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Automated Diabetic Retinopathy Image Assessment Software

Diagnostic Accuracy and Cost-Effectiveness Compared with Human Graders

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Objective: With the increasing prevalence of diabetes, annual screening for diabetic retinopathy (DR) by expert human grading of retinal images is challenging. Automated DR image assessment systems (ARIAS) may provide clinically effective and cost-effective detection of retinopathy. We aimed to determine whether ARIAS can be safely introduced into DR screening pathways to replace human graders.

Design: Observational measurement comparison study of human graders following a national screening program for DR versus ARIAS.

Participants: Retinal images from 20 258 consecutive patients attending routine annual diabetic eye screening between June 1, 2012, and November 4, 2013.

Methods: Retinal images were manually graded following a standard national protocol for DR screening and were processed by 3 ARIAS: iGradingM, Retmarker, and EyeArt. Discrepancies between manual grades and ARIAS results were sent to a reading center for arbitration.

Main Outcome Measures: Screening performance (sensitivity, false-positive rate) and diagnostic accuracy (95% confidence intervals of screening-performance measures) were determined. Economic analysis estimated the cost per appropriate screening outcome.

Results: Sensitivity point estimates (95% confidence intervals) of the ARIAS were as follows: EyeArt 94.7% (94.2%−95.2%) for any retinopathy, 93.8% (92.9%−94.6%) for referable retinopathy (human graded as either ungradable, maculopathy, preproliferative, or proliferative), 99.6% (97.0%−99.9%) for proliferative retinopathy; Retmarker 73.0% (72.0 %−74.0%) for any retinopathy, 85.0% (83.6%−86.2%) for referable retinopathy, 97.9% (94.9%−99.1%) for proliferative retinopathy. iGradingM classified all images as either having disease or being ungradable. EyeArt and Retmarker saved costs compared with manual grading both as a replacement for initial human grading and as a filter prior to primary human grading, although the latter approach was less cost-effective.

Conclusions: Retmarker and EyeArt systems achieved acceptable sensitivity for referable retinopathy when compared with that of human graders and had sufficient specificity to make them cost-effective alternatives to manual grading alone. ARIAS have the potential to reduce costs in developed-world health care economies and to aid delivery of DR screening in developing or remote health care settings. *Ophthalmology 2016;■:1−9 © 2016 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/).*

Patients with diabetes are at risk of developing retinal microvascular complications that can cause vision loss, and indeed, diabetes is the leading cause of incident blindness among the working-age population. Early detection through regular surveillance by clinical examination or grading of retinal photographs is essential if sight-threatening retinopathy is to be identified in time to prevent vision loss.[1−4] Annual screening of the retina is recommended but presents a huge challenge, given that the global prevalence of diabetes was estimated to be 9% among adults in 2014.[5] The delivery of diabetic screening will become more problematic as the number of people with diabetic retinopathy (DR) is expected to increase threefold in the United States by 2050[6,7] and to double in the developing world by 2030, particularly in Asia, the Middle East, and Latin America.[8]

National screening programs for DR, including that of the UK National Health Service Diabetic Eye Screening Programme (NHS DESP),[9] are effective; however, they are also labor and capital intensive, requiring trained human graders. Similar teleretinal imaging programs have been

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started in the United States, including at the Veterans Health Administration and elsewhere.[10,11]

Computer processing of medical images, including ophthalmic images, has benefited from advances in processing power, the availability of large data sets, and new image-processing techniques, which means many hitherto difficult challenges associated with their wider application are now tractable. For instance, automated retinal image analysis systems (ARIAS) allow the detection of DR without the need for a human grader. A number of groups have reported success in the use of their ARIAS for the detection of DR.[12–14] These systems triage those who have sight-threatening DR or other retinal abnormalities, from those at low risk of progression to sight-threatening retinopathy. However, whereas the diagnostic accuracy of some of these computer detection systems has been reported to be comparable to that of expert graders, the independent validity of ARIAS results and clinical applicability of different commercially available ARIAS to "real-life" screening have not been evaluated.

These image analysis systems are not currently authorized for use in the NHS DESP, and their cost-effectiveness is not known. Moreover, their applicability to US health care settings is yet to be realized. There is a need for independent validation of $\geq$1 of the ARIAS to meet the global challenge of DR screening.

This study examines the screening performance of ARIAS and the health economic implications of replacing human graders with ARIAS at the UK's National Health Service or using an ARIAS as a filter prior to manual grading.[15]

Methods

Study Design and Participants

The main aim of the study was to quantify the screening performance and diagnostic accuracy of ARIAS, using NHS DESP manual grading as the reference standard.[15] The study design has been previously described,[15] and the protocol was published online.[16]

Retinal images were obtained from consecutive patients with a diagnosis of diabetes mellitus who attended their annual visit at the diabetes eye-screening program of the Homerton University Hospital, London, between June 1, 2012, and November 4, 2013.[17,18] Two photographic image fields were taken of each eye, 1 centered on the optic disc and the other on the macula, in accordance with NHS DESP protocol.[17] During the delivery of the screening service, patients previously screened at the Homerton University Hospital and known to be photographically ungradable underwent slit-lamp biomicroscopy in the clinic. This was part of the routine screening pathway set by the Homerton University Hospital. Because these patients have no photographic images, they could not be included in our study. Otherwise, all other patients who underwent routine retinal photography as part of the screening program, even if images were of poor quality or classified as *ungradable* by the human graders, were included in the data set.

Research Governance approval was obtained. Images were pseudonymized, and no change in the clinical pathway occurred.

Automated Retinal Image Analyses Systems

Automated systems for DR detection with a Conformité Européenne (CE) mark obtained or applied for within 6 months of the start of this study (July 2013) were eligible for evaluation. Three software systems were identified from a literature search and discussions with experts in the field, and all 3 met the CE mark standards: iGradingM (version 1.1; Medalytix/EMIS Health, Leeds, UK),[19] Retmarker (version 0.8.2. 2014/02/10 by Retmarker Ltd [formerly Critical Health], Coimbra, Portugal), and IDx-DR (IDx, Iowa City, IA).[14] IDx, Medalytix, and Critical-Health agreed to participate in the study. IDx later withdrew, citing commercial reasons. An additional company, Eyenuk Inc (Woodland Hills, CA), with software EyeArt, contacted us in 2013 to join the study and undertook the process required to meet the CE mark eligibility criterion.

All the automated systems are designed to identify cases of DR that is mild nonproliferative (R1) or above. EyeArt is additionally designed to identify cases requiring referral to ophthalmology (DR that is ungradable or above). A test set of 2500 images also from the Homerton screening program (but not the same patients) was provided to the vendors to optimize their file handling processes, to address the fact that in practice, screening programs often capture more than the 2 requisite image fields per eye and include nonretinal images (e.g., images of crystalline lens or cataracts) that need to be identified. During the study period ARIAS vendors had no access to their systems and all processing was undertaken by the research team.

Reference Standards

All screening episodes were manually graded following NHS DESP guidelines. Each ARIAS processed all screening episodes. The study was designed not to establish the screening performance of human graders,[20–22] but to compare the automated systems with outcomes from clinical practice. The screening performance of each automated system was assessed using a reference standard consisting of the final human grade modified by arbitration, by an internationally recognized fundus photographic reading center (Doheny Image Reading Center, Los Angeles, CA). Arbitration was carried out on a subset of disagreements between the final manual grade and the grades assigned by the ARIAS, without knowledge of the assigned grade. All discrepancies with final human grades for proliferative retinopathy (R3), preproliferative retinopathy (R2), or maculopathy (M1) were sent to the reading center for arbitration. A random sample of 1224 screening episodes (including 6000 images) for which 2 or more systems disagreed with the final human grade of mild nonproliferative (R1) or no retinopathy (R0) was also sent for arbitration.

Reader Experience

The Homerton diabetes eye-screening program has a stable grading team of 18 full-time and part-time optometrists and nonoptometrist graders holding appropriate accreditation for their designation within the program. Performance against national standards is reviewed and reported quarterly at board meetings. In addition, the program has been quality assured externally by the NHS DESP. Primary and secondary graders both meet minimum requisite standards to grade retinopathy and are continuously monitored to maintain quality assurance.[23] In the current screening pathway,[24] all retinal images are reviewed by a primary grader (level 1 grader), and any patients with mild or worse retinopathy or maculopathy are reviewed by an additional grader (secondary grader; level 2 grader), with discrepancies between the primary and secondary grader reviewed by an arbitration grader (level 3 grader).

Sample-size Calculations

A pilot study of 1340 patient-screening episodes revealed that the prevalence of no retinopathy (R0), mild nonproliferative (R1; approximately equal to Early Treatment Diabetic Retinopathy Study

level 20−43), maculopathy (M1), preproliferative (R2; Early Treatment Diabetic Retinopathy Study level >43), and proliferative retinopathy (R3)[18] was 68%, 24%, 6.1%, 1.2%, and 0.5%, respectively. One of the ARIAS (iGradingM) was compared with manual grading as the reference standard. The sensitivity for mild nonproliferative (R1), maculopathy (M1), preproliferative (R2), and proliferative (R3) was 82%, 91%, 100%, and 100%, respectively, and 44% of R0 cases were graded as *disease present*. The number of unique patient-screening episodes (not repeat screens) undertaken in a 12-month period at the Homerton University Hospital was 20 258. The pilot data suggested that this sample size would provide sufficient R3 events to estimate sensitivity with an acceptable level of precision of 95% confidence intervals (CIs) for sensitivity ranging from 80% to 95% for each grade (and combination of grades) of retinopathy.[15] All manual grades of screened patients were stored and accessed using the Digital Healthcare OptoMize system version 3.6 (Digital Healthcare, Cambridge, UK).

Statistical Analysis

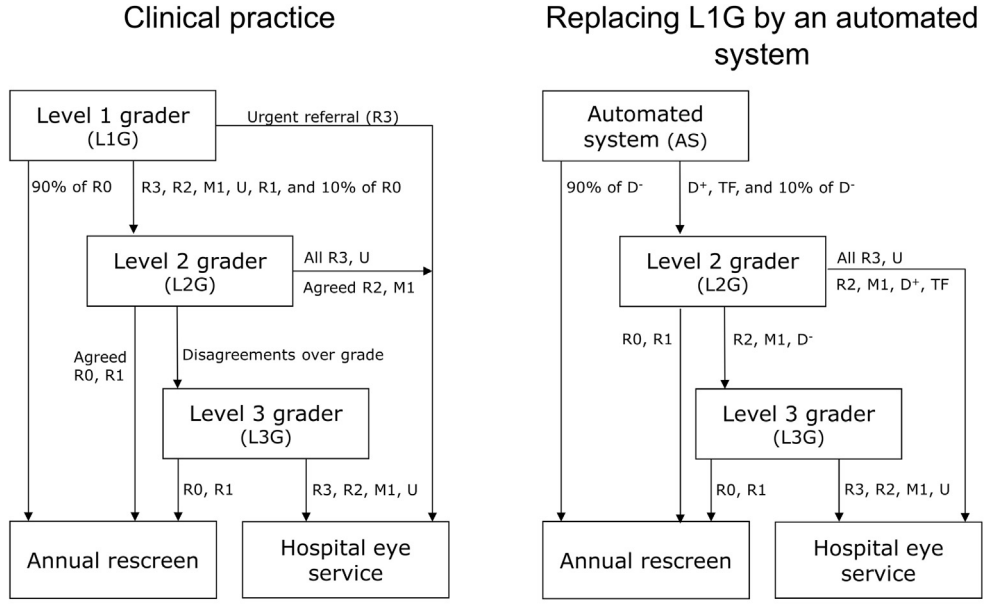
Screening performance (sensitivity, false-positive rates) and diagnostic accuracy of ARIAS (95% CI of screening-performance measures) were quantified using the final manual grade with arbitration by the reading center as the reference standard for each grade of retinopathy, as well as combinations of grades. The diagnostic accuracy of all screening-performance measures was defined by 95% CI obtained by bootstrapping. Secondary analyses used multivariable logistic regression to explore whether camera type and patients' age, gender, and ethnicity influenced the ARIAS output.

Health Economic Analysis

A decision-tree model was used to calculate the incremental cost-effectiveness of replacing initial grading undertaken by human graders (level 1 graders) with an ARIAS (Fig 1, Strategy 1) and of using an ARIAS prior to manual grading (Fig 2, Strategy 2). The decision tree was designed to reflect patient-screening pathways, shown in Figures 1 and 2,[25] and incorporated the screening levels through which images were processed (levels 1, 2, and 3 human graders) as well as grading outcomes (e.g., referral to ophthalmology/hospital eye services or rescreening as part of the annual screening program).

The health economic model used the following data: (1) the probabilities associated with the likelihood of a patient image continuing down each step of the retinopathy-grading pathway shown in Figures 1 and 2, (2) the overall likelihood of correct outcome classification of each screening strategy (true positives and true negatives correctly identified), and (3) bottom-up costing of manual screening strategies and cost analysis of ARIAS via interviews and analysis estimates. The model therefore took into account the screening performance of automated systems (sensitivity and false-positive rates), the efficacy of manual screening, the likelihood of rescreening, and referral rates to ophthalmologists. For the ARIAS, an *appropriate outcome* was defined as (1) identification of *disease* present by the ARIAS when the reference human grade indicated the presence of potentially sight-threatening retinopathy or technical failure (including grades M1, R2, R3, and U); (2) identification of *no disease* by the ARIAS when the reference human grade indicated absence of retinopathy or background retinopathy only (grades R0, R1; resulting in annual rescreening).

The model focused on assessing the relative performance of potential screening strategies and did not incorporate quality- or time-related elements. Probability parameters were modeled on the basis of Homerton hospital screening data for manual-grading performance. ARIAS performance was mapped onto tentative implementation protocols for automated screening software in the National Health Service screening program for DR (Figs 1 and 2).



D- = disease absent classification by automated system
D+ = disease present classification by automated system
TF = technical failure
R0 No retinopathy; M0 no maculopathy; R1 background retinopathy;
U ungradable images; M1 maculopathy; R2 pre-proliferative retinopathy;
R3 proliferative retinopathy (R3) [17;18]

Figure 1. Decision-tree model used to calculate the incremental cost-effectiveness of manual grading versus replacing initial grading undertaken by human graders (level 1 graders) with automated retinal image analysis system.

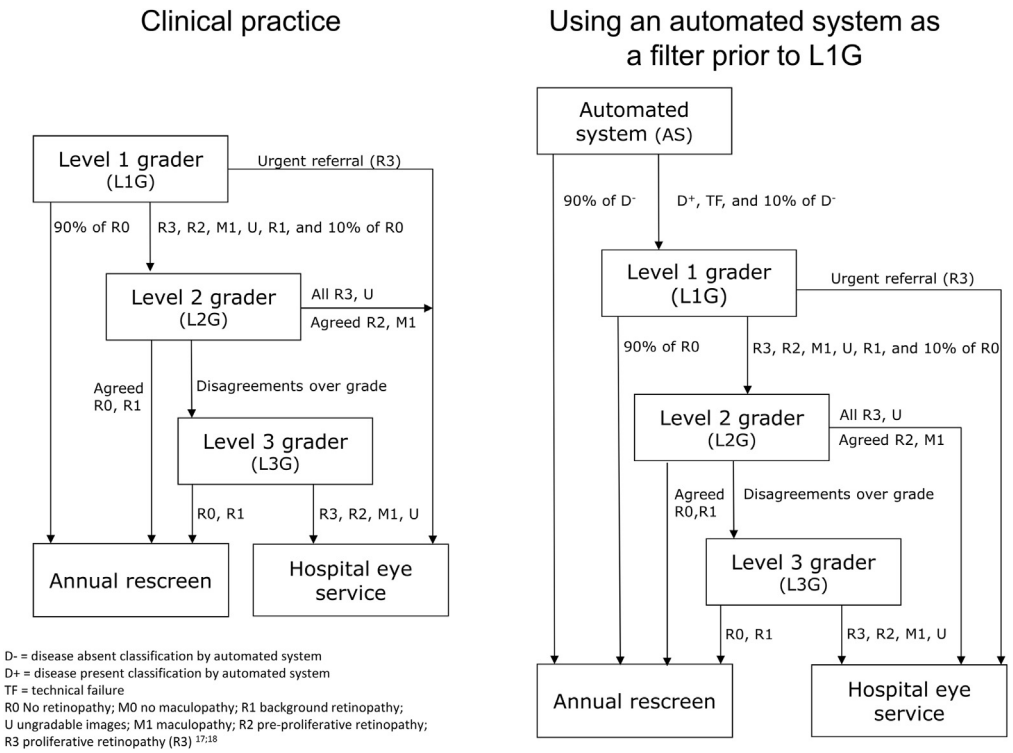


Figure 2. Decision-tree model used to calculate the incremental cost-effectiveness of manual grading versus replacing initial grading undertaken by human graders (level 1 graders) with automated retinal image analysis system prior to manual grading.

Fixed and variable screening cost data were obtained through a survey of the local study center, National Health Service National Tariffs, hospital cost data, phone/e-mail conversations with automated screening system manufacturers, the existing literature, and expert opinion. All costs were standardized to UK pounds sterling for 2013–2014 and, where appropriate, inflated using the 2014 Personal Social Services Research Unit costs, hospital and community health services pay, and prices index.[26] Screening center full-time equivalent staff costs and productivity (i.e., grading rate per hour) were used to derive unit costs per screened patient across the entire screened population. Recurrent costs (e.g., capital costs, periodic charges on technologies) were discounted to reflect opportunity costs over the life span of investment. Medical capital equipment and hospital capital charges, including overhead charges for utilities and floor space, were discounted at 3.5% per annum over the expected lifespan of the equipment or the ARIAS. All discounted charges were annualized and incorporated into the model in terms of per-patient costs. Costing results were converted into US dollar equivalents using yearly average exchange rates for 2014 from the Internal Revenue Service.[27]

Costing information regarding technological adoption was sought directly from manufacturers, as the systems are not yet available to the English National Health Service. This yielded system costs for manufacturers that were framed as an estimated cost for screening per patient image set and included similar components in this estimate. Pricing would be contingent on the number of patients for a given guaranteed contracted volume, which has major price implications. Hence, the base case estimates used reflect the size of the screening program for which we have manual screening data. We present models for EyeArt and Retmarker that incorporate cost information gathered from manufacturers using a universal ARIAS cost-per-image set as a base case figure. Costing elements of automated screening included software purchase, licensing, user training, server upgrades, and software installation and integration.[28,29] We undertook extensive deterministic and threshold sensitivity analysis to examine the impact of these pricing figures on results, because there are many uncertainties related to costing a system that have not yet been implemented in the health service.

Results

Figure 3 shows the degree of data completeness for manual grades. Data from 20 258 consecutive screening episodes (102 856 images) were included in the analysis. Data available for each episode included a unique anonymized patient identifier; episode screening date; patient age, gender, and ethnicity; image file names associated with each screening episode; camera type used; retinopathy grade; maculopathy grade; and associated assessment of image quality for each eye from the grader who assessed the image. The median age was 60 years (range, 10–98 years), with 37% of patients >65 years of age. The main ethnic groups were white (41%), Asian (35%), and black (20%). Table 1 shows the ARIAS outcome classifications for EyeArt and Retmarker, using the worst eye manual retinopathy grade refined by arbitration as the reference standard. The sensitivity (detection rates) point estimates and 95% CIs of the ARIAS are presented in Table 2. For EyeArt, sensitivity for any retinopathy (defined as manual grades of mild nonproliferative [R1], preproliferative [R2], proliferative [R3], maculopathy [M1], and ungradable [U] combined) was 94.7% (95% CI 94.2%–95.2%), 93.8% (95% CI 92.9%–94.6%) for referable retinopathy (defined as manual grades, preproliferative

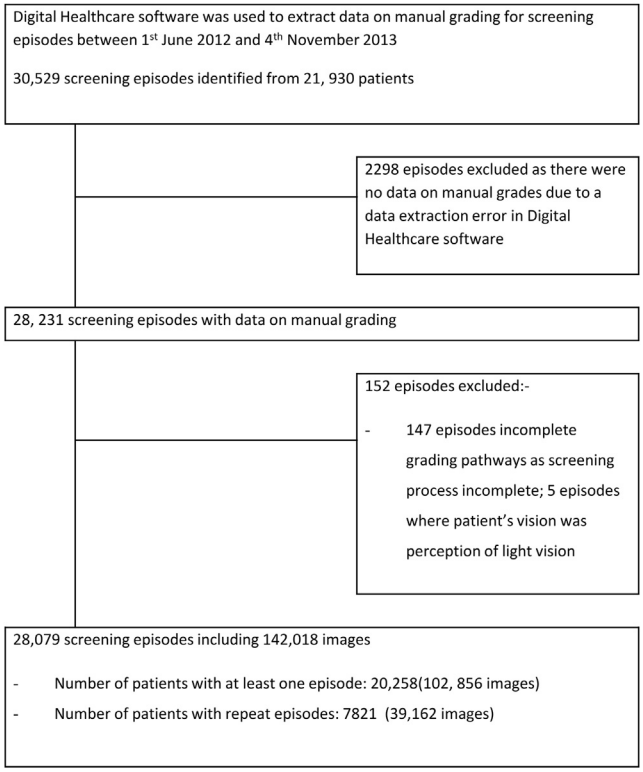


Figure 3. Data extraction of patients with diabetes attending the Homerton diabetic eye-screening program.

[R2], proliferative [R3], maculopathy [M1], and ungradable combined), and 99.6% (95% CI 97.0%−99.9%) for proliferative disease (R3). The corresponding results for Retmarker (Table 2) were 73.0% (95% CI 72.0%−74.0%) for any retinopathy, 85.0% (95% CI 83.6%−86.2%) for referable retinopathy, and 97.9% (95% CI 94.9%−99.1%) for proliferative retinopathy (R3). This means that of 100 screening episodes with referable retinopathy, 94 would be correctly classified as *disease* by EyeArt and 6 would be incorrectly classified as *no disease* (false negatives), whereas for Retmaker, 85 would be correctly classified as *disease* and 15 would be incorrectly classified as *no disease*. The false-positive rate for EyeArt was 80.1% for retinopathy graded R0M0, meaning that of 100 screening episodes without any retinopathy, 80 would be incorrectly classified as *disease* and the remaining 20 would be correctly classified as *no disease* (specificity of 20%). The corresponding false-positive rate for Retmarker is lower, at 47.7% (specificity of 52.3%).

Unfortunately, iGradingM classified all screening episodes as *disease* or *ungradable*; hence, although the sensitivities were 100%, the false-positive rate was also 100%. Examination of a subset of images showed that the software was unable to process disc-centered images. Sensitivity and false-positive rates for EyeArt were not affected by ethnicity, gender, or camera type, but there was weak evidence of a marginal decline in sensitivity with increasing patient's age. Retmarker performance seemed to be marginally influenced by patient's age, ethnicity, and camera type.

Because of the performance of the iGradingM ARIAS, health economic analysis was undertaken for EyeArt and Retmarker only. This study explored the cost-effectiveness of EyeArt and Retmarker ARIAS using 2 different strategies versus manual grading: replacing initial manual grading (level 1 graders) with ARIAS (strategy 1), or using ARIAS as a filter prior to manual grading (strategy 2).

Table 3 shows the costs of screening patients in our sample under either strategy 1 or strategy 2 and using either EyeArt or Retmarker. The results for both software systems were similar in that the ARIAS were both cheaper but also less likely to correctly identify the presence or absence of disease than the current manual grading system. Although the misclassification of R0 and R1 as *disease* was relatively high for the ARIAS (Tables 1 and 2), the proportion of potentially sight-threatening retinopathy correctly identified was

Table 1. Outcome Classification of EyeArt and Retmarker Automated Retinal Image Analysis Systems Compared with Manual Grade Modified by Arbitration

Manual Grade (Worse Eye)	No. of Screening Episodes (Column %)	EyeArt Outcome (Row %)		Retmarker Outcome (Row %)	
		No Disease	*Disease*	*No Disease*	*Disease*
Retinopathy grade					
R0M0	12 796 (63%)	2542 (20%)	10 254 (80%)	6730 (53%)	6066 (47%)
R1M0	4618 (23%)	217 (5%)	4401 (95%)	1585 (34%)	3033 (66%)
U	427 (2%)	98 (23%)	329 (77%)	194 (45%)	233 (55%)
R1M1	1558 (8%)	73 (5%)	1485 (95%)	207 (13%)	1351 (87%)
R2	626 (3%)	4 (1%)	622 (99%)	22 (4%)	604 (96%)
R2M0	193 (1%)	3 (2%)	190 (98%)	5 (3%)	188 (97%)
R2M1	433 (2%)	1 (0%)	432 (100%)	17 (4%)	416 (96%)
R3	233 (1%)	1 (0%)	232 (100%)	5 (2%)	228 (98%)
R3M0	71 (0.4%)	0 (0%)	71 (100%)	1 (1%)	70 (99%)
R3M1	162 (1%)	1 (1%)	161 (99%)	4 (2%)	158 (98%)
Combination of grades					
R0M0, R1M0	17 414 (86%)	2759 (16%)	14 655 (84%)	8315 (48%)	9099 (52%)
U, R1M1, R2, R3	2844 (14%)	176 (6%)	2668 (94%)	428 (15%)	2416 (85%)
R1M0, U, R1M1, R2, R3	7462 (37%)	393 (5%)	7069 (95%)	2013 (27%)	5449 (73%)
Total	**20 258 (100%)**	**2935**	**17 323**	**8743**	**11 515**

M0 = no maculopathy; M1 = maculopathy; R0 = no retinopathy; R1 = background retinopathy; R2 = preproliferative retinopathy; R3 = proliferative retinopathy; U = ungradable images.[17,18]

Table 2. Sensitivity and False-Positive Rates (%) for EyeArt and Retmaker Automated Retinal Image Analysis Systems Compared with Manual Grade Modified by Arbitration

Manual Grade (Worse Eye)	Classified by ARIAS as Disease Present, % (95% Confidence Interval)	
	EyeArt	*Retmarker*
Retinopathy grade		
R0M0*	80.1 (79.4–80.8)	47.7 (46.5–48.3)
R1M0	95.3 (94.7–95.9)	65.7 (64.3–67.0)
U	77.0 (72.8–80.8)	54.6 (49.8–59.2)
R1M1	95.3 (94.1–96.3)	86.7 (84.9–88.3)
R2	99.4 (98.3–99.8)	96.5 (94.7–97.7)
R2M0	98.4 (95.3–99.5)	97.4 (93.9–98.9)
R2M1	99.8 (98.4–100)	96.1 (93.8–97.5)
R3	99.6 (97.0–99.9)	97.9 (94.9–99.1)
R3M0	100	98.6 (90.7–99.8)
R3M1	99.4 (95.8–99.9)	97.5 (93.6–99.1)
Combination of grades		
R0M0, R1M0	84.2 (83.6–84.7)	52.2 (51.5–53.0)
U, R1M1, R2, R3	93.8 (92.9–94.6)	85.0 (83.6–86.2)
R1M0, U, R1M1, R2, R3	94.7 (94.2–95.2)	73.0 (72.0–74.0)

M0 = no maculopathy; M1 = maculopathy; R0 = no retinopathy; R1 = background retinopathy; R2 = preproliferative retinopathy; R3 = proliferative retinopathy; U = ungradable images.[17,18]
*For manual grades R0M0, classified as *disease present* by the automated retinal image analysis systems, the percentages correspond with false-positive rates.

93.8% for EyeArt and 85% for Retmarker. In this sample of 20 258 patients screened, with 2844 cases of potentially sight-threatening retinopathy, 2668 cases were correctly classified by EyeArt and 2416 cases by Retmarker. The proportion of these 2844 cases missed was therefore 6% (176 cases) for EyeArt and 15% (428 cases) for Retmarker. Reassuringly, for the most severe retinopathy grade (R3, proliferative retinopathy), all cases received the appropriate classification via EyeArt and 98.6% via Retmarker. Because the incremental cost-effectiveness ratio (ICER) lies in the southwest quadrant of a cost-effectiveness plane (intervention being less costly and less effective than the status quo), we have to think carefully about interpretation. Here, a lower ICER means that the intervention is less cost-effective.[30] For both Retmarker and EyeArt, strategy 1 provides more cost savings per appropriate outcomes missed than strategy 2 does. With strategy 2, ICER results for Retmarker still lie in the southwest quadrant. However, in comparison with strategy 1, there would be lower cost savings per appropriate outcome missed, at $15.36. The effectiveness measures of strategies 1 and 2 for the same software system were nearly identical. This outcome likely reflects the fact that the presence of a level 1 grader has no bearing on the disease classification given to patient episodes from automated screening systems. The cost implications emerge because patients are more likely to see more graders in strategy 2, and level 1 grader costs per patient are higher than those of level 2 graders, reflecting a proportionally larger share of full-time equivalents dedicated to the screening clinic. The average difference in cost in the *no disease* arm between strategy 1 and strategy 2 for Retmarker was $0.38 per patient and in the *disease* arm $2.33. Therefore, the biggest cost difference comes for those patients who were more likely to see a higher number of human graders when the automated screening system acts as a filter rather than a replacement.

Of key importance to our findings was the cost of automated screening. We undertook 1-way sensitivity analysis to check the robustness of our findings to 50% changes in ARIAS pricing. When used as a replacement for level 1 grading (strategy 1), both ARIAS saved costs relative to manual grading but offered lower effectiveness (appropriate identification of disease status in patient episodes). However, although both ARIAS are deemed less effective overall than human graders, this was due to oversensitivity, and the ARIAS very rarely missed any preproliferative/proliferative retinopathy or maculopathy with mild grades of retinopathy. When used as a filter prior to level 1 grading (strategy 2), thus reducing the volume of level

Table 3. Base Case Results for 20 258 Patients

Screening Strategy and ARIAS	Total Cost of Grading	Incremental Cost	Appropriate Outcomes	Incremental Appropriate Outcomes	Cost Reduction per Appropriate Outcome Missed (ICER)*
EyeArt					
Strategy 1†					
MG	$795 164.60	–	19 684	–	–
ARIAS	$693 344.48	$(101 820.13)	5427	14 257	$7.14
Strategy 2‡					
MG	$795 164.60	–	19 684	–	–
ARIAS	$675 138.67	$(63 063.91)	5428	14 256	$4.43
Retmarker					
Strategy 1†					
MG	$795 164.60		19 684		
ARIAS	$627 913.75	$(167 250.85)	10 731	8953	$18.69
Strategy 2‡					
MG	$795 164.60	–	19 684	–	–
ARIAS	$658 012.58	$(137 152.07)	10 760	8923	$15.36

ARIAS = automated diabetic retinopathy image assessment systems; ICER = incremental cost-effectiveness ratio; MG = manual grader.
*If the ARIAS were more costly and more effective the ICER would be stated in terms of cost per appropriate outcome. ICER can also be interpreted as cost savings per appropriate outcome missed.
†Strategy 1 replaces the initial grading (level 1 grader) with ARIAS.
‡In strategy 2, ARIAS is used as a filter prior to manual grading by a level 1 grader.

2 grading episodes, both ARIAS saved fewer costs than if used as a replacement for level 1 graders. Threshold analysis testing was used to identify the highest ARIAS cost per patient before which they become more expensive per appropriate outcome than human grading. For Retmarker, this figure was $6.04 under strategy 1 and $5.19 for strategy 2. For EyeArt, ARIAS pricing above $4.29 and $3.24 per patient would make the system more expensive than manual grading under strategy 1 and strategy 2, respectively.

Discussion

The detection of DR is a complex image-interpretation task and a key step in any successful screening program. We have shown that Retmarker and EyeArt ARIAS achieved acceptable sensitivity for referable retinopathy compared with that of human graders, at a level of specificity that makes them cost-effective alternatives to a purely manual grading of DR. Whereas these 2 ARIAS have good sensitivity, their low specificity makes them less effective in detecting appropriate outcomes overall than manual grading is, but they are less expensive per patient, with these cost results being robust to significant variations in ARIAS pricing. Although both ARIAS are deemed less effective overall than human graders because of excessive sensitivity, they rarely missed any preproliferative/proliferative retinopathy or maculopathy with mild grades of retinopathy (e.g., EyeArt picked up 95% of cases of maculopathy with mild retinopathy [R1M1]). In light of the screening program protocols evaluated, even if an automated screening software is overly sensitive, the patient is likely to achieve the appropriate outcome at the end of his or her acute episode. This is expected to come at a total grading cost that is cheaper regardless of whether a replacement or filter strategy is chosen for implementation of the automated screening system. For implementation into screening pathways, some additional technical issues have to be addressed, including system integration, which this study showed was a problem in a real screening environment.

This study was not designed to look at the accuracy of human graders. In the Scottish Diabetic Retinopathy Screening Programme, which used similar feature-based grading with 1-field photography and a reference standard defined as a consensus grade from the top-level graders, the sensitivity for referable retinopathy for human graders was found to be 91.1% on average. Sensitivity varied by center, from 81.9% (75.2%−87.1%) to 95.0% (91.5%−97.1%). The intergrader agreement for referable retinopathy across all grading episodes was 88.7% (95% CI 88.0%−89.4%).[31] A recent modeling study of a DR screening data set from the United Kingdom showed an estimated 11% of cases would have sight-threatening retinopathy missed by human graders.[32] These findings suggest that similar screening programs using trained human graders have test performance comparable to that of the ARIAS used.

This study, in keeping with the remit of established DR screening programs such as the NHS DESP, was not designed to diagnose non-DR eye disease. However, Retmarker and EyeArt did not miss any vision-threatening non-DR retinal conditions from the subset of images that went to the reading center for arbitration.

As one of the ARIAS processes images using cloud-based technology, governance issues associated with this form of data storage need to be addressed before implementation. Health economic models may be used to evaluate the cost-effectiveness of ARIAS under different circumstances, including in developing-country settings. Additional studies are also required to shed light on the sensitivity of ARIAS software to non-DR eye disease.

The ARIAS shown to be effective in this study have the potential to support the impending challenge of DR screening in developed, as well as developing, countries. China, for instance, faces the challenge of currently having an estimated 92 million patients with diabetes,[33] of which at least 50% receive no retinopathy check.[34,35] In India, even though diabetes is projected to affect over 100 million people by 2035,[36] it may be problematic to deliver screening even with low labor costs. Introducing ARIAS in these settings could help scale eye-screening delivery programs while also reducing the number of manually read images by $\leq$200 million images per year in each country, assuming all patients were screened. If properly implemented, ARIAS may offer the opportunity to widen provision of a needed health service while also freeing resources for other areas in health care. The use of ARIAS, in conjunction with the availability of low-cost retinal digital cameras and information technology infrastructure, may therefore help make the prevention of diabetic-associated blindness a tractable problem.

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References

1. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. *Arch Ophthalmol*. 1985;103(12):1796-1806.
2. Cheung N, Wong IY, Wong TY. Ocular anti-VEGF therapy for diabetic retinopathy: overview of clinical efficacy and evolving applications. *Diabetes Care*. 2014;37(4):900-905.
3. Aiello LP, Gardner TW, King GL, et al. Diabetic retinopathy. *Diabetes Care*. 1998;21(1):143-156.
4. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA*. 2007;298(8):902-916.

5. World Health Organization. Global status report on noncommunicable diseases 2014. http://www.who.int/nmh/publications/ncd-status-report-2014/en. Accessed June 2016.
6. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol*. 2004;122(4):477-485.
7. Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States*; 2011. https://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed June 2016.
8. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(1):4-14.
9. Public Health England. Diabetic eye screening: programme overview. https://www.gov.uk/guidance/diabetic-eye-screening-programme-overview. Accessed June 2016.
10. Murchison AP, Friedman DS, Gower EW, et al. A Multicenter diabetes eye screening study in community settings: study design and methodology. *Ophthalmic Epidemiol*. 2016;23(2):109-115.
11. Kirkizlar E, Serban N, Sisson JA, et al. Evaluation of telemedicine for screening of diabetic retinopathy in the Veterans Health Administration. *Ophthalmology*. 2013;120(12):2604-2610.
12. Abramoff MD, Folk JC, Han DP, et al. Automated analysis of retinal images for detection of referable diabetic retinopathy. *JAMA Ophthalmol*. 2013;131(3):351-357.
13. Soto-Pedre E, Navea A, Millan S, et al. Evaluation of automated image analysis software for the detection of diabetic retinopathy to reduce the ophthalmologists' workload. *Acta Ophthalmol*. 2015;93(1):e52-e56.
14. Goatman K, Charnley A, Webster L, Nussey S. Assessment of automated disease detection in diabetic retinopathy screening using two-field photography. *PLoS One*. 2011;6(12):e27524.
15. Kapetanakis VV, Rudnicka AR, Liew G, et al. A study of whether automated Diabetic Retinopathy Image Assessment could replace manual grading steps in the English National Screening Programme. *J Med Screen*. 2015;22(3):112-118.
16. Tufail A, Egan C, Rudnicka A, et al. Detailed project description: can automated Diabetic Retinopathy Image Assessment Software replace one or more steps of manual imaging grading and is this cost-effective for the English National Screening Programme?. http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0019/81154/PRO-11-21-02.pdf. Accessed June 2016.
17. NHS Diabetic Eye Screening Programme. Diabetic eye screening feature based grading forms: Guidance on standard feature based grading forms to be used in the NHS Diabetic Eye Screening Programme. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/402295/Feature_Based_Grading_Forms_V1_4_1Nov12_SSG.pdf. Accessed June 2016.
18. Taylor D. Diabetic eye screening revised grading definitions: To provide guidance on revised grading definitions for the NHS Diabetic Eye Screening Programme. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/402294/Revised_Grading_Definitions_V1_3_1Nov12_SSG.pdf. Accessed June 2016.
19. Philip S, Fleming AD, Goatman KA, et al. The efficacy of automated "disease/no disease" grading for diabetic retinopathy in a systematic screening programme. *Br J Ophthalmol*. 2007;91(11):1512-1517.
20. Stellingwerf C, Hardus PL, Hooymans JM. Two-field photography can identify patients with vision-threatening diabetic retinopathy: a screening approach in the primary care setting. *Diabetes Care*. 2001;24(12):2086-2090.
21. Taylor R, Broadbent DM, Greenwood R, et al. Mobile retinal screening in Britain. *Diabet Med*. 1998;15(4):344-347.
22. Kinyoun JL, Martin DC, Fujimoto WY, Leonetti DL. Ophthalmoscopy versus fundus photographs for detecting and grading diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 1992;33(6):1888-1893.
23. Taylor D, Widdowson S. The management of grading quality: good practice in the quality assurance of grading. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/512832/The_Management_of_Grading.pdf. Accessed June 2016.
24. NHS Diabetic Eye Screening Programme. Diabetic eye screening pathway overviews: Overview diagrams for patient pathway, grading pathway, surveillance pathways and referral pathways. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/403074/Pathway_Diagrams_V1_2_29Oct12_SSG__1_.pdf. Accessed June 2016.
25. UK National Screening Committee. Essential elements in developing a diabetic retinopathy screening programme. Workbook 4.3. http://rcophth-website.www.premierithosting.com/docs/publications/published-guidelines/ENSPDR_Workbook_2009.pdf. Accessed June 2016.
26. Personal Social Services Research Unit. Unit costs of health and social care 2014. http://www.pssru.ac.uk/project-pages/unit-costs/2014/index.php. Accessed June 2016.
27. Internal Revenue Service. Yearly Average Currency Exchange Rates Translating foreign currency into U.S. dollars. Available from https://www.irs.gov/individuals/international-taxpayers/yearly-average-currency-exchange-rates. Accessed June 2016.
28. Scotland GS, McNamee P, Fleming AD, et al. Costs and consequences of automated algorithms versus manual grading for the detection of referable diabetic retinopathy. *Br J Ophthalmol*. 2010;94(6):712-719.
29. Scotland GS, McNamee P, Philip S, et al. Cost-effectiveness of implementing automated grading within the national screening programme for diabetic retinopathy in Scotland. *Br J Ophthalmol*. 2007;91(11):1518-1523.
30. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-effectiveness Analysis in Healthcare*. Oxford, UK: Oxford University Press; 2011.
31. Goatman KA, Philip S, Fleming AD, et al. External quality assurance for image grading in the Scottish Diabetic Retinopathy Screening Programme. *Diabet Med*. 2012;29(6):776-783.
32. Oke JL, Stratton IM, Aldington SJ, et al. The use of statistical methodology to determine the accuracy of grading within a diabetic retinopathy screening programme. *Diabet Med*. 2016;33(7):896-903.
33. Yang W, Lu J, Weng J, et al. Prevalence of diabetes among men and women in China. *N Engl J Med*. 2010;362(12):1090-1101.
34. Peng J, Zou H, Wang W, et al. Implementation and first-year screening results of an ocular telehealth system for diabetic retinopathy in China. *BMC Health Serv Res*. 2011;11:250.
35. Wu B, Li J, Wu H. Strategies to screen for diabetic retinopathy in Chinese patients with newly diagnosed type 2 diabetes: a cost-effectiveness analysis. *Medicine (Baltimore)*. 2015;94(45):e1989.
36. Guariguata L, Whiting DR, Hambleton I, et al. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*. 2014;103(2):137-149.

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Abbreviations and Acronyms:
ARIAS = automated diabetic retinopathy image assessment system; **CE** = Conformité Européenne; **CI** = confidence interval; **DR** = diabetic retinopathy; **ICER** = incremental cost-effectiveness ratio; **M0** = no maculopathy; **M1** = maculopathy; **NHS DESP** = National Health Service Diabetic Eye Screening Programme; **R0** = no retinopathy; **R1** = background retinopathy; **R2** = preproliferative retinopathy; **R3** = proliferative retinopathy; **U** = ungradable images.

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