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Artificial Intelligence for Glaucoma:

Creating and Implementing Artificial Intelligence for Disease Detection and Progression

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Abstract

On September 3, 2020, the Collaborative Community on Ophthalmic Imaging conducted its first 2-day virtual workshop on the role of artificial intelligence (AI) and related machine learning techniques in the diagnosis and treatment of various ophthalmic conditions. In a session entitled "Artificial Intelligence for Glaucoma," a panel of glaucoma specialists, researchers, industry experts, and patients convened to share current research on the application of AI to commonly used diagnostic modalities, including fundus photography,OCT imaging, standard automated perimetry, and gonioscopy. The conference participants focused on the use of AI as a tool for disease prediction, highlighted its ability to address inequalities, and presented the limitations of and challenges to its clinical application. The panelists' discussion addressed AI and health equities from clinical, societal, and regulatory perspectives.

Keywords

Artificial intelligence; Deep learning; Glaucoma; Imaging

On September 3, 2020, the Collaborative Community on Ophthalmic Imaging (CCOI) conducted its first workshop to discuss state-of-the-art artificial intelligence (AI) algorithms for ophthalmic imaging and to clarify challenges, best practices, and strategies for implementing these algorithms in 4 key clinical areas: macular degeneration, retinopathy of prematurity, ocular oncology, and glaucoma. The conference served as a forum for experts from around the world and across academia, government institutions, patient groups, and the private sector to share and reflect on major opportunities and challenges involved in the application and integration of AI in ophthalmology.

As a field, ophthalmology lends itself well to the use of AI technologies for several reasons: (1) ophthalmic diagnostics are often reliant on numerous testing modalities, many of which are based on image-recognition patterns; (2) recent developments in teleophthalmology have vastly expanded access to and the availability of digital eye care services, and with that, there has been an explosion of available data; (3) in the United States alone, although the number of Americans with visual impairment or blindness is expected to double to 8 million individuals by 2050, national trends have shown a steady decline in the number of ophthalmologists,[1] such that the need for eye care specialists will outweigh the supply; and (4) modern ophthalmic practices already involve task redistribution to personnel such as optometrists and ophthalmic technicians. If used correctly, AI has the potential to facilitate some portions of disease management, allowing ophthalmologists to perform at the top of their training.

Glaucoma is one area that can benefit greatly from the implementation of AI. Glaucoma remains one of the leading causes of irreversible blindness worldwide.[2] Because early detection can be challenging and glaucoma generally remains asymptomatic in its initial stages, there is a high rate of undiagnosed and untreated advanced disease.[3] In a cross-sectional study published in 2014, it was found that in the United States, the overall prevalence of "definite" glaucoma, based on the Rotterdam Eye Study criteria, was 3.7% and the prevalence of undiagnosed and untreated glaucoma was approximately 2.9% in adults aged > 40 years, thus implying that roughly 78% (2.9 of 3.7) of those with definite glaucoma are currently undiagnosed and untreated.[4] The prevalence of undiagnosed disease is even higher in minority populations in the United States.[5–11] The potential to leverage AI technology to bridge inequities in the screening, detection, and monitoring of glaucoma served as a foundation on which many of the panelists' discussion points were based, and it was among the many topics addressed by the group of speakers during the "Artificial Intelligence for Glaucoma" segment of the CCOI 2020 conference.

To begin with, the Glaucoma Working Group of the CCOI delineated key issues that need to be addressed to expedite the innovation of AI for glaucoma diagnosis and prognostication. They proceeded to formulate a set of key questions. These questions broadly included, but were not limited to, the following:

1. Can AI algorithms or devices potentially be used to detect glaucoma or glaucoma progression?
2. What reference standards and degrees of accuracy are needed to validate newly proposed AI algorithms or devices?
3. What can be considered as successful population-based screening for glaucoma? What special considerations need to be made while implementing AI-based screening protocols?
4. How can AI be leveraged in everyday clinical practice to allow for patient-centered disease management?
5. What medico-legal considerations need to be made while implementing AI systems for glaucoma?

These questions formed the framework for the "Artificial Intelligence for Glaucoma" segment of the CCOI 2020 conference. The research presented by the panelists as well as a subsequent discussion, which was moderated by Dr Jeffrey Goldberg and included Dr Felipe Medeiros (Duke University), Dr Bhavna Antony (IBM Research), Dr Hiroshi Ishikawa (NYU Langone Health), Dr Naama Hammel (Google Health), Dr Tin Aung (Singapore Eye Research Institute), Dr Lama Al-Aswad (NYU Langone Health), Dr Michael Abramoff (University of Iowa), and Dr Minguangat (University of Melbourne), aimed to address 1 or multiple of the abovementioned key questions.

Diagnosing Glaucoma

The clinical diagnosis and characterization of glaucoma are based on a combination of elevated intraocular pressure, optic nerve cupping, visual field testing, anterior chamber angle appearance, and, ultimately, a clinician's judgment. The lack of a unified "gold" standard for glaucoma diagnosis is perhaps one of the biggest challenges that the field faces.[12–15] This is because each test focuses on a different aspect of the disease, and none is 100% sensitive or specific. For example, an evaluation of the optic nerve head (ONH) speaks to structural damage, but individuals tend to either overestimate or underestimate optic nerve damage and miss subtle structural damage, with poor reproducibility and intergrader agreement. Furthermore, although the glaucoma hemifield test is the most commonly suggested test for assessing glaucomatous functional damage using standard automated perimetry (SAP), it is by no means the only tool for visual field analysis. Moreover, the relationship between structural and functional glaucomatous changes is complex. Particularly in the early stages of the disease, there may already be structural damage on the ONH, without detectable damage in the visual field (preperimetric stage). To this end, the panelists began the session by discussing how current AI research focuses on standardizing the interpretations of several of the diagnostic modalities used for glaucoma. The current AI research domains and future research interests are summarized below. Although this is by no means a comprehensive review of the application of AI to the field of glaucoma, several noteworthy publications directly mentioned by the panelists or related to the panelists' works have been included.

AI and Fundus Photography

The application of AI to fundus photographs is attractive for many reasons. Fundus photographs are easy to obtain and are relatively inexpensive. With advancing technology, there is also a possibility of using portable cameras for nonmydriatic photography.

Although to date, there are no AI systems authorized by the Food and Drug Administration (FDA) for glaucoma, there are numerous publications describing research in this area. Li et al[16] published one of the first studies evaluating the efficacy of a deep learning (DL) system for detecting glaucoma based on fundus photographs. Over 48 000 photographs, classified as either referable glaucoma or not by 21 glaucoma specialists, were used to train and validate the DL model. The authors reported their DL algorithm to have a sensitivity of 95% and a specificity of 92%.[16] A more recent study was conducted by Al-Aswad et al.[17] Clinicians (2 ophthalmologists, 2 glaucoma fellows, 1 second-year resident, and 1 third-year resident) and Pegasus,[18] a cloud-based DL system provided by Visulytix Ltd to screen retinal imagery, graded 110 color fundus photographs. These fundus photographs were collected from the Online Retinal Fundus Image Database for Glaucoma Analysis and Research as a part of the Singapore Malay Eye Study.[19] The original clinical diagnosis, based on comprehensive clinical criteria delineated by the International Society for Geographical and Epidemiologic Ophthalmology, was set as the gold standard and used for comparison. Pegasus achieved an area under the receiver operating characteristic curve (AUROC) of 93% compared with ophthalmologist AUROCs, which ranged from 70% to 85%. The agreement between Pegasus and the gold standard was 0.715, whereas the highest ophthalmologist agreement with the gold standard was only 0.613. Moreover, the DL system took approximately 10% of the time taken by ophthalmologists to determine the classifications.[17]

Some researchers are taking DL algorithms further. Gheisari et al[20] have even been able to combine a convolutional neural network and a recurrent neural network model to extract spatial and temporal information, such as alterations in spontaneous venous pulsations or blood column variations, using not just fundus photographs but also sequential imaging with fundus videography to distinguish glaucomatous eyes from healthy eyes (F-measure, 96.2%). Additionally, using an approach called machine-to-machine learning, Medeiros et al[21] used 30 000 pairs of fundus photographs to train a DL model to predict the thickness of the retinal nerve fiber layer using fundus photographs. These were subsequently compared with nerve fiber layer thickness measurements calculated using OCT. The resultant DL algorithm achieved a very good correlation, with an R of > 0.8 and with the mean predicted nerve fiber layer thickness almost identical to the OCT-measured mean observed nerve fiber layer thickness. Interestingly, an analysis of heat maps showed that the DL algorithm used both the area of the optic nerve and the surrounding nerve fiber thickness to predict the nerve fiber layer thickness. The results of this study are exciting because having a quantitative output from a fundus photograph analysis means that one can theoretically set cutoffs based on disease severity for potential screening protocols and monitor longitudinal progression using fundus photographs in an automated fashion.

The application of AI to fundus photographs has yet another advantage. As stated previously, several studies have shown that the subjective assessment of fundus photographs can be problematic, given its poor reproducibility.[12,22–24] Unlike research conducted on the detection of diabetic retinopathy using retinal fundus photographs,[25] there are no objective criteria to differentiate optic discs with glaucoma from normal but “suspicious”-appearing optic discs. The optic disc features suggestive of a glaucomatous optic nerve include, but are not limited to, the loss of neuroretinal rim tissue, particularly at the superior and inferior poles, resulting in an increased vertical cup-to-disc ratio (CDR); asymmetry between the 2 eyes; changes in vessel configuration; flame hemorrhages; increased visibility of the lamina cribrosa; and focal notching. However, even with such criteria, clinicians place differing weightage on the presence or absence of particular features. To address this variability, Phene et al[12] summarized the work performed by the Google Health team to come up with a highly comprehensive, standardized list of specific ONH features that can be used to classify a nerve as a “referable optic disc.” In their study, when 1205 images were reviewed by 3 fellowship-trained glaucoma specialists via 2 rounds of adjudication, even with access to each other’s comments and annotations, there was full agreement on referable glaucomatous nerves on < 50% of the images.[12] For this reason, Mariottoni et al[14] used OCT imaging and SAP, rather than clinicians’ evaluations, to classify fundus photographs. Although the specific criteria used to interpret these independent modalities are still, in essence, arbitrary and, in fact, may introduce further biases into an algorithm that is yet to be validated in clinical practice, this method of setting predefined OCT and SAP parameters may still be considered more objective than a “specialist” judgment of the optic nerve. In their study, the DL algorithm achieved an overall AUROC of 0.92 and an AUROC of 0.96 for severe glaucoma, with a sensitivity of 85% and specificity of 95%.[14]

Both clinicians and AI algorithms face challenges in cases in which the neuroretinal rim is difficult to assess, which include cases with peripapillary atrophy, pathological myopia, shallow cups, or skewed or tilted discs. Further, the careful discrimination of glaucomatous features depends on high-quality scans. To this end, Liu et al[26] developed a DL system to detect glaucomatous optic neuropathy that was purposely trained on a large-scale and diverse data set that included 241 032 retinal fundus images obtained from the Chinese Glaucoma Study Alliance. This DL algorithm subsequently underwent distinct clinical, population-based, multiethnic, and multiquality directed validations. Across all the validation sets, the area under the curve (AUC) values, sensitivities, and specificities ranged from 0.823, 82.2%, and 70.4%, respectively (multiquality validation), to 0.996, 96.2%, and 97.7%, respectively (local validation).

AI and OCT

OCT technology, as a noninvasive, efficient, and reproducible modality of evaluating glaucomatous optic neuropathy, has become a mainstay of glaucoma diagnosis and management. While incorporating traditional OCT images into clinical practice, clinicians often rely on segmentation-based features such as peripapillary retinal nerve fiber layer (RNFL) thickness measurements and CDRs derived from intensity- and texture-based edge detection algorithms.[27] Motion-artifact, scan-positioning, and algorithmic-segmentation errors can all affect the machine's thickness measurements. Artifacts in the measurement of RNFL or macular thickness using spectral-domain OCT occur in 15.2% to 36.1% of scans.[28]

To overcome these challenges, researchers have explored AI's ability to integrate conventional markers with feature-agnostic approaches.[29,30] Ran et al[31] used 6921 spectral-domain OCT volumes from 1 384 200 cross-sectional 2-dimensional scans to develop a 3-dimensional DL system to identify glaucomatous disease via agnostic feature extraction, which achieved AUCs between 0.893 and 0.897 on external validation sets. Their findings showed that the 3-dimensional DL system performed similarly to experienced glaucoma specialists who reviewed conventional spectral-domain OCT printouts. Similarly, Maetschke et al[32] compared a DL technique that classified eyes as healthy or glaucomatous based on raw, unsegmented OCT volumes of the ONH using a 3-dimensional convolutional neural network (feature-agnostic) with various feature-based machine learning (ML) algorithms. In the feature-based approach, a total of 22 features, such as quadrant and clock-hour RNFL thickness measurements, rim area, disc area, cup volume, and CDRs obtained using the service scanner, were used to train a random forest support vector machine and a logistic regression classifier. It was found that although the best-performing classical ML technique achieved an AUC of 0.89, the feature-agnostic DL method achieved a substantially ($P <$ 0.05) higher AUC of 0.94. When applied to macular scans, the DL model had a mean AUC of 0.85 across a 5-fold cross-validation compared with the best-performing random forest model, which had a mean AUC of 0.81. Similarly, when compared with the average RNFL thickness (AUC, 0.938), average retinal ganglion cell + inner plexiform layer thickness (AUC, 0.949), and mean deviation on SAP (AUC, 0.889), Lee et al[33] found that their DL model outperformed all of these traditional measures (AUC, 0.99). Further, their DL system achieved a sensitivity of 94.7% and a specificity of 100.0% in detecting glaucomatous changes in a test set of 85 eyes. Artificial intelligence has even been applied to OCT, with varying degrees of success, to differentiate patients with early glaucoma from healthy controls.[31,34,35]

More recently, DL algorithms have started to incorporate and predict the minimum rim width relative to Bruch's membrane opening using both fundus photography and OCT scans.[2] This is supported by the class activation mapping analyses of several pertinent studies, which have found that DL networks assign weightage to not only the optic disc area but also the adjacent peripapillary area[36] and the anterior surface of the lamina cribrosa, whenever visible.[21,32] We still do not know whether the regions used by DL algorithms implicate the size, texture, or gradients of elements being considered, and therefore, it is possible that what we presently believe to be random noise in OCT actually contains structurally useful information. Further research is needed to clarify these imaging features observed using OCT, which might, in fact, be most highly associated with glaucoma.

While clinically applying DL to OCT scans, algorithms need to overcome challenges related to differential image acquisition, registration, and postprocessing protocols, all of which affect the final quality scores. Thus, the use of many current algorithms is restricted to only 1 OCT device or scan pattern, limiting their generalizability. In addition, OCT can fall prey to overinterpretation or misinterpretation in the absence of careful clinical scrutiny. This means that the interpretation of OCT thickness values can be influenced by factors such as the interindividual variability of RNFL thickness, the cyclotorsion of the eye, refractive error's and axial length's effect on the angular distribution of RNFL bundles, artificially increased RNFL thicknesses due to gliosis, myelinated RNFL, edema, or artificially decreased RNFL thicknesses due to peripapillary atrophy. Even with feature-agnostic approaches, it is difficult for AI alone to differentiate these cases from glaucoma.

AI and SAP

Historically, SAP has been a key test for identifying and following functional loss in both research studies and clinical practice. However, visual fields are tedious, time consuming, expensive, and, to date, inaccessible outside of the standard clinical office setting. Even with conventional visual field testing, the data collected are often noisy because of both patient reliability and the inherent variability of the test. Although AI cannot solve the practical problems of SAP test administration or the learning curve associated with obtaining reliable results, DL algorithms can help eliminate some of this noise. Asaoka et al[37] used DL models to successfully differentiate the visual fields of patients with preperimetric glaucoma from those of healthy patients, whereas Wen et al[38] used DL algorithms to predict the point-wise visual field loss up to 5.5 years in the future using just a single visual field test.

Artificial intelligence algorithms that analyze structural tests, such as OCT, to replicate corresponding visual field loss have recently been investigated. These can potentially allow the prediction of functional field loss in patients who are unable to undergo the visual field examination because of geographic, physical, or mental constraints. Yu et al[39] conducted a study in which a DL algorithm was trained using raw OCT images as input to be able to estimate the visual field index using the corresponding OCT scan at the same visit. The DL model had a Pearson coefficient correlation of 0.88 for ONH cube scans and 0.86 for macular disc cube scans, which were better than even the best-performing conventional ML model (random forest, $r = 0.74$).

AI and Anterior Chamber Angle Assessment

Although much work on glaucoma detection focuses on its effect on the optic nerve, AI can potentially be used for better evaluation of the anterior chamber angle, which is an important contributor to glaucoma. Similar to fundus photograph evaluation, gonioscopy, which is the current standard for evaluating the angle, can be subjective and dependent on the observer. Gonioscopy varies according to clinician experience, lighting conditions, lenses used, and variability in grading systems. Even with anterior-segment OCT, a subjective assessment is needed to determine whether there is apposition between the iris and the angle because it is not always clear where the scleral spur lies.

There are several publications that employed DL algorithms to localize the scleral spur, demarcate anterior segment structures, and quantify anterior chamber depth, thereby aiding in the detection of angle closure.[40–43] Fu et al[40] were among the first to compare the angle grading of their DL model using > 4000 images from 2000 subjects with that of a physician's grading. They found that there was very good agreement, with an AUC of 0.96. Taken further, a team from the Singapore Eye Research Institute has been collaborating with others around the world to develop an AI software algorithm that can not only read 360° of anterior-segment OCT images to indicate the degree of angle closure but also pinpoint the location of angle closure. They tested their AI software by comparing it with ophthalmologists' grading of the angle in a clinical setting. They analyzed 39 936 swept-source OCT scans (128 scans per subject) for this study, with good diagnostic performance (AUC, 0.85).[44] These studies point toward the potential to not only automate clinical evaluations of the anterior chamber angle but also identify and quantify other anterior-segment features related to angle closure, such as lens vaulting.

One problem with AI algorithms for gonioscopic assessments is that there is no consistent and objective gold-standard method of characterizing angles, which is needed to build and train generalizable DL models. Furthermore, many analyses are based on a single quadrant and are then applied to the overall angle, citing patient discomfort or the position of the eyelids while evaluating the superior or inferior angle. Finally, the diagnostic ability of such algorithms still needs to be validated on large, mixed-race populations and on very narrow angles when there are no visible anatomic landmarks.

Detection of Glaucoma Progression

Although some researchers and glaucoma specialists are less interested in using AI to detect the earliest stage of the disease, most agree that AI can be a powerful tool if it can be used to identify those that are likely to have disease progression in their lifetime. Predicting the rate of visual field loss is an area in which AI can be used for prognostication. Literature has indicated that DL models can be used to predict RNFL thickness measurements using both fundus photography and OCT images as well as map out corresponding functional changes.[38,45] One such study conducted by Sedai et al[45] used clustering analyses to assess the DL model-generated visual field indices in a longitudinal manner to extrapolate the trajectory of glaucoma progression. They included all available information in this analysis, including patient demographics; conventional biomarkers, such as intraocular pressure and follow-up duration; and raw OCT image data, for training the DL system. Compared with the guided progression analysis, performed using the Cirrus OCT software, which uses linear regression-based models, the DL model showed statistically significantly smaller mean absolute errors in the prediction of mean deviations and visual field index metrics. In addition, disease status did not affect the DL model's performance as much as it affected the performance of the standard, trend-based analysis.[45] Practically speaking, differentiating slow progressors from fast progressors can embolden providers to offer more aggressive surgical interventions at earlier stages of the disease, before severe damage can occur.

Patient-Centered Glaucoma Management

Physician Cognitive Support

Beyond diagnostics and prognostics, AI has a role in illuminating our current clinical practices. If the goal in the field of glaucoma is to create a more universally accepted disease definition and, thereby, the standard of patient care, being able to make explicit our own comprehension of glaucomatous damage would be helpful.[12,15] Artificial intelligence can be used in the future to help aggregate all data available for a single patient, place weighted importance on features that are conventionally relied on most heavily by specialists, and develop a proposed patient-specific diagnosis and management pathway. We can work in conjunction with AI algorithms to better understand individual and collective clinical judgments, standardize these judgments, and encode decision making into a set of rules that computers can execute for each patient.

To begin with, this would mean using AI for clinical decision support systems that integrate all available tests for assessing optic nerve structure and function as well as background clinical information.[46] Similar systems are being implemented in other fields, and it is only a matter of time until they can be modified for ophthalmology. By integrating a multitude of variables, AI allows for more holistic and meaningful modeling; that is, one can imagine an algorithm design that includes intraocular pressure trends or family history to evaluate whether a change in visual field parameters is likely to be clinically meaningful. With data sets that are large enough, AI can even go so far as to help specialists predict which patients will respond to certain medications or interventions, a process that, at present, involves much trial and error. In an increasingly automated world, AI can even be used to drive intraocular medication depots to release medication when an intraocular pressure sensor detects an abnormal and potentially sight-threatening deviation from that patient's normal pressure curves.

Promoting Health Equity

We know that glaucoma does not affect all ethnic groups equally. The Baltimore Eye Survey first showed that Black Americans had 4 to 5 times higher age-adjusted prevalence of glaucoma than White participants and had a 19% rate of blindness, compared with 3% in the White participants.[8,10] The Los Angeles Latino Eye Study showed that older Latinos aged >61 years with predominantly Mexican ancestry in Los Angeles have rates of open-angle glaucoma comparable with those of Blacks in the United States, which are significantly higher than those seen in non-Hispanic Whites.[9,11]

Attributing such epidemiologic variations simply to genetic differences rather than to socioeconomic factors is misguided. First, racial biases in the United States have led to the labeling of persons as Black even if their ancestry was more European than African. For example, Virginia's "Racial Integrity Act" of 1924 defined a White person as one "who has no trace whatsoever of any blood other than Caucasian." Yet, we know through genome-wide ancestry estimates that the genetic proportions of African Americans equate more to 73% African, 24% European, and 1% Native American ancestries.[47] Such genetic misclassification leads to the overestimation of biologic contributions to disease disparity. Instead, one must also assess more upstream health determinants to better understand the causes of inequity. Several studies have found that factors such as sex, age, insurance status, and geographic factors, as well as race and ethnicity, all contribute to disparities in screening for glaucoma, diagnosing glaucoma, monitoring glaucoma via ancillary testing and, ultimately, managing glaucoma.[5–11]

Artificial intelligence has the potential to greatly expand health care access and bridge the inequality gap. Teleophthalmology is already being used[48] to bring care directly to patients rather than expecting them to travel to the provider, bridging the urban–rural divide seen globally, particularly in places where there is a shortage of physicians and ophthalmologists. Artificial intelligence can be used to integrate glaucoma-related information and replicate decisions currently deferred to glaucoma specialists, thus bringing specialist-level care to settings in which it is lacking. Artificial intelligence can be invaluable in interpreting and processing large quantities of collected data, such as patient-monitoring sensor outputs, home tonometry, remote and virtual reality visual fields, and mobile OCT and fundus images. These systems help facilitate clinical decision making between office visits. Finally, AI can be used to streamline the screening process for glaucoma to be efficient, effective, and labor sparing. It could parallel the experiences of the United Kingdom and Singapore of using fundus photography–based DL techniques for diabetic retinopathy screenings.[49] These population-based screenings can be used to bring care to previously underserved neighborhoods. In the fight against glaucoma, there is little debate that there is a need for education and screening in these high-risk populations.

The panelists could not agree on the level of the disease that should be targeted for detection by AI models. Some participants advocated for training the DL models only on well-established cases of glaucoma. They felt that this would lead to improved diagnostic accuracy and effectiveness when applied to large screening protocols. Because symptomatic complaints in patients with glaucoma can sometimes not be present until severe stages of disease, detection at almost any stage before the onset of the symptoms can still be considered as "early" from the point of view of screening. If AI can be used to bring those with obvious glaucomatous damage to the clinic before functional loss is visually significant or before they would normally present to the eye doctor's office, then this will be where efforts should be targeted. In addition, given the difficulties in discriminating very-early disease from its normal variation, focusing efforts to train DL models on early disease states would likely lead to failure. One study applied a simple logistic classification model to fundus photographs with varied stages of glaucomatous optic neuropathy and found that the accuracy of advanced disease classification was 98.6% compared with only 73% for early disease.[50] Furthermore, it is easier to secure funding for AI projects, with a greater chance of success. Another issue with targeting glaucoma screening to early disease is that because there are no universally agreed-upon reference standards, particularly for early disease, there can be many false-positive cases.[12,15] This can lead to unnecessary glaucoma specialist referrals, placing an extra burden on an already overstretched health care system, both from cost and labor perspectives.

In contrast, other panelists argued that the early detection of glaucoma, particularly in high-risk communities, is still a worthwhile pursuit. As Dr Lama Al-Aswad and others brought up during the panel discussion, “if you were a patient, then when would you want to be diagnosed?” Studies have shown the potential success of DL algorithms to discern even early disease better than traditional markers.[51,52] Kucur et al[51] developed a convolutional neural network to discriminate visual field data between patients with early glaucoma and healthy controls, which outperformed standard visual field metrics such as mean deviation. Similarly, Bhuiyan et al[52] developed and validated a fully automated glaucoma-suspect screening system that can be integrated into cloud-based teleophthalmology platforms for population-based screening efforts. Glaucoma screening, even with stand-alone software as a medical device or as a part of a larger teleophthalmology screen, could be the only opportunity to ensure that vulnerable individuals are brought into a larger health care system. Therefore, the proponents of broader screening targets believe that AI algorithms should be more generalizable and targeted toward the whole spectrum of the disease rather than trained to detect just those with moderate or severe glaucoma.

Large screening programs also raise other challenges. It is not possible to select participants just based on disease severity because there is often a mix of both patients with advanced disease and those with early disease. The prevalence of the condition that is being screened for affects the performance of the screening test. Consequently, the primary means of increasing the yield of a screening program is to target the screening test to groups of people who are at a higher risk of developing the disease. Software as a medical device for glaucoma screening needs to adequately address these issues to maximize its impact. Once AI-based glaucoma screening becomes a part of a routine, comprehensive eye health evaluation, the medical community can focus on improving follow-up adherence after screening. A combination of these efforts can significantly improve the cost-effectiveness of community-based screening programs.

Bringing AI to Patient Clinics

Next, the panelists at the CCOI session identified practical considerations that need to be addressed to transition AI from the research setting to clinical practice in a fair, equitable manner.

First, clinicians often do not know what the AI judgments are based on in a “black box” ML algorithm. Although DL models have consistently been able to outperform traditional algorithms, interpreting the results is not always straightforward. It is not possible to backtrack to a single determinant prognostic feature even with the use of class activation mapping. The issue is then one of trust and whether physicians can trust the clinical judgment of a machine. As brought up by the discussants, if clinicians do not trust the output, then how can it be applied to the care of patients? Other panelists believed that clinicians do not really need to understand a system or technology to use it. After all, how many routine practitioners know the precise algorithms used to evaluate optic nerve structure and function presently? The argument here is that instead, it is more clinically meaningful to understand how the DL algorithms perform compared with human clinicians.

The workshop participants also described the need to evaluate and address algorithmic biases as well as promote algorithm robustness. When building models, developers exclusively depend on the training set and, therefore, are prone to racial or ethnic biases. It is imperative for all AI-based glaucoma devices to be well suited for a racially and ethnically diverse patient population. Importantly, numerous features that are important in patients with glaucoma, including CDRs, intraocular pressure measurements, central corneal thicknesses, and even baseline RNFL measurements, can be dependent on race.[49,53,54] Overreliance on models without critically analyzing the source data has the potential to exaggerate and multiply these biases. The validation of AI models across diverse data sets is mandatory to protect against biases and avoid the optimization of data. To this end, based on the 2021 FDA's AI/ML-based action plan, the agency committed to supporting numerous regulatory science research efforts to develop methods for the identification and elimination of biases and increase the robustness and resilience of AI/ML algorithms to withstand changing clinical inputs and conditions.[53]

The data demand associated with DL models is already incredibly high. It currently takes thousands of images or data points to train AI models, as opposed to just tens or hundreds when it comes to training clinicians. Particularly in regions with limited resources, often in underserved neighborhoods, collecting such data is challenging. The workshop participants highlighted the importance of balancing an appropriate quantity and quality of data, with quality being defined as data that are diverse, are relevant, and have agreed-upon labels by various graders. As previously discussed, objective labels are particularly challenging when applied to the diagnosis of glaucoma.

Finally, training an AI model is only the first step to the clinical application of AI. Deploying these models in clinical settings and seeing how they integrate into the work-flow—how usable they are for doctors, nurses, patients, and technicians—are even more important when it comes to actual patient impact. The successful integration of technology into practice can become more challenging in resource-poor environments.

Incorporating the Patient Voice

Artificial intelligence–based devices for glaucoma need patients' input to ensure usability, equity, trust, and accountability. For example, to facilitate the incorporation of patients' input into glaucoma devices, the Center for Devices and Radiological Health at the FDA formed a collaboration with Johns Hopkins University and the University of California, San Francisco, Stanford Centers of Excellence in Regulatory Science and Innovation.[55–57] These academic institutions were funded by the FDA to conduct a patient-preference study (Johns Hopkins University)[58,59] and develop a patient-reported outcome measure (University of California, San Francisco, and Stanford Centers of Excellence in Regulatory Science and Innovation) sensitive to patients with mild-to-moderate glaucoma who are eligible for minimally invasive glaucoma surgery.[56,57,60] These studies, which identified key issues from the patients' perspective, including both psychosocial and financial concerns associated with glaucoma diagnosis and treatment, can be mimicked in the future while developing and introducing new AI/ML-based devices into clinical practice. Artificial intelligence algorithm recommendations must be considered in the context of an individual's unique circumstances and preferences.

To help promote and protect public health, the Center for Devices and Radiological Health at the FDA has undertaken many efforts to engage with patients, understand their concerns, and proactively integrate the patients' perspectives into the total product life cycle of medical devices. To gain an insight into factors that affect the patients' trust in AI/ML-based technologies, the FDA held a Patient Engagement Advisory Committee meeting.[61] Furthermore, the agency committed to supporting a patient-centered approach, including the need for a manufacturer's transparency to users about the functioning of AI/ML-based devices to ensure that users understand the benefits, risks, and limitations of these devices.[53] To that end, the CCOI workshop was fortunate to have included patient representation. Patient participation in the workshop demonstrated the CCOI's commitment to promote a patient-centered approach to AI/ML-based technologies.

Ethical and Legal Considerations in the Application of AI

A recently published review article by Abdullah et al[62] identified 6 key ethical areas of concern related to AI in medicine and ophthalmology. These areas included machine training ethics, machine accuracy ethics, patient-related ethics, physician-related ethics, shared ethics, and the roles of regulators. Undoubtedly, the research on diabetic retinopathy has cleared the way for future applications of AI in glaucoma by delineating regulatory and reimbursement pathways, demonstrating the manners of developing and expediting clinical trials, and emphasizing concrete end points and reference standards. However, the workshop discussants raised several additional questions, some of which are mentioned below.

First, how willing are we as a medical community to accept a "black box" device compared with the current standard of care? Moreover, how does the concept of a "black box" factor into discussions regarding informed consent and transparency? Do existing privacy laws, such as the Health Insurance Portability and Accountability Act, apply to data obtained by third-party, private technology companies? At present, most state medical boards do not consider an autonomous AI output to have the same medicolegal status as physician documentation. The issues of liability are further complicated by the lack of established AI suppliers, making health care systems vulnerable to companies exaggerating their offerings, and the limited understanding of how best to apply AI's abilities. Finally, who takes the ownership of the massive influx of data that will be generated, and whose responsibility is it to ensure that these data are collected in a manner that complies with regulatory standards and legislation? Is the oversight of software as a medical device implementation the responsibility of the medical community, technology providers, or federal regulations? Ultimately, the answers to these questions need to be established through dialogues between health care systems, physicians, ethicists, technology developers, law-makers, and, of course, patients.

In conclusion, there has been a plethora of publications focused on AI's use to interpret and replicate the output of several commonly used diagnostic modalities, including fundus photography, OCT technology, SAP, and gonioscopy, for glaucoma. However, there are currently no legally authorized AI-based medical devices for glaucoma. Grounded in a conviction that AI can be an invaluable tool to not only advance the field of glaucoma but, more importantly, bridge the blindness gap seen in underserved communities, the discussants at the "Artificial Intelligence for Glaucoma" segment of the CCOI 2020 conference shared research findings, debated upon current controversies, and addressed key issues to help expedite worldwide access to AI-based technologies for glaucoma detection and prognostication. Although several practical, legal, and clinical considerations must be addressed before the implementation of AI for glaucoma in clinical settings, workshops, such as the CCOI, bring together physicians, researchers, patients, and industry experts to overcome such challenges.

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Abbreviations and Acronyms:

AI	artificial intelligence
AUC	area under the curve
AUROC	area under the receiver operating characteristic curve
CCOI	Collaborative Community on Ophthalmic Imaging
CDR	cup-to-disc ratio
DL	deep learning
FDA	Food and Drug Administration
ML	machine learning
ONH	optic nerve head
RNFL	retinal nerve fiber layer
SAP	standard automated perimetry

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