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Feasibility and acceptance of artificial intelligence-based diabetic retinopathy screening in Rwanda

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Synopsis: This clinical study on the practical application of using artificial intelligence for diabetic retinopathy detection in Africa demonstrates the feasibility of using artificial intelligence-based screening for diabetic retinopathy in low-resource settings.

ABSTRACT

Background Evidence on the practical application of artificial intelligence (AI)-based diabetic retinopathy (DR) screening is needed.

Methods Consented participants were screened for DR using retinal imaging with AI interpretation from March 2021 to June 2021 at four diabetes clinics in Rwanda. Additionally, images were graded by a United Kingdom National Health System Certified Retinal Image Grader. DR grades based on the International Classification of Diabetic Retinopathy with a grade of 2.0 or higher were considered referable. The AI system was designed to detect optic nerve and macula anomalies outside of DR. A vertical cup to disc ratio of 0.7 and higher, and/or macular anomalies recognized at a cut-off of 60% and higher, were also considered referable by AI.

Results Among 827 participants (59.6% women (n=493)) screened by AI, 33.2% (n=275) were referred for follow-up. Satisfaction with AI screening was high (99.5%, n=823), and 63.7% of participants (n=527) preferred AI over human grading. Compared to the human grader, the sensitivity of the AI for referable DR was 92% (CI 0.863, 0.968), with a specificity of 85% (CI 0.751, 0.882). Of the participants referred by AI: 88 (32.0%) were for DR only, 109 (39.6%) for DR and an anomaly, 65 (23.6%) for an anomaly only, and 13 (4.73%) for other reasons. Adherence to referrals was highest for those referred for DR at 53.4%.

Conclusion DR screening using AI led to accurate referrals from diabetes clinics in Rwanda and high rates of participant satisfaction, suggesting AI screening for DR is practical and acceptable.

KEY MESSAGES

What is already known on this topic: Artificial intelligence (AI) for referrable diabetic retinopathy (DR) detection has demonstrated acceptable performance in an under-resourced African population.

What this study adds: This study demonstrates the feasibility of and high satisfaction with AI-based screening for DR at diabetes clinics in sub-Saharan Africa. This is the first clinical study on the practical application of using AI for DR detection from Africa.

How this study might affect research, practice or policy: This study assessed a currently-available AI tool in a variety of clinical centers in a low-middle income country, an under-studied setting. The feasibility suggests this study could be replicated in similar under-resourced settings as a strategy for DR detection. For long-term sustainability, an AI-based DR screening program will need to be integrated into existing national healthcare funding models.

INTRODUCTION

Globally, the incidence of diabetes and the impact of diabetic retinopathy (DR) on visual impairment are increasing.[1] DR, a complication of diabetes, is the leading cause of vision loss among working age persons globally,[1] and recent reports project the largest increase in the prevalence of DR in sub-Saharan Africa.[2] This presents a significant challenge in human resource support to detect and treat DR given the low numbers of ophthalmologists in sub-Saharan Africa, with the mean being 3.7 per million population.[3]

Screening programs, which support early diagnosis and treatment of DR, are known to be effective at preventing visual impairment.[4] DR screening aims to identify an unnoticed complication of diabetes, as most patients with diabetes do not realize they have DR until their vision is already affected.[5] One Hong Kong study showed that patients with diabetes who do not attend screening are up to 4 times higher risk for developing sight-threatening DR.[6] Further, DR screening has the potential to detect retinal and microvascular conditions other than DR contributing to improved overall eye health.[7]

While DR screening is critical for disease management, low-resource settings, such as Rwanda often lack the infrastructure and trained personnel to implement DR screening programs effectively.[8,9] Additionally, the labor-intensive aspect of traditional DR screening programs hinders their ability to scale. Expansion and sustainability of human resource-focused screening models will be challenging given the projected increases in diabetes and associated complications. Alternative, efficient and effective DR screening models are needed. One such solution is shifting DR screening to non-ophthalmology providers, which has been implemented successfully in low- and middle-income countries (LMIC) and is routine in many high-income countries.[10]

Furthermore, recent advances in artificial intelligence (AI) for DR screening have the potential to support such programs. There is a growing body of evidence on the accuracy of AI systems for DR, and reviews have highlighted potential advantages of using AI in the reduction of personnel and as a cost-effective screening tool.[11] Using AI for DR screening allows non-clinicians to be trained on retinal

imaging, with AI interpretating the images onsite, providing patients instant feedback. As suggested by Mathenge,[12] in Africa, such task shifting to non-clinical staff benefits ophthalmologists with increased valuable time to accomplish more specialized tasks, and allows patients, who often travel long distances, to return home or progress to eye clinics with an immediate answer on their DR status. Bellemo et al.[13] previously demonstrated the validity of using AI for DR screening in an under-resourced African population. However, additional evidence on not just the accuracy of AI models, but also the practical application of AI-based DR screening programs in low-resource clinical settings, is needed. This study aims to expand that evidence base by analyzing the clinical implementation and community acceptance of an AI-based DR screening and service-delivery project in and around Kigali, Rwanda.

METHODS

Screening for DR using retinal imaging with AI interpretation was implemented from March 2021 to June 2021 at four diabetes clinics in and around Kigali, Rwanda: three government clinics (two secondary-level, one tertiary-level) and one private primary level clinic funded by the World Diabetes Foundation. Participants provided written informed consent during routine visits to the diabetologist before enrolment. The study was approved by the Rwanda National Health Research Committee (NHRC/2020/PROT/025) and the Rwanda National Ethics Committee (945/RNEC/2020). The tenets of the Declaration of Helsinki were followed throughout.

The study inclusion criteria were diagnosis of type 1 or 2 diabetes, age 18 years and older, ability to give informed consent, availability of gradable digital retinal images for at least one eye, and lack of any current treatment or participation in any on-going study requiring regular appointments for eye care. Participants were consecutively enrolled from among patients presenting to the four diabetes clinics. Unconsented participants and those with ungradable images received appropriate clinical care but were excluded from the study.

AI model

The AI model is based on the Inception-ResNet-v2 Convolutional Neural Network (CNN) architecture[14] trained to classify fundus photographs into one of five categories based on the International Clinical DR Disease Severity Scale (non-proliferative normal, non-proliferative mild, non-proliferative moderate, non-proliferative severe, and proliferative). The input to the CNN is a single (or batch thereof) fundus photograph. Preprocessing includes: (i) removal of black Fundus border, if present; and (ii) resizing of the image to 448×448 pixels with preserved aspect ratio. The output of the model is a L1-normalized vector (i.e. sums to one), where each element corresponds to one of the DR grades. The predicted DR grade is the argmax of the raw output vector, and the referable DR score is the sum of the last three elements of the output vectors.

The model was trained on a total of 90,073 photographs that were quality-controlled by at least one board-certified Ophthalmologist, which included verifying image quality and image labeling. Training was carried out "from-scratch", based on randomly initialized weights. There was no former knowledge encoded in the neural network as opposed to a pre-trained model. To improve generalization to unseen images, data augmentation techniques such as random zoom, flipping, and rotation were applied during training. While not a direct comparison, in a previous study, the model's referable DR performance validation was carried out based on an independent dataset containing 200 photographs per DR grade (for a total of 1000 photographs), which resulted in an area under the operator receiver characteristic curve (AUROC) of 96% and 98·5%, respectively.[15]

For this study specifically, the AI system was designed to detect optic nerve abnormalities or macula anomalies outside of DR. The data used for training was similar to that used for the DR models. Images were labelled as containing macular anomalies or not (irrespective of whether caused by specific conditions) by at least one board-certified ophthalmologist. For the optic nerve head, the only assessment included in this study was the vertical cup to disc ratio (VCDR) with a VCDR of 0.7 and higher considered referable by AI.[16] The AI additionally referred macular anomalies, at a cut-off of 60% and higher on a scale of zero to 100%, which reflected the degree of certainty in recognizing an anomaly.

Thresholds and cut-offs for all models used as part of this study were obtained on a hold-out validation dataset based on maximisation of the relevant target metrics.

Procedures for screening

Participants' baseline demographic data and clinical characteristics were collected on electronic devices using KoBoToolbox (Cambridge, MA, USA) prior to retinal imaging. Following imaging, a questionnaire was administered to all participants inquiring about satisfaction with the screening process and their eye care history and knowledge. Trained personnel captured 2-field (optic disc and center-cantered), digital color, non-stereo, non-mydriatic 45° retinal fundus photographs of each eye (Topcon NW400, Tokyo, Japan). Retinal images were captured in the JPEG (Joint Photographic Experts Group) format, with a dimension of 2592 × 1944 pixels. If image quality was deemed poor due to a small pupillary aperture (<2.5 mm), the eye was dilated with a single drop of tropicamide 0.5%, and the image was reacquired after 15 minutes.

Once completed, all images were anonymized with a unique patient registration number and uploaded to Orbis International's Cybersight AI (New York, USA). A mobile device or laptop and an Internet connection are required to access Cybersight AI, which generates a response regarding the presence or absence of referable DR based on a macula-centered image from each available eye of a participant within 60 seconds. The system confirms automatically for each image that it contains the correct features and is of sufficient quality for grading. Cybersight AI is available free of charge to eye health professionals in LMICs and is accessible upon completion of no-charge registration on Orbis International's telehealth platform, Cybersight. Patients that screened negative for DR and showed no other anomalies were informed that no referral was needed, but they should continue to screen annually for DR. Patients that screened positive for DR or had an anomaly present as detected by the AI model were suggested to complete the referral within 30 days of screening.

In addition to screening by AI, all images were uploaded to Labelbox (Labelbox, Inc, San Francisco, USA) for grading by a United Kingdom National Health System Certified Senior Retinal

Image Grader. DR grades at the patient level were obtained by taking the most severe outcome across both eyes and compared between AI and the human grader based on the International Classification of Diabetic Retinopathy (ICDR) with a grade of 2.0 or higher considered referable.[17] The human grader used a VCDR value of 0.7 and higher to identify disc anomalies, whereas macula anomalies were documented as a binary outcome (present or absent). Discrepancies between AI grades and human grades were reviewed and any patients that were screened negative by AI, but positive by human grading were contacted and referred to the eye hospital for a full eye exam.

Statistical analysis

Means and standard deviations are presented for age, and blood glucose (mg/dL). Basic frequencies and percentages are used for categorical variables, with participant responses of "I don't know" categorized as lack of knowledge regarding diabetes eye care knowledge and beliefs. The AI system for referable DR compared to human grading was evaluated with the following metrics: sensitivity, specificity, area under the receiver operator curve (AUC-ROC), area under the precision recall curve (AUC-PR), Kappa, and Mathew's correlation coefficient (MCC). Participant referrals were categorized into four types: Referrable DR only, Referrable DR and an anomaly, Anomaly with no referrable DR, Referral for other pathology or other reason. Adherence was defined as presentation for recommended referral within 30 days and was calculated for all participants referred and by type of referral. The Chi-square test was used to assess adherence rate differences across referral types.

RESULTS

Between March to June 2021, 827 persons (59.6% women (n=493)) with an age range of 18 to 91 years were screened by AI at one of four diabetes clinics participating in the project. Among these, 82.8% (n=685) self-reported being in the middle-income class and 88.9% (n=735) had public insurance. Type 1 diabetes was reported by 41.2% (n=341) and 57.4% (n=475) reported having Type 2 diabetes, while a small percentage of participants (1.33%, n=11) were unaware which type of diabetes they had. Approximately one-quarter (26.4%, n=218) of participants were diagnosed with diabetes ten or more

years ago, 30.4% (n=251) were diagnosed five to ten years ago and the remainder less than five years ago. The mean blood glucose for participants for which it was documented (n=728, 88.0%) was 9.40 mmol/L (SD 4.79). Nearly half of participants (44.5%) came from rural locations, and one-third (n=275) were suggested by the AI to receive referral for further examination. (Table 1)

Table 1. Demographic and clinical characteristics of the study population

Variable	n = 827
Demographic	
Mean age in years (SD)	47.8 (16.1)
Female sex, n (%)	493 (59.6%)
Educational level, n (%)	
None	109 (13.2%)
Primary	319 (38.6%)
Secondary	280 (33.9%)
Tertiary	119 (14.4%)
Socioeconomic status*, n (%)	
Highest	66 (7.98%)
Medium	685 (82.8%)
Lowest	24 (2.90%)
Unknown	52 (6.29%)
Health insurance, n (%)	
None	32 (3.87%)
Public	735 (88.9%)
Private	39 (4.72%)
Other	21 (2.54%)
Occupation, n (%)	
Professional	53 (6.4%)
Skilled work	158 (19.1%)
Unskilled work	172 (20.8%)
Unemployed	411 (49.7%)
Retired/Pensioner	33 (3.99%)
Diabetes status	
Type of diabetes, n (%)	
Type 1	341 (41.2%)
Type 2	475 (57.4%)
Unknown	11 (1.33%)
Duration, years, n (%)	
< 5	358 (43.3%)
5-10	251 (30.4%)
>10	218 (26.4%)
Blood glucose (mmol/L) Mean (SD) <7%	n=728 9.40 (4.79) 261 (35.8%)
Residence	
Urban	459 (55.5%)
Rural	368 (44.5%)
AI Outcome	

Referral recommended	275 (33.2%)
Did not refer	552 (66.8%)

*Status based on official Ubudehe classification that exists for all Rwandans (https://rwandapedia.rw/hgs/ubudehe/poverty-level-categories) and which has most recently been reviewed in 2020. Category A is highest, categories B and C are combined into medium, and categories D and E are the lowest.

There was very high satisfaction with the AI screening process (99.5%, n=823), and 63.7% of participants (n=527) reported that they preferred AI screening over human grading. Fewer than 10% (n=80) of participants reported having had an eye examination with dilation of the pupil in the last year, while 21.8% reported having ever had an eye exam of any kind. Among all participants, 18.7% (n=155) were aware of the results of their last eye test. The majority of participants (87.1%, n=720) knew that diabetes can cause eye problems and 80.4% (n=665) were worried about losing their sight. (Table 2)

Table 2. Diabetes eye care knowledge and beliefs

Eye Care History and Knowledge	**n (%)**
Reports eye exam in the past year	180 (21.8%)
Reports previous dilated eye test in past year	80 (9.7%)
Aware of results of last eye test	155 (18.7%)
Aware diabetes causes eye problems	720 (87.1%)
Believes it is the doctor who decides timing of eye exam*	300 (36.3%)
Knows good blood sugar control reduces risk of eye problems*	659 (79.7%)
Personally knows a blind person	355 (43.1%)
Worried about losing sight	665 (80.4%)
High satisfaction with screening processes	823 (99.5%)
Complained of delays when screening time > 30 minutes	439 (53.2%)
Patient preference of AI versus human expert	527 (63.7%)

*Responses of “I don’t know” are categorized as lack of knowledge.

Compared to human graders as a standard, the sensitivity of the AI for referrable DR with the AI internal threshold of 0.5, as used during the screening program, was 92% (Confidence Interval (CI) 0.863, 0.968), with a specificity of 85% (CI 0.824, 0.874). The area under the precision recall curve (AUC-PR) and the receiver operating curve (AUC-ROC) for referable DR were 82% (CI 0.751, 0.882) and 96% (CI 0.941, 0.975) respectively. (Table 3)

Table 3. AI and Human Outputs for Referrable DR.

	Threshold	Sensitivity	Specificity	AUC-PR	AUC-ROC	Kappa	MCC
Referable DR (95% CI)	0.5	0.92 (0.863, 0.968)	0.85 (0.824, 0.874)	0.82 (0.751, 0.882)	0.96 (0.941, 0.975)	0.53 (0.454, 0.604)	0.58 (0.515, 0.643)

Among 827 consenting participants, 275 (33.2%) were referred by the AI for follow-up: 88 (32.0%) for DR only, 109 (39.6%) for DR and an additional anomaly, 65 (23.6%) for an anomaly only (that is, DR if was detected it was not at a referable level) and 13 (4.73%) had other pathology or reasons (Table 4). Adherence to referrals was highest for those referred for DR (with or without an additional anomaly) at 53.4%. The overall adherence to referral was 45.4% (n=125). (Table 4) Upon examination at the eye hospital, n=110 (88.0%) were confirmed to have a referrable diagnosis, n=8 (6.4%) were diagnosed with mild NPDR and no other eye conditions, and n=7 (5.6%) were diagnosed as normal eyes.

Table 4. Participant Referrable Type by AI and Adherence to Referral.

Referral Outcome	All Referrals	Referrable DR only	Referrable DR + anomaly	Anomaly with non-referrable DR	Other pathology or ungradable image
# Participants	275	88	109	65	13
Adhered with referral, n (%)	125 (45.4%)	47 (53.4%)	55 (50.5%)	22 (33.8%)	1 (7.7%)

Note: Chi-square test p=0.002 indicating significant differences in adherence overall by the four referral types. Pairwise comparison indicates that patients with Referrable DR only and Referrable DR+ anomaly had significantly higher rates of adherence compared to patients referred for anomaly with non-referable DR (p=0.02 and p=0.03, respectively) and other pathology or ungradable images (p=0.003 and p=0.002, respectively).

DISCUSSION

This study demonstrates the feasibility of and high satisfaction with AI-based screening for DR at diabetes clinics in sub-Saharan Africa. DR screening utilizing AI has been successful in other countries including China and Australia;[18-21] however, this is the first clinical study from Africa. Notably, almost two-thirds of respondents reported a preference for AI over human grading, and the very large majority were satisfied with the AI screening process.

Factors that may have contributed to high participant satisfaction include receiving the exam during their diabetes appointment, as opposed to scheduling a separate appointment. The reduction of appointments and travel time, an important barrier to DR screening,[22] was likely of particular importance to rural patients, comprising nearly half the sample. The AI screening model was supported by clinic diabetes specialists and integrated into existing workflows, which is shown to improve delivery of services for patients.[8] Further, no patients refused consent to participate in the study, which could be attributed to their familiarity with the diabetes care provider seeking consent. Low numbers of participants with ungradable images is also a likely factor contributing to patient satisfaction and is attributed to selection of a stationary fundus camera to capture high-quality images.

The low rate of prior recent full eye exams suggests that incorporating eye health screenings into primary care and diabetes appointments could increase adherence to recommended screening schedules.[23] The high proportion of participants worried about their vision and aware of the impact of diabetes on the eye suggests that barriers of access rather than knowledge are particularly important in this setting, underscoring the importance of enhanced convenience delivered by the new model.[24]

The very low requirements for pupillary dilation to obtain images acceptable for AI grading (only 3 participants [0.363%]) is a further indication of the feasibility of this model, and likely contributes to the observed high patient satisfaction and the value of having a good non-mydriatic camera. Avoiding dilation reduces patients' time commitment and enhances convenience by avoiding blurred vision. While internet connectivity has been cited as a challenge for implementing AI screening programs in Africa,[25] no such problems were encountered in the four locations involved in this study, including one center located well

outside of Kigali. Additionally, this model incorporated printed reports for patients, providing an opportunity for health education, an important factor in increasing uptake of DR referral.[24]

Accuracy of the AI system is an important aspect of the feasibility of the screening model. The figures of 92% sensitivity and 85% specificity observed in the current study when comparing AI with the human grader are in accordance with performance reported for programs in Kenya[13] (sensitivity 87%) and Zambia[26] (92.3% sensitivity and 89.0% specificity), the latter of which also utilised images captured by technicians. As a further indication of accuracy, results in the current paper align with those from a recent global meta-analysis of primary care-based DR deep learning screening models (87% sensitivity and 90% specificity).[27] Upon examination at the eye hospital of patients that adhered to the referral, the majority (88.0%) were confirmed to have a referrable diagnosis, with only 6.4% diagnosed with mild NPDR and no other eye conditions and 5.6% diagnosed as normal eyes. While false-positives want to be avoided to minimize unnecessary examinations for both the healthcare system and the patients, meeting with an eye-care professional provided an opportunity for patient education and awareness on the importance of eye health, especially important for those with mild NPDR, which could escalate.

This study specifically incorporated referrals for eye pathology besides DR. This increased the number of referrals by 33%, and enhanced the impact of the program and convenience to patients. To further improve impact, additional strategies will be needed to increase adherence to referral beyond the observed figure of 45%. A randomised controlled trial associated with the current study demonstrated one such strategy: use of AI increased uptake of DR referral services by 30.1%.[28]

A significant strength of the study was its assessment of a currently-available AI tool in a variety of clinical centers in a low-middle income country, an under-studied setting. Limitations must also be acknowledged: when detecting macula anomalies, the AI detects any deviation from the healthy images on which it was trained, whereas human graders review a checklist of features for disease, making it challenging to quantify and compare outcomes. For example, light reflections seen in the macula of younger patients, would be ignored by an experienced human grader as artifacts whereas it would be

flagged as an anomaly by the AI due to the fact it is not expected to be observed in the vast majority of the patients. Future versions of the system will allow the user to differentiate between artifacts and other benign anomalies and those likely to be related to DR. The prevalence of Type 1 diabetes was high, and likely not representative of the population, due to the existence of a free insulin program at one of the participating centers. As discussed above, the adherence to referral was 45%, so the overall true- and false-positive case numbers are unknown. Finally, this study provided DR screening at no additional cost for participants; however, for long-term sustainability, an AI-based DR screening program will need to be integrated into existing national healthcare funding models. Encouragingly, DR screening has been prioritized in the Rwandan National Strategic Plan for Eye Health.[29]

With the projected global rise in diabetes, managing the workload associated with DR screening is an essential pre-requisite for sustainability in under-resourced settings. A key barrier to the implementation of screening programs in LMICs is the low numbers of trained ophthalmologists.[3] Therefore, effective task-shifting to non-ophthalmologists is a necessity.[10] Quinn et al.[30] have suggested that automated technology for DR screening in low-resource settings significantly reduces demand for human graders. Using non-ophthalmologists trained in capturing retinal images, in tandem with AI-supported interpretation for referrals as this study did, will be crucial to improve access to sight-saving screening services in Africa, the global region poised for the greatest rise in the diabetes burden. Additionally, automated DR screening systems have the potential to reduce unnecessary referrals, further contributing enhancing efficiency for both providers and patients. In the current study, DR screening using AI led to accurate referrals from diabetes clinics in Rwanda, and high rates of participant satisfaction. This suggests AI screening for DR is practical and acceptable in this high-need setting.

Ethics Statement

The study was approved by the Rwanda National Health Research Committee (NHRC/2020/PROT/025) and the Rwanda National Ethics Committee (945/RNEC/2020).

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Competing Interests Statement

There are no competing interests for any author.

Contributorship Statement

Conception or design of the work: JN, NJ, GL, DHC, NC, WM

Data collection: JN, NJ, GL, WM

Data analysis and interpretation: NW, JLP, NJ, GL, NC, WM

Drafting the article: NW, JLP, NJ, GL, NC, WM

Critical revision of the article: All

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