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TechFlash: Artificial intelligence for automated detection of diabetic retinopathy

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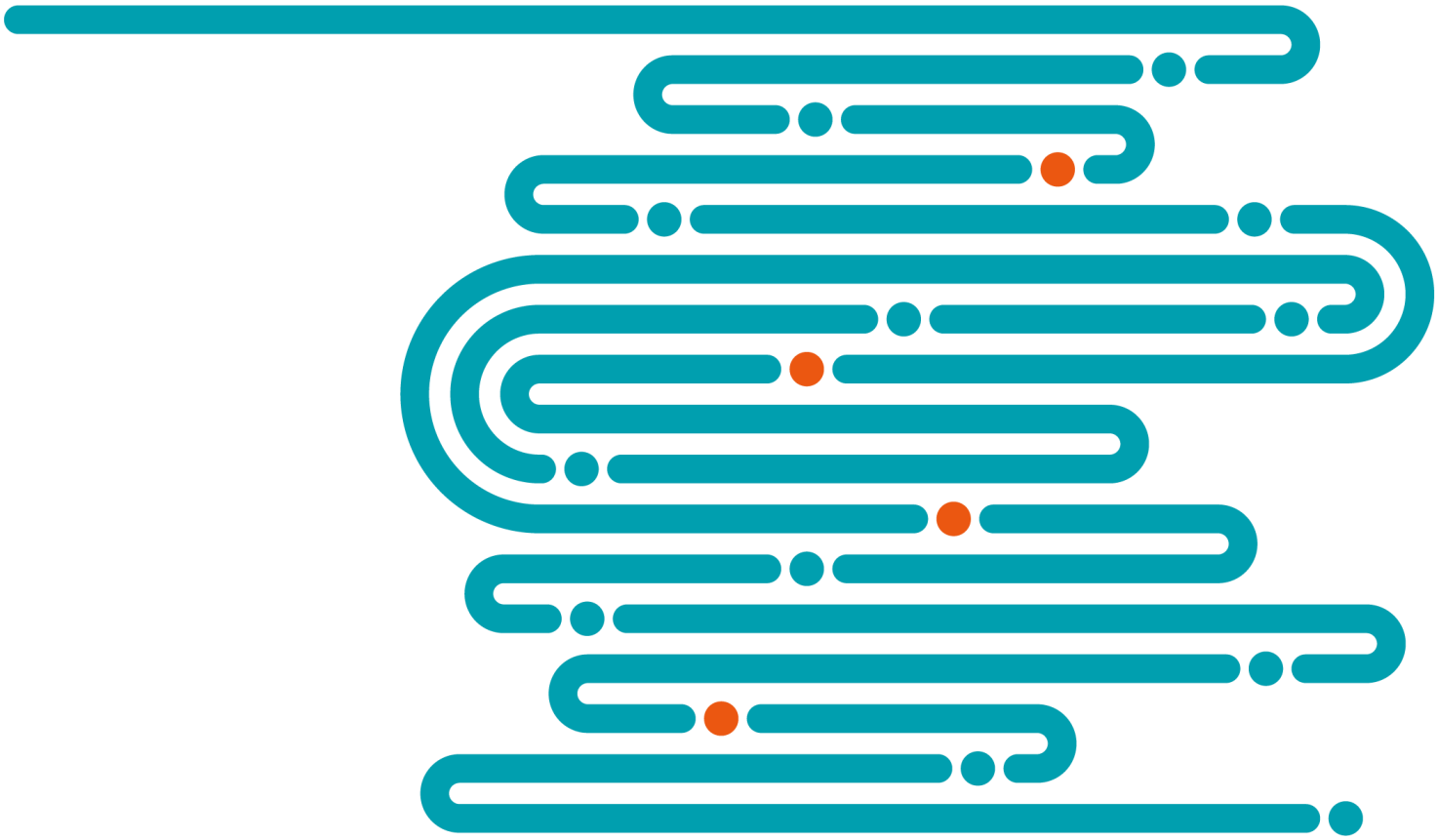

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This report comprises a review of abstracts identified through a search of the recent biomedical literature and does not constitute a comprehensive analysis. The report focus is on clinical evidence and outcomes.

For more information, contact Joe Cummings, PhD, at joe.cummings@vizientinc.com

Technology overview and status

Artificial intelligence (AI) is a rapidly emerging disruptive technology with numerous applications in health care. The use of AI for detection and triage of diabetic retinopathy (DR) is an innovative application in the field of ophthalmology. Potential advantages of screening patients for DR using autonomous AI algorithms without the need for a human reader include rapid return of results, better consistency, increased accuracy, scalability and lower costs. By enabling more widespread availability of DR screening, autonomous AI algorithms may improve health care access and equity.

DR is a significant complication in patients with type 1 or 2 diabetes caused by damage to the blood vessels in the retina with secondary effects on retinal neurons. Microvascular complications include the formation of retinal lesions, like hemorrhages, microaneurysms, infarcts, exudates, edema and vascular or fibrous proliferation.[1] DR may therefore be diagnosed by visual retinal examination that detects these lesions and their extent. Staging may progress from no DR to mild, moderate or severe non-proliferative DR to proliferative DR and macular edema.[2]

Preventive measures in early stage DR are crucial to slowing disease progression. However, early stage disease is typically asymptomatic and therefore requires detection through a screening strategy. Professional societies typically recommend annual screenings in patients with known diabetes. But, these may not occur due to many factors, including socioeconomic issues and lack of access. Further, type II diabetes itself often goes undiagnosed and this complicates an early detection strategy. Diagnoses of moderate or higher stage DR significantly increases the risk of visual deterioration and blindness; hence requires referral to a specialist for preventive measures and/or interventional treatment.

Numerous AI algorithms have been developed for DR detection. These programs typically analyze color fundus (retina) images pushed to a cloud-based server for AI analysis. Pre-processing of the images for color and contrast-enhancement may be conducted at the point-of-use or server level. If the image is of insufficient quality, however, no diagnosis is made. Some systems have been validated only for specific camera types, though images from other image types in the proper format may also be analyzable.

Different AI algorithms vary in programming architecture, training data, learning method, feature detection and diagnostic output. Deep learning (DL) image analysis algorithms, like convolutional neural networks, have shown advantages in learning ability and accuracy and are the most widely used.[3-9] Results are typically output as a binary yes/no for a given severity grade, like more than mild DR or sight threatening DR. AI analytic times typically range from one to a few minutes with real-time reporting of results.

As of July 2021, there were two AI systems for DR detection with Food and Drug Administration (FDA) marketing clearance: IDx-DR (Digital Diagnostics; Coralville, Iowa) and EyeArt (Eyenuk; Woodland Hills, California). The IDx-DR system was the first to receive FDA clearance in April 2018 through the *de novo* process, which is an FDA pathway intended for certain low risk devices with no comparable previously approved predicate (DEN180001).[10] Once the new FDA category (product code PIB) was created, subsequent AI applications could be approved through the conventional 510(k) process. EyeArt received 510(k) marketing clearance in August 2020 (k200667) and IDx-DR received a further 510(k) clearance for a modified device in June 2021 (k203629).

Both of these systems are labeled for *automatic* detection of more than mild DR in diabetic patients with no previous DR diagnosis. Use in a general population without a previous diabetes diagnosis would be off-label. EyeArt is also labeled for detection of vision-threatening DR indicative of the need for expedited referral. Both systems require two high-quality, undilated pupil (non-mydriatic) fundus images -one macula-centered and one disk-centered.

In addition to IDx-DR and EyeArt, there are numerous other AI systems for DR detection that are commercially available outside of the US and/or in various phases of development. These also may differ in algorithm architecture, diagnostic output and other characteristics. For example, some algorithms may run offline on smartphones or mobile browsers and some may be designed for use with handheld or smartphone-based cameras.[11-17] Some alternative DR platforms in the pipeline include: AEYE Health, Cognizant, D-EYE, Diagnos, DreamUp Vision, Iris, Medios AI, OphtAI, Retina-AI Health, RetinAI Medical, RetinaLyze, Retmarker, SigTuple, Spect and VisionQuest.

Overall, the AI-enabled platforms for DR detection are in the early adopter phase of dissemination. Basic science and clinical research on current generation platforms, however, has rapidly amassed over the last five years and now includes reported usage in hundreds of thousands of patients. FDA clearance in the US was in early 2018 for the first system and about one-year ago for the second system. Both systems also have the CE Mark as a class IIA medical device enabling commercial marketing in Europe. Some countries with nationalized health care systems have reportedly begun to implement AI systems as part of nationwide DR screening programs. Collective experience to date is estimated at a few million cases interpreted with AI.

Of note, the creation of a new Current Procedural Terminology (CPT®) reimbursement code (92229) specific to automated detection of DR and coverage by the Centers for Medicare and Medicaid Services (CMS) effective January 1, 2021 is a major milestone expected to significantly accelerate more widespread technology usage in the US.

Technology significance

Diabetes is a highly prevalent and rapidly growing chronic disease. According to CDC estimates, ~10% of the US population (~34 million people) have diabetes and about one in five adults with diabetes may not even know they have the disease. Type 2 diabetes is the most prevalent type and accounts for more than 95% of cases. Type 2 diabetes rates show a strong correlation with age and race/ethnicity. For example, American Indians/Alaska Natives have the highest incidence followed by people of Hispanic origin and non-Hispanic blacks.

Almost all type 1 diabetic patients will develop some degree of DR during the course of their disease and about 21% of type 2 patients may have some DR at the time of their first diagnosis.[1] The overall prevalence of DR in US adults may include more than 8 million people. In patients with DR, approximately one-third may have vision threatening DR. The CDC estimates that ~24,000 Americans may go blind each year due to DR.

Screening is a widely accepted and effective practice for early DR detection. Prognosis and outcomes are much better when DR is identified in its early stages.[1] Glycemic, lipid and blood pressure control have been shown to prevent or delay DR progression and photocoagulation therapy can prevent blindness. In addition to improved outcomes, costs and health care resources may also be saved by early intervention.

Automated AI-based detection algorithms may have some potential advantages for DR screening. Importantly, they may increase availability of DR screening by reducing the need for on-site trained readers. This could allow for use in primary care offices or other convenient screening locations. Further, rapid AI results at the point-of-care could lead to higher likelihood of compliance with referral to a specialist and enhanced educational opportunities compared to delayed diagnosis received days later. In addition, the capability to rapidly analyze large test volumes may help to address shortages in trained readers and reading backlogs.

There is also some evidence for significant inconsistency, low sensitivity and inter-reader disagreement for images read by human analysts.[18] Use of automated AI may decrease this inconsistency and potentially improve on accuracy compared to human readers. AI system performance can also be optimized to balance

sensitivity and specificity for screening purposes. Choosing diagnostic cut-offs with high sensitivity minimize false negatives so that DR cases are not missed during screening. However, if this lowers specificity, there may be an increase in false positives that increase referrals leading to unnecessary follow-up tests.[19]

Despite the potential advantages, there are also potential disadvantages common to an early stage emerging AI technology. The clinical evidence for safe and effective use in a screening paradigm is still undergoing investigation. Though showing high accuracy in controlled reference datasets, real world studies have shown less accuracy, particularly when low quality images are used. Safety and liability issues when an inaccurate diagnosis is made by an autonomous AI are also still being worked through.

Explainability of AI is another potential issue. DL algorithms often involve complicated, non-linear relationships among interconnected hidden programming layers. These can sometimes obscure the ability to explain how an AI algorithm arrived at its result. This issue needs to be addressed in order to instill trust in the AI result and to provide a warning in cases where the AI may have developed biases or other types of inaccuracy. As a software product, data protection, patient privacy and cybersecurity are also implementation issues that need to be fully addressed.

Finally, at this stage in development, ophthalmic AI algorithms are mostly directed at a very narrow diagnosis of DR. Human-based comprehensive eye exams typically also evaluate the patient for other important eye diseases, like glaucoma, and identify other incidental eye findings. It is possible that some cases of these other diseases could go undetected in a paradigm where autonomous AI for DR screening is available. The AI algorithms also narrowly focus on findings from retinal images and hence may not be as sensitive as a diagnosis made with some of the more advanced diagnostic tools available to an eye specialist.

Current practice and alternatives

There are a large number of variable methods comprising the DR screening paradigm. Screening may be conducted in hospitals, clinics, physician offices, pharmacies, mobile clinics, kiosks and other non-healthcare sites that offer opportunistic testing. Methods may use pupil dilation or no dilation, numerous different types of cameras with different lenses, light sources and viewing angles, live in-person reading, remote telescreening and readers with different training and experience levels. Because of the many variables, evidence-based comparative studies are mostly lacking among the many options and choices may often be based on a trade-off involving accuracy, availability and cost-effectiveness.

Traditional DR diagnosis typically involves pupil dilation and retinal imaging using a narrow view ophthalmoscope with multiple fields (e.g., up to 7 images) to evaluate the entire central and peripheral retina with live reading by a trained eye professional. Drawbacks include the need to wait 15 to 30 minutes for dilation, time to examine multiple fields and labor-intensive manual mapping of lesions for DR grading.

More contemporary approaches tend to use non-dilation imaging with fewer, wider fields and digital color image capture. Though diagnostic accuracy tends to be higher with pupil dilation, systematic review data suggest high accuracy can be obtained with non-dilation digital imaging and these methods may be adequate for screening purposes.[20] For screening, digital imaging has largely replaced traditional ophthalmoscopy because it is faster and more convenient and storage and sharing of the images is more straightforward.

Telescreening using asynchronous (store and forward) telediagnosis is a common alternative to in-person reading. After the digital retinal images are taken, they are sent to a specialty reading center, where they are read by experienced professionals and results may be relayed back to the patient with the diagnosis.

Depending on volume, results may take a few days for processing. Different computer-assisted lesion detection systems may also be used in specialized centers to speed-up the reading process.

Fundus camera set-ups vary considerably in size, weight and costs. These cameras may include classic stable hard-mounted devices, mobile hard-mounted devices and portable devices.[21] The latter now include handheld and smartphone mounted cameras capable of image capture, processing, storage and transmission. The high availability and relatively low cost of smartphone-based adaptor-type devices make this set-up a growing focus area for DR screening applications in atypical settings.

Camera field of view may typically be 30º, 45º or 60º. Ultra-wide field of view cameras capturing up to a 200º angle are also now available. A narrower field of view requires more images to cover the retina. The ultra wide cameras can capture about 80% of the retina in a single image. For a given field of view, more images may increase DR diagnostic accuracy.[22] However, American Academy of Ophthalmology guidelines suggest a high-quality single field image interpreted by an experienced reader may be sufficient for screening purposes in most cases.

Alternative diagnostic methods for DR include optical coherence tomography (OCT) and fluorescein angiography (FA). FA uses an intravascular dye and retinal imaging to identify vasculature, vascular leakage and other abnormalities. OCT angiography similarly provides high resolution imaging of the retinal vasculature. Both techniques can detect DR with very high accuracy, but typically require specialized equipment and expertise; thus limiting availability for widescale screening.

Clinical evidence summary

The Medline/PubMed bibliographic database was searched in August 2021 to identify clinical evidence related to the use of AI for DR detection and screening. Keywords used in the literature search strategy included*: artificial intelligence, AI, automated, deep learning, diabetes, diabetic retinopathy, macular edema, fundus, retina, screening* and/or various company/product names. Manufacturer websites (IDx-DR and Eyenuk) were also searched to identify pertinent clinical evidence.

Key performance indicators include the percent of exams/images that are interpretable, accuracy, sensitivity, specificity and positive and negative predictive values (PPV and NPV). A good accuracy result for DR screening may include sensitivity/specificity >85% and a technical failure rate <5%.

Diagnostic accuracy conclusions may be confounded by the use of different software versions over time. Further, accuracy may be measured against different reference standards and using different classification scales. For example, pivotal trials have typically used a nationally-known fundus photo reading center using dilated widefield (45º to 60º) stereoscopic images (4 stereoscopic pairs of digital images per eye) graded by highly experienced readers as the gold standard.[23] Other studies have used consensus from two or more expert human graders and/or various different imaging techniques of lesser quality as a comparator.

The literature review identified a large amount of published clinical evidence, including multiple recent systematic reviews and meta-analyses.[8, 24-26] The meta-analyses included between 20 and 40 studies analyzing between 400,000 to 700,000 retinal images, depending on the different meta-analytic study inclusion criteria. Overall, accuracy was reported to be very high with area under the receiver operating curves (AUCs) ranging from 0.97 to 0.99. Pooled sensitivity was in the range from 74% to 92% and pooled specificity ranged from about 91% to 95% for detection of referable DR. Image-related factors, such as image size and number of fields, was noted to play a significant role in diagnostic performance.[27]

The IDx-DR system was tested on a reference fundus image data set and demonstrated sensitivity of 96.8% and specificity of 87% for detecting referable DR.[28] The NPV was 99% (6/874 false negatives) with an AUC of 0.98. In a real-world, multi-center pivotal clinical trial (NCT02963441) enrolling 900 patients at 10 sites,

IDx-DR demonstrated sensitivity of 87.2% and specificity of 90.7%, with a 3.9% technical failure rate.[23] Trials have reported avoidance of ~91% of unnecessary specialty visits through use of the AI system.

IDx-DR has also been validated in screening trials in Poland, Spain and the Netherlands.[29-32] In the Poland study, the AI system demonstrated sensitivity of 94%, specificity of 95%, PPV of 82% and NPV of 99% for detection of referable DR compared to a single human grader standard.[29] The Spanish study reported 100% sensitivity and 81.8% specificity.[30] In the Netherlands, one study reported a sensitivity of 91%, specificity of 84%, PPV of 12% and NPV of 100% to detect referable DR.[31] Another Netherlands study with screening in a primary care setting reported sensitivity of 79.4% and specificity of 93.8% for referable DR.[32] Overall, these studies demonstrate high diagnostic accuracy in a variety of settings and populations.

The EyeArt multi-center, pivotal clinical trial (NCT03112005) conducted as part of the FDA submission process reported sensitivity of 96% and specificity of 88% for referrable DR and sensitivity of 92% and specificity of 94% for detecting vision threatening DR. EyeArt has also been studied in some very large real-world type screening studies. In a retrospective review analyzing images from more than 100,000 consecutive patients, reported sensitivity was 91.3% and specificity was 91.1% for referrable DR.[33] In a 30,000 patient prospective UK screening study, reported sensitivity was 95.7% and specificity was 68% for referrable DR.[34] Overall, these studies demonstrate high diagnostic accuracy, safety and utility in a real-world screening program and the capability to reduce the referral workload by ruling out unnecessary specialty visits.

EyeArt has also been studied for use on different types of images, including those taken with ultra-wide field systems, portable cameras and smartphones.[35-38] These studies demonstrated high sensitivity and specificity for referrable DR. Further, they showed high accuracy despite different imaging techniques, operators with little previous retinal imaging experience and in most cases without the need for pupil dilation.

Because of differences in diagnostic scales, readers, imaging techniques and settings, it is difficult to compare AI algorithms across studies. However, a direct comparative study in the VA Healthcare system compared 7 different AI algorithms head-to-head on a dataset consisting of 20,000 patients and more than 300,000 retinal images from 2 different sites.[39] High NPVs (82% to 94%) were noted for all algorithms, but there was a range of variation in reported sensitivity (51% to 86%). Two algorithms in this study reportedly achieved higher sensitivity and one achieved comparable sensitivity compared to human graders. The researchers concluded that different AI algorithms may have different diagnostic performance for DR screening. Other direct comparative studies have also noted differences in performance between AI systems.[40-42]

Financial issues

Automated AI usage for DR screening may typically be based on a fee for each analysis. For example, manufacturer charges may be around $30 to $50 per analysis, but can vary with contract terms and volumes. In addition to AI usage costs, DR screening may include direct costs for medical imaging equipment and labor, such as a technologist, to set-up and take the images and a specialist reader to grade the images. Indirect costs may include administrative and overhead costs.

Direct reimbursement for automated AI-based DR screening may be available using new CPT code 92229 (imaging of retina for detection or monitoring of disease; point-of-care automated analysis and report, unilateral or bilateral).[43] Effective January 1, 2021, CMS reported a $55.66 valuation for hospital outpatient use of CPT code 92229. However, actual CMS reimbursement rates have been left to individual Medicare Administrative Contractors (MACs) and these MACs have announced rates ranging between ~$28 to $55. Though helpful, in some scenarios, this reimbursement rate may not cover all incurred AI costs.[44]

The main economic value associated with automated analysis in DR screening may be accrued through potential labor savings.[42, 45] Automated algorithms with high specificity and NPV may be used to rule out DR in a high proportion of patients; thus, reducing the costs associated with reading of all images by trained specialists. Though analysis is highly dependent on AI pricing, one study noted potential savings of ~$15 to $18 compared to a system using ophthalmologists for reading and ~$7 to $9 compared to optometrists used as the graders.[39] Similarly, an economic modeling study found the use of a hybrid (automated/manual screening) protocol to cost ~$62 per patient per year, which was better than a fully automated model at $66 per patient per year or a fully human-based model at $77 per patient per year.[46]

Cost-effectiveness may also be achieved by showing improved outcomes and reduced costs associated with treating DR secondary to an effective DR screening program.[47] In one economic study in diabetic pediatric patients, autonomous AI screening was shown to be cost saving when screening adherence rates were high.[48] Notably, this study accounted for many factors, including out-of-pocket costs, probability of DR screening, ophthalmology visits and DR treatment.

Further studies incorporating automated AI analysis and collection of financial outcomes, however, are still needed to show the cost-effectiveness of the AI approach. Other patient outcomes of interest include overall quality-of-life, independent living ability and working ability associated with DR progression. Special populations of interest may include rural patients with high transportation costs and low-income populations with reduced access to healthcare and therefore low screening adherence rates.

Patient selection criteria

Current FDA product labeling for the approved systems (k200667, k203629) is for adult diabetic patients without a previous diagnosis of DR. Labeling is based on pivotal trial patient inclusion/exclusion criteria and trial design criteria. These trials included a specified camera type and imaging protocol, but the setting was broader and could be a primary care or eye care site. Contraindications include serious vision symptoms or vision loss, history of eye or retina interventional procedures and retinal hypersensitivity to light that would contraindicate fundus imaging.

Education of the patient and full disclosure of AI weaknesses are needed to safely implement these systems. Warnings for both approved devices (IDx-DR, EyeArt) emphasize the inability to diagnose eye diseases other than DR and therefore the need for patients to see an eye care provider to screen for other eye diseases like glaucoma. Further, in patients where the image quality is insufficient, dilation may be needed and/or the patient should be promptly re-tested or referred to an eye care professional for testing.

Future developments

AI is a rapidly emerging technology with expansion into many areas of ophthalmology. Its rapid evolution is due to many factors, including faster and more powerful computer hardware, advances in cloud computing, fine-tuning of existing deep learning algorithms and larger annotated data sets available for training purposes. All of these factors are expected to continue with rapid progress in the years ahead leading to enhancement of current applications and creation of new applications.

Some new applications in progress include detection and screening for age-related macular degeneration (AMD) and glaucoma. One study, using a deep learning algorithm and OCT, was able to accurately diagnose more than 50 different retinal diseases.[49] Further, because of the relatively easy visualization of the vasculature, retinal imaging with AI analysis may also be used as a biomarker for the risk of other cardiac and vascular diseases, such as stroke and heart disease. Retinal imaging has also been used to

predict a patient's gender, smoking status, systolic blood pressure, renal function, Alzheimer's disease and even autism.[50]

The availability of low-cost portable cameras and smartphone-based cameras capable of taking high resolution color fundus images without pupil dilation may drive rapid growth in DR screening in the future. These types of cameras may enable DR screening in a wide variety of settings. The use of automated AI analysis may be critical to reduce the burden associated with the high volumes created by all these new cameras and screening sites. FDA clearance of AI-enabled algorithms for use with more convenient camera set-ups may be expected in the near future.

Continued maturation of clinical evidence regarding the safety and efficacy of automated AI for DR screening is underway. Clinical trials have moved beyond proof of technical performance and accuracy in contrived cohorts ("in silico" analysis) and into real-world studies collecting data on patient outcomes and cost-benefit. Because of rapid developments in the field, efforts should be made to update the literature search included in this report to account for new clinical evidence.

Summary and recommendations

The following conclusions and recommendations are based on the material presented in this report:

- Diabetes care is a high-impact focus area for hospital performance improvement. DR is a highly prevalent complication of diabetes that can significantly affect patient quality of life, lead to visual deterioration and result in blindness. DR complications, however, can be largely prevented through early detection. Therefore, hospitals should examine their current paradigms for DR screening and implement practices that increase compliance with annual retinal exams in diabetic patients.
- Automated AI algorithms for detection and triage of DR is a rapidly emerging innovative technology that can improve patient access and thus adherence with guideline directed screening. For example, AI may enable DR testing at primary care sites. These sites may often refer patients for retinal screening, but do not typically have the equipment or expertise necessary for on-site testing. In this scenario, AI is an enabling technology that allows for non-ophthalmic personnel, like primary care clinicians or endocrinologists, to perform DR screening exams in their clinic in a relatively convenient and cost-efficient manner.
- In the last few years, two companies have received FDA marketing clearance for automated detection of more than mild DR. Numerous other companies worldwide have also developed DR screening algorithms and these may be expected to enter into the marketplace in the near future. Usage of AI has been reported in clinical studies involving hundreds of thousands of patients and overall it has been used in a few million patients to-date.
- In-person fundus image analysis by trained eye specialists, however, remains the most widely utilized approach for DR diagnosis. Telescreening with off-site human readers is an alternative approach to AI that can also improve patient access and convenience. There are a wide array of fundus cameras and techniques that can provide retina images with a quality sufficient for screening purposes.
- Generally, clinical trials supporting the currently FDA-approved technologies for automated AI-based DR detection have reported high diagnostic accuracy, sensitivity and specificity. Some studies have also noted results similar to or better than human readings. Though further studies may be needed to corroborate and expand on these results, the current evidence base provides a significant foundation for the use of AI algorithms in DR screening.

- DR detection algorithms are typically optimized to achieve high sensitivity and negative predictive value to minimize false negatives in patients who would benefit from referral for follow-up. By design, specificity may be somewhat lower secondary to false positives. The latter will require referral and unnecessary use of resources. Overall, however, the automated algorithms may accurately rule out a large proportion of those screened, thus reducing the overall burden on specialist readers.
- CMS reimbursement policies that became effective in 2021 may be a significant factor facilitating the adoption of this new technology. Under the CMS paradigm, reimbursement of up to $55 may be available to offset the automated analysis cost. Not all MACs are providing this level of reimbursement, however, and hospitals should conduct their own financial analyses using their unique payer mix and reimbursement rates to determine financial viability.
- AI algorithms are a medical technology used in the clinical care paradigm, hence should be reviewed through hospital processes and committees equipped to evaluate innovative new technology. Deliberative processes should include consideration of the clinical evidence, financial issues and overall hospital strategic plan.
- There are many different AI-based systems for DR detection and many different variables involved in the screening process. These differences can be expected to affect diagnostic performance and some data are available that show different accuracy outcomes among systems. However, most systems have not been rigorously compared and therefore strong evidence-based system choices can't be made at this time.
- Other system characteristics to consider include the camera type, setting and technician skill level. Selected DR screening systems should be validated for the specific camera and setting scenario. It should also be validated for local patient demographics.
- Hospitals implementing AI at this early stage may experience many barriers to implementation. Medicolegal issues, cybersecurity, clinician concerns, explainability of results, patient education and acceptance, and financial viability are challenges that may need to be addressed during implementation.
- AI is a rapidly growing field expected to disrupt and transform many of the current paradigms in ophthalmology. Because of this, hospitals and health systems should be actively involved in learning about the technology, applications, evidence and economics. Where warranted, hospitals should proactively implement AI technologies as a strategy to maintain current and future market competitiveness.

Related links

Manufacturer web pages: Digital Diagnostics, Eyenuk

FDA documents: IDx-DR DEN180001, k203629; EyeArt k200667

Select full text articles: PubMed Central articles, Google Scholar articles

Other AI ophthalmology product manufacturers: AEYE Health, Cognizant, D-EYE, Diagnos, DreamUp Vision, Iris, Medios AI, OphtAI, Retina-AI Health, RetinAI Medical, RetinaLyze, Retmarker, SigTuple, Spect, VisionQuest

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290 E. John Carpenter Freeway
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(800) 842-5146

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