Peer Review File

Article information: https://dx.doi.org/10.21037/jmai-22-33

Reviewer A

Comment 1: The manuscript is well written. However, too long to understand the authors' proposal.
It is a comprehensive review about glaucoma, AI developments for glaucoma, QOL related to glaucoma, and economics. I was surprised at the volume of this paper. I have several comments about the paper.

Reply 1: We are thankful to Reviewer A for his positive comments on our article. We believe that the initial examination of this very complex subject necessitates its large size.

Comment 2: The authors should highlight why FRS is an important issue. How about other diseases or other fields? Is there a successful case using the FRS concept?

Reply 2: Our article addresses several groups of stakeholders (including healthcare executives, medical practitioners, glaucoma patients, and software developers), most of whom are unfamiliar with each other's ongoing practices and terminologies, which is highly challenging. Development and ongoing maintenance of Functional Requirement Specifications is a well-established initial step for mid-size and large software development projects. As such projects are conceptually risky, with the majority failing to deliver desired outcomes, the main goal of the FRS is to balance the needs of stakeholders managing 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 knowledge zone. Several new references and our additional explanations listed in the Changes in the text 2 below, in addition to the list of fairly recent (2019-2021) review publications given in lines 155-157, hopefully cover this important issue.

Changes in the text 2: 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%. (Healthcare Services Global Market Report 2022). 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% (Statista 2022), 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% (Zion Market Research 2022).

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 (Goodwin 2017; Ebad 2020; Doyen 2022; Abouzahra 2011; Kim 2017; Hung 2014; Kaplan 2009). 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 (Swords 2020; Shah 2019).

Large software development projects are conceptually risky, with the majority failing to deliver desired outcomes. The main goal of the 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 Functional Requirements Specifications (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 (Market Trends 2022; Team Asana 2021; Kozhakhmetova 2019).

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 1.1. Addressing these requirements will identify our project's scope, cost and chance of success.

Comment 3: Table 1.1 - I cannot find the concept of "a sustainable ecosystem platform". Please clarify this concept. The contents should be summarized in a table form.

Reply 3: This mostly socio-economics concept of platforms has been covered in detail in Section 6.1. Ensuring sustainability of the healthcare ecosystem.

Changes in the text 3: 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 (Polese 2018; The Economist Intelligence Unit 2018; Stephanie 2019).

To clarify it further, and to stress that we are not analyzing here the attributes of a generic sustainable ecosystem but are focusing on the healthcare ecosystem, we have also added the term 'healthcare' to the heading of Table 1.1.

Comment 4: The literature related to AI for glaucoma diagnosis should be summarized in one table.

Reply 4: This article is not attempting to conduct a comprehensive review of the existing literature related to AI for glaucoma diagnosis, as the 'General AI' methods that we discuss in our article have a far wider scope and substantially differ in their computer science theory and practical approaches. Also, AI for diagnosing glaucoma has been extensively covered and there are numerous review articles, such as Camara J, Neto A, Pires IM, Villasana MV, Zdravevski E, Cunha A. Literature Review on Artificial Intelligence Methods for Glaucoma Screening, Segmentation, and Classification. J Imaging. 2022 Jan 20;8(2):19.; Mursch-Edlmayr, A. S., Ng, W. S., Diniz-Filho, A., Sousa, D. C., Arnould, L., Schlenker, M. B., … & Jayaram, H. (2020). Artificial intelligence algorithms to diagnose glaucoma and detect glaucoma progression: translation to clinical practice. Translational vision science & technology, 9(2), 55-55.; Devalla, S. K., Liang, Z., Pham, T. H., Boote, C., Strouthidis, N. G., Thiery, A. H., & Girard, M. J. (2020). Glaucoma management in the era of artificial intelligence. British Journal of Ophthalmology, 104(3), 301-311.; Girard, M. J., & Schmetterer, L. (2020). Artificial intelligence and deep learning in glaucoma: current state and future prospects. Progress in Brain Research, 257, 37-64.; Xu, J., Xue, K., & Zhang, K. (2019). Current status and future trends of clinical diagnoses via image-based deep learning. Theranostics, 9(25), 7556., to name just a few recent reviews.

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 reduce costs while simultaneously providing individualized support to millions of glaucoma patients globally. A comprehensive review of the existing literature related to AI for glaucoma diagnosis would also substantially increase the size of this article, which the authors would like to avoid.

Comment 5: "Artificial Neural Network Approach for Differentiating Open-Angle Glaucoma From Glaucoma Suspect Without a Visual Field Test" should be included in the literature review part.

Reply 5: We are thankful to the reviewer for this valuable suggestion.

Changes in the text 5: This critical publication has indeed been added to the body of references in our article.

Comment 6: Figure 4.1. - Some boxes of some digits should be removed. (~20%)

Reply 6: Without boxes around some percentages, it might be unclear to which group of diagnoses on the chart the particular numbers might relate.

Comment 7: The last figure - please edit the plot to understand the patterns and concepts easily. The authors may have the raw data.

Reply 7: This figure was reproduced from another article to illustrate certain trends related to our line of arguments. As its detailed explanation would be quite complex while not essential to our line of arguments, we have decided to drop this figure and simplify corresponding explanations.

Comment 8: An additional figure is needed to summarize the authors' proposal.

Reply 8: Figure 2.1. Critical building blocks and enabling commercial and proprietary engines of the integrated approach to define functional requirements and Chapter 7 Conclusions and future perspectives already provide a condensed chart and brief summary statements of the authors' proposals.

Changes in the text 8:
7. Figure 2.1. "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.

Comment 9: Smartphones may play an important role for monitoring glaucoma. Discuss this issue

Reply 9: Predictions of various future commercial channel delivery options and technologies (including the use of smartphones) are unreliable and not essential for our subject but would increase our article size substantially. Also, the importance of smartphones has been extensively covered and there are numerous review articles, such as Aboobakar, I. F., & Friedman, D. S. (2021, May). Home monitoring for glaucoma: current applications and future directions. In Seminars in Ophthalmology (Vol. 36, No. 4, pp. 310-314).; Vilela, M. A., Valença, F. M., Barreto, P. K., Amaral, C. E., & Pellanda, L. C. (2018). Agreement between retinal images obtained via smartphones and images obtained with retinal cameras or fundoscopic exams–systematic review and meta-analysis. Clinical Ophthalmology (Auckland, NZ), 12, 2581.; Rodriguez-Una, I., & Azuara-Blanco, A. (2018). New technologies for glaucoma detection. The Asia-Pacific Journal of Ophthalmology, 7(6), 394-404.; Taylor & Francis. Mohammadpour, M., Heidari, Z., Mirghorbani, M., & Hashemi, H. (2017). Smartphones, tele-ophthalmology, and VISION 2020. International journal of ophthalmology, 10(12), 1909; Chang, R. (2015). The role of smartphones in glaucoma care. Glaucoma Today, 26-28., and many others.

Reviewer B

Comment 10: Goldmann et al. discuss the potential requirements and obstacles relevant to creating a comprehensive AI-based glaucoma treatment and care ecosystem. They focus on subcategories within this system, including the biomedical model, quality of life (QoL) and quality-adjusted life years (QALYs). They provide an adequate review of these subcategories and make general suggestions of which aspects could be incorporated into a comprehensive AI glaucoma treatment model. The length of the article is far too long with multiple redundancies – this is particularly an issue given the lack of actual detail on how such a model could begin to exist outside of listing all things important to glaucoma and its cost. I suggest a restructuring of the manuscript to cut the length down by about half, which would allow for a listing of the requirements of such an idealist model with briefer explanations. There are several tangential discussion points that felt more like a manifesto on the limitations of current healthcare systems over useful information on how such a model should be designed or incorporated into current healthcare systems. There are many sections that could be written in a few sentences instead of a few pages. I do not think discussing an ideal healthcare system out of touch with the current reality of healthcare, and then saying we will use this ideal healthcare system to create a comprehensive glaucoma model provides many benefits to the research community. It is unlikely the healthcare economy is going to change to a degree in the suggested 5-to-20-year window that could accommodate their proposed model.

The overall concept is agreeable but the content lacks true detail or guidance for those interested in this line of research outside of the categories suggested to be in the model. Many of the points presented are valid, and guidelines for developing models are needed, but the authors make suggestions that, in the current healthcare climate, are unrealistic. Several times in the manuscript there are statements that say ‘we need an AI model to incorporate – list of 20 variables – and output useful information.’ I do not feel these statements provide any useful information and seem rather obvious. They give little detail on how such a model would incorporate all of these variables and where the data would come from. However, the issues and suggestions that are discussed for the development of such a model are logical. The review of QoL and QALY in glaucoma is well done. They use strong wording suggesting that such a large-scale model incorporating the disease, its progression forecast, patient preferences, treatment options, treatment efficacy, quality of life goals, patient families, caregivers, varying cultures, genetics, healthcare economics in different countries, over and under treatment, cost, etc., all into one model is the only way that AI will improve patient care. I think something like this is decades away, if even possible, and takes away from current AI research in glaucoma, that may be beneficial to patients and physicians in the immediate future.

There is little discussion about where we would get data to begin training such a model, even if just for the biomedical/disease forecasting. Discussing this would be more helpful to those in the field. Would you get data from insurance claims, governments, large ongoing eye care datasets like IRIS or the SOURCE consortium? How do you get QoL metrics so frequently that an AI model could use them? If patients will not take drops what would motivate them to answer questions on their phone or another platform about their quality of life frequent enough that the data could be used in such a model in a useful way?

A better review of the current use of AI in glaucoma research would be beneficial. Work by Josh Stein at Michigan, using Kalman filtering to predict glaucoma progression and target IOP values and Filipe Medeiros at Duke, using Deep Learning to diagnose glaucoma and progression from fundus photos are important examples of how AI can be used to help glaucoma patients in the more immediate future. Also, more discussion/examples of the real-world limitations/failure of scaling such systems (e.g., its use in breast cancer or Google’s attempt to use AI for diabetic retinopathy screening in India) would be helpful.

Major questions and concerns for such a global model that should be addressed:
How to check for the efficacy of/evaluate such a model over time.
What frequency would QoL data need to be obtained and how could you motivate patients to consistently give this data
Why is a global model, which would need to share data across countries, be so important? Why not have adaptive systems at local levels instead of one large model for the world. This seems more practical.
There is very little discussion about the use of actuarial tables for predicting the intersection between functional vision loss and age of death. This seems like it would be a key output for a model like this.

Should be discussions on how something like this would be integrated into EMRs, or would this be a completely separate system that would need to be purchased by clinics?
Discuss how patients may view and adopt the idea of AI helping to diagnose and treat their disease
Such a model would need to be able to automatically track surgeon outcomes as well given the variety of procedures and techniques being used across the world for glaucoma surgery.
The difficulties of such a model for diagnosis given the lack of a clear definition of glaucoma itself
Concern for the 5–20-year plan for this model. Neuroprotection trials in glaucoma take several years itself. How do you do you propose to systematically evaluate such an algorithm compared to those not using the algorithm. Patient satisfaction? Disease progression? Cost savings? This should be discussed.
More detail on current state of liability of such systems. If a physician uses it to guide treatment, who is to blame when poor outcomes happen.
Discuss how to track medication compliance. Refills from pharmacy, smart bottles? – this would be important data for a model like this.
It would be useful to have figure explaining concepts and differences between decision trees, Markov models, DES models

Reply 10: We are thankful to Reviewer B for some positive comments on our article and also have great empathy for the list of critical issues that Reviewer B raises here. Indeed, we would also be much interested in the research publications on numerous subjects raised above. Regretfully, such a massive research agenda would require a set of skills and resources that the authors of this article lack. Some other proposed research subjects would substantially increase the size of this article, which the authors would like to avoid.

Comment 11: The COVID-19 references do not seem to have much relevance

Reply 11: We thank the reviewer for this suggestion.

Changes in the text 11: We've deleted most of the COVID references in sections 1.2, 2.3, 2.4, 3.2, 3.7, 4.3.

Other specifics:
Comment 12: 155 – Need examples of how these ecosystems have been applied to healthcare. Many readers will not understand the concept.

Reply 12: We agree.

Changes in the text 12: Several new references and our additional explanations listed in the Changes in the text 2 above, in addition to the list of fairly recent (2019-2021) review publications given in lines 155-157 address this issue.

Comment 13: 218 – On the contrary, glaucoma treatment, although still requiring IOP reduction, has changed massively in the last 15 years and is not entrenched.

Reply 13: Although there have been many advances in medical and surgical IOP-lowering and in exploring other academic research subjects, the overall glaucoma clinical approach is still focused on lowering IOP. Many leading glaucoma experts, patients, and other healthcare stakeholders are also aware of wide variations in approaches to glaucoma care. While leaders in the field have changed their approach massively, many front-line non-glaucoma specialists continue to utilize older strategies. We provide a list of relatively recent references to the corresponding views of practicing clinicians in lines 220-221 and to other relevant texts throughout this article.

Comment 14: 224 – Citation for this statement is needed.

Reply 14: We cover this issue in more detail with many references in section 3.3. Self-management model to help patients with chronic conditions and also in section 3.4.

Comment 15: 330 –Why not mention structural tests as well – OCT and disc photos

Reply 15: Thank you.

Changes in the text 15: Although challenging, telehealth methods need to incorporate equivalents to structural tests such as 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.

Comment 16: 362 – gonioscopy also likely needed in an exam. Most important for new patients. Why not discuss the potential for local glaucoma testing centers.

Reply 16: Thank you.

Changes in the text 16: Although challenging, telehealth methods need to incorporate equivalents to structural tests such as 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.

Comment 17: 573 – how would you incorporate legacy scientific and clinical information into the system?

Reply 17: Thank you.

Changes in the text 17: 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 (Colacino 2017; Corish 2018; Densen 2011; Geddes 2018). 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.

Comment 18: 715-717 AI tools can be useful to clinicians now, even if fragmented from their proposed all-encompassing model.

Reply 18: We agree that AI tools might be useful even now in the bio-medical research environment. Their application in the clinical environment is, however, some years ahead, especially if critical risk management, regulatory and professional liability issues are taken into account.

Comment 19: 738-740 citation of examples of this

Reply 19: Thank you.

Changes in the text 19: We have added references to the paragraph:
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 (Kelly 2019; Brocklehurst 2017; Antoniou 2021; Carleton 2020; Martin 2020).

Comment 20: 754-755 Why couldn't they be scaled?

Reply 20: Thank you.

Changes in the text 20: We have modified the text and added references to the sentence:
Due to well-known AI scalability challenges (Chen 2019; Varghese 2020; Shaw 2019; Lwakatare 2020; Rahman 2020a), AI algorithms that only handle subtasks could not be easily scaled up into commercial medical products.

Comment 21: 935-937 Are you referring to ensemble models here? This is quite common in machine learning in healthcare and not theoretical.

Reply 21: These are two different concepts in AI. Multistrategy learning employs multiple constituent learners drawn from diverse paradigms, thus attempting to achieve superior performance to any single learner (see Michalski R and Tecuci G, eds. Machine Learning: A Multistrategy Approach. Morgan Kaufmann . San Mateo CA.) It could improve planning efficiency and the quality of plans. In contrast, an ensemble is a machine learning model that combines the predictions from two or more models. The models that contribute to the ensemble, referred to as ensemble members, might be the same type or different types and may or may not be trained on the same training data. To improve accuracy over a single model, the base classifiers in an ensemble must be diverse (meaning they must make different mistakes), which is not that easy to achieve in the clinical setting.

Comment 22: 1360-1367 Again, seems obvious that something like this would be great. Why not make suggestions based on the literature on standardized ways the input data for a model like this could be obtained (e.g., a patient's short- and long-term visual goals or quality of life metrics)

Reply 22: Thank you.

Changes in the text 22: 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 (Janz 2001; Quaranta 2016; Teipel 2016; Ho 2020; Ghaleb 2022).

Comment 23: 1436 Authors go into a long discussion about dry eye, which I suppose has relevance, but authors continually go from far too broad to very specific in their discussion. If you are going to discuss dry eye from eye drops, why not discuss orbitopathy from prostaglandin eye drops, COPD exacerbations from topical beta blockers, endothelial dysfunction from topical carbonic anhydrase inhibitors, stinging with drops with pH differences, drops in heart rate and blood pressure with topical beta blockers, allergic responses to brimonidine and other active ingredients, not just BAK. Dry eye could simply be mentioned as a QoL in the model and does not need such a discussion unless you are going to be inclusive of other side effects of drops.

Reply 23: We are thankful to the reviewer for this valuable suggestion.

Changes in the text 23: 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.

Comment 24: 1517-1524 Why not suggest the need for more research on functional outcomes of glaucomatous vision loss so the model can understand what visual end points tested in a glaucoma clinic result in specific functional losses (e.g., driving, reading, playing golf). Or will the model "figure this out" from the massive amount of QoL data it will obtain.

Reply 24: Thank you.

Changes in the text 24: 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.

Comment 25: 1595-1596 this is a good suggestion and would likely be motivating to patients.

Reply 25: Thanks! Your good feedback matters to us.

Comment 26: 1879-1881 Citation for this?

Reply 26: This wish list is based on the informal discussions and patients' and clinicians' feedback to the World Glaucoma Patient Association and the World Glaucoma Association's Patient's Committee, with which several authors have actively been involved.

Comment 27: 1891-1892 Would add OCT ganglion cell imaging as well

Reply 27: Thank you.

Changes in the text 27: Depending on the resources available, some glaucoma experts also conduct OCT ganglion cell imaging (Arintawati 2013; Bussel 2014; Mwanza 2014; Tan 2009; Jeoung 2013).

Comment 28: 2050-2053 I would think a model of the size would be able to stratify to the individual level, especially assuming the type of glaucoma would presumably be an input for the model. Stratifying may be beneficial to the model for a smaller training cohort. Also, I doubt such a model of this magnitude would be using simple decision trees to make decisions.

Reply 28: We agree. Much will depend on the inevitable disruptive advances in theoretical AI, especially in support of quantum computing, whose approaches will be different from current AI engines.

Comment 29: 2102-2137 Nice review on neuroprotection but not sure it is relevant for the purpose of this manuscript. At the very least, why not suggest the use of the database to find eligible patients for clinical trials and so on that could benefit from these new treatments as they arrive to market.

Reply 29: Our key point here is that to control the high risks of long-term discontinuity innovation, non-medical participants must include the wide range of new and diverse subjects and sub-disciplines to be considered in the successful design and implementation of complex Computerized Glaucoma Treatment and Care Ecosystems. What might be obvious to MDs is often unknown to other stakeholders, such as system developers, regulators and investors (and vice versa).

Comment 30: 2494-2495 A good doctor-patient relationship is critical, especially for care of a chronic disease. Is it possible that such a model and the potential for physicians to rely on such a model something that could deteriorate the doctor-patient relationship? I think this is a topic worth discussing over many of the others currently in the manuscript. How well will patients accept the output of such a model that cannot be fully explained to them. What sort of training will a physician or healthcare worker need to work with such a model?

Reply 30: We agree.

Changes in the text 30: 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 (Vasudevan 2022; Buchwald 2022; Varonen 2008; Buranapanitkit 2005; Lo 2010)? 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.

Comment 31: 2729-2731 Examples of these?

Reply 31: Some examples are listed in the references (Erturkmen 2019; Chin 2018; Cordis 2016; Christensen 2012). As discussed in our article, success rates for such projects are dismal; the initial failure often can be traced to deficiencies in the project's Functional Requirement Specification. System integrators deliver what the wording of the sign spec said, whether or not it makes sense; not what the medical clients meant, assume or imagine. Often, the results of a multiyear project are obsolete on arrival. This is not entirely the techies' fault. Unless medical professionals and investors are willing to formulate their long-term vision while understanding the constraints of discontinuity innovation within the standard technology frameworks of FRS, not much is likely to change. We hope our article is a small step towards clarification and finding a practical solution.

Comment 32: 2811-2812 This has not been proven.

Reply 32: It is impossible to prove that data needed to create new robust and powerful glaucoma programs are not yet in mainstream practice.

Changes in the text 32: We modified this sentence to:
We believe that much data needed to create novel robust and powerful glaucoma programs is not in the mainstream practice.

Comment 33: 2842-2846 Discuss this topic more. Need more details on how such a model could be built, not just what would be nice to have in a model.

Reply 33: As we discuss, the global glaucoma healthcare community is currently at an early healthcare AI system definition stage, attempting to define just the overall vision for the future system. Specific FRSs are developed for bidding and usually consist of voluminous comprehensive and expensive documents that quantify desired outcomes rather than exact ways to implement the system. It takes much time to formulate the client's vision and to ascertain that the technological basis exists for its implementation before any ecosystem project has been announced. An FRS for a system of this magnitude would attract bids from some world-top System Integrators (Capgemini, Cognizant, Deloitte, IBM, Accenture, Tata Consultancy Services, Infosys, CGI) and others, each with its own system design and implementation proposal. Costs for each vendor's bid run to millions of dollars and involve specialized technical, operational and financial expertise. Long-term system implementation success depends on the client's ability to engage top System Integrators actively. It is usually a good SI procurement strategy not to constrain the diversity of such vendor approaches, especially with any projects involving such ambitious targets as healthcare AI. Unless the stakeholders of such systems start to formulate their vision now, they won't be ready to successfully define a specific system's FRS and initiate a preliminary RFP process in about five years.

Comment 34: 2872-2875 What about decision curve analysis (DCA). Wouldn't this be a key component to integrating decision making based on a patient's concern and the models predictions? See Ul Banna et al. Scientific Reports 2022

Reply 34: Diagnostic and prognostic models and decision-analytic techniques, such as DCA, could be valuable to assess clinical outcomes and to address biomedical issues for a particular disease. However, predicting models that address chronic patients' concerns (that typically suffer from several progressing chronic diseases) must also include many other critical factors, such as QoL, financial, technology optimization, and ongoing patient lifecycle management, which are mostly outside the objectives and capabilities of the current medical diagnostic and prognostic models.

Comment 35: 2923-2924 Examples or citations of these failure?

Reply 35: Thank you.

Changes in the text 35: 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 (Sant Fruchtman 2021; He 2019; Vinsard 2019; Patel 2020; Fernandes 2020; Ebenso 2022; Marongwe 2022; Petersson 2022; Wallis 2017; Tomlinson 2013.)

Comment 36: 3037 Not sure why such an emphasis on global infrastructure. Seems highly impractical and a model that works locally could incorporate all of the criteria mentioned in the paper while also fitting into local healthcare economies and patient groups.

Reply 36: Development and ongoing advancement of a patient-focused system envisioned requires massive innovation investments, far beyond the capability of the national government and investment industry of one country, even the USA. I.e., by annually investing trillions of dollars in R&D, top global digital platform players, like Amazon, Alphabet, Meta, Alibaba, Netflix, PayPal, Salesforce, Baidu, Uber, eBay, Expedia, Airbnb, and numerous other global players easily destroy local competitors, by outspending them, hiring away their best executives and developers, and making their offerings obsolete. A recent bibliometric and mapping analysis of glaucoma research (López-Muñoz, F., Weinreb, R. N., Moghimi, S., & Povedano-Montero, F. J. (2022). A bibliometric and mapping analysis of glaucoma biomedical research between 1900 and 2019. Ophthalmology Glaucoma, 5(1), 16-25.) clearly illustrates the global character of this field of biomedical innovation. Why should healthcare high-tech applications be any different?

Comment 37: 3251 Where is the quantitative analysis?

Reply 37: Thank you.

Changes in the text 37: As a result of our quantitative analysis (Figure 1.1), from being a 'nice to have', AI has been found to be a 'must have' enabler.

Comment 38: 3294 – 3298 Should incorporate individual surgeon outcomes as well for different procedures given breadth of surgeries available now for glaucoma

Reply 38: Thank you.

Changes in the text 38: 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 (Gazzard 2019; Fingeret 2018; Philippin 2021), the ecosystem should also exhibit surgeons track records for different procedures.

Comment 39: 3331 No evidence for this statement

Reply 39: Thank you.

Changes in the text 39: We believe radical improvement in global glaucoma care is possible with the aid of a patient-centric computerized treatment and healthcare ecosystem.

Comment 40: 3380 – 3385 A model this powerful should have no problem handling different glaucoma classifications without stratification.

Reply 40: We agree. Every technology, however, could have unforeseen problems, especially when several negative factors might simultaneously collide.

Reviewer C

Comment 41: This is a very nice paper that provides and review of the literature and a summary of the authors' thoughts about a computerized care ecosystem for glaucoma. The ideas are well-presented and clear. This paper brings together many interesting concepts.

Reply 41: We are thankful to Reviewer C for the positive comments.

Comment 42: I have just a few small concerns:

1) In a few places (for example, the bottom of page 12 the authors discuss that a major problem with glaucoma care is late identification of the disease. I may have missed this, but how will the ecosystem address this challenge?

Reply 42: Thank you. Although our article does not focus primarily on this issue, we discuss various aspects of the proposed glaucoma ecosystem effectively dealing with it. In particular:

- Lines 224-249 We cite the stats on the high incidence of undiagnosed glaucoma globally, especially, in developing countries, and stress its effect on QoL.
- 798-808 Discuss shortcomings of current AI systems, such as overfitting, as related to undiagnosed glaucoma.
- 899-910 Outline some solutions to the undiagnosed glaucoma challenge that a computerized care ecosystem enables to address (i.e., cloud computing enabling supervised learning algorithms to associate various patients' diagnoses with their corresponding annotations, providing more clinically relevant results.)
- 1213-1216 We've noted that newly diagnosed glaucoma patient has a high probability of developing a second chronic disease (could it also be a factor the other way around?).

- 1757-1777 Difficulties with subjectively establishing the initial diagnosis in the absence of objective tests. 1952-1953 and 3089-3092 half of the newly diagnosed patients found through screening have seen an ophthalmologist or an optometrist. 3093-3098 This is explained by a nonoptimal combination of diagnostic and follow-up tests conducted less frequently, leading to low specificity.
- 1820-1833 Introduction of intelligent medical diagnostic systems is important for providing accurate glaucoma diagnoses (with examples given).
- 1852-1878 Misdiagnosis and the need for a trusted second opinion.
- 2038-2039 Disc hemorrhage as the single most significant predictor of visual field loss.
- 2338-2344 Costs decrease and QoL improves with early glaucoma diagnosis and treatment. Opportunistic detection with routine eye examinations is cost-effective and should be encouraged.

Changes in the text 42: 5. 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.

Comment 43: 2) On page 19, the authors bring up an important issue—the need for changes in financing and administration for an ecosystem such as this to function. Again, I may have missed this, but do the authors have thoughts about how to make these nationwide changes to health system financing and structure to allow for an ecosystem such as this to function?

Reply 43: Thank you. In our article, we discuss various approaches dealing with ecosystem administration and financing. In particular:

- Lines 831-856 Healthcare ecosystem platform administration must support the collaboration and networking of health and non-health sectors; public (local, national and global), 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.

- It would be difficult, if not impossible, to predict today the exact nature of various dynamic user interfaces (visual? voice? command neural?) and service delivery channels that might evolve even in 10 years; but the necessity for their eventual development for administering healthcare ecosystems is quite apparent. 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, in turn, could allow forthcoming system integrators to develop 'modern' user-friendly interfaces that would satisfy the evolving platform management, information and cost-sharing needs of all ecosystem stakeholders.
- 1744-1748, 2164-2166 Regarding financing system development and maintenance, measures such as reducing the costs of overdiagnosis should cover such costs with good ROI. 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.
- Whole sections 6.2. Economics, finance and QoL, and 6.3. Attracting financial support
- 3191-3194 We have noted that 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.

Changes in the text 43: Healthcare ecosystem platform administration must support the collaboration and networking of health and non-health sectors; public (local, national and global), 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.

Comment 44: 3) The authors discuss glaucoma care from many different countries. I may have missed this, but do they envision a single glaucoma ecosystem that could meet the needs of all of these different countries? Or would a system need to be uniquely developed for each country given the big differences in health systems, financing, resources, etc.?

Reply 44: Ideally a non-profit or transactional private single glaucoma ecosystem could be developed to meet the needs of different countries. This is essential as required huge academic research, industrial R&D and innovation financial and human investments in such a system would be far larger than even the USA or other rich countries could afford. Current technology 'cloud' support infrastructure is already inherently global. Only the global approach could provide large-size glaucoma patient databases necessary to train AI systems for academic and clinical applications.

However, our research could be useful to any national, state, or local jurisdiction that decides to build such a platform or parts of it on its own, whether or not they'd recognize the limitations of local or partial approaches after they had performed a sound feasibility study.