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Validation of artificial intelligence algorithm LuxIA for screening of diabetic retinopathy from a single 45° retinal colour fundus images: the CARDS study

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ABSTRACT

Objective This study validated the artificial intelligence (AI)-based algorithm LuxIA for screening more-than-mild diabetic retinopathy (mtmDR) from a single 45° colour fundus image of patients with diabetes mellitus (DM, type 1 or type 2) in Spain. Secondary objectives included validating LuxIA according to the International Clinical Diabetic Retinopathy (ICDR) classification and comparing its performance between different devices.

Methods In this multicentre, cross-sectional study, retinal colour fundus images of adults (≥18 years) with DM were collected from five hospitals in Spain (December 2021–December 2022). 45° colour fundus photographs were captured using non-mydriatic Topcon and ZEISS cameras. The Discovery platform (RetinAI) was used to collect images. LuxIA output was an ordinal score (1–5), indicating a classification as mtmDR based on an ICDR severity score.

Results 945 patients with DM were included; the mean (SD) age was 64.6 (13.5) years. The LuxIA algorithm detected mtmDR with a sensitivity and specificity of 97.1% and 94.8%, respectively. The area under the receiver-operating characteristic curve was 0.96, indicating a high test accuracy. The 95% CI data for overall accuracy (94.8% to 95.6%), sensitivity (96.8% to 98.2%) and specificity (94.3% to 95.1%) indicated robust estimations by LuxIA, which maintained a concordance of classification (N=829, kappa=0.837, p=0.001) when used to classify Topcon images. LuxIA validation on ZEISS-obtained images demonstrated high accuracy (90.6%), specificity (92.3%) and lower sensitivity (83.3%) as compared with Topcon-obtained images.

Conclusions AI algorithms such as LuxIA are increasing testing feasibility for healthcare professionals in DR screening. This study validates the real-world utility of LuxIA for mtmDR screening.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Diabetic retinopathy (DR) is one of the most common microvascular complications associated with diabetes mellitus (DM) (in any of its modalities, either type 1 or type 2), and its global burden is projected to reach approximately 160.5 million patients by 2045.

⇒ There has been increasing interest in developing and substantiating automated analysis using deep learning or artificial intelligence-based algorithms (LuxIA) for the analysis of retinal images in patients with DR.

WHAT THIS STUDY ADDS

⇒ As demonstrated in our study, the validated LuxIA has good performance when screening DR in patients with DM and is proposed as an accessible and affordable tool for use in clinical settings in Europe and other extrapolatable populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementation of this algorithm may promote timely screening of DR and, therefore, would contribute to decreasing the risk of vision loss and blindness in patients with DM through more timely treatment.

INTRODUCTION

Diabetes mellitus (DM) is a major public health challenge,[1] and as per the International Diabetes Federation (IDF), the number of patients with DM is projected to reach around 783 million globally by 2045.[2] Diabetic retinopathy (DR) is one of the most common microvascular complications associated with DM[3] and the fifth-leading cause of preventable blindness in the elderly (age ≥50 years).[4] The global prevalence of DR was

estimated at 22.3% in 2020, accounting for 103.12 million adults (age ≥20 years).[5] Of these, 28.5 million adults had severe non-proliferative DR (NPDR) and proliferative DR (PDR).[5] Due to the rapidly ageing population and increasing lifespan, DR will continually increase the healthcare burden worldwide. In fact, by 2045, the number of affected patients is projected to reach approximately 160.5 million.[5]

In Spain, the prevalence of DM according to the IDF (in 2021) was estimated at 10.3%, and the rate of DR in the context of DM (in 2022) was 15.3%.[6] Early detection and timely treatment, along with systemic management of DM, are important measures to reduce rates of DR and associated vision impairment.[7] Even so, only a small fraction of patients with DM attend DR screening clinics (19%), and only 60% undergo yearly eye examinations.[8] These numbers are concerning since one of the main factors contributing to the development of DR is a lack of early diagnosis.[9]

Traditionally, colour fundus photography has been used to screen DR; however, this technology relies on a skilled grader.[10] In recent years, several successful alternative methods such as telemedicine have been developed for the screening of DR to respond to the increasing demand for diabetic care and to complement standard in-office eye examinations.[11] These methods have demonstrated an increase in screening of DR and did not require referral to eye specialists.[11] Additionally, these methods have been shown to achieve pooled sensitivity and specificity exceeding 80% and 90% for DR, respectively.[12] In addition to telemedicine, one such advanced method is artificial intelligence (AI)-based automated retinal imaging analysis, which has demonstrated high screening performance and greater sensitivity and specificity in screening the more-than-mild DR (mtmDR) when compared with reading centres.[13]

Hence, there has been an increasing interest in developing and substantiating automated analysis using AI algorithms for the analysis of retinal images in patients with diabetes. Nevertheless, some concerns have been raised when using AI-based technology, including bias in data collection and analysis, as well as generalisability in terms of populations, different algorithms and devices, among others.[14] For these reasons, additional clinical studies are required to assess the performance of this novel method in an unbiased way and to better characterise its clinical benefits. The current study (MultiCentre Study to valiDate an Artificial intelligence algorithm for screening of diabetic Retinopathy-CARDS) validated the clinical performance of a new AI-based algorithm (LuxIA) to screen mtmDR in adult patients with diabetes.

MATERIALS AND METHODS

Study objectives

The primary objective of the CARDS study was to evaluate the performance of LuxIA[15] in screening patients for mtmDR. The screening was performed on Topcon retinal colour fundus images of patients with DM in routine clinical settings in Spain, using retina specialists' manual grading as a reference standard. The secondary objectives of this study were (1) to measure the robustness of LuxIA performance; (2) to validate LuxIA on Topcon images according to five DR severity classifications: no apparent DR, mild NPDR, moderate NPDR, severe NPDR and PDR; (3) to evaluate the generalisability of LuxIA by validating it using images from ZEISS devices and to compare LuxIA scoring (in units and in the five DR severity classification) obtained using Topcon and ZEISS images and (4) to describe sociodemographic and clinical characteristics of the patients according to DR classification.

More information about the development of the LuxIA algorithm to detect DR from a single fundus image was previously published.[15]

Ground truth

Operators performed the first image quality check before manually uploading the images to the RetinAI Discovery platform (RetinAI Medical AG, Bern, Switzerland). A second image quality check was performed by a retinal specialist with proven experience in the diagnosis and management of DR to ensure the images were of high-enough quality to be used in the study. All images that passed the image quality checks were graded based on the DR international severity classification.[16] Three retina specialists with proven experience in the diagnosis and management of DR from three university hospitals in Spain independently evaluated the images in the RetinAI Discovery platform and classified the image according to the 1–5 score (online supplemental table 1). During this process, the algorithm was not used, and the graders were blinded to the algorithm assessment and to the demographic data attached to the patient. The ground truth used in the validation process corresponded to the mean of the ratings provided by the three experts. Electronic case report forms were used to collect patient data, image quality information and DR grades. Data collection workflow is summarised in online supplemental figure 1.

Study design and patient population

A multicentre, cross-sectional, observational study was conducted to assess the capacity of LuxIA to identify DR in retinal colour fundus images from adults (aged ≥18 years old) with DM. In this real-world study, patient data were recorded from routine clinical practice of five Spanish university hospitals during December 2021–December 2022. Among these five university hospitals, patients were equally distributed. Both primary care settings and tertiary referral centres were included in the study, as the centres evaluated images taken in the primary care settings related to the site. Patients with DR primary care settings were referred by general physicians or ophthalmologists to retinologists in tertiary referral centres. Patients with a diagnosis of DM (in any of its modalities, either type 1 or type 2) that accomplished one of the five DR severity classifications (no apparent DR, NPDR, mild

Table 1 Baseline characteristics of patients in total sample and DR severity groups

Characteristics	Total (N=945)*	DR severity classified by retina specialists (n=830)†				
		No apparent DR N=620	Mild NPDR N=69	Moderate NPDR N=113	Severe NPDR N=19	PDR N=9
Study centre‡						
Centre 1, n (%)	185 (19.6)	140 (22.6)	12 (17.4)	5 (4.4)	1 (5.3)	0 (0)
Centre 2, n (%)	177 (18.7)	124 (20)	8 (11.6)	21 (18.6)	2 (10.5)	4 (44.4)
Centre 3, n (%)	200 (21.2)	116 (18.7)	22 (31.9)	21 (18.6)	8 (42.1)	4 (44.4)
Centre 4, n (%)	186 (19.7)	119 (19.2)	12 (17.4)	31 (27.4)	3 (15.8)	0 (0)
Centre 5, n (%)	197 (20.8)	121 (19.5)	15 (21.7)	35 (31)	5 (26.3)	1 (11.1)
Age, years						
Mean (SD)	64.6 (13.5)	64.7 (13.3)	60.7 (15.0)	65.2 (13.1)	64.1 (9.5)	51.4 (18.2)
Median	67	67	63	67	64	49
n valid§	937	615	68	112	19	9
Gender						
Male, n (%)	508 (55.0)	322 (52.4)	31 (47)	75 (66.4)	13 (68.4)	6 (75)
n valid§	924	615	66	113	19	8
Ethnicity						
Caucasian, n (%)	874 (92.5)	573 (92.4)	65 (94.2)	101 (89.4)	18 (94.7)	8 (88.9)
Mixed, n (%)	35 (3.7)	23 (3.7)	4 (5.8)	6 (5.3)	1 (5.3)	0 (0)
Black/African/Caribbean, n (%)	7 (0.7)	4 (0.6)	0 (0)	2 (1.8)	0 (0)	0 (0)
Asian, n (%)	4 (0.4)	4 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Other, n (%)	25 (2.6)	16 (2.6)	0 (0)	4 (3.5)	0 (0)	1 (11.1)
n valid§	945	620	69	113	19	9
Smoker status						
Non-smoker, n (%)	597 (63.2)	387 (62.4)	44 (63.8)	67 (59.3)	14 (73.7)	6 (66.7)
Former smoker, n (%)	220 (23.3)	149 (24)	18 (26.1)	26 (23)	3 (15.8)	2 (22.2)
Smoker, most or all days, n (%)	115 (12.2)	74 (11.9)	7 (10.1)	17 (15)	2 (10.5)	1 (11.1)
Smoker, occasionally, n (%)	7 (0.7)	6 (1)	0 (0)	1 (0.9)	0 (0)	0 (0)
Do not answer, n (%)	6 (0.6)	4 (0.6)	0 (0)	2 (1.8)	0 (0)	0 (0)
n valid§	945	620	69	113	19	9
BMI, kg/m^2						
Mean (SD)	28.6 (5.4)	29.1 (5.8)	28.1 (5.0)	27.6 (4.5)	26.9 (2.9)	28.5 (6.8)
Median	27.9	28.1	27.1	27	26.1	26.4
n valid§	566	384	38	62	9	6
Fasting HbA1c, %						
Mean (SD)	7.3 (2.5)	7.2 (2.9)	7.7 (0.8)	8.1 (1.5)	7.8 (1.3)	8.9 (2.4)
Median	6.9	6.7	7.7	7.9	8	8
n valid§	362	251	23	31	5	5
HDL cholesterol, mg/dL						
Mean (SD)	51.0 (14.8)	51.6 (13.1)	45.7 (13.0)	51.5 (27.5)	48.0 (7.0)	42.8 (17.2)
Median	49	49	45	43	48	48
n valid§	341	235	19	31	5	5
Use of phakic lenses						
Yes, n (%)	667 (70.7)	467 (75.3)	43 (62.3)	72 (64.3)	9 (47.4)	7 (77.8)
n valid§	944	620	69	112	19	9

Continued

Table 1 Continued

Characteristics	Total (N=945)*	DR severity classified by retina specialists (n=830)†				
		No apparent DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
		N=620	N=69	N=113	N=19	N=9
First DR screening						
Yes, n (%)	212 (22.5)	146 (23.5)	14 (20.3)	15 (13.4)	3 (15.8)	5 (55.6)
n valid§	944	620	69	112	19	9

*Number of patients with any sociodemographic and clinical information.
†Total of patients with a DR score.
‡N valid corresponds to number of images not number of patients. A total of 115 patients did not have DR scores: 70 because DR scores were missing and 45 because there was no consensus regarding DR scores among the specialists.
§Patients with valid DR score in Topcon images.
BMI, body mass index; DR, diabetic retinopathy; HbA_{1c}, haemoglobin A_{1c}; HDL, high-density lipoprotein; NPDR, non-progressive diabetic retinopathy; PDR, progressive diabetic retinopathy.

NPDR, moderate NPDR, severe NPDR, PDR) and had a pupil diameter ≥3 mm to ensure minimal image quality were included. The detailed patient selection criteria are presented in online supplemental figure 2. When both eyes were suitable for the study, only one was randomly selected by the principal investigator of the site.

Data collection

All images had a quality assessment. For each patient, a single 45° retinal colour fundus image centred on the fovea was captured from the target eye using a commercially available CE-certified non-mydriatic Topcon camera (NW200, NW400 or equivalent) and, when available, a ZEISS camera was used to acquire an image from the same patient. Each image was acquired by a camera operator according to the advanced algorithm (IADR) imaging protocol and underwent image quality assessment by a retinal specialist. Camera operators had previous professional experience in ophthalmic photography or were specially trained for this study purpose. The fundus images were collected at a single routine visit, along with the sociodemographic and clinical characteristics, which were checked for quality by a retinal specialist and recorded on the RetinAI Discovery platform. The output of LuxIA was an ordinal score from 1 to 5. The final score used in the validation process corresponded to the mean ratings provided by the three independent retina specialists based on the international DR grading guidelines. During this process, the algorithm was not used, and the graders were blinded to the algorithm assessment and to the demographic data attached to the patient.

Sample size and statistical analysis

The sample size was computed at a per-subject level for statistical significance of sensitivity and specificity by applying an exact binomial test, assuming a one-sided, 2.5% type 1 error for both and at least 85% power for sensitivity and 90% power for specificity. The lower bounds for sensitivity and specificity for the whole population and sample proportions were assumed to be 75.0% and 77.5%, respectively, the same as in a previously published AI algorithm study.[17] In this study, a sample size of 900 patients was used for the validation of the AI algorithm.[17] In our study, the ideal sample size was estimated to be 960 patients, assuming a loss of 13.3% of patients due to ungradable images that were to be excluded from the primary analysis. The estimated number of referable subjects (with mtmDR) was 149 (172 before loss) and non-referable subjects (no apparent or mild DR) were 682 (787 before loss).

The analyses were descriptive, and continuous variables were described using means, medians, SDs, 95%

Table 2 Performance of LuxIA in screening mtmDR using Topcon cameras

LuxIA scoring	Ophthalmologists' scoring		Accuracy (%)	Sensitivity (%)	Specificity (%)
	mtmDR	≤mild DR			
	n=140	n=689			
mtmDR, n (%)	TP 136 (16.4)	FP 36 (4.3)	95.2	97.1	94.8
≤mild DR, n (%)	FN 4 (0.5)	TN 653 (78.8)			
n valid*	829				

mtmDR=patients with score equal to 3 or 4 or 5 based on ICDR severity scale. ≤mild DR= patients with score equal to 1 or 2 based on ICDR severity scale.
*Patients with valid DR score in Topcon images.
DR, diabetic retinopathy; FN, false negative; FP, false positive; ICDR, International Clinical Diabetic Retinopathy; LuxIA, artificial intelligence-based algorithm; mtmDR, more-than-mild DR; TN, true negative; TP, true positive.

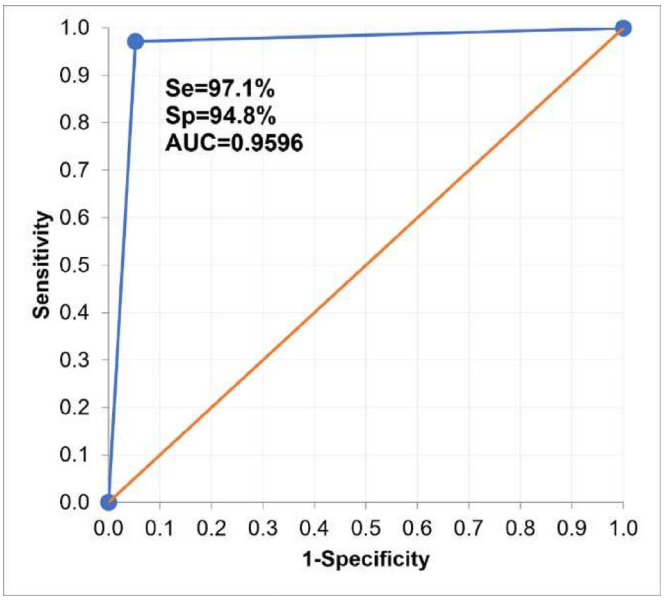

Figure 1 ROC curve. AUC, area under the curve; ROC, receiver operating characteristic; Se, sensitivity; Sp, specificity.

CIs, minimum and maximum values, and IQRs. Categorical variables were described using the number and percentage of patients. All descriptive analyses were performed using Statistical Analysis System (V.9.4 or later for Windows), R (V.4.1.1) and R Studio (V.1.4.1717).

The scores provided by LuxIA were compared with those provided by the experts. The overall accuracy (probability of a patient being correctly classified), sensitivity (probability of the test result being positive when the disease was present) and specificity (probability of the test result being negative when the disease was not present) of LuxIA for the screening of mtmDR were calculated.

The comparison of the accuracy metrics obtained by Topcon and ZEISS cameras was performed using McNemar's χ^2 test for paired data. The robustness of LuxIA was estimated by applying it to 100 randomly selected images and repeating the process 100 times (ie, bootstrapping).

RESULTS

The baseline characteristics of the total number of patients included in the study and across different DR severity classifications are presented in table 1. Of the 945 patients who met the inclusion criteria (online supplemental figure 2), 508 (55%) were male and 597 (63.2%) were non-smokers. The mean age (SD) of the study population was 64.6 (13.5) years. A mean (SD) body mass index of 28.6 (5.4) kg/m^2 indicated overweight, a fasting mean (SD) haemoglobin A_{1c} (HbA_{1c}) level of 7.3% (2.5) indicated DM, and a mean (SD) high-density lipoprotein-cholesterol level of 51.0 (14.8) mg/dL was categorised as low level. The sociodemographic characteristics of the patients were similar across the five DR severity classifications, except for sex, which showed a higher proportion of men in the more severe DR stages. Furthermore, clinical characteristics were similar across all types of DRs, except for HbA_{1c} levels, which were higher in patients with moderate/severe NPDR and PDR. The DR screening performed in the framework of this study was the first one done for more than 22% of the study participants (table 1).

The quality of the images was rated from 1 to 5, 1 being the worst quality and 5 being the best quality. For all the DR cohorts, more than 90% (n=905) of patients had images corresponding to quality 4 (25.8%, n=251) or 5 (67.3%, n=654). In total, 88.6% of images (n=801) showed no quality problems. The most frequent quality issue was image shadowing (5.8%, n=52) (data not shown).

Table 3 Validation of LuxIA in screening mtmDR in randomly selected Topcon images using scoring provided by retina specialists as reference standard

	Confusion matrix						
Ratings made by	TP	FP	FN	TN	Accuracy %	Sensitivity %	Specificity %
LuxIA	mtmDR	mtmDR	≤mild DR	≤mild DR	–	–	–
Retina specialists	mtmDR	≤mild DR	mtmDR	≤mild DR	–	–	–
Descriptors (N=100)							
Mean (SD)	17.0 (3.2)	4.3 (1.7)	0.5 (0.7)	78.2 (3.7)	95.2 (1.8)	97.5 (3.8)	94.7 (2.1)
Median	17.3	4.2	0	77.7	95.3	100	94.8
95% CI	16.4 to 17.6	4.0 to 4.6	0.4 to 0.6	77.5 to 78.9	94.8 to 95.6	96.8 to 98.2	94.3 to 95.1
n valid*	100	100	100	100	100	100	100

mtmDR=patients with score equal to 3 or 4 or 5 based on ICDR severity scale. ≤mild DR= patients with score equal to 1 or 2 based on ICDR severity scale. These outcomes were obtained by applying the algorithm to 100 randomly selected images in 100 iterations using bootstrapping.
*Patients with valid DR score in Topcon images.
DR, diabetic retinopathy; FN, false negative; FP, false positive; ICDR, International Clinical Diabetic Retinopathy; LuxIA, artificial intelligence-based algorithm; mtmDR, more-than-mild DR; TN, true negative; TP, true positive.

Table 4 Performance of LuxIA in classifying images based on ICDR severity scale using Topcon cameras

	Gold standard (retina specialist)					Concordance		
LuxIA predicted score	No DR n (%)	Mild NPDR n (%)	Moderate NPDR n (%)	Severe NPDR n (%)	Proliferative DR n (%)	P value	Kappa	95% CI
No DR	602 (72.6)	17 (2.1)	0 (0)	0 (0)	1 (0.1)	<0.001	0.837	0.805 to 0.869
Mild NPDR	11 (1.3)	23 (2.8)	3 (0.4)	0 (0)	0 (0)			
Moderate NPDR	7 (0.8)	29 (3.5)	102 (12.3)	5 (0.6)	4 (0.5)			
Severe NPDR	0 (0)	0 (0)	7 (0.8)	14 (1.7)	4 (0.5)			
Proliferative DR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)			
n valid*	829							

*Patients with valid DR score in Topcon images.
DR, diabetic retinopathy; ICDR, International Clinical Diabetic Retinopathy; LuxIA, artificial intelligence-based algorithm; NPDR, non-proliferative DR.

Performance of LuxIA on Topcon-obtained images

As described in table 2, LuxIA was demonstrated to be highly accurate (95.2%), sensitive (97.1%) and specific (94.8%) in screening mtmDR on Topcon retinal 45° colour fundus images (n=829) when validated against retina specialists' manual grading as a reference standard. Test accuracy was measured by plotting specificity vs sensitivity, as presented in figure 1. The area under the receiver-operating characteristic curve value was 0.96, suggesting the algorithm was highly accurate.

Robustness of the performance of LuxIA

LuxIA was validated on 100 randomly selected Topcon images per 100 times to assess its robustness. As per validation results, data for the 95% CI for overall accuracy (94.8% to 95.6%), sensitivity (96.8% to 98.2%) and specificity (94.3% to 95.1%) indicated that the algorithm estimations were robust (table 3).

Performance of LuxIA in classifying images based on International Clinical Diabetic Retinopathy severity scale

When classifying retinal fundus images based on a five-point International Clinical Diabetic Retinopathy (ICDR) severity scale using Topcon cameras, LuxIA maintained a concordance of classification (n=829, kappa=0.837, p=0.001). The algorithm was validated against retina specialists' manual grading (table 4).

Validation of LuxIA on ZEISS-obtained images and comparison of LuxIA scoring obtained using Topcon and ZEISS images

The validation of LuxIA on ZEISS-obtained retinal fundus images (n=32) demonstrated high accuracy (90.6%) and specificity (92.3%) (online supplemental table 2). However, the sensitivity of screening mtmDR using the ZEISS camera (83.3%) was lower than that of the Topcon camera (97.1%) (table 2).

When the five DR severity classifications were scored as categorical variables, no significant difference was observed between the classifications made with Topcon and ZEISS images (p>0.05). Similarly, the scores obtained by LuxIA when using the two cameras were not statistically different when expressed as ordinal variables (online supplemental table 3).

DISCUSSION

DR is one of the leading causes of blindness in subjects over 50 years old.[4] However, vision loss from DR can be prevented by well-implemented screening programmes that could lead to timely treatment and increasing public awareness regarding this disease and the importance of retinal screening.[18] Nevertheless, screening increasing numbers of patients with DM[4] is an intensive process and requires extensive resources.[9 19] The effectiveness of AI algorithms has the potential to alleviate the burden of DR screening.[20–23] Specifically in Spain, increased awareness of DR screening using AI and online retinography has improved its prognosis, promoted timely treatment and reduced the economic burden on health services.[17 22 24]

Our study demonstrated that LuxIA was accurate, sensitive and specific in screening mtmDR from a single Topcon-obtained 45° colour fundus image ofc patients with diabetes in clinical settings. This algorithm also maintained a concordance of classification when used to classify Topcon retinal fundus images based on a 5-point ICDR severity scale. Like the Topcon camera, LuxIA was accurate and specific when used to classify ZEISS images; however, it was not as sensitive for ZEISS images as for Topcon images.

Multiple studies have demonstrated the utility of AI algorithms for early diagnosis of DR in Spain and other countries. In 2018, the first AI algorithm was approved by the FDA for use in real-world settings.[20] Similar to our study, they validated their AI algorithm to screen DR in primary care clinics by using a Topcon non-mydriatic retinal camera (NW400).[20] However, their overall accuracy, sensitivity and specificity were much lower than those of LuxIA used in our study. This could be attributed to differences in the characteristics of our patient population (eg, elderly age and most being Caucasian patients). In another study that was validated in Valencia (Spain),

an AI algorithm showed 95%–100% sensitivity and specificity for screening of severe NPDR and PDR, and 100% sensitivity but only 81.8% specificity when identifying mtmDR.[21] Other studies also had several limitations, such as different patient population types,[22] screening less prevalent forms of DR,[22] low performance in terms of both specificity and sensitivity,[25] and not detecting all forms of DR.[23] Contrary to these studies, LuxIA had high accuracy metrics when screening mtmDR, and it also classified the patients according to DR severity. In addition, LuxIA also showed high generalisability since the scoring for ZEISS and Topcon images was similar.

Building on the results of a prior study,[26] LuxIA could enhance patient access to screening and offer reliable testing methods, enabling prompt treatment. Additionally, this algorithm is likely to reduce costs and expedite screening decisions.[27]

Due to the rising prevalence of DM across Europe,[28] including Spain,[28] the rising ageing population,[1] the requirement of early DR diagnosis[29] and limited ophthalmology resources,[9] there is an urgent need for enhanced DR screening. In this context, LuxIA could be a viable option to help healthcare providers undertake DR screening and to support the assessments performed by retinal experts. In addition, LuxIA could be more cost-effective compared with conventional ophthalmologist screenings and reduce the burden on medical or nursing resources, as reported previously.[30–32] Given the need for high-quality images for optimal operation of the algorithm, it would be desirable for future research to incorporate an image quality evaluation that might aid camera operators in determining its usefulness. Future clinical studies should also assess the impact of the algorithm on clinical practice outcomes and the feasibility of implementing it in real-world settings.[33]

The CARDS study was completed using the Discovery platform, a cloud-based platform facilitating distributed data collection and grading, as well as collaboration for ophthalmic data. This enabled the acceleration of the study across multiple clinical sites and review by multiple experts in real-time. By deploying LuxIA with Discovery, it will enable fast sharing of data between consultants and specialists, before the patient has booked a visit, as a step toward telemedicine.

One of the strengths of our study included its prospective design, which allowed us to predefine and standardise study procedures. Second, our study included the patients from five Spanish university hospitals which covered the Spanish population. It is also important to note that although the study was conducted in Spain, the study population can be extrapolated to Europe in terms of prevalence, incidence and future projection.[34] For this reason, and although further studies should be conducted in other countries, our results could help to mtmDR screening in other European primary care centres. Third, our study used two different cameras and hence reinforced the results for LuxIA and showed its high generalisability.

In addition, there were a few limitations that should be considered while interpreting the outcomes. First, this study presented a potential for misdiagnosis during manual rating of less severe DR cases by experts. However, this limitation was mitigated and likely avoided by the inclusion of only retinal specialists as graders. Second, the study had a cross-sectional design, which did not allow the assessment of changes in the study outcomes or the performance test–retest validation. Third, sensitivity with the Topcon camera was higher versus the ZEISS camera. The decreased sensitivity of the ZEISS camera could be attributed to the small sample size used in our study. Additionally, our investigation conducted an evaluation of images' quality, recognising that such an assessment may encounter feasibility constraints within the practical context of clinical applications. This inherent limitation could potentially impact the precision and robustness of the outcomes achieved. Finally, while the type of centres where images were captured could influence the results, this study did not account for their impact. However, no significant differences in DR scoring were observed across the various study centres.

CONCLUSIONS

LuxIA was highly accurate, sensitive and specific in screening DR in Topcon-obtained retinal fundus images from patients with DM (in any of its modalities) in Spain from primary care settings. LuxIA is a readily accessible tool that can provide retinal-specialist-level diagnosis when used as part of a DR screening programme. Implementation of this algorithm may promote the timely screening of DR and, therefore, contribute to decreasing the risk of vision loss and blindness in patients with DM.

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