we need an effective, patient-centric, integrated self-management module within the computer-aided system.

Self-management model to help patients with chronic conditions

Without a radical innovation for each disease, cure of a chronic disease is impossible. While slow deterioration is likely, rapid decline is also possible (208). Successful treatment requires personalized therapeutic targets for each patient that cannot be based solely on the results of a patient's biomedical testing.

The strategic goal of guided self-management is to improve both health status and lifestyle of patients with multiple chronic conditions. Ideally it could be achieved through individual responsibility and tools for living well despite illness. Evolving self-management practices might benefit chronic patients physically and mentally, their business activities, personal behavior and QoL, thus improving healthcare outcomes and containing costs (208,257).

Self-management aims to empower patients by building knowledge and skills to maintain independence and to minimize disease impact on their lifestyle. It means to engage chronic patients in treatment decisions, problem-solving and proper administration of medication (180,202,208,252,258-264). Developing self-management plans depends on the various chronic diseases affecting a particular patient, as well as the stage of these diseases. It is a dynamic process adapted to a patient's changing state of health using effective computer-based tools.

Clinician and patient collaboratively derive agreed quantitative personal goals for health and QoL, as well as risk assessment profiles for various kinds of medical treatments. Personalized QoL goals can help select a patient's therapeutic biomedical targets. Active patient participation to develop self-management plans is imperative: they are best positioned to observe and communicate the impact of their lifestyle decisions, accept or reject recommended treatments and follow healthy lifestyles (179,202,204,205,208).

Chronic patients' healthcare delivery policies, practices and costings are based on their ability to develop and maintain skills, tenacity, diligence and dexterity required to administer self-treatment, self-monitoring and self-assessment, with the support of family and periodic visits to their clinician (205,208). Families, friends and employers need to provide support for their life activities. Such support could be enabled by technology, such as online personal health records, mobile applications, voice input devices, emerging self-driving cars, medical, domestic and business robots. The general community could help by creating a friendly environment for affected individuals at work, in public spaces, on the street and with appropriate public transport. Novel teleglaucoma care might add inexpensive and effective ways to implement ongoing biomedical testing and monitoring run by patient's physicians (208,257,265).

According to Deloitte 2019 Global health care outlook (13): "*Standing at the epicenter of the new health care value system will likely be informed and empowered consumers—change agents and active caretakers of their health who have high expectations of their health care ecosystem. These consumers will likely be "pulling" solutions rather than being "pushed" services, flipping the current health care delivery model from business-to-consumer (B2C) to consumer-to-business (C2B). In response, stakeholders are expected to use innovative technologies and personalized programs to engage with consumers and improve the patient experience. Data interoperability, security, and ownership should move to the forefront as consumers join other stakeholders in accessing, analyzing, and sharing information. In addition, disruptive trends in health care delivery and mobility may radically alter everything from the site of care to who delivers care and how. […] patient behavior, [is] one of the key components of disease management amid an increasing prevalence of chronic conditions.*"

Regretfully, beyond the motivational hype, reports of successful implementation of self-management programs are at present rare to nonexistent. It is well documented in the specialized literature that private discussions between patient and caregiver, as well as group tutoring, are insufficient to provide patients with the necessary understanding and skills to manage their disease and minimize complications; nor do conventional approaches ensure essential behavior changes. Even the positive impact of improved patients' medical knowledge on self-management has been questioned. Management of several simultaneous chronic diseases by elderly patient becomes too complex, even demotivating (208).

This 'policy-practice mismatch' is a major obstacle preventing health professionals and patients from proactive implementation of self-management. With self-management not translated from idea to practice, it runs the risk of 'blaming and shaming' chronic patients for failing to manage their health status and lifestyle. Any resulting

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additional stress has negative effects (266,267).

Many patients are unable, unwilling, or cannot afford to participate actively in their own treatment (180,202,208). There is an alarming lack of glaucoma awareness among patients and health professionals worldwide. While numerous glaucoma patients would accept any treatment decided by their health care providers, many would not (208,258-264).

Scores of patient information trials and campaigns have proven to be ineffective, unless they include extensive, individualized, expensive multiyear and face-to-face patient counseling with glaucoma experts that consider a patient's specific needs. To be at least moderately successful, such counseling must change patients' health behavior with disease education; even then, this only succeeds for a few well-educated, committed patients and not for long (13,202,205,208,258-264,268-271). Reports on various educational measures for glaucoma patients do not show a substantial impact on long-term behavior or on health outcomes, unless counseling and education are but a starting point in a long-term patient's support program (208,272).

Advancing treatment of elderly patients, with many chronic diseases, is expensive in developed countries, and economically unsustainable in the developing world even before COVID-19 ["*A system on the verge of bankruptcy. […] a disastrous course*" (203)]. Aging and growing populations, greater prevalence of chronic diseases, rising labor costs, and exponential advances in costly digital technologies increased global healthcare spending at an annual rate of 5.4% in 2018–2022, a near doubling from 2.9% in 2013–2017 (13,273). Chronic diseases are a major cause of a family's poverty and they hinder countries' economic development (202,274).

Technological approaches to self-manage glaucoma as a chronic illness

We introduced five critical building blocks for the integrated approach to defining a healthcare ecosystem (*Figure 1*). The Chronic diseases self-management block enables new, more effective approaches compared to conventional patient information and education techniques. The key research and development challenge is that the methodological foundation for the self-management block is less advanced than for all other system's blocks.

New technologies integrated into the self-management block (such as telehealth, technology enablers for AI's ability to reason and learn new concepts, online personal health records and mobile applications) could effectively facilitate essential but occasional collaborative interaction of several clinical experts with each patient. This complex long-term process would establish mutually agreed and personalized quantitative therapeutic targets for each patient.

Healthcare ecosystem platform administration must support the collaboration and networking of health and non-health sectors; public (local, national and global), non-governmental organization (NGO), and private organizations; as well as clinicians, academics, and patients. Such a complex system also requires the introduction of new and interdependent general, health, QoL and financial legislation.

While it is difficult to predict the exact nature of various dynamic user interfaces (visual? voice? command neural?) and service delivery channels that might evolve over even 10 years, the necessity for their development to administer healthcare ecosystems is clear. By providing a diagram of critical building blocks and enabling commercial and proprietary engines of the platform, and by outlining its features and functions, we enable future stakeholders of such systems to define decision-making mechanisms and their exact sharing among stakeholders for each module and the overall healthcare system. This will allow forthcoming system integrators to develop novel user-friendly interfaces that would satisfy the evolving platform management, information and cost-sharing needs of all ecosystem stakeholders.

By balancing patients' health status and QoL values and preferences with state-of-the-art biomedical knowledge against the health system's treatment limitations and costs, a healthcare ecosystem could proactively engage chronic patients and their families in individualized treatment decisions, problem-solving and proper administration of medication. Personalized QoL goals could lead to selection of a patient's therapeutic biomedical targets. Clinical experts would guide and control a proactive computerized AI system, permanently engaged in ongoing diagnosis, continuum of care and patient support.

Smart computerized systems could implement a new long-term medical treatment and QoL support through personalized knowledge building. Such a dynamic process should be highly adaptable to the patient's current state of health coupled with insurance and lifestyle challenges, and provide on-demand transactional delivery of relevant information. The input data for such a model could be obtained from the patient's short- and long-term visual goals or quality of life metrics, such as proposed or reviewed in numerous publications related to glaucoma and other neurodegenerative diseases (36,275-278). Being efficient

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and cost-effective, it would impact patients' long-term behavior. By coordinating multiple health appointments, prescriptions and procedures, such systems could effectively support each patient in managing glaucoma.

The Chronic diseases self-management block should provide each patient with timely information to build appropriate healing skills. It should alert physicians and the patient when a medication is prescribed that conflicts with other chronic illnesses. It could avoid oversupplying patients with medical data they perceive to be irrelevant. Such a goal is impossible with conventional patient information and education approaches.

AI support for glaucoma patients' daily lifecare requirements

For chronic diseases, sophisticated self-management tools help maintaining lifestyle. Computerized AI methods could ensure consistent ongoing support for vital daily routines.

Lifestyle factors that adversely affect IOP include:

- Obstructive sleep apnea syndrome and supine/head-down position during nightly sleep (279-282).
- Excessive coffee consumption, especially in men (283) and in patients with the highest genetic susceptibility to elevated IOP (284).
- Various fitness exercises and professional sports. Thus, head-down yoga might increase the IOP by two-fold (285-287).
- Swimming with goggles and weightlifting (288-290).
- Tight neckties, excessive water drinking, exposure to pesticides (291-294).
- Playing a wind instrument might increase the IOP due to Valsalva breath-holding (295,296).
- Extensive nearsighted tasks, working overtime and staying up late, typical for the current Internet and Smartphone age, transiently raises IOP both in normal individuals and in glaucoma patients (297,298).
- IOP is usually higher in winter (299).
- Airborne particules might trigger ocular hypertension through ocular surface inflammation, as suggested in animal models (300,301). Both internal and external factors have been proven to affect the IOP.

Although there is supportive evidence that some products, supplements, life habits and lifestyles might be beneficial, indications generally are variable, precarious, and not well-characterized. They include:

- Vegetables and fruits (302);
- More W-3 fat (129,303);
- Saffron (304);
- Vitamin C (305);
- Nicotinamide—vitamin B3 (306);
- Magnesium (307);
- Ubiquinol (Coenzyme Q10 or CoQ10) (308,309);
- Normal sleep circadian rhythms (310);
- Relaxation music (311,312);
- Meditation (313,314);
- Aerobic exercises (315).

While others appear to be harmful, such as:

- Tobacco (316);
- High-salt intake (317);
- Obesity (318,319).
- IOP might be elevated by some medications, i.e., mydriatics, antipsychotics, antihistamines and steroids (320,321). With more detailed information included in drug documentation, continuously tracked by AI systems, stronger adherence might be achieved, while possible side effects avoided.

A healthcare ecosystem should record and control crucial activities directly correlated with glaucoma risk, thereby guiding patients' choices in everyday life. Patients should be treated holistically rather than by addressing each chronic disease separately. An AI system's assistance to each patient and to all attending clinicians could simplify multi-factorial, comprehensive and complicated decision-making required to maintain QoL. By providing condition-related health-promoting suggestions to each individual, it would reduce the potential for discord between various chronic disease treatments prescribed for the same patient.

Managing dry eye syndromes

From glaucoma patients' perspectives, dry eye is one of many chronic drop-related side effects that impacts significantly on QoL. We have selected dry eye as an example of a common co-occurring condition that future developers of Patient-centric Computerized Glaucoma Treatment and Care Ecosystems must take into account at the system's design level. Other drop side effects, each important for sub-segments of glaucoma patients, necessitate dynamic customization of such systems for individual patient.

Glaucoma patients often experience impaired ocular surface with long-term treatment from the active compounds in eye drops and preservatives, and due to individual sensitivities. Signs and symptoms of ocular surface disease are observed in 15–50% of glaucoma patients, substantially higher than in the general population (322-326).

Low-grade, chronic inflammation often follows topical

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glaucoma medications, resulting in various clinical disorders (322,324,327). Such medications might cause or exacerbate ocular surface diseases such as dry eye, meibomian gland dysfunction and chronic allergy, thereby further diminishing QoL, adherence, and surgical outcomes.

Several studies correlate ocular surface impairment with benzalkonium chloride (BAK), the most frequently used preservative in eye drops (322,323). BAK and other preservatives cause various inflammatory, toxic and physical damage effects on the ocular surface. An impaired tear film causes dry eye symptoms and corneal damage from exposure and cytotoxic inflammatory mediators. Tear film alterations might stimulate biological changes in the ocular surface, leading to neurogenic inflammation and further tear film impairment, creating a 'vicious circle' (328).

Non-preserved drops might improve the ocular surface (322,329). Most tear substitutes are preservative-free or BAK-free.

It is preferable to use preservative-free eye drops to prevent ocular surface diseases than to add supplementary eye drops to treat another chronic eye disease, a side effects of administered medication. Removal of an aggravating factor might be insufficient for treating drop-induced dry eye syndrome. Specific dry eye therapies that address inflammatory reactions are preservative-free tear substitutes, osmoprotectants, topical cyclosporine, or punctual plugs; each carrying its own risks (328).

Not all patients are sensitive to active compounds and preservatives and not all side effects from anti-glaucoma medications are induced by preservatives. In some patients, preservatives disrupt epithelial cell barriers, increasing drug penetration. Some patients find the larger preserved bottles easier to handle than the typically smaller preservative-free ones. Larger bottle prescriptions might be more cost-effective and easier to store. Preservative-free multidose bottles might combine both advantages. Not all public or private insurance bodies cover preservative-free medications with their shorter shelf life, a significant financial barrier for their use.

Glaucoma patient's risk of developing dry eye syndrome depends on active compounds in eye drops, potential effects of preservatives and the state of the patient's ocular surface. Simple clinical tests help to detect ocular surface diseases, such as eyelid margin redness, positive corneal and conjunctival fluorescein staining and rapid tear film break-up time.

When QoL, adherence, surgical outcomes and overall glaucoma care might be affected, a clinician should consider treatment alternatives, such as preservative-free products, minimizing preserved eye drops, fixed combinations, recognition and treatment of the ocular surface with unpreserved tear substitutes, addressing meibomian gland dysfunction (e.g., better eyelid hygiene) and considering laser trabeculoplasty or surgery to decrease the number of eye drops.

Effective treatment of glaucoma while minimizing dry eye symptoms is complex, challenging and time-consuming. Optimization of various medical and nonmedical management strategies for millions of individual glaucoma patients can be achieved with support from a powerful patient-centric digital ecosystem. *Figure 1* shows a dry eye syndrome managing engine as a part of the chronic disease self-management block.

Key points

(I) The paradigm shift from acute to chronic care has substantial implications for the definition of functional requirements and for developing underlying methodologies for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem.

(II) Treatment of glaucoma patients requires personalized care with the establishment of individualized therapeutic targets to minimize deterioration and, especially, to prevent rapid visual field decline. Elderly glaucoma patients often suffer from severe physical and/or psychological problems caused by several co-existing chronic diseases. To minimize health deterioration and to manage treatment risks, each chronic patient needs a 'whole care' approach rather than treatment of each disease separately.

(III) Chronic diseases often affect many aspects of a patient's life, requiring various forms of health monitoring, home-based self-testing and drug self-administration, use of mobile apps, health support and implantable devices. Such diseases impact a patient's mobility, transport, family, social networks, financial resources, housing, education and employment opportunities. The chronic diseases self-management block enables the introduction of new, proactive and effective approaches by individual chronic patients compared to the conventional patient information and education.

(IV) New technologies integrated within the self-management block could effectively and cost-efficiently facilitate the collaborative interaction

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of several clinical experts with the patient. They could establish mutually agreed and personalized quantitative therapeutic targets; and proactively engage chronic patients and their carers into individualized treatment decisions, problem-solving and optimal administration of medication. Through personalized knowledge building, based on expert observations and know-how, as well as by correlating the massive amount of biomedical and QoL data and functional outcomes of glaucomatous vision loss, smart computerized systems could quantify how visual endpoints tested in worldwide glaucoma clinics affect specific functional losses, including driving, reading, or various physical activities, vital for all chronic patients but especially elderly. Intelligent systems could also implement new kinds of long-term medical treatments and ongoing QoL support that are highly adaptable to suddenly change the states of health of patients with multiple chronic diseases.

(V) Worldwide financial constraints on public health services exposed the need to simultaneously balance treatments for several chronic illnesses that are characteristic for glaucoma patients, to reduce their side effects, and to guide the patients who seek better management of their QoL. Only an effective integrated self-management block within the computer-aided system could accomplish such a complex optimization task.

(VI) To be effective, a healthcare ecosystem needs quantitative digital modeling of chronic disease progression, responsive to each patient's real-time treatment outcome data, taking into account specific features of a patient's glaucoma type that might influence prognosis. It should record and control crucial patient activities directly correlated with glaucomatous risks, thus guiding patients' choices in everyday life.

(VII) It is challenging and time-consuming to treat glaucoma effectively while minimizing dry eye symptoms. Optimization of various management strategies to contain these two conditions individually is best achieved by a powerful healthcare ecosystem. A dry eye syndrome managing engine should be an integral part of the chronic diseases self-management block.

Conventional Biomedical Model in glaucoma treatment

Even with its limited application to chronic disease treatment, the Biomedical Model is an important component of the glaucoma healthcare ecosystem. Smart computerization of glaucoma treatment requires advance in this model.

Despite success, the conventional biomedical approach lacks diagnostic precision, contains errors, fails to improve patients' QoL, and does not address day-to-day challenges living with the disease and its treatment, including side effects (35,53-55,227,330-340). The full range of biological complexity characteristic of glaucoma could be analyzed with novel computational AI tools. Each patient's online personal health record could be used as the granular basis for such analysis. Actionable information could be communicated back to each patient and their healthcare providers based on ongoing decision-analytic output; this might improve adherence to treatment (13,202,205), in particular for glaucoma patients (258-264,268-272).

New approaches for the Biomedical Model

Essential digitization of biomedical test outputs data could benefit glaucoma patients by supporting management decisions with AI tools (341,342). Ongoing biomedical monitoring and maintenance of normal values are not as well developed for key health metrics required for chronic outpatients as they are for acute, hospital-based medical conditions (202).

We need to improve and automate biomedical testing in support of glaucoma computer-aided diagnosis and treatment decision-making. For this, we need a complex and interconnected workflow of biomedical testing, patient treatment, QoL assessment and socioeconomic conditions that could enable a comprehensive quantitative glaucoma treatment decision methodology. Various quantitative glaucoma treatment decision methods and guidelines for glaucoma treatment (45,54,238,343-348) could enable implementation of an all-encompassing treatment decision system.

The diagnosis stratification layer of the Biomedical Model block (*Figure 1*) should reflect most worldwide state-of-the-art, credible glaucoma treatment decision methods and guidelines. The block's AI engine should be able to rank and select treatment methods and guidelines most applicable to a particular patient. A patient's treatment course must align with the local medical laws and regulations, as well as pharmaceutical legislation and guidelines.

Development of a computerized healthcare decision support platform requires resolving many challenging health/analytical, technical, regulatory, security and

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privacy issues necessary for its implementation globally. The platform would be able to output a medical treatment strategy and forecast critical milestones in the health state of the particular patient. Periodically updated, such biomedical forecasts could help glaucoma patients to predict how any deteriorating state of their vision might affect their future lifestyle, self-reliance and the financial well-being of their family.

An intelligent glaucoma management decision system should also be able to monitor and provide recommendations for other eye illnesses that they might develop, as well as treatment side effects and risk factors. The Biomedical Model should determine and take into account a patient's biological age and lifespan, which could be predicted by available machine learning methods, especially for those with chronic diseases (170,349-355).

Based on test data that includes critical parameters, the Biomedical Model block of the healthcare ecosystem should be able to analyze a glaucoma patient's multivariate progression to the comprehensive treatment model. Such a powerful biomedical testing and diagnostic ecosystem needs an advanced AI/deep learning analytic platform. The application of AI could provide reliable means to forecast glaucoma progression, devise rehabilitative strategies, outline lifestyle and financial choices and recommend improvements for the patient's safety and their QoL. This combination could guide clinicians and patients towards a more successful, less risky and less expensive management strategy. AI-based biomedical diagnostic functionality should also support optometrists, medical and paramedical specialists, especially in developing countries.

New approaches in glaucoma treatment that could affect the architecture and functioning of the Biomedical Model block include:

- Use of long-lasting injections of medications (e.g., intracameral bimatoprost) to help patients with difficulties using or remembering to instill their drops (18,356,357).
- Changes to grading systems of glaucoma severity to integrate ganglion cell loss and visual field deterioration, instead of the cup-to-disc ratio (358-360).
- Better defined target IOP for individual patients.
- Routine home monitoring of IOP that might help understand why some patients progress despite 'normal' office IOP.
- Treatment based on OCT progression rather than on changes in the patient's IOP.
- Improved accuracy in clinical glaucoma testing required for AI applications.

Medical overtreatment

Reducing overtreatment and misdiagnosis is seldom a top priority for clinicians who concentrate on successful patient treatment (361-367). In contrast, confidence in a precise diagnosis and appropriate treatment is a top priority for patients; although many are reluctant to challenge their doctors about any unexpected results (362) or to request a second opinion. Overdiagnosis and overtreatment for chronic diseases are pervasive problems for patients and health systems, often negatively affecting patients health (54,204,207,339,340,368-387). They endanger patient safety and have been classified as medical errors (383). AI medical platform development must account for patient concerns, including reduction of overtreatment, misdiagnosis and optimization of QoL.

Reducing overtreatment and misdiagnosis could support the business case to fund a comprehensive glaucoma healthcare ecosystem, with release of resources necessary for the system's development and ongoing maintenance. According to Oakes *et al.* (373): "*Overuse—the provision of care where the potential for harm exceeds the potential for benefit—has been cited as a leading contributor to the high cost of the US health care system. Overuse is often physically and psychologically harmful to patients and is a definitive misuse of resources. Such wasteful utilization helps to explain why health care spending is inconsistently associated with measures of health care quality. More is not always better. The identification and elimination of overused services could improve health outcomes and reduce spending, while redirecting important resources toward the delivery of high-value care.*"

Patients with several chronic disorders undertake a range of treatments, including different drugs. Multiple treatments, medications, surgeries and stress associated with each condition might conflict with the risk of deterioration in overall health, common side effects and reduced QoL.

For people with a low risk of glaucoma, there are few benefits from treatment that wastes government and insurer resources while more urgent matters and health innovation are neglected. Overdiagnosis and overtreatment significantly contribute to the resource crisis facing the worldwide health system (372,374-377). The US spends $3.6T (or about 18% of the GDP) on healthcare, of which 20–30%, or even more, are wasted (373,380,381,383) while similar loss numbers have also been quoted for the UK (385), Germany (386,387), Italy (388), Canada (389), Australia

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(374,390,391), Sweden (374) and Switzerland (392). Across OECD about one-fifth of healthcare spending is wasted while according to WHO 20–40% of healthcare spending globally is wasted (382).

The estimated annual cost of US overtreatment or low-value care is $75.7B to $101.2B (380), perhaps even larger (371). Healthcare finance might be a function of the measurement of overuse and underuse of services while physicians are paid according to the quality of care they deliver and penalized for overuse/underuse (377).

Concerning overdiagnosis and overscreening (368): "*Biological abnormalities that will not affect either life expectancy, or life quality, are called pseudo-disease. Pseudo-disease is very common. As a result, efforts to screen populations for health problems will result in a lot of 'disease' and may produce significant expenditures on treatment. However, it is not clear that population health will improve. Organizations such as the American Heart Association, the American Lung Association, and the American Cancer Society (ACS) argue that mass screenings for the disease are necessary because observed disease represents only the tip of the iceberg. Clearly, the greater screening will produce more cases. On the other hand, what will be detected includes both true disease and pseudo-disease. […] diseases that are progressing extremely slowly may never cause clinical problems. Ironically, advances in screening technology have a greater likelihood of detecting cases for which a clinical manifestation will never materialize.*

In summary, we typically assume that the more sensitive the test, the more it will contribute to population health status. However, tests can also do harm because false-positive tests can lead to other investigation that might be physically or psychologically harmful."

With stretched resources, rapid changes in pharmaceuticals and surgical treatments, and increasing specialization of medical experts, patients cannot rely on their GPs for awareness, monitoring and balancing contradictory requirements of several divergent treatments. According to Deloitte (13): "*Health care, public health, social services, and other sectors typically function and are funded in silos, with different funding requirements and often-incompatible data collection and information systems. This can make it difficult to coordinate efforts, integrate data, and assess shared impact. […] The multiple sectors that affect health—often driven by a variety of stakeholder and interest groups—may have different cultures, values, and vocabularies and generally lack experience working together. This can likely impede partnership and collaboration.*"

The goal of diagnosis is detection of clinically meaningful disease stages (372). For chronic diseases like glaucoma, the challenge is to establish meaningful objective thresholds for biomedical diagnosis in the context of the patient's projected longevity and other co-morbidities. Such thresholds should be based on the patient's relevant subjective QoL factors and individual risks, and be balanced against the cost of ongoing treatment.

A factor of overdiagnosis is lowering disease and treatment thresholds by expert panels and Clinical Practice Guidelines (CPG) committees—by expanding disease definitions (376), thus creating a new group of patients eligible for treatment. Changing regulatory thresholds for disease and treatment of chronic patients often result from pressure of special interest groups, based on statistical results from therapeutic trials that might not apply to an individual patient. Some trials might not stratify trial participants according to specific disease stages or consider, baseline risks, a patient's prognosis, or possible harm.

Test values from a sample of healthy people beyond two standard deviations from the mean are considered statistically anomalous in standard epidemiological definitions. For a bell-shaped distribution, 2.5% of the people would be 'abnormal', and might receive unnecessary treatment for a disease that is not present. A rational definition of objective biomedical thresholds that reduce rates of overuse and underuse requires substantial advances in the theoretical framework from which this problem is addressed (377).

A "modern epidemic" of unnecessary management of overdiagnosed diseases mainly afflicts high-income countries (372). Changes to disease definitions do not consider potential human and financial costs from overdiagnosis, especially as they are often made by conflicted panels. Treatment thresholds need to ensure that potential benefits exceed harms.

Other principal reasons for overtreatment are (368,371,372,374-377,383,386): new, more sensitive biomedical and biomarker tests that detect subtle symptoms and abnormalities. For a low risk of future illness or a false positive, the pseudo-disease label and subsequent treatment may do more harm than good.

- Care 'occurs too frequently' or is delivered in the wrong dose or duration.
- Diagnosis is subjective; it varies for different physicians or even for the same physician at different times (186). "*The threshold for deciding whether or not someone has the disease can be ambiguous. This occurs not only in the definition of the disease, but also in the interpretation of clinical*

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data. Using their experience, clinicians examine and interpret clinical information. Like any judgment, these perceptions are not always reliable. For example, it is known that physicians are highly variable in their interpretation of clinical data. They disagree with one another when examining the same clinical information. Further, they disagree with themselves when presented with the same information at two points in time. […] study showed that the clinicians disagreed with one another in about 60% of the cases. […] At the second assessment, they disagreed with their own first judgment in between 8 and 37% of the cases. … one pathologist saw cancer in 12% of the slides while another saw DCIS in 33% of the same slides. […] These variations in diagnostic patterns imply that patients with the same problem, going to different doctors, may get different diagnoses. […] The variation studies suggest that there is room for providers to make different decisions about what care is required. These decisions may be influenced by training, availability of hospital beds and methods of reimbursement." (368).

- Unjustifiable geographic and jurisdictional frequency variations for medical procedures and care intensity.
- Use of a binary 'disease/no disease' approach traditional for acute diseases versus a 'continuum progressive spectrum of disease severity' more befitting chronic diseases. Overestimation of benefits and underestimation of harms of medical interventions lead to unjustified enthusiasm for health services from both patients and clinicians. A lack of full disclosure to chronic patients of potential harms versus benefits for their treatments and overprescription of drugs can be dangerous for elderly patients with several slowly progressing chronic conditions, as glaucoma medications decrease QoL and increase risks for accidents (54).
- Behavioral economics-based analyses of overtreatment are strategies for health professionals to deal with uncertainty and to avoid regret, explaining why overtreatment might appear to be the 'rational' choice in clinical decision-making, even when it causes harm (371,375,377).
- Cultural beliefs in preventive measures, uncritical faith in early detection, and good clinical practice regarded as 'more is better'. More 'medicalized' terminology in discussions with patients often leads to more aggressive treatment and overuse.
- Legal punishment for missed diagnosis but not for overdiagnosis. Fear of malpractice lawsuits and discomfort with medical uncertainty are drivers for unnecessary care. Patients might mistrust efforts to reduce care, equating them with rationing health services.
- Health system model of business (more tests and treatments bring in more income). A merger of diagnostic, therapeutic and surgical practices might lead to a conflict of interest among health professionals.
- Effective, low-cost interventions might be neglected in favor of profitable but less useful interventions.

Overtreatment has diverse contexts and numerous causes; addressing them requires several strategies (371). Physicians should be able to predict a specific treatment as proven low value before delivery, based on published biomedical evidence, a challenging task. They do not contemplate care with unknown effectiveness or apparent no value after use. Identified causes of overtreatment mostly include categories focused on service value from a medical perspective rather than from patients' preferences.

- A rigorous and well-structured German study has prioritized recommendations against the overuse and underuse of healthcare services, with standardized diagnostic aids providing the best tools to combat them (386). No medical needs should be overlooked and service should not be offered to the patient population that might not benefit from it.
- Introduction of intelligent medical diagnostic systems is important for providing accurate glaucoma diagnoses, especially in developing countries that lack glaucoma experts. Academic examples of AI medical diagnostic systems include:
- A smartphone-based deep learning system for glaucoma detection based on visual field deterioration, which demonstrated a superior accuracy and rapidity compared with visual field review by general ophthalmologists (393);
- A deep learning algorithm analyzing color fundus images or visual field results that predicts glaucomatous optic neuropathy with greater sensitivity and specificity than ophthalmologists (394-396);
- A high accuracy three-dimensional deep learning system for the detection of glaucomatous optic neuropathy using spectral domain-optical

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coherence tomography (397).

Soon such AI image diagnostic systems could be used clinically. Overdiagnosis and overtreatment might be reduced for some low-risk or non-glaucoma patients, with limited social public health resources more reasonably allocated.

However, more powerful 'General AI' methods, suitable for a patient-centric computerized glaucoma healthcare ecosystem, as conceptualized in this article, have to be far more complex and sophisticated compared with current specialized diagnostic systems. They need substantial, multifaceted discontinuity research of AI systems based on a new paradigm quantum computing and other state-of-the-art innovative solutions (141,160,398-402). Defining functional requirements for such a healthcare ecosystem could greatly facilitate and accelerate their introduction.

In the current healthcare services and socioeconomic environment, money is scarce. Reducing overuse could release funds for critical care. Functional requirements and underlying methodology for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem should be able to reduce over- and underuse of healthcare services.

Misdiagnosis and the need for a trusted second opinion

The relatively common glaucoma misdiagnoses (53,54,56,403) propel patients to a second opinion. This need increases when surgery is recommended. Other queries concern ongoing medical treatment if IOP is low, when treating the second still healthy eye, or reconfirming accurate diagnosis with rare types of glaucoma. Another common reason driving a second opinion could be side effects from treatment or seeking potential strategy options. A trusted second opinion could provide reassurance and enhance adherence.

US outpatient diagnostic error rates exceed 5%, i.e., approximately 12 million adults annually (403). About half of these errors could be harmful. Up to 66% of patients obtaining a second opinion will refine their diagnosis, while in 21% second opinion diagnoses differed from initial diagnoses. Misdiagnoses delay treatment, cause complications and increase costs. Just 12% initial diagnoses were the same as final diagnoses (404).

Scarcity in glaucoma experts often renders a second opinion very difficult or impossible to arrange. Often the initial appointment takes months or years. A patient-friendly output from a computerized glaucoma healthcare ecosystem would reduce the need for a second opinion by a clinician. It could improve the patient's chances of optimal treatment, minimizing strains on the overall health system.

There are practical difficulties with a second opinion, such as transferring relevant medical history, and with finding out historic success rates for procedures a particular clinician performs. Most health practitioners expect and encourage second opinions. However, while some clinicians outline risks clearly, many overstate their own success rates. Patients worry whether clinicians might be offended that their judgment or experience is being questioned.

Patients would appreciate a clinical printout generated by an AI system independently recommending the same treatment, or explaining why it differs, even though the AI-based system does not recommend it. Lifelong consequences follow an unsuccessful operation. A patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem should enhance trust in the clinical diagnosis and recommended treatments.

Overdiagnosing and overtreating glaucoma

For glaucoma, indirect biomedical testing methods increase the likelihood of overdiagnosis and overtreatment. Direct and accurate assessment of the health state of over one million optic nerve fibers and their surrounding tissue is currently impossible. Glaucoma diagnosis depends on results from five biomedical tests; i.e., IOP, gonioscopy, visual field, optic disc images, and retinal nerve fibre layer (RNFL) images. When all five tests cannot be performed, at least three are required. Test results are compared with population-based quantitative thresholds that vary with age, family history, genetic makeup, exfoliation and myopia. Also analyzed are qualitative differences with normalized ocular images (34,54,405,406). Depending on the resources available, some glaucoma experts also conduct OCT ganglion cell imaging (407-411).

Assessment of uncovered abnormalities depends on the examination method and requires experienced interpretation, as there are considerable variations even among skilled ophthalmologists (56,406). We do not know the optimal tests for mass screening. Overtesting incurs unnecessary costs for no gain.

Glaucoma clinicians currently observe the 'primary glaucoma injury' by the visible changes in optic nerve head structure. Optic disc images are two-dimensional, a view possible with the monocular direct ophthalmoscope. Glaucoma has been defined as an 'optic nerve headopathy' (412).

The paucity of direct pathological evaluation of glaucoma

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damaged optic nerves, individual neurons, and nerve fiber bundle distributions within the brain will hopefully be resolved with the development of advanced noninvasive biomedical tests. Diagnosis of glaucoma versus other eye diseases or no disease present is uncertain, especially for inexperienced examiners, with variations in equipment quality, state of maintenance, and the selection of different thresholds and determination of image abnormalities. "… *The gold standard diagnostic assessment may be the consensus of expert opinion*." (412).

Challenges in selecting biomedical tests concern establishing exact thresholds for each change related to age, disease progression, unilateral blindness, and other factors. Progression varies in rate and timing compared with results indicating mild glaucoma diagnosis (406). Listed below different glaucoma sub-types have different speeds of damage; exact determination of glaucoma type is essential for individualized patient treatment.

Other eye conditions, like myopia, might complicate glaucoma diagnosis by mimicking its features. Yet glaucoma is more prevalent among myopes (413). Do IOP-lowering drugs control glaucoma progression effectively in high myopia combined with suspected glaucoma with IOP within the 'normal' range? This is being currently assessed by a prospective study (414) and a randomized controlled trial (415) at the Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. Resolution would optimize the allocation of public resources.

Lowering IOP is the major modifiable risk factor for all glaucomas, even though its efficacy might be limited for some sub-types (33,44,412). Acute situations with very high IOP must be treated aggressively but they affect a small number of patients. Glaucoma patients whose IOP falls in the normal range are often treated with IOP-reducing drugs and surgeries, even though evidence for efficacy is not as strong as for those with abnormally elevated IOP. Perhaps half of all glaucoma patients are overdiagnosed and overmedicated, which can be harmful and takes limited resources from other health priorities (53,54,56,126,406).

"*When applying the current diagnostic criteria for open-angle glaucoma, a total of 40% of patients did not to display any structural or functional damage suggesting glaucoma after 11 years of continuous medical treatment and follow-up*" (54). Up to 50% of patients thought to have glaucoma do not actually suffer from it (53,54,56). These studies were mostly from Finland, a universal healthcare country rated among the top healthcare providers in the world, one of a few global jurisdictions which proactively monitor overdiagnosis, compare costs, effectiveness and efficacy of available glaucoma treatments. This sorry situation, especially common for the elderly in developed countries, is aggravated by neglect of QoL issues (330).

Conversely, many people with glaucoma are unaware of their disease and not being treated. Approximately half of people with glaucoma in developed countries are not diagnosed (46,56,330) even though half of the newly diagnosed patients found through screening have seen an ophthalmologist or an optometrist (56).

Standard treatments for glaucoma patients are not always successful, might have side effects and be expensive (55,104,330,416). Routine cataract surgeries might increase visual field losses even if IOP values have been improved (416). In addition to treating the optic nerve head and the eye, ophthalmologists should also address patients' psychosocial conditions, as the clinician's relationship with patients is a key determinant of quality of life [Dr. Peter Shah quoted by (330)]. "*In everyday practice the challenge lies in trade-off between overconsumption of care and too little care.*" (417).

"*We overtreat some of our glaucoma patients. This occurs for a variety of reasons. In some cases, we may overestimate risk in ocular hypertensive patients and treat patients with low risk of developing glaucoma. These patients might be better off if observed closely without treatment over time. In other patients, we may fail to recognize that therapy is ineffective and continue its use unnecessarily, gaining only side effects without efficacy. In addition to local side effects, some of our medications have systemic issues that often go unrecognized.*" [Dr. Robert D. Fechtner quoted by (330)].

Optimizing QoL requires ongoing feedback between initial and evolving diagnoses and individual patient's response to treatment. Failure of feedback disrupts dynamic balancing of divergent responses. Effective biofeedback might stabilize a patient's health and QoL (45,238).

To minimize over- and under-treatment, the Therapy feedback response layer of the Biomedical Model block is necessary (*Figure 1*). It also balances the effects of contradictory events and interactions characteristic of glaucoma progression (418). Regretfully, most AI medical treatment platforms currently being developed do not include effective feedback mechanisms. Some AI applications are too risk-averse, requesting unnecessary testing and treatment, which leads to overdiagnosis or overprescription (381,419-421). Overcoming overtreatment is impossible to achieve cost-effectively without recent advances in AI/deep learning decision-analytic methodologies to be implemented in a healthcare

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ecosystem.

Differentiating glaucomas: the value of stratification

Glaucoma subtypes differ by age of onset, gender and racial predilection, speed of progression, risk of blindness, response to medical or surgical treatments, genetic influence, and IOP fluctuations. Advances in computerized diagnosis and treatment plus improvement in QoL could be achieved by analyzing glaucomas as a stratified group of neurodegenerative brain diseases (33,81,225,239,412,422-424). Stratification of patients could simplify analysis of this complex problem and facilitate cost-effective personalized healthcare (81,109,235). A computerized glaucoma healthcare ecosystem enhanced by AI engines is a prerequisite for the required decision-analytic stratification of glaucoma.

By focusing on the causes of disease, stratification could improve diagnostic accuracy and intervention costs, and lead to new, individualized and more effective drug targets for the pharmaceutical industry. Stratification allows smaller patient populations to be tested at earlier disease stages and with more accurate monitoring to achieve more effective results (109). For some glaucomas, vision deterioration might be faster than for others, calling for more aggressive treatment. Recently, many chronic diseases, such as cancers, Crohn's, diabetes, are being stratified into subgroups based on more precise decision-analytic criteria (13).

With stratification, computerized glaucoma healthcare ecosystems could facilitate personalized forecasts, better risk models, improved treatment efficacy with decreased variations in medication responses, and fewer side effects—all useful for glaucoma patients, their health practitioners, government budget authorities, and private insurers (81,109). Including a patient's QoL choices is essential, as lifestyle might have a bigger effect than genetic variants on disease risk and medication response (103). An AI engine could analyze how all elements in this complex system interact with each other and quantify, predict and optimize each individual's health, QoL and costs.

In *Figure* 7 and Tables S1-S3 we have updated patient-focused classifications (225,424) with data presented in other publications (33,80,405,406,422). For some patients, the chart could clarify the factors affecting their QoL in the future.

Glaucoma patient stratification does not necessarily mean sizeable differences between outcomes. After adjusting for age, central corneal thickness, peak IOP, beta-zone parapapillary atrophy and disc hemorrhage, visual field change (dB/year) in faster progressing exfoliative glaucoma is only moderately faster than in other slower progressing glaucomas (422). Fast visual decline in the early years often means rapid decline later too. In this scenario, the 'usual' gradual escalation of treatment is inadequate (425). High-risk patients require swift intervention with more aggressive individualized treatments. Addressing this complex challenge necessitates computerized management to be cost-effective. In contrast, patients with slow progression require less frequent long-term follow-up (425).

Visual field values are not all-encompassing characteristics of visual health; its loss is not the only factor to evaluate glaucoma progression. Up to 30–40% of retinal nerve fiber loss precedes detectable visual field defects (33,34,406,412,422) and disc hemorrhage is the single most significant predictor for visual field loss (422). Categorization of glaucoma patients phenotypically (426-430) correlates with subgroups and might simplify AI deep learning models.

Each stratified model should address a global slice of data, with resulting subproblems easier to analyze. Every subproblem needs deep domain expertise (109). For AI training, stratification of glaucoma patients (*Figure* 7) is advantageous. More aggressive subgroups, such as exfoliative glaucoma, have greater patient care costs (81,423). Objective stratification of glaucoma diagnosis would improve quality and granularity of QoL costs and facilitate reimbursement models for healthcare systems.

Clinicians debate whether to lump together or separate glaucoma subtypes, given that all treatment depends on IOP reduction. A potential downside of diagnosis stratification would be to create multiple computerized systems and decision trees for essentially similar treatments.

On the road to personalized or precision medicine

Contemporary medical therapeutics is shifting from a 'one-size-fits-all' approach based on diagnoses that fit normalized combinations of patients' medical histories, physical examinations, and laboratory data. Evolving treatments will include different well-targeted actions derived from objective biomedical data. Disease severity and response to treatment likely vary based on mutations in glaucoma genes, as well as the patient's phenotype. Genetic data will help to identify which patients to treat and how to do so. Genetically targeted pharmacotherapy would take into account all relevant mutations found in the patient's DNA.

Personalized or precision medicine is based on accurate assessment of variability in a patient's clinical, genetic, lifestyle, risk factors and environmental data. Biomarkers

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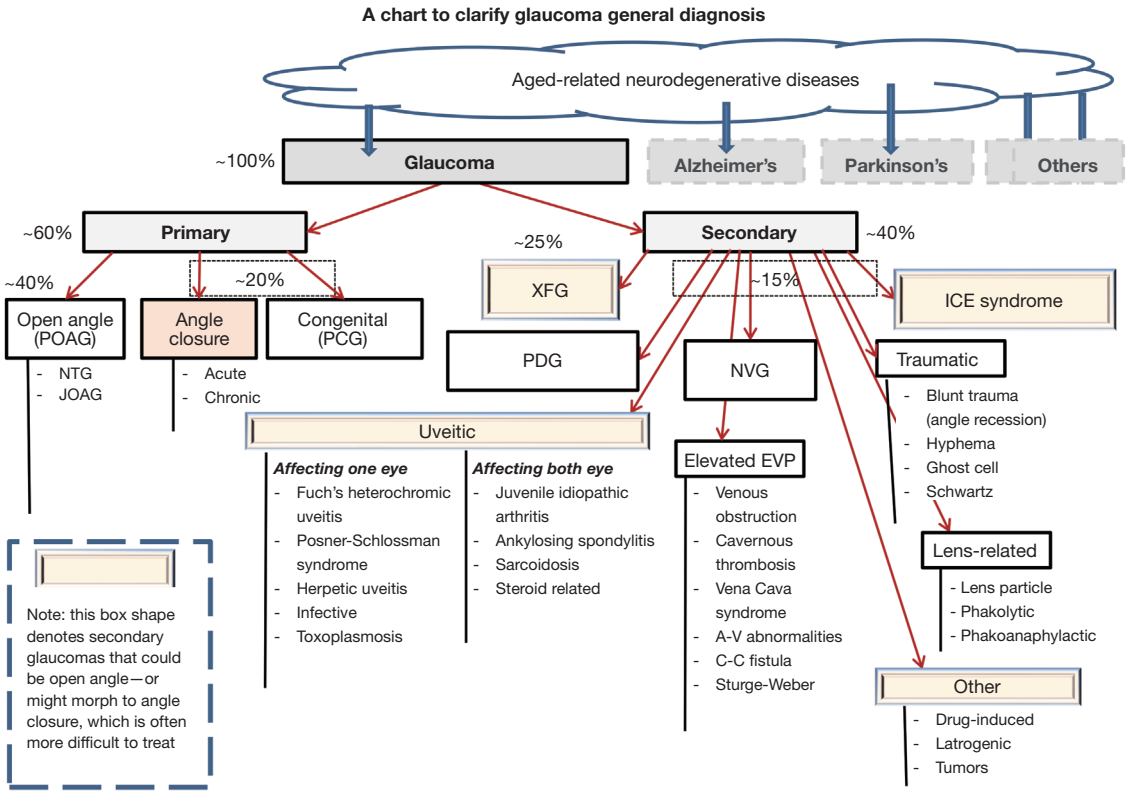

Figure 7 A chart to clarify glaucoma's general diagnosis. Percentages shown on the chart are approximate total occurrences of glaucoma in the global population, typically experienced by ophthalmologists in their clinical practices. The exact statistics might differ significantly in developed vs. developing countries, within geographic regions and individual countries, and even among ophthalmological clinics in the same city, especially as a large proportion of the population affected by glaucoma has not been diagnosed. Based on the original classifications that have been introduced in (33,225,424). POAG, primary open-angle glaucoma; PCG, primary congenital glaucoma; NTG, normal-tension; JOAG, juvenille-onset open angle glaucoma; XFG, exfoliation; PDG, pigmentary dispersion; EVP, episcleral venous pressure; A-V, atrioventricular; C-C, carotid-cavernous; NVG, neovascular glaucoma; ICE, iridocorneal endothelial.

and diagnostic pathways could allow patient stratification based on risk, prognosis, and treatment response. Patients' relatives might also benefit from genetic screening, to calculate better their risk of developing glaucoma (431-433).

Personalized medicine presumes that a person's genome would allow targeted repair without disturbing anything else. Identify the specific gene and its disordered molecular pathway, correct them pharmacologically or genetically, one patient at a time. As the glaucoma biological process involves multiple genes, complexity increases further with environmental/lifestyle interactions, individual's polygenic traits, and specific epigenetic factors. We are unlikely to hit target for a specific patient, certainly not for an entire populace.

There are already examples in glaucoma therapeutics. PTGFP gene polymorphisms influence IOP-lowering from latanoprost in Chinese, Japanese and Mediterranean patients (434-436). Genomic knowledge might resurrect medications like betaxolol that enhances IOP lowering in patients with variations in the beta-1 adrenergic receptor (437). Genome-Wide Association Studies has identified genes that influence steroid responsiveness (438,439). As more loci are identified and validated, genetic testing will predict the steroid response.

Using a patient's genetic makeup to predict efficacy and adverse effects from medications, pharmacogenomics needs to be included in any computerized glaucoma ecosystem. Fifteen to 30% of Caucasians with polymorphisms of the *CYP2D6* gene might be 'poor metabolizers', elevating systemic drug levels and bradycardia (440), which is also found with topical beta-blockers (441).

Genomic engineering will enable precision medicine. A single copy of dominant alleles of the *MYOC* gene increases

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risk for juvenile open angle glaucoma. Clustered regularly interspaced short palindromic repeat technology selectively inactivates the disease-causing allele, sparing the normal copy. The feasibility of this approach has been demonstrated in a mouse model of myocilin-induced glaucoma, as well as in human trabecular meshwork cells (442). It would also apply to other dominantly-inherited Mendelian glaucomas, like those with optineurin mutations.

Soon therapeutic options and expected outcomes will match known mutations to the expected phenotype (309,443-445) and enable other kinds of gene and stem cell therapies (446-452). Genome-wide association study has identified many glaucoma risk genes (453-455) but there is no single 'curative' gene therapy for mid- to later-in-life glaucoma. Genetic information could support development of computerized treatment algorithms and guidelines, and it should be included in every comprehensive database of glaucoma patients.

Gene therapy principal targets are:

- ❖ Neuroprotection;
- ❖ Increasing conventional outflow;
- ❖ Increasing unconventional or uveoscleral outflow;
- ❖ Decreasing aqueous humor production;
- ❖ Controlling wound healing post drainage surgery.

It is not always necessary to replace a defective gene with a corresponding normal. In organ culture, regulation of 'conventional' pathways (i.e., trabecular meshwork, Schlemm's canal, and downstream outflow channels) reduce outflow resistance. By turning down the resistance of an alternative molecular pathway, the altered pathway compensates for one with abnormally high resistance (446).

Some medications lower IOP through the 'unconventional' or 'uveoscleral' outflow pathway (446,456-458). Both pathways might be managed by viral vector/gene constructs to reduce IOP (459-461). Similarly, the aqueous secretory system could be 'turned down' by drugs and various constructs to lower IOP (462-464). Stem cells might restore functionality by infusing cultured outflow pathway cells or induced pluripotent stem cells grown in outflow pathway medium (446,465,466).

New anti-apoptotic neuroprotective, neurorescue and neuroregenerative approaches are part of the US National Eye Institute's Audacious Goals effort (467). Pharmacologic and gene therapeutic strategies are being assessed to save, regrow and reconnect retinal ganglion cells to their afferent partners in the retina, in the midbrain, and beyond in the visual cortex. All these factors will affect technical choices in a computerized glaucoma diagnosis, medical treatment, and QoL ecosystem.

Key points

(I) The Biomedical Model is one of the most important components of a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem. Smart computerization of glaucoma treatment requires advancement of this model to support the interconnected workflow of biomedical testing, patient treatment, assessment of both QoL and corresponding socioeconomic conditions; and better model representation of the chronic character of glaucoma. This section described the requirements for a sophisticated digital platform that could quantify, model and balance various health, treatment, QoL, and economic factors characteristic of numerous chronic diseases for each patient. These requirements have dynamically changed over many years and will likely even more rapidly change in the future.

(II) To develop an effective computerized healthcare decision support platform, we need to resolve challenging health/analytical, technical, regulatory, security and privacy issues inherent in global implementation. Quantitative outcomes of such a complex dynamic process might be the system's decisions on medical treatment strategies and on critical milestones in an individual's health state that might affect a patient's lifestyle, self-reliance, and financial well-being. We have formulated several new approaches within the Biomedical Model to support radical improvements in biomedical testing necessary for computer-aided glaucoma diagnosis and treatment.

(III) Increasingly in chronic disease management, overdiagnosis and overtreatment have been recognized as problems for patients and health systems. This contributes to the crisis in the worldwide health system. According to WHO, across OECD nations about one-fifth of healthcare spending is wasted. Some governments consider financing healthcare services based on the assessment of overuse and underuse. As reasons for overuse are diverse, addressing them requires a range of effective strategies.

(IV) Up to half of the glaucoma patients are overdiagnosed and overtreated, which can be harmful and reduce resources for other health priorities. A confluence of several indirect biomedical testing methods to diagnose and monitor glaucoma

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likely exacerbates overdiagnosis and overtreatment. Assessment of abnormalities depends on examination methods and examiner experience. Conversely, many people with glaucoma worldwide are unaware of their disease, undiagnosed and untreated. Overcoming overtreatment cannot be achieved rapidly and cost-effectively without recent advances in AI/deep learning decision-analytic methodologies incorporated within a healthcare ecosystem.

(V) In the absence of objective tests, a computerized healthcare ecosystem could also improve initial glaucoma diagnostics. This could be achieved by raising the learning and reasoning abilities of current AI systems and addressing their shortcomings; so that they would be able to treat patients, support them in arranging their daily activities, and provide them and their physicians with a trusted second opinion. With the current shortage of glaucoma experts worldwide, most newly identified patients (a relatively large share of whom are likely to be overdiagnosed) would likely be unable to easily find qualified clinicians to treat them. This reinforces the need for introduction of a computerized glaucoma treatment and care ecosystem that could help a limited number of glaucoma experts in supporting the growing number of patients all their lives.

(VI) Optimized use of medical services could divert needed funds to critical care. Functional requirements and underlying methodologies for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem should achieve this goal.

(VII) Analyzing glaucomas as a set of distinct subgroups of patients could advance computerized glaucoma diagnosis, treatment and QoL optimization; simplify digital decision analytics; and facilitate cost-effective personalized healthcare. Categorization by glaucoma phenotypes might facilitate simplification while running AI deep learning models could fuse complex patient assessments. Such objective glaucoma diagnosis stratification would support the evaluation of quality and granularity of QoL costs, as well as optimize healthcare reimbursement models. Yet, there is valid debate among the clinicians whether to lump various glaucoma types together, keep them separate, or simultaneously build computerized models and conduct data analysis for both scenarios, as the potential downside of diagnosis stratification would be the creation of multiple computerized systems and decision trees for essentially similar treatments.

(VIII) Medical therapeutics is shifting to personalized medicine. Complex genetic information could inform choices of which patients are best to treat, by which means, and how aggressively. Various biomarkers and diagnosis pathways could stratify patients on their likely disease, prognosis and treatment response. We are approaching the ability to match therapeutic options and expected outcomes with known mutations, as well as gene and stem cell therapies. All these new factors would affect technical choices in the development of a computerized glaucoma diagnosis, medical treatment and QoL system.

Use of interactive QoL assessment questionnaires for glaucoma patients

The design of the QoL assessment block is critical to define functional requirements and develop a methodology for patient-centric computerized glaucoma diagnosis, medical treatment and QoL system. Successful treatment of glaucoma patients requires personalized care with the establishment of individualized therapeutic and QoL targets, which would guide a patient's biomedical targets.

Achieving integrated patient-centered eye care

The World Health Organization recommended integrating into health systems the delivery of people-centered eye care services. Integrated people-centered eye care is defined as services:

- Managed to deliver a continuum of health interventions covering promotion, prevention, treatment and rehabilitation;
- For the full spectrum of eye conditions as needed;
- That recognize people as participants and beneficiaries throughout their lives (22).

All patient-centered care components must be customized according to patient preferences, which include involvement in decision-making. Quality eye care services must be affordable and tailored to population needs. Technological advances facilitate care access by underserved populations.

For this, effective strategies are needed. One is empowerment of patients, engaging them and communities—by raising awareness of glaucoma, prevention of vision impairment, and improving ways to access eye care. Patients and the public expect to become more involved in the care and more informed about health (468).

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'Patient engagement' is the process of building the capacity of patients, families and healthcare providers to facilitate active patient involvement in their care (469). As engaged patients make informed decisions about their care options according to their priorities, it is integral to lifelong healthcare (470).

With the rapidly aging population, glaucoma patients have to self-administer eye drops throughout their lives, in addition to managing medical treatments, pharmaceuticals and clinical appointments for other acute and chronic diseases that multiply with time passing. Not surprisingly, they usually have dismal adherence to the IOP self-treatment.

Effective functional support could only be provided by a smart and action-oriented computerized healthcare ecosystem that would monitor health and well-being, activate alarm in an emergency, arrange an appointment with a clinician or reconfirm medical treatments when necessary, explain the optimal actions, provide second opinions, continuously prompt drops restock and control their proper administration. It would advise glaucoma patients on evolving QoL states of mobility, reading, general self-care, work, driving and other lifestyle decisions. Patients could benefit from support groups, online educational resources and facilitated communication. The system will support patients in taking care of themselves and extending independent living.

Using the Biomedical Model block, QoL assessment within the computerized healthcare ecosystem would estimate secondary risks to daily function, particularly as the disease progresses (471). Many patients would appreciate a rolling 5–10 years forecast on ongoing fitness to drive, dangers of legal blindness, ability to work, need for personal care, likelihood of major surgeries, estimating risks of a rapid QoL reduction with increased glaucoma visual loss in the less affected eye (55,56,472,473). For glaucoma patients, QoL is mostly affected in later disease stages. Psychological problems (social withdrawal, depression) and loss of the general ability to live independently often accompany increasing glaucoma severity (349).

All individualized glaucoma diagnostic, treatment and care management approaches are complex, with many dynamically changed functions and variables. Coherent methodology to treat glaucoma patients should support the digitization of this interconnected data.

For optimal care outcomes in chronic patient care, a strong long-term doctor-patient relationship with mutual trust is critical. Could an AI-driven, computerized treatment ecosystem impinge on this (474-478)? Could it be an obstacle to implementation? However rational, user-friendly and intuitive novel computerized platforms might be, physicians and other healthcare workers will need to train to work with them.

Defining QoL

Glaucoma patients QoL is being increasingly examined (36-41,47-51,479-483). Progress in treatments and technologies has increased survival, with healthcare focus shifting from acute diseases to living a full life with chronic diseases (484).

Inherently subjective and culturally dependent, a universal QoL definition would be challenging (484-488). A common definition for glaucoma QoL (36) has been based on published data (36,480): "*QoL is defined as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a wide-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of their environment. QoL is thus the sum of a range of objectively measurable life conditions experienced by an individual. These may include physical health, personal circumstances (wealth, living conditions, etc.), social relationships, functional activities and pursuits, and wider societal and economic influences. The subjective response to such conditions is the domain of personal satisfaction with life. The QoL of an individual or subgroup can be established by comparing their position to that of the total population.*"

As populations increase and age, numbers with visual impairment grow rapidly. Major living factors contribute to QoL, each with a sight-dependent component (36,481). QoL defines glaucoma patients' ability/inability to perform specific tasks, especially those most important to them (39).

Patient engagement in care and decision-making improves their QoL. Patient-centered care variously measures cost-effectiveness, to provide patients, clinicians and other stakeholders the information needed for optimal treatment and QoL.

Glaucoma, collective health and social impact: developing countries' perspective

Even though glaucoma QoL has mostly been coped with in developed countries, it is also a major cause of irreversible visual impairment in developing communities. Compared with European populations, glaucoma is more prevalent

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among African, East Asian and Latin American peoples (79,489,490). With population growth and aging, increased socio-economic impact has to involve individual and collective strategies.

Introduced in Brazil, Collective Health has been further developed by the Brazilian Association of Postgraduate Programs in Collective Health, incorporating health, social sciences and humanities (491,492). While Public Health focuses on population diseases, injuries, risks and deaths, Collective Health is broader. It embraces all the conditions required to avoid disease, prolong life, and also improve QoL by enhancing human freedom through individual and collective happiness (491).

In Public Health, health promotion, prevention (secondary, tertiary and quaternary), treatment and rehabilitation are all part of the push against glaucoma (469,493), including social inequities and facilitated access to effective and safe management resources. Promotion of glaucoma health involves awareness for early detection and of the main risk factors. Awareness-raising campaigns in developing countries guide primary care professionals in targeting those at greatest risk, such as the elderly and family members of diagnosed patients.

As glaucoma is genetic, its primary prevention is impossible. Secondary prevention (early diagnosis, effective treatment), tertiary prevention (limiting negative consequences of disease, rehabilitation) and quaternary prevention (minimizing inappropriate diagnosis and medical interventions, overdiagnosis, overtreatment and overmedication) are the strategies to prevent progression to disability (53,54,207,330,372).

Secondary prevention searches for glaucoma with targeted screening aim to identify disease early. Costs decrease and QoL improves with early glaucoma diagnosis and treatment (494,495). At more advanced stages resources needed for control are more costly (81,494) or unattainable in developing countries.

Glaucoma population screening is not cost-effective (496). Opportunistic detection with routine eye examinations is cost-effective and should be encouraged (497).

In Brazil, the National Policy of Glaucoma Care established Glaucoma Reference Centers, where patients access specialized consultations, ancillary tests and eye drops within the Brazilian Unified Health System (SUS), supported by the ophthalmologic society. The Ministry of Health's DATASUS database estimated that by 2020 about 140,000 patients were supposed to be registered (498). Still, with glaucoma prevalence in Brazil of more than 1 million people, this coverage of care remains inadequate.

Many patients using medical treatment in glaucoma referral centers continue to lose vision from challenges with chronic use of eye drops, such as low adherence, negative impact on QoL, and side effects. The more medications needed and the higher the frequency of adverse effects, the worse is the QoL (499). Add to this the toxicity of eye drop preservatives on eye tissues (324).

Optimally glaucoma treatment should not depend on patient actions. Success of novel therapies (laser trabeculoplasty, micro-invasive surgical techniques) depends on facilitated access and wide acceptance of updated treatment guidelines. Early-stage glaucoma treatments that postpone eye drop use could control the disease better. Laser treatment is growing as a primary cost-effective therapy (495,500). Micro-invasive surgeries might be a cost-effective option for initial to moderate glaucoma (81,501). In advanced glaucoma, filtering surgeries might be the most cost-effective option (502).

Rehabilitation of those visually impaired is important to reduce glaucoma's social impact. Public policies need to raise community and health professional awareness about rehabilitation opportunities.

As glaucoma impacts not only the individual and his/her family but also the general community, strategies against it must involve all of society. With the shortage of qualified glaucoma experts, especially in developing countries, an effective and efficient integrated healthcare ecosystem could provide within the scope of Collective Health much-needed support to combat the debilitating effects of glaucoma.

Conventional QoL questionnaires: strengths and constraints

QoL questionnaires that assess various chronic diseases and account for cultural differences (484,488) are mostly based on patient-reported outcome (PRO) questionnaires and surveys developed by WHO, Medical Outcomes Study (MOS), EuroQol Group, US FDA, National Eye Institute, US Congress Office of Technology Assessment, UK's National Institute for Health and Care Excellence, by other international and national health institutions and on input by patients (51). Reflecting a wide variety of cultures and diseases, they are often further adapted to particular medical conditions, like glaucoma (424), to the local language, and a jurisdiction's health requirements (479).

The healthcare ecosystem QoL block (*Figure 1*) might include a computer adaptive testing (CAT, personalized assessment) system and a conventional database of globally

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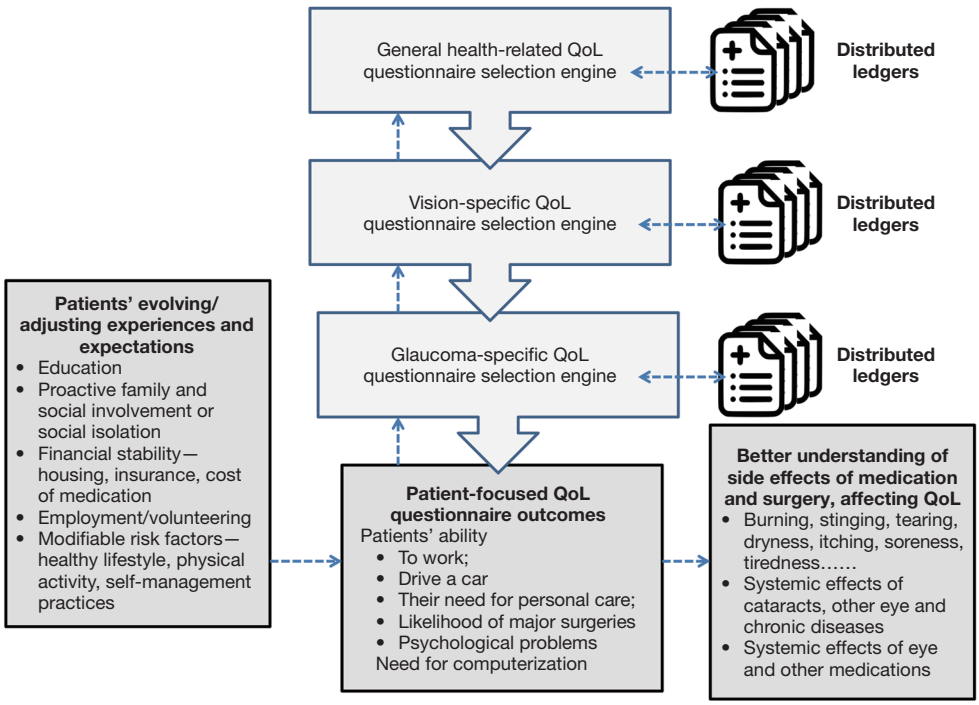

Figure 8 A functional hierarchy, key affecting factors and outcomes of QoL questionnaires that could be processed by a DLT-based QoL block (*Figure 1*). QoL, quality of life; DLT, distributed ledger technology.

standardized glaucoma QoL questionnaires. In CAT questions can be added or deleted, increasing flexibility, accuracy and efficiency. AI-guided choice of questions would be based on local treatment settings, individual patients' ability and their prior answers.

To ensure reliability, CAT needs to be trained on large representative data for each patient subgroup, which limits clinical application (503-505). Any rigid centralized approach based on just one standardized database of questions would not cover the possible permutations of medical factors, or socioeconomic, financial, cultural, language, geographic and ethnic variations evolving constantly. It would fail to explore unexpected correlations important for the personalized patient QoL improvement.

For clinical use of QoL questionnaires, more attractive is a functional hierarchy, a typical workflow, key affecting factors, patient- and clinical-focused outputs, and effectiveness feedback loops (*Figure 8*). A global peer-to-peer assembly of independently derived and standardized QoL questionnaires could be realized with a distributed ledger technology (DLT), which has recently evolved from the cryptocurrency blockchain model (506-508).

DLT could improve the data necessary for interconnected QoL questionnaires and application flexibility. With increasing information complexity, DLT rather than conventional databases might be beneficial, as it does not impose one-size-fits-all requirements on its components and records. DLT could reduce costs of non-uniform questionnaires, improve customer experience, and support introduction of new value-added services for glaucoma patients.

DLT for health applications allows 'privacy by design', enabling individual records to be encrypted, while conventional databases typically encrypt the whole data set, with compromising one record results in penetration of all. Peer-to-peer DLT also eliminates the need for a single authority to administer all component questionnaires.

General health-related ('generic') QoL questionnaires provide a patient-derived measure of the overall impact of sickness or surgery, allowing various diseases to be compared (56,488,509). Often, they do not well correlate with glaucoma's QoL impact.

Vision-specific ('disease-specific') QoL questionnaires' assess more accurately ocular symptoms and difficulties with vision-dependent tasks (483,488). They do not allow comparison with non-ocular diseases.

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Glaucoma-specific QoL questionnaires respond to the relative weaknesses of vision-specific questionnaires. They include (86,483,510,511):

- Glaucoma Symptom Scale (GSS): scores ten symptoms commonly experienced by glaucoma patients on a five-point rating scale.
- Viswanathan questionnaire: ten questions asking for a binary 'yes' or 'no' response.
- Glaucoma Quality of Life (GQL-15): asks 15 rating-scored questions to assess glaucoma functional disability.
- Symptom Impact Glaucoma (SIG): 43 questions, including psychological and systemic inquiries, derived from patient focus groups and ophthalmologists.
- Glaucoma Health Perceptions Index (GHPI): six questions to assess stress caused by glaucoma and levels of concern about blindness.
- Glaucoma Activity Limitation (GAL-9): German revised scale 9 items evaluating activity limitation and mobility.
- Glaucoma Activity Limitation (GAL-10): Indian revised scale 10 items evaluating activity limitation and mobility.
- Spratt (481): classification of conventional QoL assessment approaches as they relate to glaucoma diagnoses.
- Performance-based testing of visual function films patients undertaking tasks. Offering advantages over self-reported evaluation of visual ability, such tests are difficult to arrange and administer. Labor- and time-intensive, they are rarely used beyond academic studies.

QoL assessment approaches

People assess their health-related QoL subjectively, comparing expectations with experience, rather than objectively on its merit (512). QoL is "*the gap between expectations and experience*" (513). Patients with severe damage do not necessarily report a poor QoL, while some with good health might report a significant impact on their QoL from a mild illness. Most older people in the United Kingdom self-rate their health as 'good' or 'excellent', and say they do not have a 'life-limiting' ailment, even though the majority live with one or more long-term conditions (204,514).

Even though they are supposed to evaluate health rather than disease (488), QoL assessments complement biomedical tests, being doctor- and disease-centric. Although they could help clinically (513), their application to patient personal, family, financial and business planning is limited to research (43,483-485,487,511,515).

Patients' wellbeing is affected by education, family and social involvement versus isolation, financial stability, housing, employment or volunteer activities, adaptability with aging for modifiable risk factors like healthy lifestyle and exercise (516,517), and even local climate (204,518,519). Experiences change expectations, resulting in shifts in the QoL meaning (512).

Dissatisfied patients are more likely to experience a poor outcome by not attending appointments or adhering to prescribed treatments. Reported adherence to glaucoma medications varies between 5% and 80%, with pharmacy refills producing the lowest numbers contrary to patients' self-reporting; while half of new patients discontinue their glaucoma treatment within six months. Most glaucoma patients cannot instill eye drops correctly (33,520-523). Adherence to medications to control IOP is important to prevent glaucoma progression.

The impact of chronic diseases on patients' QoL could be minimized with help to adjust their expectations and to adapt to their changed status. Adherence management improves if personalized information and guidance are provided.

To improve health status and QoL, self-efficacy scales have been proposed, such as the general, chronic disease management and glaucoma medication self-efficacy questionnaires (523-525). Improvement in self-management efficacy boosts patients' medication compliance (523) while dealing with feelings of helplessness and depression helps patient confidence. Health education and proper communication with clinicians improve self-management efficiency (526-528). Computerized systems help clinicians to maintain individualized dialogs with patients beyond the limitations of office visits.

Costs of medications, clinical visits and fears of blindness, anxiety, and depression are all important to patients (36,37,47-50,482). Confidence in the doctor and the correct direction of treatment improve QoL. A good doctor-patient relationship is vital (479).

According to Barcaccia *et al.* (484), citing (485): "*It is obvious that different interpretations of QoL, different points of view, different definitions, will lead to different decisions on very important topics. In truth, ethical consequences stem from different QoL definitions: Health professionals often make quality of life judgments when making decisions about the care of patients*

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and their perspective on expected quality of life is the crucial factor in deciding whether treatment for a life-threatening condition will be administered or not."

Efficacy of QoL assessment of glaucoma patients

Conventional QoL glaucoma assessments are subjective, ill-defined, ambiguous and conceptually elusive because their definitions are complicated and their statistical methods used inconsistently and incorrectly (86,483,484,487,510,511,529). Many patients cannot complete QoL self-assessments due to questionnaire complexity and their health, emotional, cognitive and communication challenges (485,487,510).

Patients with similar glaucoma disability rate their QoL differently, depending on personality, mood, family support, and other interests and activities, concomitant health issues, financial challenges and side effects from treatment (324,530-536). Also contributory are other eye diseases and risk factors for secondary glaucomas (537-539), corticosteroids and other drugs (540-543), and systemic effects of eye medications (544,545). While QoL decreases right from early stages in glaucoma patients compared with the general population, differences have been found in some studies to be substantial only at later stages (54,55).

The primary focus of current QoL assessment of glaucoma patients is on the effects of visual impairment (36). Decreased QoL has links with medication inconvenience; for many eye surgery provokes more discomfort than do medications (54); strokes have the greatest effect on QoL compared with diabetes or high blood pressure (515). Patients are not interested in glaucoma classification, but rather the impact of their disease on QoL (42).

QoL tests were meant to assess the impact of glaucoma on a patient's life, to establish suitability for surgery or a feasible medical regime, and then to guide a patient through difficult choices for therapeutic decisions. They were intended to customize treatment options based on a patient's profile. For many patients, ability to recognize people, read, drive and climb stairs is more important than biomedical testing characteristics (36,39,86). Maximizing the patient's QoL is the principal goal of the therapeutic alliance between clinician and patient (36,37,39,47-50,54,511).

Mobility independence is particularly important in the United States, where driving provides the primary transport; elderly persons who stop driving are five times more likely to move to a long-term care facility, to suffer higher rates of depression, and to report lower QoL. Many patients, even with advanced visual field loss and a prior collision continue to drive, subjecting themselves and their community to increased risk (40,81,546). In contrast, for Japanese glaucoma patients, with their excellent public transport system, driving is relatively unimportant (547).

Assessing glaucoma QoL is restricted mainly to academic research, not clinical practice (39,511). Current QoL questionnaires are parochial and focus on physical symptoms, not the personal or social aspects of the disease (55). Of 27 QoL assessment questionnaires expressly developed for glaucoma patients all: "*…demonstrated poor developmental quality, more specifically a lack of conceptual framework and item generation strategies not involving the patients' perspective. […] this review revealed that most authors did not try to improve the quality of their instrument, even if the results from validity and reliability tests show unsatisfactory evidence.*" (510).

Despite recommendations on how to improve or delete current questionnaires, they have not improved. Rapid, accurate, precise and sensitive ophthalmology-specific QoL assessments need computerized adaptive testing from a large bank of pre-calibrated questions. Improvements for each novel treatment require validation.

In turn, effective validation requires comprehensive multidimensional testing of eye health and patient wellbeing, based on an individualized approach to issues of greatest relevance for each patient (86,529). This is what we suggest to implement with Functional Requirements for QoL ecosystem. Its development and validation will need labor-intensive, expensive research efforts (511).

Conventional QoL glaucoma assessments have been designed in developed countries with advanced biomedical test equipment and with glaucoma patients' expectations of employment, mobility and driving. In developing countries like India, with different culture, social life, financial concerns and high unemployment, QoL questionnaires are less effective (37). Even in Singapore, cultural differences, financial burdens and psychological impact of disease necessitate localization of questionnaire content (43).

Treatment cost and value

Treatment cost has a major impact on glaucoma QoL assessment.

"*The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life, at a sustainable cost. The cost of treatment in terms of inconvenience and side effects as well as financial implications for the individual and society requires careful evaluation.*" (345).

The more expensive the treatment, the worse the QoL (479), as costs and side effects of treatment are the

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most significant negative factors claimed by patients. From an overall cost perspective, the value of some standard tests has not been established. Patients with diagnosed open-angle glaucoma from two geographically different regions in Finland were compared. One region had 25% higher per patient treatment costs than the other. There was no statistically significant difference in quality-of-life scores of life questionnaire (15D) between them. The region with higher treatment costs had less severe case glaucomas and early-stage glaucoma patients who used more resources reported worse QoL (54). Equal outcomes for Medicare expenditures for Medicare recipients in different regions of the United States were reported where expenditures per recipient vary by as much as twice (368). Healthcare decisions might be influenced by physician training, availability of hospital beds, and methods of reimbursement rather than by medical needs.

The need for computerization

Conventional QoL glaucoma assessment scores are complex (54,55), patients need to respond to many questions (43,547), administration costs are high and physicians need health psychology training to achieve valid outcomes. They are not covered by medical insurance, disincentivizing practitioners from using them. Unable demonstrably to support treatment strategies, QoL scores are meaningless (41).

"*In the daily medical setting, a careful clinical history is more relevant than all these (conventional QoL assessment) methods and essential to assess the patient's QL, knowing their potential limitations in daily life activities.*" (349).

"*Standard QoL assessment approaches are a highly subjective form of self-evaluation and draw heavily upon a patient's own perception, expectations and belief system. As such their usefulness will perhaps always be limited. A superior method of assessing the impact of glaucoma on our patients' visual abilities may be the direct observation of how well they perform visually demanding tasks.*" (481).

Conventional QoL assessments are handicapped by subjectivity of and volatility in QoL meaning as well as divergence of patients' life goals, experiences and socioeconomic conditions, superimposed on changing expectations. There is no 'gold standard', universal, globally applicable, one-size-fits-all QoL assessment scale for all glaucoma patients (38,41,54,55,479,483).

Usefulness of any one QoL assessment scale can only be established for an individual patient or a select group of patients at a given moment. Ranked output of any QoL assessment scale should guide biomedical testing targets. This process is personalized, requiring analysis of non-uniform data streams. Algorithmizing is not feasible.

For all these reasons, an agile, user-friendly, cost-effective glaucoma patient's QoL assessment questionnaire is possible only with an advanced AI/deep learning decision-analytic platform. Our QoL assessment block in *Figure 1* includes the AI enablers to implement such a QoL assessment questionnaire.

Key points

(I) Most glaucoma patients are elderly, often with declining cognition and with several chronic diseases; usually, they meet their eye clinicians briefly and just a few times a year. They have to self-administer one or more eye drops indefinitely while managing other medical regimens, including pharmaceuticals and clinical appointments for their concomitant diseases, which likely multiply and worsen over time. Many of them also have to endure their diminishing QoL. Realistically, their daily functional support could only be provided by a comprehensive healthcare ecosystem.

(II) A powerful, smart and action-oriented computerized platform could monitor patients' health and well-being; activate alarms in case of emergency; confirm their ongoing medical treatments; arrange a physical or virtual appointment. It should also be able to explain treatment options available; assist with a second opinion for any proposed surgery; remind patients in real-time to restock and to administer drops. As well, it should be able to advise glaucoma patients on their evolving QoL related to mobility, ability to read, use of interactive interfaces, general self-care, work, driving and many other often critical lifestyle decisions.

(III) We outline the architecture of the QoL assessment block that is critical to define functional requirements as well as the underlying methodology for developing a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem, based on personalized care and individualized therapeutic and QoL targets. This could help to select a patient's biomedical targets. The coherent methodology should provide a viable foundation to digitize this complex and highly interconnected workflow.

(IV) With the shortage of qualified glaucoma experts, especially in developing countries, an effective and efficient integrated patient-centric digital

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system could combat glaucoma within the scope of Collective Health, including communal action at primary, secondary and tertiary care levels.

(V) Conventional QoL assessments are based on various patient-reported outcome (PRO) questionnaires and surveys. These are adapted to particular medical conditions, to the local language, and the jurisdiction's distinctive health needs. General health-related QoL questionnaires provide a patient-derived measure of the overall impact of sickness or surgery; they allow comparison across various diseases. Vision-specific QoL questionnaires assess ocular symptoms and specific difficulties with vision-dependent tasks. Glaucoma-specific QoL questionnaires focus on glaucoma-related symptoms.

(VI) Conventional QoL assessments have been criticized as inherently subjective, ill-defined, ambiguous and conceptually elusive. As they are based on complex definitions, their statistical methods might be inconsistent. Although possibly helpful in academic research, their usefulness to chronic glaucoma patients is quite limited. For many glaucoma patients, it might be more valuable to follow their ability to recognize people, read, drive and walk on stairs than to follow the results of their biomedical testing.

Economic foundations of a glaucoma healthcare ecosystem

Development of a sustainable healthcare ecosystem depends on macro- and microeconomic analysis of its components, and on addressing strategies to mitigate risks. Prolonged and expensive, such analysis needs top platform experts to reconcile diverse political, socioeconomic, regulatory and legal, long-term investment, bio-medical, QoL, clinical, technology and security goals.

Ensuring sustainability of the healthcare ecosystem

A global ecosystem must be implemented as a transactional technology platform. Platform technology is important but not critical while human factors and access to capital are usually decisive (548-550). Current 'Platform-as-a-Service' paradigm allows developers to select technologies from infinite and relatively inexpensive choices. An infrastructure is assembled from building blocks with limited customization, as opposed to dicey capital investment in a custom-built rigid IT structure (551-553).

After a program budget has been allocated to deploy a healthcare ecosystem, a draft FRS for its operational platform is usually released. Then this document is negotiated with service stakeholders and potential vendors (usually SIs).

Regretfully, the interests of beneficiaries (patients) and system operators (clinicians) are not always taken into account upfront. If they are evaluated after completion, it is too late to change the course of platform development. Success rates of such health system development projects are dismal, as with other information technology projects, such as in finance, governance, or infrastructure (554-565). With this article, we hope to reverse this tendency for the development of a glaucoma healthcare ecosystem.

The platform economy disrupts legacy industries and introduces new global-reach platforms (i.e., Amazon, Alibaba, Google, Facebook) that allocate resources more efficiently than conventional corporations because their independent participants collaborate and compete more vigorously. They reduce shared search costs with economies of scale; especially after reaching a critical mass, where for new users the value of the ecosystem exceeds the cost of joining (566-570). "*…Practically any industry in which information is an important ingredient is a candidate for the platform revolution*" (566).

Governments also formulate their platform policy strategies (571,572), particularly in the delivery of digital healthcare (13,573-577). New concepts of collaborative ecosystems and platforms to manage chronic diseases have emerged (578-581). So far, the implementation of a comprehensive patient-focused ecosystem to manage chronic diseases has not been announced.

Economics, finance and QoL

How could financial support be attracted for an effective healthcare ecosystem? Economic, financial and regulatory factors include:

(I) It should provide substantial benefits to the glaucoma patient's vision and QoL.

(II) It should present interpretable and explicable algorithms for health regulatory frameworks (i.e., US HIPAA, FDA, MDR, GDPR; AMA June 2018 Policy on Augmented intelligence in health care (582) and clinicians (583-585).

(III) It should transparently save costs compared with existing fragmented systems.

(IV) Its financial sustainability and technology development should be assured over the next 10–25 years.

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Annual medical costs for glaucoma in the US are projected to be $12 billion by 2032 and $17.3 billion by 2050 (81,586,587). Direct annual costs for glaucoma treatment increase with severity—$8,157 for no vision loss to $18,670 for blindness in 2008 (588). Add to this social security benefits, lost income tax revenue and long-term care (589). Similar amounts prevail globally (500,590-592).

Glaucoma management is expensive, including medical evaluation, testing and decision making, medications, laser and surgical procedures. Increased knowledge about glaucoma progression, with and without treatment, has encouraged earlier and more aggressive interventions to prevent visual loss in an aging population. As disease awareness expands and diagnosis is made earlier, costs escalate. The risk of unilateral blindness in a patient with POAG 10 years from diagnosis is 7.4%, jumping to 13.5% after 20 years (84,593). Patients with severe visual loss strain financial resources, as their independence is lost and support services increase.

Although glaucoma is incurable, treatment slows progression of visual loss. How long does a patient live after diagnosis? Years of observation to determine an individual's rate of progression show that many patients are overtreated. If prior variables were known, we might forgo treatment for some patients. The corresponding epidemiological model is 'the number needed to treat' (NNT) (594-596).

In the Ocular Hypertension Treatment Study (OHTS), the NNT to prevent one person from developing glaucoma was 20 (597). If we had a reliable way to identify that person, treatment would be unnecessary for 95% of patients with ocular hypertensive symptoms. Cost savings become far greater when disease is advanced, as surgery, multiple medications and more frequent observation all rise (500,586-592).

A patient-focused global glaucoma ecosystem could attract government and insurer support. To save, only patients at risk of vision loss would be treated. Genetic predictor tools might help to rationalize costs (598). The platform accurately making those predictions would be valuable. A controlled utilization of therapy would save further with reduced comorbidities, side effects from medical and surgical therapies, doctor visits, diagnostic testing and remote monitoring.

A robust glaucoma decision-making platform would use clinical information obtained over a few patient visits to determine optimal frequency for monitoring, testing and treatment to prevent visual loss. Clinicians will continue to be essential, deciding what information is required to be captured and overriding a treatment algorithm deemed in error.

The US AMA June 2018 Policy on Augmented intelligence in health care endorses a human 'second opinion'. Diagnostic systems should enhance physician clinical decision-making, not replace them. AMA calls for AI systems advancing the delivery of care in a way that outperforms what either can do alone; are transparent; and take into account the legal implications of healthcare AI, such as issues of liability, and professional and governmental oversight (582).

With glaucoma AI ecosystem, fewer clinicians would care for more patients with less overtreatment, overdiagnosis and visits to healthcare providers. Those needing more frequent monitoring would be more accurately identified and able to benefit from it. Equally important is the overall benefit to patient QoL. Maintenance of functional vision would also allow for increased patient mobility and independence, prevention of falls and injuries, and yielding better outcomes. An FRS should denote rigorous microeconomic modeling of the resulting cost-benefit balance.

Attracting financial support

The ability to predict glaucoma progression is complex (*Figures 3*,*4*). Glaucoma's 'landmark studies', such as OHTS, CIGTs, EMGT, AGIS, Baltimore Eye Study, have cost hundreds of million dollars and taken many years to complete (599-601). While data from those studies could be incorporated into AI algorithms, they are insufficient to support a fully functional and effective ecosystem. Government and private investments in new technologies, therapies and data will also be required.

We believe that much data needed to create novel robust and powerful glaucoma programs is not in the mainstream practice. For example, IOP levels 'around the clock' are needed to predict glaucoma progression and to monitor therapy. Remote monitoring remains non-autonomous but is in development or early implementation (e.g., Triggerfish/Sensimed—sensimed.ch; Implandata Eyemate—implandata.com; Qura—qura.biz; Injectsense—injectsense.com; to name just a few).

OCT technology cannot predict future loss of nerve fiber layer. Visual field testing is subjective, with variability and errors. Objective measures of visual function, such as pattern electroretinogram, are time-consuming and not accurate. With evolution, accuracy will improve. Venture capital will drive biomedical innovation.

Start-up capital for glaucoma patient-focused and QoL-oriented infrastructure projects will be essential. Venture

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investors might be attracted to their early development phase with large returns possible. A glaucoma healthcare ecosystem might also pave the way for patient-focused platforms for other chronic diseases (such as Alzheimer's, Parkinson's, cystic fibrosis, cardiovascular, cancer, and diabetes). Successful ecosystem development would be monetizable.

Patient-centered outcomes models

Conventional Biomedical Models of acute diseases consider people as either sick or healthy. 'Outcomes models' (the Donabedian model, The Quality Health Outcomes Model - QHOM, Kaplan's Outcomes Model) are based on the observation that diagnosis and treatment do not necessarily improve life expectancy and QoL of patients with chronic diseases; they might even lead to deterioration in a patient's health (368,529,546,602-606).

Outcomes models require more comprehensive patient-centric socioeconomic, financial and risk analyses. They are more quantitative and objective, even when they produce counterintuitive results (487). Using government-supplied statistical indicators, outcomes models overcome the subjectivity of questionnaires while not negating QoL subjective assessment methods but complementing them.

Unlike a linear Donabedian model, QHOM is a dynamic model that could cope with multiple factors and relationships, tying quality of care to desired outcomes. It could guide database development to improve outcomes management, compare treatment options and suggest key variables and policies in a clinical and organizational intervention (603).

Chronic diseases are gradual processes with multiple causes, and are not easily cured. Many patients have several chronic conditions (368). As elderly patients typical for glaucoma must adapt to their several diseases, psychological and social factors along with epidemiological data are key. Data imprecision and the need for ongoing massive data collection necessitate a powerful ecosystem.

QALY as a measure of health status in chronic diseases

Patient-centered outcomes models use Quality Adjusted Life Year (QALY) to measure health status in chronic diseases. QALY combines two assessments—benefit or harm of new treatments and their effects on a patient's QoL (42,43,86,368,509,546,547,602-609).

QALY is the cornerstone of economic analysis (86,509,608), which is the basis of rational health care decisions (86). More expensive than for acute diseases, chronic disease management has to account for both society and the individual. QALY also provides stakeholders with the cost-effectiveness factors to allocate limited resources optimally (45,86,509).

Initially embraced by governments and medical insurance industry as a cost-utility measure to maximize the value of healthcare spending, QALY use has expanded to affect decision-making by medical researchers, clinicians and patients. It assigns appropriate values to medical and QoL impacts for each patient's treatment, its side effects, and overall program costs. The cost/QALY ratio might be useful to compare relative efficiencies of treatment programs. Integration of QALY assessment could facilitate global adoption of our proposed platform.

Kaplan's conventional survival analysis used to evaluate QoL in chronic diseases, such as cancers and diabetes, gives a unit of credit for each year of life (368); or for glaucoma, for prevented years of blindness. Thus, a person with severe glaucoma with some sight is scored as if in perfect health. In contrast, in QALY, years of wellness are scored on a continuum from 0 for death to 1.0 for full functioning.

A disease that reduces QoL by one-half will take away 0.5 QALYs over 1 year. If it affects two people, e.g., including a caregiver, it would take away from this family 1 year over 1 year because caregivers experience stress and endure a substantial cost (610-614). A drug treatment that improves wellness or QoL would equivalently improve QALY if the benefit were maintained over 1 year (42,43,283,368,509,546,547,602-608).

Based on QALYs, Kaplan's Outcomes Model might be interpreted differently from the conventional Biomedical Model. QALY analysis shows the relatively minor impact of high-profile acute diseases compared with chronic diseases like glaucoma. "…*The disease burden patterns of Westernized developed countries will begin emerging in the developing world*." (368).

Kaplan's Outcomes Model does not consider biological abnormalities problematic unless they threaten life expectancy or reduce QoL. In contrast to the Biomedical Model, the Outcomes Model can make decisions that maximize the quality-adjusted life expectancy.

Certain QALY assumptions and the universality of its methodology have been challenged, particularly related to equity and efficiency (509). However, as no alternative measure of similar evaluation power and universality has emerged, contemporary research focuses on improving the QALY approach.

Quality assurance of an outcomes model

Glaucomatous visual loss creates a huge economic burden.

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Quality assurance is essential to ensure user's confidence in a complex health economics outcomes model with many input variables (615). In QALY modeling, quality assurance could be accomplished with sensitivity analysis, which assesses how each input contributes to output's uncertainty (616,617). It could clarify the model's recommendations to decision-makers, test the robustness of the model's results, and facilitate recalculating outcomes with alternative assumptions, thus improving the model.

Computationally intense, a rigorous sensitivity analysis demands mathematical proofs of theoretical assumptions. For simplicity, sensitivity analysis calculations use a univariate output model; yet real-life processes result in multiple outputs of signal- or time-dependent data. Thus, a discrete sensitivity analysis is needed for each output of interest. For widespread models with mutually correlated and nonlinear outputs, sensitivity analysis results are hard to interpret (616,617).

Development methodologies and functional requirements of computerized diagnosis and treatment systems do not reflect the need for comprehensive quality assurance. After a long and expensive R&D phase, most such systems fail when scaled commercially to the complex clinical environment, especially in developing countries that need to benefit most from this approach (182,618-625).

Quality assurance prevents mistakes, avoids medical treatment problems, and boosts patient confidence. It aims to hold health services publicly accountable (606). The technical aspect of quality of care is proportional to its effectiveness, and dependent on the best knowledge and technology (605). With quality management, our glaucoma healthcare ecosystem must continually modify, extend and improve itself by self-learning.

The DES model for Glaucoma evaluates model outcomes sensitivity with univariate analyses (45,238,347,348). Designed for healthcare cost/utility evaluation, this univariate model supports discrete sensitivity analyses for each time-dependent data output. AI engines shown in *Figure 1* could be used to compare cost-effectiveness among glaucoma treatments, as well as no treatment, subgroup analyses for different IOPs and degrees of glaucomatous damage, visual deterioration in the less affected eye, frequency of visual field testing, effects of local factors and regulatory environments, risks of testing, procedures and pharmaceuticals, effects of costs for informal care, low-vision services and aids, transport and production losses.

With glaucoma biomedical testing, patient treatment, QoL assessment and socioeconomic conditions often correlated, interpretation of discrete output sensitivity measures might be hard, especially for glaucoma types, each requiring a different decision-analytic approach (45). A new AI-based methodology is necessary for such complex analysis, along with regulatory acceptance of tiered cost-effectiveness acceptability thresholds by governments or private insurance companies. Healthcare procedure is cost-effective if it is efficient and cheaper, or if its cost does not exceed the determined threshold of cost-effectiveness.

In the Netherlands, such a threshold has been recommended at a maximum of €80,000 (~US$95,000 in August 2020) per QALY; the UK uses a range of £20,000–£30,000 (~US$26,000–40,000) per QALY; in Canada a range of CAN$20,000–CAN$100,000 (~US$15,000–76,000) per QALY (45); in the US willingness-to-pay thresholds lie between $100,000 and $150,000 per QALY (626,627); while WHO considers interventions cost-effective if it costs less than three times the national annual GDP per capita and highly cost-effective if less than the national annual GDP per capita (628). Brazil follows the WHO guidelines, which in 2014 was equivalent to BRL 81,000 (~US$15,000) (495).

Outcomes models and shared decision making

Outcomes models enable shared decision-making by clinicians with patients while accounting for resource limitations. Treatment strategies involve evaluation of risk/benefit profiles for various options.

While the Biomedical Model seeks to eradicate the disease whatever the side effects, treatment costs or harm to QoL, the Outcomes Model recognizes a chronic disease diagnosis does not necessarily result in better patient outcomes (56). If left undetected, some glaucomas for some patients might not impact life expectancy or QoL (368). This affects shared decisions for public policy, clinical policy and treatment.

A patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem should generate individualized forecasts of disease progression. Biomedical testing results and QoL criteria forecasts would be updated, depending on scenarios within the probable digital range for a particular patient. Such forecasts facilitate joint decisions by clinicians with patients on the appropriate individual biomedical targets to trigger clinical actions. As laser trabeculoplasty and other kinds of surgery are offered as a first-line glaucoma treatment for patients who have problems with remembering to instill eye drops, eye drop cost, allergies, or dry eyes (629-631), the ecosystem should also exhibit surgeons track records for different procedures.

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Depending on the biomedical tests results and conventional QoL assessments, clinicians could outline treatment options and probabilities for various outcomes. As complex and jargon-ridden biomedical data are often difficult to interpret (632), for clinicians the most important challenge to derive a shared decision is to ensure that risk information has been well understood by patients. As elderly patients often have several chronic conditions, they can put values on possible treatment outcomes within the context of their own circumstances and objectives.

Use of QALY to evaluate healthcare systems

Outcomes models have been used to forecast the progression of chronic diseases, evaluate their effects on patients' everyday activities and long-term treatment, and facilitate family- and business-related planning. Limited health resources must be optimized to help people live longer and feel better. Focused on the most efficient use of resources, QALY is used as an outcome measure to evaluate healthcare systems by decision-makers (governments, public and private insurance services, medical researchers, health economists and long-term investors) (608).

As economic and risk factors affect all healthcare decisions, QALY helps global health services to address growing pressures to determine the optimal use of limited resources. With novel and more expensive treatments, healthcare systems need additional resources for new cures, even while health budgets barely afford legacy solutions. Widely used but ineffective treatments surge public perception of healthcare underfunding. Hence, clear priorities must be established and tough choices made (56).

Credible decision-analytic modeling of cost-effective resource allocation for chronic healthcare is not trivial, especially in real-time. As noted (86): "*The best way to measure the economic benefit of glaucoma care remains controversial, with some measures lacking precision, and others lacking generalizability. […] Innovation in glaucoma care requires accurate, validated tools to assess the improved utility of each novel treatment otherwise we cannot justify the broad-scale societal uptake of such new technologies.*"

Use of QALY to assess glaucoma patients

The Outcomes Model has been used to evaluate health and behavioral outcomes. It is based on an analysis of QALY as a measure of health status in a chronic illness, considering benefits, side effects and program costs specific to this particular disease. Although QALY has been used in glaucoma academic research and long-term effectiveness analysis of government and private healthcare systems (53,54,86,511,633-635), rarely has it been applied to evaluate real-time healthcare outcomes for individual glaucoma patients. Personalization of treatment is impossible without simultaneous optimization of biomedical testing, QoL assessment and corresponding socioeconomic conditions for every patient.

Accurate but challenging bottom-up microcosting, starting with each patient and progressing up to national and global healthcare systems is 'the gold standard' in costing. Modeling at the patient level is effective when considering health interventions owing to patient heterogeneity (412,626,636). Its use also supports proactive development of global infrastructure, which must be widespread, comprehensive and smart. Such a global infrastructure is vital to capture and forecast biomedical testing, treatment, QoL assessment and corresponding socioeconomic conditions for each chronic patient.

The QALY approach should help to find the right balance between benefits of a particular treatment and its risks, QoL costs for individual patients and cost-effectiveness for society. Such balance should avoid waste in public and private insurance services (56). Higher resource allocation that leads to overtreatment might not provide measurable benefits to patients or improved healthcare service (86).

For example, by exploring whether it is cost-effective to treat selected individuals who are unlikely to develop functional impairment from glaucomatous damage, the QALYs elucidate difficult treatment decisions, especially for elderly glaucoma suspects or younger individuals with stable, early glaucoma. Ongoing improvements in technology, effects of therapy, medication, relative prices, demography and life expectancy would benefit all stakeholders (53). It might be possible to correlate QALY with the percentage of ganglion cell loss.

Several QALY studies, covered in a recent in-depth review (86), have attempted to analyze comparative cost-effectiveness of various glaucoma treatment scenarios for a range of durations and patients' ages. QALY has been used in a comprehensive health economic modeling of glaucoma treatment options in the UK (633), Finland (53,54), France (633), Germany (633), Japan (608), the Netherlands (45) and elsewhere.

To evaluate treatment cost-effectiveness, health economists have used the Markov model for QALY decision analytics, which is simple to implement in academic environments and can provide estimates of

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disease advancement. By dividing overall progression into time cycles and assigning resource use and health outcomes to every cycle, this model estimates probability of advancement, long-term costs and outcomes for various disease scenarios (56,86). With its inherent limitations, the Markov model cannot be used for clinical or insurance applications. We make a detailed examination of QALY decision analytic modeling in the next section.

Analyzed glaucoma treatments cover eye drops versus laser trabeculoplasty versus surgery for equal visual outcomes. Each treatment (or absence of treatment) has been assumed to have positive factors and substantial risks. QALY helped to quantify that patients with visual loss in one eye can serve as accurate predictors of outcome values that would develop if the visual loss were to occur in both eyes (86,472).

These decision-analytic results were divergent and country dependent, for both acceptance of direct and indirect treatment costs, as well as local expectations and tolerance for deteriorating QoL. Final values and conclusions are affected by many assumptions and estimates built into the models, especially as they do not account for downstream effects and risks related to long-term medical and QoL outcomes and corresponding utilization of healthcare services (86).

Several Finnish studies based on the Outcomes Model and QALY have confirmed Dr. Fechtner's above-cited views that physicians overtreat some glaucoma patients (53,54,56). In Finland approximately half the patients diagnosed with glaucoma do not suffer from it but have been prescribed unnecessary medications for over 10 years. Likewise in Australia, in a 1990s population-based cohort study conducted over 7 years, more than half the patients treated for glaucoma did not have the disease (634). On the contrary, in Australia and Sweden more than half of the patients with newly diagnosed glaucoma had seen an ophthalmologist, but their disease was not diagnosed (633,635). All three countries have first-rate socially supported health systems.

Similar to Kaplan (368), Vaahtoranta-Lehtonen (53) explains this by: "*Compared to studies performed in academic centres, in everyday practice ophthalmologists often apply a nonoptimal combination of diagnostic and follow-up tests and do so far less frequently, leading to a low specificity.*"

Health economic modeling supports analyzing glaucomas as a stratified group of chronic diseases. Comparing resource utilization for patients with various types of glaucomas shows healthcare costs are higher for some types (i.e., exfoliation versus POAG) (512). Such quantifiable data is critical to run comparative evaluations of reimbursement models (fee-for-service versus bundled payments), as cost forecasts depend on the granularity of glaucoma diagnosis (56,637,638).

QALY might ensure better decision-making and a different treatment strategy regarding the need for intervention for populations in developing countries. In the Indian population, it is difficult to separate mild glaucoma patients from controls because demographic characteristics differ from those in developed countries (37). However, QALY is not sensitive to small changes in glaucoma severity or therapies (639,640).

For instance, a cross-sectional analysis of glaucoma patients under different therapies demonstrated QALY's utility values that did not differ much between groups (639). Unlike conventional QoL glaucoma assessments techniques, the more comprehensive and granular QALY approach, fortified by stronger analytics and modeling methods, should better handle the impact of extensive demographic differences.

QALY decision analytic modeling in an academic environment

Decision analytic assessments of QALY are conducted to evaluate the efficiency and cost-effectiveness of healthcare and to administer social services to glaucoma patients. Several decision-analytic modeling methods are used to estimate disease advancement, such as decision tree, Markov and DES models. Each decision-analytic model of healthcare economics evaluates different tradeoffs and quality assurance approaches in and out of academia (616,617,626,636,641-643).

The model selected to evaluate QALY outcomes for glaucoma patients must represent a complex, interconnected workflow of biomedical testing, patient treatment, QoL assessment, and corresponding socioeconomic conditions. It must be powerful enough to cover chronic effects of glaucoma regulatory disclosure requirements, and be agile enough to explore alternative strategies. The model should also consider robustness, in-field conditions, accuracy, speed and computational efficiency, granularity, transparency, ease of use, quality assurance, and cost of development and maintenance.

QALY outcome applications for chronic diseases must be properly designed, tested and constantly improved; their output has to be monitored for continuously changing inputs, especially for longer cycles. Despite this, modeling

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approaches might differ in QALY estimates and decision outcomes, especially if the number of analyzed patients is insufficient (616,617,626,636,641-643). Choice of a viable QALY model outside of the R&D environment depends on the functional requirements formulated by academic, clinical, policy, financial and computer technology experts.

The decision tree is a simplified legacy model, which estimates probability of potential outcomes without accounting for effects of time. It is straightforward but labor-intensive to implement, inflexible and taxing to derive far-reaching conclusions (616,617,626,642).

Commonly used in economic research, the Markov model is relatively uncomplicated and fast to implement with Excel spreadsheets and Visual Basic scripts. While it provides an advantageous mix of accuracy and run-time, it introduces complexity when calculating cost and QALY outcomes with large numbers of events. It can be used for evaluation of idealized models with a mutually exclusive chain of limited events. As the Markov model is forced to constantly check clinical events at the end of each cycle, its processing is slowed down, a major limitation, especially in non-basic applications (616,617,626,636,641-643).

DES modeling provides higher accuracy, reliability and speed for more complex, larger models, with interdependent multiple health conditions competing for clinical events. It allows comparison of therapeutic effects of a medicine including adverse reactions with the use of an alternative treatment. Originally developed for physics and engineering applications, DES is currently extensively utilized in microeconomics, as well as in the insurance and biotechnology industries. With the introduction of personalized medicine, DES could better reflect individual patients' characteristics and clinical profiles rather than rely on the population level statistics used by conventional methods.

DES modeling has been proposed for comprehensive costing analysis of different approaches to the treatment of glaucoma patients (45,238). Theirs and similar novel costing methods could link biomedical and QALY model blocks shown in *Figure 1*, supporting the implementation of an effective glaucoma treatment decision support platform.

DES is more complex to implement than alternatives, as it runs stochastic modeling, which estimates probability distributions of potential outcomes and possible risks by exploring many random variations in process inputs. Such random variations are based on fluctuations in historical data, such as the effect of IOP changes on the visual field in glaucoma patients. DES models could incorporate patient heterogeneity of costs and risks. It could handle historic data and plan future events, while Markov's is a 'memory-less' model (616,617,626,636,641-643).

The selection of decision-analytic models and the choice of key modeling assumptions, inputs and outcomes robustness have been insufficiently justified (642,644). Many QALY academic researchers continue to use simplified decision trees and Markov modeling. A 2017 comprehensive evaluation of 41 model-based studies on the cost-effectiveness of treatments for depression found that 21 used decision trees, 15 Markov models, and three DES models. Based on 11 predefined quality of modeling criteria, decision trees scored positively in just four of the 11 criteria, Markov models in five, and three DES models in seven (642).

In a 2020 review of 22 decision-analytic modeling on the cost-effectiveness of treatments for primary open-angle glaucoma, undertaken for more than 35 years in 15 different countries, 14 were Markov models, four were decision trees and four DES (644). Mass digitization of glaucoma care, financing and administering cycles in the clinical environment would require a more powerful and robust implementation approach compared with academic research conditions.

QALY decision analytic modeling in the clinical environment

In 2002, with 42 brands of five pharmacological classes of drugs that were then commonly used to treat glaucoma (either as monotherapy or in combination), medical therapy for glaucoma offered 56,159 different options (645). Today, with eight pharmacological classes available and new treatments (laser options, minimally invasive glaucoma surgical devices), as well as generic and new drug combinations, that number has increased substantially (18,646-650).

Yet for a glaucoma specialist, all but a few options are inappropriate for initial treatment in most cases. Like much in AI, what comes easily to trained humans is often hard for computers. Experience and learning hone treatment options for the specialist.

For AI systems, each treatment option is an extra input to be considered, an additional burden for the system to quantify potential outcomes. With exponential growth, input options for QALY decision-analytic modeling from biomedical factors offer trillions of choices, especially with the chronic character of this illness, far exceeding human cognitive capacity (*Figure 9*).

In 2011, more than 27 million possible inputs (different

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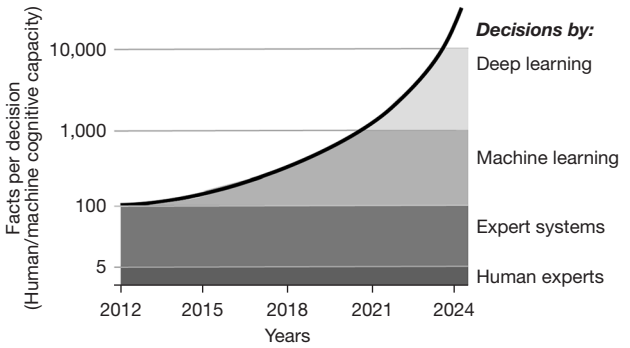

Figure 9 Growth in facts affecting provider decisions versus human cognitive capacity. Inspired by a forecast by William W. Stead in 2008 that the absorption by physicians of the information published in 1990–2020 in exponentially growing genetics journals will inevitably be limited by the human processing capacity (108).

utilities, utility respondents, cost bases, cost perspectives, time frames, discount rates, currencies, years) might go into a QALY analysis alone (627,651-654). A decade later, this has ballooned. Boundless data growth is characteristic of modeling the output span.

No medical expert can comprehend and analyze such colossal volumes of incongruous data in real-time. This is why 'consensus of expert opinion' is often regarded as the gold standard of diagnostic assessment (412). Hopefully, potentially unlimited processing abilities of AI will address this complex challenge.

The DES model, one of the most analytically powerful, can be computationally demanding, especially for probabilistic sensitivity analyses. In 2019 it simulated 100,000 individual women with postmenopausal osteoporosis, to estimate the average total per-patient costs and QALYs in a 10-year time horizon (626). It performed 100 million simulations (10,000 samples, each containing 10,000 individual patients) for each treatment strategy in 7.5 hours. For a medium-size ophthalmological practice with a dozen clinicians and a similar number of patients, modeling a more complex and more computationally intensive glaucoma treatment would be too expensive, and too slow to optimize meaningful multidimensional data for each patient.

In daily practice, clinicians stick to a dozen or so treatment plans they regard as viable and effective, based on training and experience. This pragmatic approach runs contrary to individualization of patient treatments. It limits the potential for treatment optimization for an individual, as well as accounting for possible QoL criteria that force patients to abandon their treatments (125,655,656). Even though computationally effective modeling is necessary to better understand glaucoma academically, no existing algorithmic modeling method could be scaled up for practical use in its global clinical environment, as it would be too slow and too expensive to implement.

Hence, functional requirements and underlying methodology for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem must reflect the fundamental quantitative barrier between radically different digitizing approaches in the institutional research and worldwide clinical environments. Such a wall between two polar approaches reinforces our conclusion that only effective implementation of a powerful AI-based healthcare ecosystem could optimize numerous input and output parameters for individual patients globally, overcoming the quantitative barrier between academic and clinical approaches.

As a result of our quantitative analysis (*Figure 9*), from being a 'nice to have', AI has been found to be a 'must have' enabler.

Key points

(I) By considering the interests and opinions of users and stakeholders, we would like to ensure the successful development of a sustainable patient-centric computerized glaucoma healthcare ecosystem. How could such a critical system attract government and/or private insurance financial support? This depends on the economic, financial and regulatory factors formulated and discussed in this section.

(II) AI systems incur costs, but these would be offset at least in part by less overtreatment, less overdiagnosis, fewer visits to healthcare providers, less under-treatment, with more optimal treatment outcomes. By avoiding unnecessary doctor visits and treatments, with potential side effects, patients' QoL should be enhanced; there should be significant cost savings. It would be possible to conduct rigorous economic modeling to reveal break-even points.

(III) The multifactorial processes causing glaucoma visual loss make progression prediction complex and costly. With significant investment by VCs to develop novel technologies to facilitate diagnosis and treatment, venture funding will drive biomedical innovation and improve patient QoL. The extensive costs of new

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glaucoma research will also require institutional and government financial contributions.

(IV) Venture financing of complex healthcare ecosystems is more challenging than the funding of early-stage biomedical products and services. Longer timelines for returns on investment from the development of an integrated healthcare ecosystem compare poorly with development of a new pharmaceutical or device. Many expensive and slow-to-resolve regulatory requirements and legal challenges that are difficult to predict, amplify this problem. A successful glaucoma healthcare ecosystem might prompt recognition of the need for similar patient-focused platforms for other chronic diseases (e.g., Alzheimer's, Parkinson's, cystic fibrosis, cardiovascular diseases, cancers, diabetes) and thus become monetizable in its own right.

(V) We could use QALY to evaluate healthcare outcomes, which requires comprehensive and quantitative patient-centric socioeconomic, financial and risk analyses. QALY combines into a single measure two disparate assessments of health status in chronic diseases: how much a new drug or treatment could extend (or shorten) a patient's life and how much it might improve (or diminish) their QoL. It provides the healthcare system's stakeholders with the cost-effectiveness factors necessary for the optimal allocation of limited resources.

(VI) A healthcare ecosystem should generate individualized forecasts of disease progression based on a patient's situation, personal choices and likely risk profile. It should be able to facilitate joint decisions by clinician and patient on the most appropriate individualized biomedical targets for clinical actions. It should also exhibit surgeons' track records for different procedures.

(VII) Modeling of health economics supports the analysis of glaucomas as a stratified group of diseases. Healthcare cost forecasts might depend on the granularity of glaucoma diagnosis, being different for various types of glaucoma. Cost quantifiable data enable comparative evaluations of reimbursement models.

(VIII) Decision analytic assessments of QALY evaluate healthcare efficiency and cost-effectiveness, thus optimizing social support services for glaucoma patients. The most commonly used methods to estimate disease advancement are decision tree, Markov, and DES, with each model offering different tradeoffs. DES models are more flexible and computationally efficient than decision trees or Markov models.

(IX) Biomedical and QoL factors mean the distribution of input options for QALY patient-centric decision-analytic modeling amounts to trillions of choices, far above human cognitive capacity; they grow exponentially. Computationally effective modeling is necessary to understand glaucoma. No existing algorithm could be scaled up for the worldwide implementation that could ensure reliable analysis, as it would be too slow and expensive.

(X) Functional requirements and underlying methodology for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem must reflect very different digitizing approaches in global academic research versus clinical environments. Such a formidable wall between these two polar approaches reinforces our conclusion that only effective implementation of a powerful AI-based decision-making system could effectively optimize numerous input and output parameters for individual patients. As a result of our quantitative analysis, from being a 'nice to have' feature, AI has been found as a 'must have' enabler.

Discussion

We believe radical improvement in global glaucoma care is possible with the aid of a patient-centric computerized treatment and healthcare ecosystem. A smart computerized system to manage glaucoma patients holistically, over a long period should be built on a new methodological foundation. With exponential data accumulation and human limitations to make healthcare decisions, the use of AI systems that complement clinical care is vital. We outline broad criteria necessary to optimize the efficacy of the integrated computer-aided decision-making system. Although no current AI training algorithms can meet these complex challenges, one should be able to define and later implement a potent global health data infrastructure with extensive R&D.

We identify many interdependent issues (including health/analytical, ability to live independently, psychological, risk, technical, regulatory, security and privacy) necessary to resolve to create an effective treatment decision support platform on a large scale; we outline selection criteria for an

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AI engine. We also establish AI engine types likely suitable for medical diagnostic applications. Large investment is needed to develop a relevant AI healthcare solution.

A well-defined infrastructure could guide the proper structuring of each patient's data with appropriate granular analysis, of selected patients' segments, for example, the type of glaucoma, genetic predisposition and stage of the disease. AI-run testing and treatment methodologies must be individualized for each patient. A computerized medical treatment and QoL support ecosystem should support the multifaceted functionality of the critical building blocks of this defined integrated approach. It should also produce and periodically update personalized mid- to long-term forecasts useful to glaucoma patients, their health practitioners, government budget authorities and private insurers. We have listed economic, financial and regulatory factors necessary for such a critical system to attract government and/or private insurance financial support, along with the need to conduct rigorous economic modeling to reveal break-even points.

Elderly glaucoma patients often suffer from various physical and/or psychological problems caused by several co-existing chronic diseases. To minimize health deterioration and to manage treatment risks, each chronic-care patient needs a holistic approach, rather than separate treatment of each disease.

Increasingly in chronic disease management, overdiagnosis and overtreatment are challenges for patients and health systems. Up to half of glaucoma patients are overdiagnosed and overtreated, which can be harmful and reduce resources for other health priorities. This contributes to the crisis facing worldwide healthcare resources. Some governments consider financing healthcare services based on an assessment of overuse and underuse. As reasons for overuse are diverse, addressing them requires a range of effective strategies.

Conclusions

Analyzing glaucomas as a set of distinct subgroups of patients could advance computerized glaucoma diagnosis, treatment and QoL optimization; simplify digital decision analytics; and facilitate cost-effective personalized healthcare. Such objective glaucoma diagnosis stratification would support the evaluation of quality and granularity of QoL costs, as well as optimize healthcare reimbursement models. Yet, there is valid debate among the clinicians whether to lump various glaucoma types together, keep them separate, or simultaneously build computerized models and conduct data analysis for both scenarios, as the potential downside of diagnosis stratification would be the creation of multiple computerized systems and decision trees for essentially similar treatments.

The requirement-gathering process that will develop a more formal FRS for an effective, efficient, integrated patient-centric glaucoma healthcare ecosystem would be a reasonable starting point. This 'evergreen' document would need to crystallize broad agreement between clients and developers, supported by health innovation, medical and regulatory communities in many countries, on how to implement, continuously to improve and extend a glaucoma holistic ecosystem. Typical inputs required for developing a sustainable healthcare ecosystem platform are a description of services that the software must offer, demonstration of the platform's added value and economic benefits, applicable regulatory frameworks, features, functions and components of the system and its subsystems, work and data flows and risk profiles. Addressing these requirements will identify the project's scope, cost and chances of success.

In summary, *Figure 1* "Critical building blocks and enabling commercial and proprietary engines…" presents a condensed block diagram of the integrated approach to define functional requirements for a patient-centric computerized glaucoma diagnosis, medical treatment and QoL ecosystem.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jmai.amegroups.com/article/view/10.21037/jmai-22-33/coif). CB declares receiving grants and contracts from Horus Pharma, Santen and Thea; consulting fees from Abbvie, Alcon, Horus Pharma, Oculis, Santen and Thea; and participation on a data safety monitoring boards or advisory boards with Thea, Oculis and Santen. PLK reports that he consults for and/or sits on scientific advisory boards for numerous drug and device companies related to glaucoma and presbyopia.

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These are compensated at a going market rate. He and his research team at the University of Wisconsin-Madison also conduct research for companies in areas where they have the appropriate technical and intellectual capabilities. These are fee-for-service contracts that comply with the UW-Madison rules for such activities, including equipment, material and reagents. PLK and his team have no current active patents but are working with a device company on a gene therapy delivery system that could be novel. RR declares receiving honoraria for speaking at promotional events sponsored by Allergan, which sells pharmaceuticals for the treatment of glaucoma. He is a Co-Founder and Co-Managing Member of a venture capital fund that has investments within companies that are focused on the treatment of glaucoma. PH declares receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Abbvie, Alcon, JandJ Vision, Bausch and Lomb, Glaukos, Zeiss, Labtician and Thea. None of the aforementioned activities or relationships causes a conflict of interest in the matter of this paper. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Glaucoma general diagnosis

Glaucoma sub-type	Description	Share of the population affected	Forecast	References
Glaucoma	The optic nerve has been damaged.	• 0.5% at the age of 40; • 2% of over 40-year-old; • 8% of 80-year-old	Cannot be generalized; see specific diagnoses below	(225,412,424)
Primary	Intraocular pressure (IOP) might or might not be elevated. Optic nerve damage occurs without any known or detectable cause.	~60% of glaucomas	Cannot be generalized; see specific diagnoses below	(225,412,424)
Secondary	IOP is or has been elevated due to some known pathological cause. Optic nerve damage occurs as a result of clinically evident external or internal conditions; i.e., injury, eye inflammation, exfoliation or pigment dispersion syndromes (with exfoliation fibrils or pigment molecules hindering drainage in the trabecular meshwork), prolonged use of steroid medication, problems with the focusing lens or cornea.	~40% of glaucomas	Better outlook if the cause can be identified and treated; otherwise, treatment success depends on effective IOP control	(225,412,424)

Table S2 Primary glaucoma diagnosis

Glaucoma sub-type	Description	Share of the population affected	Population affected	Forecast
Open-angle [primary open-angle glaucoma (POAG), adult-onset]	Primary open-angle glaucoma occurs without any detectable cause. Normal-tension glaucoma (NTG), also called low-tension or normal-pressure glaucoma is a sub-type of primary open-angle glaucoma. The optic nerve is damaged even though the intraocular pressure (IOP) is not very high (usually between 12-20 mm Hg). The cause of damage is usually unknown. At higher risk for NTG are people: • with a family history of NTG; • of Japanese/Korean ancestry; • with a history of systemic heart disease. Juvenile-onset open angle glaucoma (JOAG)	~40% of total glaucomas	More common in people with African ancestry	Open-angle glaucomas are responsible for about half of glaucoma visual disabilities. For NTG, because IOP is 'normal' (i.e., defined as POAG with <21 mmHg in some studies (33,387), diagnosis is often confirmed later than for high-IOP glaucomas. This emphasizes the importance of optic nerve evaluation at all treatment stages.
Angle-closure [primary angle-closure glaucoma (PACG)]	This type of glaucoma usually occurs due to reduced access of aqueous humor to the eye's drainage pathways. It is caused by inherited anatomic elements of the individual's eye (typically in long-sighted individuals) and further deteriorates with age-related thickening of the cataract that pushes the peripheral iris forward, further narrowing access of fluid to the drainage angle. Usually affects both eyes. If of sudden onset, might cause severe pain, headaches, nausea and vomiting, blurring of vision, sensations of rainbow rings around lights. If untreated, could destroy sight-in days. Almost all oral medications contraindicated in glaucoma are linked to this type of glaucoma. Most commonly chronic and asymptomatic. Forms of angle-closure glaucomas: • Acute; • Chronic.	~20% of total glaucomas	Affects women more than men. More common in Chinese, Indian, other Asian and Inuit populations.	Angle-closure glaucomas are responsible for another half of glaucoma visual disabilities; in particular, because their diagnosis is often missed, even more frequently than for the open-angle glaucomas.
Primary congenital glaucoma (PCG) (childhood; juvenile)	Occurs in babies when there is an incorrect or incomplete development of the eye's drainage canals during the prenatal period.	A very small percentage of diagnosed glaucomas	Usually inherited	Microsurgery can correct structural defects. Results are often better when uncomplicated by other abnormalities.

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Table S3 Secondary glaucoma diagnosis

Glaucoma sub-type	Description	Share of the population affected	Population affected	Forecast	Angle
Exfoliative, also called pseudoexfoli-ative (XFG)	LOXL-1 gene abnormality has been associated with this particular condition. Abnormal material that looks like microscopic dandruff is released in the eye where it damages the drain and rubs on the iris, releasing its pigment granules into the watery fluid, further blocking drain channels and raising eye pressure, often rapidly and severely. This in turn might damage the optic nerve.	~25% of total glaucomas.	More common in older people and certain ethnic groups, including: • People from the Nordic and other Northern European countries; • Greeks and other Mediterranean populations; • Indians.	Tends to be a more aggressive form of glaucoma, but the underlying exfoliation syndrome might be found with no evidence of glaucoma.	Open-angle; might morph to angle-closure [secondary angle-closure glaucoma (SACG)], which is often more difficult to treat
Pigmentary dispersion syndrome (PDG)	Pigment granules from the back of the iris are dislodged by rubbing, float with the aqueous fluid, blocking and damaging the drainage channel. The eye pressure rises. This in turn might damage the optic nerve.	Small share of total glaucomas.	Although this is a relatively uncommon condition, it is more common among younger people, mostly shortsighted men in their 20s to 30s	As with the underlying exfoliation syndrome, pigmentary dispersion can occur without glaucoma. Usually treated like primary open-angle glaucoma, with some differences in the type of laser procedure performed in the affected eye.	Open angle
Uveitic	Uveitic glaucoma diagnosis usually covers numerous inflammation disorders (e.g., sarcoidosis, tuberculosis, toxoplasmosis, and various viruses) that increase eye pressure. Forms of Uveitic glaucomas that affect only one eye: • Fuchs' Heterochromic Iridocyclitis; • Posner-Schlossman Syndrome (Glaucomatocyclitis); • Herpetic uveitis; • Infective; • Toxoplasmosis. Other forms that can affect one or both eyes: • Juvenile idiopathic arthritis; • Ankylosing spondylitis; • Sarcoidosis; • Steroid related.	Small share of total glaucomas.	~20% of patients with ocular inflammatory disorders (uveitis)	With modern treatments focusing on the root cause of inflammation, as well as controlling eye pressure, many patients can maintain excellent vision.	Open angle; might morph to angle-closure (SACG), which is often more difficult to treat
Neovascular (NVG), also called new vessel, hemorrhagic, thrombotic, congestive, rubeotic, and diabetic hemorrhagic	NVG diagnosis usually covers numerous blinding diseases.	Small share of total glaucomas.	Most commonly associated with retinal vein blockage or diabetic eye disease patients	The better controlled a person's diabetes and the more efficient the treatment after a retinal vein obstruction, the less likely is NVG to develop. Treatment starts with the identification and correction of the cause. Newer medications and laser approaches have revolutionized treatment, but the outlook for visual recovery depends on the underlying cause, how much visual damage it has caused, and how amenable it is to the treatment.	Open angle; might morph to angle closure (SACG), which is often more difficult to treat
Elevated episcleral venous pressure (EVP)	• Venous obstruction; • Cavernous thrombosis; • Vena Cava syndrome; • A-V abnormalities; • C-C fistula; • Sturge-Weber.	Small share of total glaucomas.	Rare		Open angle
Irido corneal endothelial syndrome (ICE)	ICE is a rare form of glaucoma, usually found in only one eye. Symptoms include hazy vision upon awakening and the appearance of colored rings around lights.	Small share of total glaucomas.	Rare. Cause unknown.	ICE is difficult to treat; it causes visual damage through corneal decompensation, as well as glaucoma.	Open angle; might morph to angle closure (SACG), which is often more difficult to treat
Traumatic	Mostly caused by a blunt injury to the eye and occasionally injuries that penetrate the eye; occurs either immediately after an injury or years later (called angle-recession glaucoma). Blunt Trauma (Angle Recession) causes include a blow to the eye from sportsrelated injuries (in baseball, boxing, squash). Angle recession highlights the damage done to the drainage canals in the eye with pressure increases sometimes many years after the injury. • Blunt trauma (angle recession; • Hyphema; • Ghost cell; • Schwartz.	Small share of total glaucomas.	The greater the extent of injury (seen as angle recession), the higher the risk. Glaucoma might occur up to 30 years later. Other conditions, such as severe nearsightedness, previous injury, infection, or prior surgery might also contribute.	Treated similarly to a more aggressive form of primary open-angle glaucoma. If you have had an eye injury, you should have regular checks by an ophthalmologist for the rest of your life, to ensure that any subsequent glaucoma is detected early and efficient treatment offered to safeguard your vision.	Open angle
Lens-related	• Lens particle; • Phakolytic; • Phakoanaphylactic.	Small share of total glaucomas.	Rare		Open angle
Other	Various rare forms of glaucomas not covered above: • Drug-induced; • Iatrogenic; • Tumors.	Small share of total glaucomas.	Rare		Open angle; might morph to angle closure (SACG)

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