Impact of Artificial Intelligence Assessment of Diabetic Retinopathy on Referral Service Uptake in a Low-Resource Setting

The RAIDERS Randomized Trial

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Purpose: This trial was designed to determine if artificial intelligence (AI)-supported diabetic retinopathy (DR) screening improved referral uptake in Rwanda.

Design: The Rwanda Artificial Intelligence for Diabetic Retinopathy Screening (RAIDERS) study was an investigator-masked, parallel-group randomized controlled trial.

Participants: Patients ≥ 18 years of age with known diabetes who required referral for DR based on AI interpretation.

Methods: The RAIDERS study screened for DR using retinal imaging with AI interpretation implemented at 4 facilities from March 2021 through July 2021. Eligible participants were assigned randomly (1:1) to immediate feedback of AI grading (intervention) or communication of referral advice after human grading was completed 3 to 5 days after the initial screening (control).

Main Outcome Measures: Difference between study groups in the rate of presentation for referral services within 30 days of being informed of the need for a referral visit.

Results: Of the 823 clinic patients who met inclusion criteria, 275 participants (33.4%) showed positive findings for referable DR based on AI screening and were randomized for inclusion in the trial. Study participants (mean age, 50.7 years; 58.2% women) were randomized to the intervention (n = 136 [49.5%]) or control (n = 139 [50.5%]) groups. No significant intergroup differences were found at baseline, and main outcome data were available for analyses for 100% of participants. Referral adherence was statistically significantly higher in the intervention group (70/136 [51.5%]) versus the control group (55/139 [39.6%]; \( P = 0.048 \)), a 30.1% increase. Older age (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.02–1.05; \( P < 0.0001 \)), male sex (OR, 2.07; 95% CI, 1.22–3.51; \( P = 0.007 \)), rural residence (OR, 1.79; 95% CI, 1.07–3.01; \( P = 0.027 \)), and intervention group (OR, 1.74; 95% CI, 1.05–2.88; \( P = 0.031 \)) were statistically significantly associated with acceptance of referral in multivariate analyses.

Conclusions: Immediate feedback on referral status based on AI-supported screening was associated with statistically significantly higher referral adherence compared with delayed communications of results from human graders. These results provide evidence for an important benefit of AI screening in promoting adherence to prescribed treatment for diabetic eye care in sub-Saharan Africa. Ophthalmology Science 2022;2:100168 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
appointments. Poor adherence to treatment and follow-up recommendations because of financial barriers, travel time, lack of clarity in the referral process, and uncertainty among patients about the treatability of the disease remain a significant barrier to positive clinical outcomes and preventing vision loss in patients with diabetes.

Recent advances in computer-based analysis using artificial intelligence (AI) present a promising opportunity to test and refine automatic grading of diabetic retinal images for screening. Using validated AI algorithms instead of scarce trained specialists could potentially increase the efficiency and accessibility of screening programs. Systematic reviews of deep learning-based algorithms in DR screening have highlighted such advantages as reduction in demands for manpower, cost of screening, and intrgrader and intergrader variability. However, evidence from real-life screening programs is limited, and no evidence exists on community acceptance of the use of AI-supported DR screening.

Studies on the use of AI to screen for DR in Africa report good accuracy of the technology, however, the continent lags in deployment of AI in clinical settings. The present trial, piggybacking on an AI-based DR screening and service-delivery project in Kigali, Rwanda, was designed to assess whether use of Orbis International’s Cybersight AI in diabetes clinics leads to increased patient uptake of DR referral services. Our hypothesis was that adherence to referral services would be higher among patients randomized to receive AI-supported screening with immediate feedback compared with those randomized to receive delayed communication of results until after human grading was completed.

**Methods**

**Study Design and Participants**

The Rwanda Artificial Intelligence for Diabetic Retinopathy Screening (RAIDERS) study was an investigator-masked, parallel-group randomized controlled trial enrolling participants at 4 clinical sites in Rwanda. The study was approved by the Rwanda National Health Research Committee (identifier, NHRC/2020/PROT/025) and the Rwanda National Ethics Committee (identifier, 945/RNEC/2020). All participants provided written informed consent before enrollment. The tenets of the Declaration of Helsinki were followed throughout. The trial was registered on the Pan African Clinical Trial Registry (www.pactr.org; registry number, PACTR202101512465690).

Screening for DR using retinal imaging with AI interpretation was implemented from March 2021 through June 2021 at 4 diabetes clinics in and around Kigali, Rwanda (2 district-level clinics, 1 referral-level clinic, and 1 diabetes association-led clinic). Follow-up at the referral site continued through July 2021. Participants were recruited during routine visits to the diabetologist. The diabetologist or other attending clinician presented the patient information sheet and consent form to all potentially eligible patients before DR screening.

The study inclusion criteria were diagnosis of type 1 or 2 diabetes, ≥ 18 years of age, provision of informed consent, availability of gradable digital retinal images for ≥ 1 eye, willingness and ability to travel to the designated referral clinic, and lack of any current eye treatment or participation in any ongoing study requiring regular appointments for eye care. Additionally, all participants in both study groups were required to have a positive finding of referable DR or other condition requiring referral for additional investigations according to Cybersight AI.

**AI Model**

The model is based on the Inception ResNet version 2 convolutional neural network architecture trained to classify fundus photographs into 1 of 5 categories based on the International Clinical Disease Severity Scale for DR (nonproliferative normal, nonproliferative mild, nonproliferative moderate, nonproliferative severe, and proliferative).

The input to the convolutional neural network is a single (or batch thereof) fundus photograph. Preprocessing includes: (1) removal of black fundus border, if present, and (2) resizing of the image to 448 × 448 pixels with preserved aspect ratio. The output of the model is an L1-normalized vector (i.e., sums to 1), where each element corresponds to 1 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 3 elements of the output vectors.

The model was trained on a total of 90 073 photographs that were quality controlled by ≥ 1 board-certified ophthalmologist. Training was carried out “from scratch” based on randomly initialized weights. To improve generalization to unseen images, data augmentation techniques such as random zoom, flipping, and rotation were applied during training.

Referable DR performance validation carried out based on a balanced hold-out dataset (200 photographs per DR grade for a total of 1000 photographs) and based on an external benchmark dataset resulted in areas under the receiver operating characteristic curve of 96% and 98.5%, respectively.

**Procedures for Imaging and Data Collection**

Participants’ baseline demographic data and clinical characteristics were collected on electronic devices using KoBoToolbox before retinal imaging. After 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, nonstereo, nonmydriatic 45° retinal fundus photographs of each eye (Topcon NW400; Topcon). 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 because of 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.

After imaging was completed, all images, anonymized with a unique patient registration number, were uploaded to Orbis International’s Cybersight AI. 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
receiving the report on the examination (immediately for the intervention group, or after 3 to 5 days for the control group), participants were informed that they could report to the eye clinic on any working day within the next 30 days.

Assessment of Outcomes

The main study outcome is the difference between study groups in the rate of presentation for recommended referral services within 30 days of being informed of the need for a referral visit. Attendance for eye examination at the eye clinic was recorded on an outcome form by an independent research assistant who was masked to participant study group assignment. The project manager received the completed outcome forms and linked the data to the participant database for each participant. Nonattendance was defined as failure to attend the referral clinic on any occasion within 30 days of being recommended for follow-up. Participants in the control group who could not be successfully contacted by SMS or telephone (n = 5) were still included in the denominator as requiring referral.

Statistical Analysis

Patients with nondeferrible outcomes on images according to the AI were not enrolled in the trial and were excluded from the analyses. Demographic and clinical characteristics are presented stratified by study group according to the principle of intention to treat. Frequencies and percentages for categorical variables and means and standard deviations for continuous variables are presented, stratified by study group. Responses of “I don’t know” regarding awareness of eye care knowledge and beliefs are categorized as negative or incorrect responses. Rates of attendance at the referral clinic visit (main outcome) are described as unadjusted percentages, comparing the 2 study groups using the chi-square test. Univariate and multivariate logistic regression modeling was used to compare the main outcome between study groups and other potential predictors. Variables that were significant in the univariate models were included in the multivariate model if they remained significant (P < 0.05).

Role of the Funding Source

The project was supported by Orbis International and the Association for Research in Vision and Ophthalmology (Roche Award). The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 827 clinic patients with diabetes who gave consent and were screened for DR, 4 did not meet inclusion criteria, specifically the ability to travel. A total of 275 patients (33.4%) met the referral criteria on AI screening and were randomized for inclusion in the trial, with 136 (49.5%) allocated to the intervention group and 139 (50.5%) allocated to the control group. All participants (100%) in each study group received the allocated intervention, and data for the main outcome was available for all (100%) participants (Fig 1).

Baseline demographic data (Table 1) did not differ significantly between study groups. Satisfaction with the screening process was very high in both groups (intervention, 100%; control, 99.3%). A total of 5
participants (3.60%) in the control group could not be contacted by SMS or telephone, but were retained in the analysis as specified pre hoc in the registered protocol. None returned for follow-up.

Adherence with recommended referral examination was significantly higher in the intervention group (70/136 [51.5%]) versus the control group (55/139 [39.6%]; \(P = 0.048\)) in unadjusted analyses (Table 2), representing a 30.1% increase. When adjusted for age, sex, and urban or rural residence, membership in the intervention was significantly associated with acceptance of recommended referral (odds ratio, 1.74; 95% confidence interval, 1.05–2.88; \(P = 0.031\); Table 3). Participants in the AI group also sought treatment at the referral clinic much sooner after receiving referral advice than those in the control group: AI group, 6.6–7.4 days (median, 4.0 days; range, 0–30 days) versus control group, 9.6 ± 5.1 days (median, 8.0 days; range, 3–28 days; \(P < 0.0001\), Wilcoxon rank-sum test).

**Discussion**

Screening programs are a proven, cost-effective model for preventing serious complications resulting from DR, but they are dependent on adherence with referral services to succeed in preventing negative clinical outcomes. Previous studies have reported successful DR screening programs based in primary care and diabetes clinics, and Bellemo et al demonstrated the validity of using AI for DR screening in an underresourced African population. Similar to Liu et al, the current study focused on adherence with screening referral as a crucial step in the practical application of AI-supported DR screening in low-resource settings, yet the RAIDERS study strengthens the evidence because of its randomized clinical trial design. The RAIDERS trial found increased adherence to DR referral services among participants randomized to receive immediate feedback on referral status based on AI-supported screening compared with those randomized to receiving referral advice only after the human grading report was completed.

Data on adherence with follow-up after DR screening in low-resource countries are limited. The adherence rate for the intervention (AI) group in this study (51.5%) is higher than rates reported in traditional screening programs not delivering immediate feedback on need for referral, including a study in the neighboring country of Tanzania (25%), and also in more developed countries, where follow-up rates as low as 45.2% and 36% have been reported. Artificial intelligence-supported screening provides an opportunity for immediate counselling and eye health education for those requiring referral, potentially contributing to increased adherence. Other studies in low-resource settings have reported improved adherence with referral care in response to eye health education.
Provision of an instant report that includes images of the retina may support acceptance of the recommended referral, especially for those who are asymptomatic. Furthermore, in this model, participants who wished to visit the ophthalmologist on the same day as screening could do so, potentially minimizing travel and accounting for the quicker uptake of referral seen in this study, although additional research on factors contributing to increased adherence is needed. The study by Watane et al found that longer recommended intervals for follow-up led

Table 1. Baseline Demographic and Clinical Characteristics by Study Group

| Variable                        | Intervention Group (n = 136) | Control Group (n = 139) |
|---------------------------------|-----------------------------|-------------------------|
| **Demographic**                 |                             |                         |
| Mean age (yrs)                  | 50.1 ± 16.0                 | 51.3 ± 15.9             |
| Female sex                      | 79 (58.1)                   | 81 (58.3)               |
| Educational level               |                             |                         |
| None                            | 25 (18.4)                   | 22 (15.8)               |
| Primary                         | 41 (30.2)                   | 49 (35.2)               |
| Secondary                       | 47 (34.6)                   | 48 (34.5)               |
| Tertiary                        | 23 (16.9)                   | 20 (14.4)               |
| **Socioeconomic status**        |                             |                         |
| Highest                         | 18 (13.2)                   | 14 (10.1)               |
| Medium                          | 99 (72.8)                   | 113 (81.3)              |
| Lowest                          | 4 (2.9)                     | 4 (2.9)                 |
| Unknown                         | 15 (11.0)                   | 8 (5.8)                 |
| **Health insurance**            |                             |                         |
| None                            | 6 (4.4)                     | 6 (4.3)                 |
| Public                          | 117 (86.0)                  | 124 (89.2)              |
| Private                         | 8 (5.9)                     | 4 (2.9)                 |
| Other                           | 5 (3.7)                     | 5 (3.6)                 |
| **Occupation**                  |                             |                         |
| Professional                    | 8 (5.9)                     | 10 (7.2)                |
| Skilled work                    | 31 (22.8)                   | 27 (19.4)               |
| Unskilled work                  | 17 (12.5)                   | 18 (13.0)               |
| Unemployed                      | 71 (52.2)                   | 80 (57.6)               |
| Retired/pensioner               | 9 (6.6)                     | 4 (2.9)                 |
| **Diabetes status**             |                             |                         |
| Type of diabetes                |                             |                         |
| 1                               | 63 (46.3)                   | 56 (40.3)               |
| 2                               | 71 (52.2)                   | 80 (57.6)               |
| Unknown                         | 2 (1.5)                     | 3 (2.2)                 |
| Duration (yrs)                  |                             |                         |
| <5                              | 47 (34.6)                   | 36 (25.9)               |
| 5–10                            | 43 (31.6)                   | 45 (32.4)               |
| >10                             | 46 (33.8)                   | 58 (41.7)               |
| **Blood glucose (mg/dl)**       | 8.97 ± 3.69 (n = 123)       | 10.3 ± 5.01 (n = 120)   |
| **Eye care history and knowledge** |                           |                         |
| Patient reports dilated eye examination in past year | 14 (10.3)       | 23 (16.6)               |
| Aware diabetes can cause eye problems | 121 (89.0)              | 125 (83.4)              |
| Personally knows a blind person | 64 (47.1)                   | 64 (46.4)               |
| Worried about losing sight      | 110 (80.9)                  | 112 (80.6)              |
| **High satisfaction with screening processes** |  |                         |
| Mean distance of home from screening site (km) | 17.2 ± 20.1 | 15.8 ± 18.4 |
| **Residence**                   |                             |                         |
| Urban                           | 79 (58.1)                   | 85 (61.2)               |
| Rural                           | 57 (41.9)                   | 54 (38.8)               |

Data are presented as no. (%) or mean ± standard deviation.

*Status based on official Ubudehe classification that exists for all Rwandans ([https://rwandapedia.rw/hgs/ubudehe/poverty-level-categories](https://rwandapedia.rw/hgs/ubudehe/poverty-level-categories)) and that was reviewed in 2020. Category A is highest, categories B and C are combined into medium, and categories D and E are the lowest. No statistically significant differences exist between the two study groups.

Table 2. Unadjusted Comparison of Primary Outcome between the Intervention and Control Groups

| Referral Outcome                  | Intervention Group (n = 136) | Control Group (n = 139) | P Value |
|-----------------------------------|-----------------------------|-------------------------|---------|
| Adhered with referral, no. (%)    | 70 (51.5)                   | 55 (39.6)               | 0.048   |
| Did not adhere with referral, no. (%) | 66 (48.5)                   | 84 (60.4)               |         |
to increased odds of follow-up nonadherence. We hypothesized that an important reason for lower acceptance of care in the control group would be an inability to contact these participants after they left the clinic, but in fact, nonadherence for this reason was not common. Follow-up rates in the control group (39.6%) were higher than those in the intervention group in Tanzania, potentially because of high insurance coverage rates in Rwanda, which reduced barriers of cost, and the impact of phone reminders to relay the results of the DR screening. Such contact with SMS reminders\(^27\) has been shown to increase adherence with recommended eye care.

Although an increase in the uptake of referral services was observed in the intervention group compared with the control group in the current study, close to half of those undergoing AI screening did not comply with referral care within 30 days. Clearly, other interventions in combination with AI-supported screening are needed to increase adherence further.

Strengths of the study include results that are broadly applicable across AI-supported DR screening models, regardless of the AI platform used. The trial was a randomized design with good fidelity to protocol and high follow-up rates. Additionally, drawing participants from different types of facilities provided data representative of the broader Rwandan health system. Furthermore, the study provides evidence on the practical application of AI-supported DR screening in

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Table 3. Univariate and Multivariate Comparison of Primary Outcome (Referral Adherence)

| Variables                                | Odds Ratio | 95% Confidence Interval | P Value |
|------------------------------------------|------------|-------------------------|---------|
| **Univariate**                           |            |                         |         |
| Intervention group                       | 1.62       | 1.00–2.61               | 0.048   |
| Age, years                               | 1.03       | 1.01–1.05               | 0.0002  |
| Male sex                                 | 1.50       | 0.93–2.43               | 0.099   |
| Educational level                        |            |                         |         |
| None                                     | Reference  |                         |         |
| Primary                                  | 1.41       | 0.69–2.87               | 0.342   |
| Secondary                                | 0.94       | 0.46–1.91               | 0.864   |
| Tertiary                                 | 1.17       | 0.51–2.70               | 0.706   |
| Socioeconomic status                     |            |                         |         |
| Highest                                  | Reference  |                         |         |
| Medium                                   | 1.60       | 0.75–3.45               | 0.225   |
| Lowest                                   | 0.24       | 0.03–2.18               | 0.204   |
| Unknown                                  | 0.89       | 0.29–2.72               | 0.836   |
| Health insurance                         |            |                         |         |
| None                                     | Reference  |                         |         |
| Public                                   | 1.76       | 0.52–6.02               | 0.364   |
| Private                                  | 1.43       | 0.27–7.52               | 0.674   |
| Other                                    | 0.86       | 0.14–5.23               | 0.867   |
| Occupation                               |            |                         |         |
| Professional                             | 0.43       | 0.15–1.28               | 0.129   |
| Skilled work                             | 1.13       | 0.62–2.06               | 0.699   |
| Unskilled work                           | 0.59       | 0.27–1.27               | 0.175   |
| Unemployed                               | Reference  |                         |         |
| Retired/pensioner                        | 1.80       | 0.56–5.76               | 0.320   |
| Type 2 diabetes (type 1 is reference)    | 2.28       | 1.39–3.76               | 0.001   |
| Duration of diabetes (yrs)               |            |                         |         |
| <5                                       | Reference  |                         |         |
| 5–10                                     | 1.10       | 0.60–2.01               | 0.769   |
| >10                                      | 1.50       | 0.84–2.68               | 0.174   |
| Blood glucose (mg/dl)                    | 1.00       | 0.94–1.06               | 0.951   |
| Patient reports dilated eye examination in past year | 0.90 | 0.45–1.81 | 0.772 |
| Aware diabetes can cause eye problems    | 1.20       | 0.55–2.63               | 0.642   |
| Personally knows a blind person          | 0.99       | 0.62–1.59               | 0.965   |
| Worried about losing sight               | 0.92       | 0.50–1.67               | 0.780   |
| High satisfaction with screening processes| Not calculable* | Not calculable* | 0.986 |
| Distance of home from referral site (km) | 1.01       | 1.00–1.03               | 0.081   |
| Rural vs. urban residence                | 1.68       | 1.04–2.74               | 0.036   |
| Multivariate                             |            |                         |         |
| Intervention group                       | 1.73       | 1.04–2.87               | 0.034   |
| Male sex                                 | 2.08       | 1.22–3.54               | 0.007   |
| Age (yrs)                                |            |                         |         |
| >4                                       | 1.02       | 1.02–1.05               | <0.0001 |
| Rural residence                          | 1.77       | 1.05–2.99               | 0.033   |

*Not calculable because of zero cell size in the denominator.
low-resource settings, specifically in Africa, where few trial data on the programmatic impact of AI exist. Key factors that should be considered when thinking about a similar approach in other locations include support from the diabetes care providers to provide time and space for eye screening, the availability and accessibility of an accurate AI system, using a high-quality nonmydriatic camera for imaging acquisition, and ensuring confidence in the system by those presenting it to patients. Acknowledging limitations, the study included a relatively higher proportion of patients from urban areas (60%), meaning that the application of the results to rural settings must be made with caution. Accuracy of the AI platform used has not been validated in a peer-reviewed publication for those of African descent, but the accuracy of the referral was not relevant to the main trial outcome, and overread precautions were implemented. Finally, it was impractical to mask participants, but placebo effects are not of particular concern for the main outcome of this study.

In conclusion, this study demonstrated the potential of AI-supported DR screening to deliver increased uptake of referral services. Results of the RAIDERS trial provide evidence for the integration of AI for DR screening as part of a sustainable national eye care program to prevent DR-related blindness in sub-Saharan Africa. Additional research on methods to further increase adherence with referral services is needed, because early diagnosis and treatment of DR is highly effective in preventing vision loss. Further research on the use of AI-supported DR screening in low- to middle-income countries is also necessary to better understand how to integrate this technology into efficient DR care systems in low-resource settings.

**Footnotes and Disclosures**

Originally received: December 25, 2021.
Final revision: April 21, 2022.
Accepted: April 25, 2022.
Available online: April 30, 2022. Manuscript no. XOPS-D-21-00250

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Disclosure(s):
All authors have completed and submitted the ICMJE disclosures form.
The author(s) have made the following disclosure(s): W.M.: Employee — Orbis International
N.W.: Employee — Orbis International
G.L.: Employee — Orbis International
M.Y.K.: Royalties — New World Medical, SpyGlass Pharma
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Supported by Orbis International, New York, New York; and Association for Research in Vision and Ophthalmology (Roche Award).

**HUMAN SUBJECTS:** Human subjects were included in this study. The human ethics committees at the Rwanda National Health Research Committee and the Rwanda National Ethics Committee approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.
No animal subjects were included in this study.

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**Abbreviations and Acronyms:**
AI = artificial intelligence; CI = confidence interval; DR = diabetic retinopathy; OR = odds ratio; RAIDERS = Rwanda Artificial Intelligence for Diabetic Retinopathy Screening; SMS = short message service.

**Keywords:**
Artificial intelligence, Diabetic retinopathy screening, Randomized trial, Referral uptake, Rwanda.

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