INVESTIGATING THE USE OF AI-BASED ANALYSES OF FUNDUS IMAGES FOR RETINOPATHY SCREENING AND VASCULAR RISK STRATIFICATION IN PATIENTS WITH DIABETES: AN EXPLORATORY STUDY

Technical Report 1:

Performance of the AI-based system for retinopathy screening

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CONTENTS

EXECUTIVE SUMMARY

Diabetic retinopathy (DR) is one of the leading causes of preventable vision loss globally and represents a major microvascular complication of diabetes mellitus. Early detection through systematic retinal screening is essential to prevent progression to vision-threatening disease. However, conventional ophthalmologic screening pathways are resource-intensive and difficult to scale, particularly in settings where access to specialist eye care is limited. Recent advances in artificial intelligence (AI)-assisted retinal image analysis offer the potential to improve accessibility, standardisation, and cost-effectiveness of DR screening programs.

This report evaluated the first 24 months of implementation of an AI-assisted diabetic retinopathy screening programme conducted through the Retinography Project in Somerset West, South Africa. The programme integrated non-mydriatic fundus photography into routine diabetic care at an endocrinology practice, with retinal images analysed in real time by the EyeArt® AI Eye Screening System. Patients identified as having potentially referable disease were referred for specialist ophthalmologic evaluation. The study also explored the performance of an alternative AI platform, SugarwaveAI®, and conducted a preliminary cost analysis comparing AI-based screening with traditional referral pathways.

A total of 320 diabetic patients underwent screening during the study period, of whom 200 consented to participate in the evaluation. Participants were predominantly middle-aged adults with a high burden of comorbidities including hypertension, obesity, peripheral neuropathy, and kidney disease. Most participants had type 2 diabetes, and glycaemic control was suboptimal in a substantial proportion of the cohort.

The prevalence of referable diabetic retinopathy according to expert ophthalmologic grading was 11.8%, while the prevalence of any diabetic retinopathy was 43.6%. Vision-threatening diabetic retinopathy was identified in 8.7% of participants. Diabetic macular oedema was present in 7% of patients according to expert assessment. Overall image gradability was excellent, with only a small number of retinal photographs deemed ungradable by either the AI system or the ophthalmologist.

The EyeArt® AI system demonstrated excellent screening sensitivity for referable diabetic retinopathy (95.7%) and a high negative predictive value (99.3%), indicating strong performance in ruling out disease. Specificity was lower (84.9%), resulting in some over-referral of patients without referable disease, but this is generally acceptable in a screening context where minimising missed cases is prioritised. Agreement between the AI system and expert ophthalmologic grading ranged from moderate to substantial across different

diagnostic categories. The system performed particularly well in identifying vision-threatening disease.

In comparison, the SugarwaveAI® system demonstrated similarly high sensitivity but substantially lower specificity (46.5%), leading to markedly higher false-positive referral rates. Overdiagnosis was particularly evident among younger patients without diabetic retinopathy. While the system maintained a high negative predictive value, the lower specificity substantially reduced its operational efficiency and increased projected downstream healthcare costs.

The pilot cost analysis suggested that the AI-assisted screening model was consistently more cost-effective than traditional referral-based screening pathways. The AI-based programme identified more cases of diabetic retinopathy while simultaneously reducing the cost per case detected. The benefits were especially pronounced in lower-prevalence settings, where indiscriminate referral of all diabetic patients for specialist screening is economically inefficient. The analysis also demonstrated that screening performance characteristics, particularly specificity, substantially influence downstream healthcare costs.

Overall, the findings support the feasibility and effectiveness of integrating AI-assisted retinal screening into routine diabetes care at the primary or secondary healthcare level. The EyeArt® system demonstrated strong clinical utility as a high-sensitivity triage tool capable of improving access to diabetic retinopathy screening while reducing reliance on specialist ophthalmologic services. The results further highlight the importance of careful validation of AI systems before implementation, as differences in specificity can significantly affect healthcare utilisation and programme costs.

The Retinography Project provides a promising model for scalable diabetic retinopathy screening in South Africa and similar resource-constrained settings. Further research involving larger and more diverse populations, longitudinal follow-up, and real-world implementation outcomes will be valuable to confirm the long-term effectiveness, sustainability, and economic benefits of AI-assisted retinal screening programmes.

INTRODUCTION

Both microvascular and macrovascular disorders –which are different manifestations of the same underlying pathological atherosclerotic mechanism– are common complications of diabetes and primary causes of morbidity and mortality in diabetic patients.[1–3] The frequency of complications[4] and the globally rising number of diabetic people results in an already enormous and rapidly growing societal cost.[5]

A common consequence of microvascular alterations associated with diabetes is retinal damage – Diabetic Retinopathy (DR) and its complication Macular Oedema (DMO) – which is a leading cause of vision loss globally and, in many countries, the most frequent cause of acquired vision loss in middle-aged people.[6–9] A 2012 systematic review and meta-analysis of population-based studies on prevalence and risk factors for DR estimated that 34.6% of diabetic patients have some degree of DR, and more than 10% are afflicted by vision-threatening forms of the disease.[10]

Recommendations for periodic, systematic examination of the interior surface of the eye opposite the lens (*fundus*, which includes the retina, optic disc, macula, fovea, and posterior pole) for detection of microvascular alterations are included in major national and international clinical management guidelines for diabetic patients.[11–14] The recommendations are supported by robust evidence that fundus examination can detect early signs of DR and that various treatments exist (laser treatment, intravitreal injections, and eye surgery, among others) which are effective in preventing progression to severe vision-threatening forms of the disease.[15,16,8] Various techniques are used for this systematic examination, with different levels of sensitivity and specificity, requirements in terms of training of health professionals and cost. The most common techniques include direct and indirect ophthalmoscopy, slit-lamp bio microscopy, mydriatic and nonmydriatic retinal photography, and optical coherence tomography.[17]

In recent years, advances in fundus camera technology and artificial intelligence (AI) diagnostic algorithms have opened new possibilities for implementing low-cost screening programs for the early detection of DR, though automatic interpretation of retinal images obtained with fundus cameras which do not require pharmacologic dilation of the pupil and can be operated by non-specialists. AI deep learning algorithms have achieved excellent diagnostic performance in detecting early stages of DR, with diagnostic accuracy comparable to the grading by retinal specialists.[18] AI screening systems have obtained regulatory approval in many countries, and commercial products are accepted for

reimbursement under the chronic illness benefit for diabetes by private health insurers. AI systems offer substantial benefits for health care by (1) reducing the reliance on specialist work, (2) ensuring homogeneous and adequate performance (in terms of sensitivity and specificity in identifying early stages of diabetic retinopathy), which compare favourably with manual screening performed by non-specialists, (3) reducing the overall cost for the individuals and the health system. AI systems can be deployed at the primary/secondary level of care, increasing accessibility and reducing reliance on healthcare provider engagement and patient compliance with referrals.[19–21]

The retinography project

At the beginning of 2023, the Diabetic Evaluation Clinic (DEC) in the Somerset Eye practice of Dr Eric Falletisch Inc (https://www.somerseteye.co.za/) initiated a project aimed at improving the timeliness and cost-effectiveness of screening for retinopathy among diabetic patients in their catchment area, by modifying the current situation where the DEC acts as the first level of screening for patients referred by their primary care providers or self-referred. While the service has the resources to thoroughly evaluate the diabetic eye, the type of evaluation (an hour-long appointment scheduling, requiring patients to travel to the Clinic) makes it not well suited to mass screening, for reasons of cost and ease of access for patients in different locations.

The *Retinography* project (www.retinography.co.za), aims to implement an integrated screening model, where the DEC (1) supports primary healthcare providers of diabetic patients (physicians, general practitioners) in establishing easily accessible screening facilities for signs of diabetic retinopathy (including providing training to optometrists, general practitioners and other health workers for the correct use of fundus cameras) and (2) provides specialised diagnostic and therapeutic support for those at risk according to the preliminary screening.

Figure 1: The Retinography project logo

For diabetic care facilities with high numbers of patients (such as specialist endocrinology practices), fundus cameras are directly deployed to the facility, while in the case of relatively low diabetic patient load (such as for general practitioners), the facility is associated with a nearby optometrist with the availability of adequate hardware. In both cases, standardised retinal photos taken with the cameras within the practice (or nearby optometrist) are screened in real-time by an AI system and only patients failing the screening are referred to the DEC, which is more appropriately functioning at the secondary level, with only those who fail both primary and secondary screening being referred onto ophthalmology (tertiary level) for treatment. With this approach, screening is more efficiently delegated at the primary eye care level with the AI system standardising the quality of the assessment, and a network of cameras distributed throughout the territory, together with the lower cost of the screening, improving accessibility.

The first phase of the project started in March 2023 with the deployment of a fundus camera (iCare Centervue DRS Plus, https://www.icare-world.com/product/icare-drsplus/) at a specialist endocrinologist practice (https://internalmed.co.za/). Since then, the standard assessment procedure for all new adult diabetic patients attending medical consultation at the practice (and for all old patients who did not have an eye screening in the previous 12 months) includes an AI-based screening administered by the practice nurse, who has undergone training on the use of the fundus camera. The automatic report generated in real-time by the AI system is used for referral for specialist ophthalmologic evaluation and treatment for those failing the screening test. The retinal photographs taken during the assessment are saved in the electronic individual patient folders, together with the assessment report, blood test results and medical history (*Figure 2*).

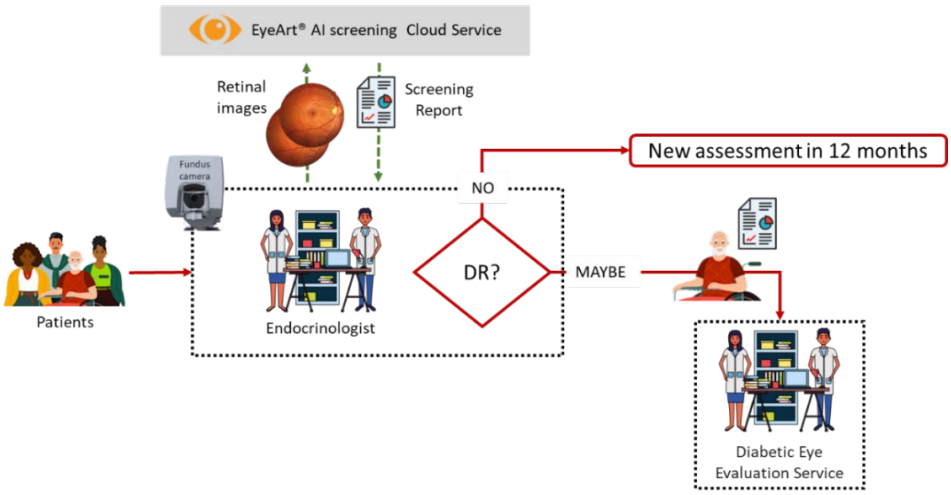


Figure 2: Summary representation of the screening process

The AI system used in the project was the EyeArt® AI Eye Screening System (https://www.eyenuk.com/en/products/eyeart/). The accuracy of the system has been confirmed in numerous studies in various populations.[22–25]

Evaluation

This study aimed to evaluate the results of the screening program for diabetic retinopathy among the patients attending the endocrinologist practice in its first 24 months of implementation, and provide insights for future developments.

METHODS

Population and sample

The target population for this study consists of all adult patients (18 years and over) of the endocrinologist practice with a diagnosis of Diabetes Mellitus (ICD-10 diagnostic codes E10-E11) who underwent AI-based screening for diabetic retinopathy between March 2023 and February 2025.

The sampling took a census approach, and all eligible patients were contacted for participation and enrolled in the study if they consented. Formal eligibility and exclusion criteria were:

Eligibility criteria:

- 18 years and older
- Diagnosis of diabetes mellitus
- Underwent AI-based screening during the study period
- Able and willing to provide informed consent

Exclusion criteria:

- Minor
- Already in the care of an ophthalmologist
- AI-screening carried out outside the study period
- Unwilling or unable (for severe mental illness or disability) to provide informed consent.

Eligible patients were contacted by email by the practice nurse. The email contained (1) a plain language description of the study, its objectives, potential benefits and risks, (2) clarification that participation/non participation in the study had no effect regarding the clinical services received in the practice, (3) the contact numbers/email of the PI for further

information, and (4) the request of consent for extraction of anonymised demographic and clinical data from their electronic folder, including retinal photographs and the AI report. A reply to the email including a signed, scanned copy of the declaration of consent was regarded as a valid expression of consent. Alternatively, the patients were able to express their consent by filling out an online form. No response was followed by a reminder after 2 weeks, and further lack of reply will be considered a refusal.

Data extraction

The practice nurse extracted demographic (age, gender) and clinical characteristics (date of diabetes diagnosis, type of diabetes, general medical history and presence of other chronic diseases) of the consenting patients from their paper folders, and entered the data in an electronic spreadsheet. The spreadsheet did not include any direct identifier of the participants, who were assigned a unique identification code for the purpose of the study.

A locally deployed large language model was used to extract information included in PDF format in the electronic patient folders, namely the results of the AI screening and the laboratory results (blood and urine tests). When multiple series of laboratory results were available, the tests carried out on the date closest to the date of the AI report were considered. The extracted data were manually checked for inconsistencies and corrected when necessary. The extracted results were linked to the demographic and clinical data by means of the study identification code.

The original, high-resolution, retinal images associated with the AI report were extracted and linked to the demographic and clinical data by means of the study identification code. Four images (2 per eye, centred in the optic disc in the macula as per common practice) were available for each patient.

All extraction and anonymisation procedures were carried out in the practice, and only the anonymised datasets (demographic and clinical information, AI screening results, laboratory results and retinal images) were uploaded to protected cloud storage and made available to the investigators for the analyses. The documents linking anonymised unique identifiers with personal information, allowing for the identification of patients (necessary in case of findings requiring referral), were kept at the practice, with the exclusive availability to the PI and clinical supervisor of the study.

Images grading

The anonymised retinal images extracted from the patient folders were sent to a trained ophthalmologist, with no additional information other than the study identification code.

The ophthalmologist graded the images for the presence and severity of DR (absent, mild non-proliferative, moderate non-proliferative, severe non-proliferative and proliferative) and macular oedema (present vs absent) in alignment with the International Clinical Diabetic Retinopathy (ICDR) severity scale,[26] as detailed in *Figure 3* and *Figure 4*.

Following standardised clinical practice, the presence of moderate NPDR, severe NPDR, PDR or DMO in one or both eyes was considered an indication for referral to the specialist ophthalmologist for confirmation of the diagnosis ("Referable DR"). VTDR was defined as the presence of severe NPDR, PDR, or markers for DMO in one or both eyes. "Any DM" included mild, moderate or severe DR, PDR or signs of DMO.

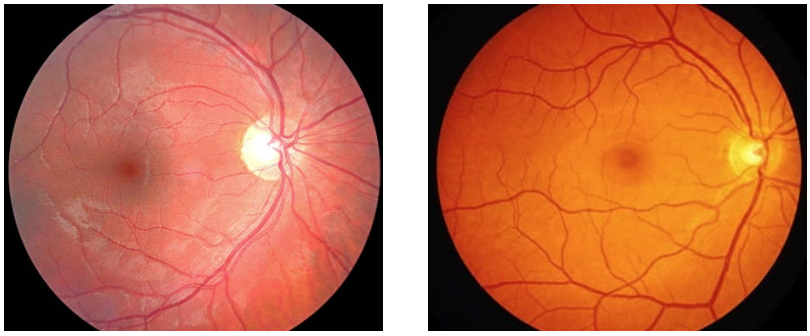
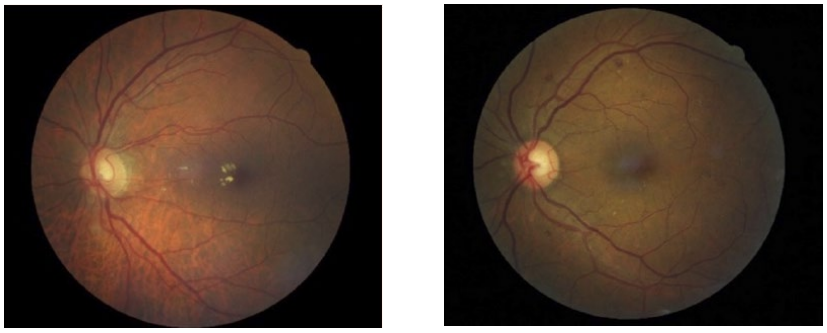
	Oedema	Example retinal images
No oedema (No DMO)	**No DMO** No exudates or apparent retinal thickening within one disc diameter of the fovea	**Normal retina** 
Macular oedema (DMO)	**DMO** Exudates or apparent thickening within 1 disc diameter of the fovea	**DMO** 

Figure 3: ICDR severity scale (macular oedema). Adapted from [29].

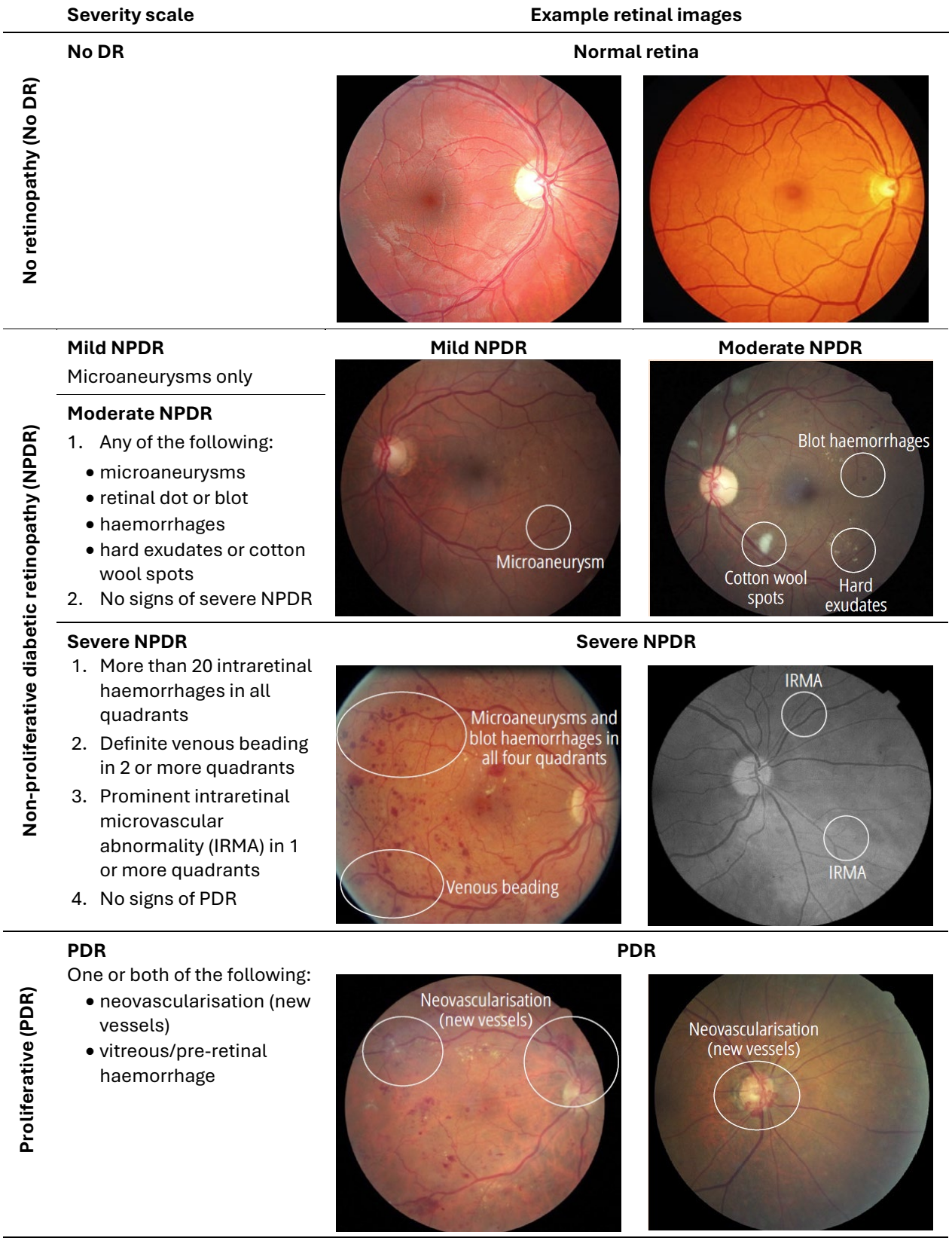


Figure 4: ICDR severity scale (diabetic retinopathy). Adapted from [29].

Alternative AI system

After the conclusion of the data collection windows for the study (March 2023/February 2025), the EyeArt® AI Eye Screening System reimbursed by the medical insurer was superseded in favour of the SugarwaveAI® system (https://sugarwaveai.co.za/). To compare the performances of the two systems, the anonymised retinal images were re-submitted for screening to the new system, and the results of the assessment (in terms of presence/absence of referable DR, as the new system does not provide finer grading of the images) were recorded and associated with the patients' unique identifiers.

Uptake rate

The study nurse contacted the ophthalmologist practice to verify the outcome of the AI referral, in terms of number of referred participants who attended the ophthalmologic evaluation.

Data analysis

The characteristics of the sample were described in terms of median and interquartile range for continuous variables and proportion for categorical variables.

We estimated the distributions of the practice patients (and each patient's eye) across ICDR severity grades according to the AI and the ophthalmologist screening results, and calculated the referral rate as the proportion of referred patients who attended the ophthalmologic evaluation. We tested for the existence of statistically significant differences between the AI and ophthalmological screening using the Spearman's rank correlation coefficient.

After excluding images deemed of inadequate quality either by the EyeArt® system or the ophthalmologist (or both), we used the Cohen Kappa statistic to test the level of agreement between the ophthalmologist and the EyeArt® system in (1) identifying the presence/absence of referable DR, (2) grading the severity of DR according to the ICDR scale. The kappa values – broadly interpretable as a measure of agreement between two graders beyond what is to be expected by chance alone – were qualitative interpreted as per Table 1.[27]

Using the ophtalmologist's evaluation as the gold-standard, we calculated the accuracy parameters of the screening test (sensitivity, specificity, area under the ROC curve, positive and negative likelihood ratios, positive and negative predictive values in the population).[28]

We quantified the uncertainty of the estimates in terms of standard errors and/or 95% confidence intervals, and considered p-values < 0.05 as indication of statistical significance when conducting statistical testing.

We assessed the screening performances (in terms of presence/absence of referable DR) of the SugarwaveAI® system, by calculating the same accuracy parameters as above, and compared the results with those for EyeArt®.

Data analyses were conducted using Stata 17 statistical software (College Station, TX: StataCorp LLC).

Table 1: Interpretation of Cohen's Kappa statistics

Kappa	Level of agreement
0.01-0.2	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
>0.9	Almost perfect

Pilot cost analysis

We conducted a preliminary cost-analysis to compare the costs of the traditional screening program (where the endocrinologist refers diabetic patients for manual screening to an optometrist/ophthalmologist) with the novel AI-based program.

We included in this preliminary analysis only the direct healthcare costs (cost of the manual screening by an ophthalmologist/optometrist, cost of the automatic screening in the endocrinologist practice, calculated as the average reimbursement cost by two major South African health insurers at the time of the study).

With the traditional screening process, all N patients are referred by the endocrinologist for further evaluation, either by a Tier 2 professional (optometrist) or directly to a Tier 3 specialist (ophthalmologist): in the first hypothesis, patients with confirmed retinopathy at Tier 2 are referred to Tier 3. With the AI-based process, the initial screening occurs at Tier 1 (i.e., a non-specialised level from an ophthalmologic point of view), and only a fraction of patients

progress to higher levels. We assume also that no error in the DR diagnosis by either with professional examination (Figure 5).

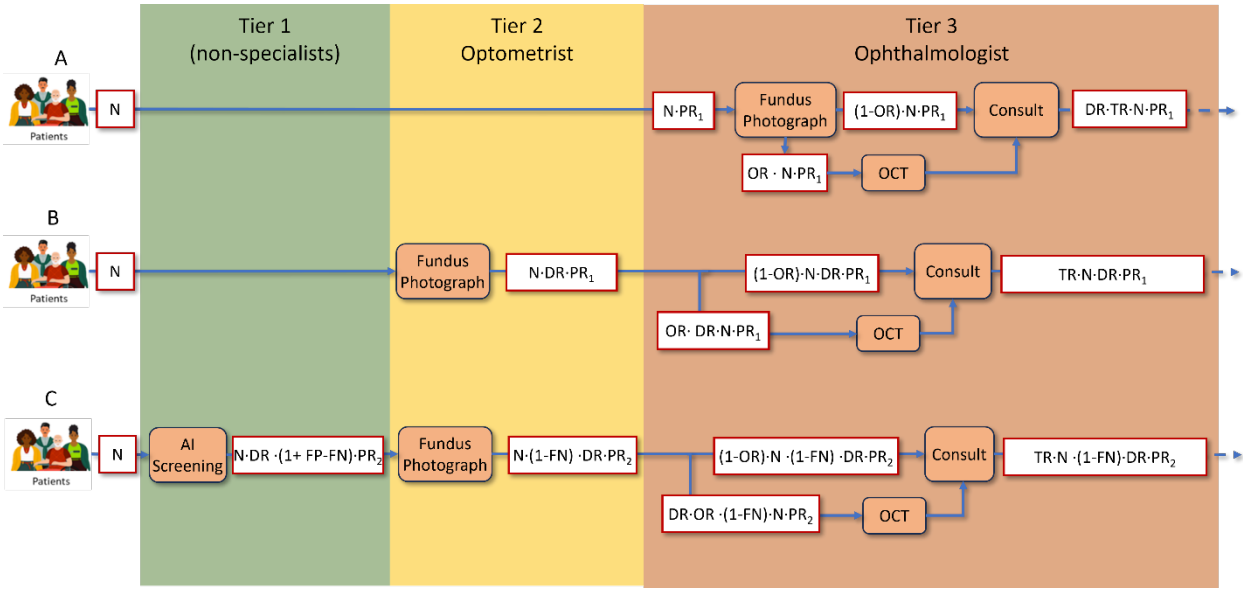


Figure 5: Comparison of the traditional screening processes with the AI-based one

The assumed costs for the procedure in Figure 5 are summarised values of the parameters that we used in the simulations to define the progression between stages are shown in Table 3 and Table 2, respectively.

Table 2: Assumed cost for the medical/screening procedures

	Cost [ZAR]		
Procedure	**Insurer 1**	**Insurer 2**	**Average**
AI Screening	150	150	150
Widefield Fundus Photograph	626.80	527.20	577
OCT	1671.46	1405.60	1539
Ophthalmologist consultation (including standard examinations)	1697.90	1283.1	1490

Table 3: Parameters for the preliminary cost analysis

Par.	Description	Values	Source
DR	True proportion of patients with retinopathy	0.15	Range of hypotheses
		0.25	
		0.35	
FN	False negative rate of the AI screening test	0.043 (0.056) EyeArt	Estimates from the study
		0.043 (0.056) Sugarwave	
FP	False positive rate of the AI screening test	0.151 (0.030) EyeArt	Estimates from the study
		0.535 (0.040) Sugarwave	
PR_1	Baseline screening rate. PR_1 independent of DR status	0.15	Plausible hypotheses for literature
		0.20	
		0.30	
PR_2	Uptake rate, as the proportion of patients screened positive by the AI who attended ophthalmologic evaluation. PR_2 independent of DR status	0.85 (0.025)	Estimates from the study
OR	Proportion of referred patients needing Optical Coherence Tomography (OCT)	0.7 (0.05)	Estimates from ophthalmologist's records
TR	Proportion of patients with confirmed DR who need treatment	0.3 (0.05)	Estimates from ophthalmologist's records

We repeated the calculation for different values of the prevalence of diabetic retinopathy (DR) and the baseline screening rate of the practice patients (PR_1), before the implementation of the new screening program. We used a Montecarlo approach to take into account the uncertainty in the values of the remaining parameters (FN, FP, TP, TR), by repeating the calculation 1000 times, with parameters' values randomly and independently sampled from normal distributions (truncated at 0), with mean and standard deviation indicated in the table, and we reported the 2.5% and 97.5% of the resulting outcome distributions.

Ethics

This study received ethics approval from the South African Medical Research Council Human Research Ethics Committee (Protocol ID: EC019-9/2024). All participants provided informed consent to participate in the study.

RESULTS

Sample characteristics

Of the 320 adult diabetic patients who were screened for diabetic retinopathy in the first 2 years of implementation of the screening program, 200 (63%, 107 males and 93 females) responded to the invitation and provided informed consent to participate in the study. Their demographic and main clinical characteristics are summarised in Table 4.

Table 4: Sample characteristics

Characteristics	**N**	**Females** (N = 90)[1]	**Males** (N = 110)[1]
Demographics			
Age [Years]	200	52 (36, 60)	57 (45, 65)
Age category	200		
<25		6 (6.7%)	5 (4.5%)
25-34		14 (16%)	8 (7.3%)
35-44		17 (19%)	12 (11%)
45-54		16 (18%)	18 (16%)
55-64		23 (26%)	35 (32%)
65-74		9 (10%)	22 (20%)
75+		5 (5.6%)	10 (9.1%)
Diabetes			
Type	200		
Type 2		51 (57%)	84 (76%)
Type 1		36 (40%)	25 (23%)
LADA		3 (3.3%)	1 (0.9%)
Duration [Years]	196		
<5		5 (5.7%)	13 (12%)

Table 4: Sample characteristics

Characteristics	N	Females (N = 90)[1]	Males (N = 110)[1]
[5,10)		34 (39%)	23 (21%)
[10-15)		17 (19%)	22 (20%)
[15-20)		21 (24%)	26 (24%)
20+		11 (13%)	24 (22%)
Comorbidities			
Hypertension	200	59 (66%)	94 (85%)
Peripheral neuropathy	200	14 (16%)	39 (35%)
Kidney disease	200	7 (7.8%)	24 (22%)
Heart disease	200	1 (1.1%)	21 (19%)
Stroke	200	1 (1.1%)	8 (7.3%)
MAFLD	200	4 (4.4%)	0 (0%)
Treatment			
Insulin	200	69 (77%)	65 (59%)
Oral antidiabetic	200	50 (56%)	85 (77%)
GLP-I	200	12 (13%)	19 (17%)
Statins	200	49 (54%)	85 (77%)
Antihypertensives	200	47 (52%)	75 (68%)
Anthropometry & biomarkers			
Body Mass Index [Kg/m^2]	200	29.8 (25.0, 36.0)	29.1 (27.0, 32.0)
BMI Category	200		
Normal weight		20 (22%)	15 (14%)
Overweight		25 (28%)	46 (42%)
Obese I		20 (22%)	30 (27%)
Obese II		12 (13%)	13 (12%)
Obese III		13 (14%)	6 (5.5%)
Systolic Blood Pressure [mmHg]	200	134 (128, 145)	138 (130, 146)
Diastolic Blood Pressure [mmHg]	200	85 (81, 92)	89 (83, 93)
Hb1Ac [%]	200	7.2 (6.5, 8.5)	7.1 (6.3, 7.9)
Hb1Ac < 7%	200	35 (39%)	48 (44%)
Other			
Smoking	199		
Current		4 (4.5%)	13 (12%)

Table 4: Sample characteristics

Characteristics	N	Females (N = 90)[1]	Males (N = 110)[1]
Former		3 (3.4%)	8 (7.3%)
Never		82 (92%)	89 (81%)

[1]Median (first quartile, third quartile); n (%)

LADA = Latent Autoimmune Diabetes in Adults; MAFLD = Metabolic dysfunction-associated fatty liver disease; GLP-I = Glucagon-Like Peptide-1; Hb1Ac = Glycated haemoglobin; BMI = Body Mass Index.

Participants were predominantly males (55%). Age ranged from 19 to 88 years (median 55 years, interquartile range 42 to 63 years). The majority of them were diagnosed with type II diabetes (67%), which was especially frequent among men. Type I diabetes affected 30% of participants, and only 4 had a diagnosis of Latent Autoimmune Diabetes in Adults (LADA).

All participants had some form of comorbidity with other chronic diseases. Hypertension was the most common condition in both genders. Other cardiovascular conditions (heart disease and stroke) were significantly more frequent among men. Peripheral neuropathy and kidney disease were the most reported complications. The large majority of patients were either overweight or obese according to the WHO cutoffs for Body Mass Index,[30] with only 22% of women and 14% of men in the normal weight range. Glycaemic control according to the cutoff commonly used in South Africa (Hb1Ac < 7%) was achieved by 39% of women and 44% of men. Only a minority of participants (8% of women and 21% of men) were current or past smokers.

Image quality and gradability

The EyeArt® system was unable to grade for signs of DR a total of 3 eyes, for inadequate quality of the images. The same images were identified as ungradable by the ophthalmologist, together with 4 additional eyes (belonging to two patients). The images for which the gradability assessment for DR differed between the EyeArt® system and the ophthalmologist are reported in Figure 6.

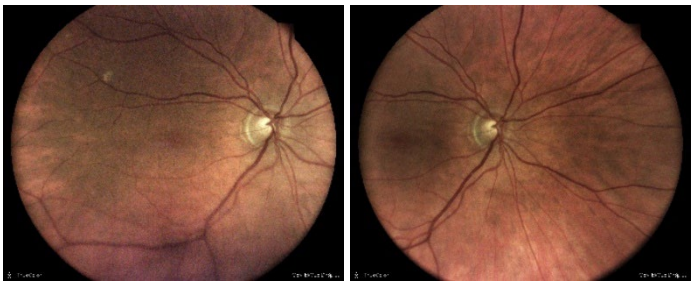
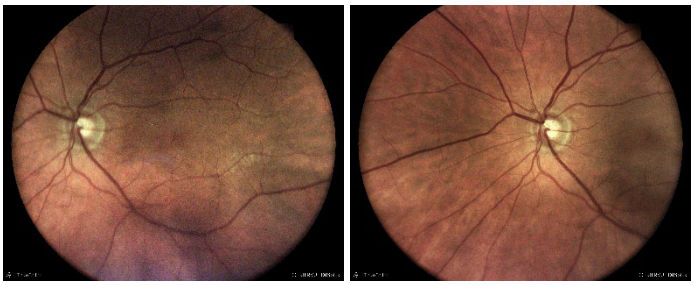
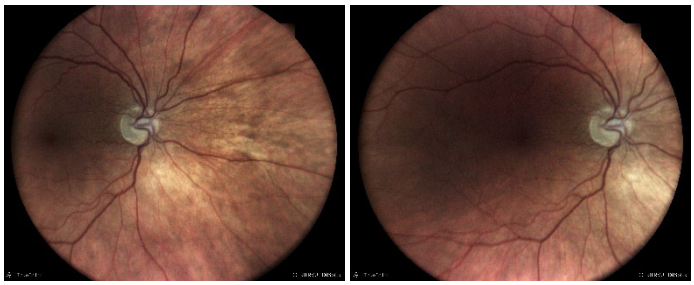
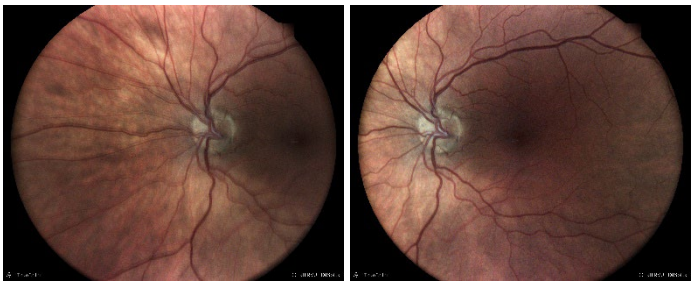
	Eye	Images	Assessment	
			AI	Ophtal.
2	Right		NDR	Ungradable
	Left		Mild NPDR	Ungradable
16	Right		NDR	Ungradable
	Left		NDR	Ungradable

Figure 6: Gradability assessment: AI vs. ophthalmologist

The reason reported by the ophthalmologist for the insufficient quality of the images was a general blurriness of the photographs (potentially due to movement during the exam) and the presence of large shadows that might have masked the presence of microaneurysms.

The 5 patients for whom no complete evaluation by both the EyeArt® system and the ophthalmologist was available (patients 2,16,92,131,184) were excluded from the DR

analyses. As per study protocol, patients 2 and 16 were contacted and referred for further ophthalmologic evaluation. The remaining 3 patients had already been referred, for the presence of referable DR in the gradable eye (patients 92 and 184) and for the inability of the AI to produce a conclusive evaluation (patient 121).

Both the EyeArt® system and the ophthalmologist deemed the images of adequate quality for the assessment of the presence/absence of DMO (absent in both cases). Therefore, the DMO analyses below include all patients.

Diabetic Retinopathy

Table 5 compares manual vs AI grading according to the broad categories of "any DR", "referrable DR" or "vision-threatening DR".

A more detailed grading, according to the 5 ICDR categories is shown in Table 6.

Table 5: Identification of DR

Classification		Manual grading		AI grading	
		N	%	N	%
Any DR	No DR	110	56.4	107	54.9
	Any DR (one eye)	25	12.8	37	19
	Any DR (both eyes)	60	30.8	51	26.1
	Total	195	100	195	100
Referable DR	Not referrable	172	88.2	147	75.4
	Refer (one eye)	5	2.6	20	10.3
	Refer (both eyes)	18	9.2	28	14.4
	Total	195	100	195	100
VTDR	Not vision-threatening	178	91.3	176	90.3
	Vision-threatening DR (one eye)	3	1.5	2	1
	Vision-threatening DR (both eyes)	14	7.2	17	8.7
	Total	195	100	195	100

Table 6: ICDR classification

		Manual grading		AI grading	
Eye	**Classification**	**N**	**%**	**N**	**%**
Right	**No DR**	123	63.1	127	65.1
	Mild NPDR	59	30.2	36	18.5
	Moderate NPDR	10	5.1	28	14.3
	Severe NPDR	3	1.5	6	3.1
	PDR	1	0.5	1	0.5
Left	**No DR**	123	63.1	129	66.1
	Mild NPDR	59	30.2	31	15.9
	Moderate NPDR	8	4.1	28	14.3
	Severe NPDR	5	2.5	11	5.6
	PDR	2	1	2	1

The prevalence of referable DR was 11.8% according to the expert evaluation, and 24.7% according to the AI screening system.

Diabetic Macular Oedema

Table 7 compares manual vs AI screening for the presence of DMO. The total prevalence of DMO (in one or both eyes) was 7% according to the expert evaluation, and 8.5% according to the AI screening system.

Table 7: Identification of DMO

	Manual grading		AI grading	
Classification	**N**	**%**	**N**	**%**
No DMO	186	93	183	91.5
DMO (one eye)	5	2.5	11	5.5
DMO (both eyes)	9	4.5	6	3
Total	200	100	200	100

As indicated by the higher AI-estimated prevalence, in the majority of cases the discrepant evaluations consisted in the AI identifying referable DMO and the ophthalmologist excluding it. Only in one case (patient 137) was the discrepancy in the opposite direction.

Figure 7 compares the two evaluations for that patient, who, in accordance with the study protocol, was contacted and referred for further ophthalmologic evaluation.

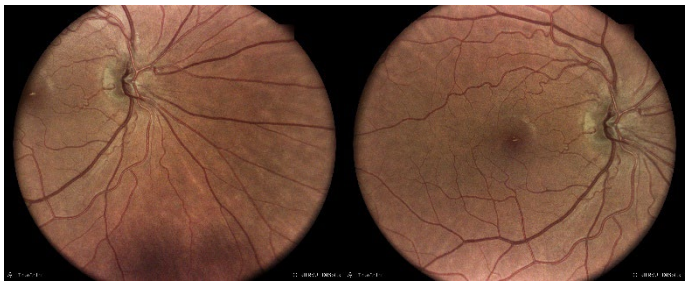
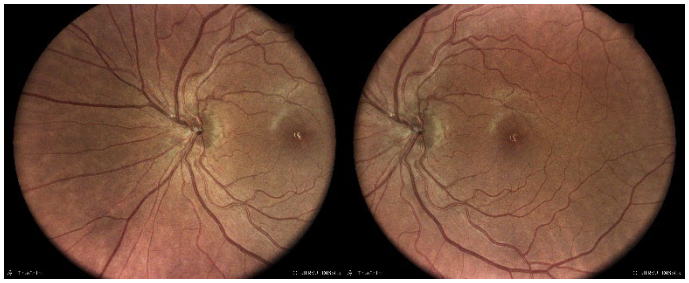
	Eye	Images	Assessment	
			AI	Ophtal.
137	Right		No DR	Mild NPDR DMO
	Left		Mild NPDR	Mild NPDR DMO

Figure 7: Referability assessment: AI vs. ophthalmologist

Level of agreement

Table 8 shows the results of the analysis of the level of agreement between manual and AI-based screening. Levels of agreement varied from a minimum of 81% for the identification of any DR, to 92.3% for VTDR. Kappa coefficients indicated a moderate level of agreement for referrable and vision-threatening DM (Kappa = 0.47 and 0.55, respectively), and substantial agreement (Kappa = 0.68) for any DR. Overall level of agreement across all 5 ICDR category was also moderate and slightly higher for the right eye, albeit the differences were not statistically significant (Table 9).

Table 8: Level of agreement in the identification of and DR, referable DR and vision-threatening DR

ICDR classification	Agreement [%]	Expected agreement [%]	Kappa	se
Any DR	81	41.4%	0.68	0.053
Referrable DR	83.1	68.1%	0.47	0.052
Vision-threatening DR	92.3	83%	0.55	0.064

se = Standard error

Table 9: Level of agreement in the grading of DR across 5 ICDR categories

	Agreement [%]	Expected agreement [%]	Kappa	se
Right eye	78.5	46.3	0.6	0.05
Left eye	73.3	46.4	0.5	0.048

se = Standard error

Accuracy of the screening

Table 10 and Table 11 summarize the characteristics of the EyeArt® system as a screening tool for referable DM, in comparison with expert ophthalmologic evaluation as the gold standard.

Results indicate excellent sensitivity of the EyeArt® system, at 95.7% (95%CI: 78.1%-99.9%), with only 1 out of 23 referable patients not identified as such. Specificity was slightly lower (84.9%, 95%CI: 78.6%-89.9%), with 26 out of 172 not-referable patients incorrectly categorized. Consequent to the high sensitivity, the screening text excelled in ruling out the presence of referable DM, with a negative test result almost certainly predictive of the absence of referable DR (NPV = 99.3%, 95% CI = 96.3%-100%). The lower specificity, and the relatively low true prevalence in the population resulted in a more modest positive predictive value, with a positive test result confirmed in less than 50% of the cases (PPV = 45.8%, 95% CI: 31.4%-60.8%).

Table 10: Referrals (EyeArt®)

		Manual grading (gold standard)		
		Referable	**Not referable**	**Total**
EyeArt® grading	**Referable**	**22**	26	**48**
	Not referable	1	**146**	**147**
	Total	**23**	**172**	**195**

*Table 11: Estimated accuracy parameters of the EyeArt® system for referable DR in the target population**

	Estimate	95% Confidence Interval	
Sensitivity	95.7%	78.1%	99.9%
Specificity	84.9%	78.6%	89.9%
Area under the ROC curve	0.9	0.85	0.95
Likelihood ratio (+)	6.3	4.4	9.1
Likelihood ratio (-)	0.1	<0.1	0.3
Positive predictive value [PPV]	45.8%	31.4%	60.8%
Negative predictive value [NPV]	99.3%	96.3%	100%

* With estimated referable DR prevalence of 11.8% (95% CI: 7.6-17.2%)

Overall, the accuracy of the EyeArt® screening test, as summarised by the area under the ROC curve, was 88.2% (Figure 8).

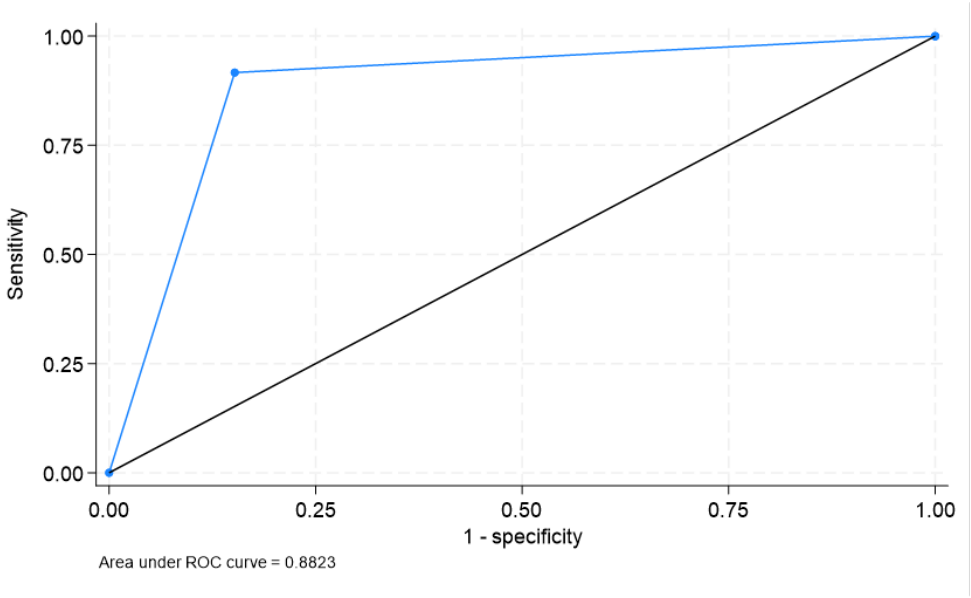


Figure 8: Receiver Operating Characteristics (ROC) curve of the EyeArt® *screening test for referable DM*

SugarwaveAI® grading

The SugarwaveAI® system did not flag any image as ungradable, and produced a screening result for all 200 patients. The results of the assessment for the 195 patients who were deemed gradable by the ophthalmologist are summarised in Table 12 and Table 13.

Table 12: Referrals (SugarwaveAI®)

		Manual grading (gold standard)		
		Referable	**Not referable**	**Total**
SugarwaveAI® grading	**Referable**	**22**	92	**114**
	Not referable	1	**80**	**81**
	Total	**23**	**172**	**195**

*Table 13: Estimated accuracy parameters of the SugarwaveAI® system for referable DR in the target population**

	Estimate	95% Confidence Interval	
Sensitivity	95.7%	78.1%	99.9%
Specificity	46.5%	38.9%	54.3%
Area under the ROC curve	0.71	0.65	0.77
Likelihood ratio (+)	1.79	1.52	2.11
Likelihood ratio (-)	0.09	0.01	0.64
Positive predictive value [PPV]	19.3%	12.5%	27.7%
Negative predictive value [NPV]	98.8%	93.3%	100%

* With estimated referable DR prevalence of 11.8% (95% CI: 7.6-17.2%)

Overall, the accuracy of the SugarwaveAI® screening test, was 71.1%.

Similarly to the EyeArt®, results indicate excellent sensitivity of the SugarwaveAI® system, at 95.7% (95%CI: 78.1%-99.9%), with only 1 out of 23 referable patients incorrectly. Specificity, however, was remarkably lower (46.5%, 95%CI: 38.9%-54.3%), with 92 out of 172 not-referable patients incorrectly categorized. An analysis of the classification performance by age group (*Figure 9*) clearly shows that this low overall specificity is due to the large level of overdiagnosis of younger patients with no DR.

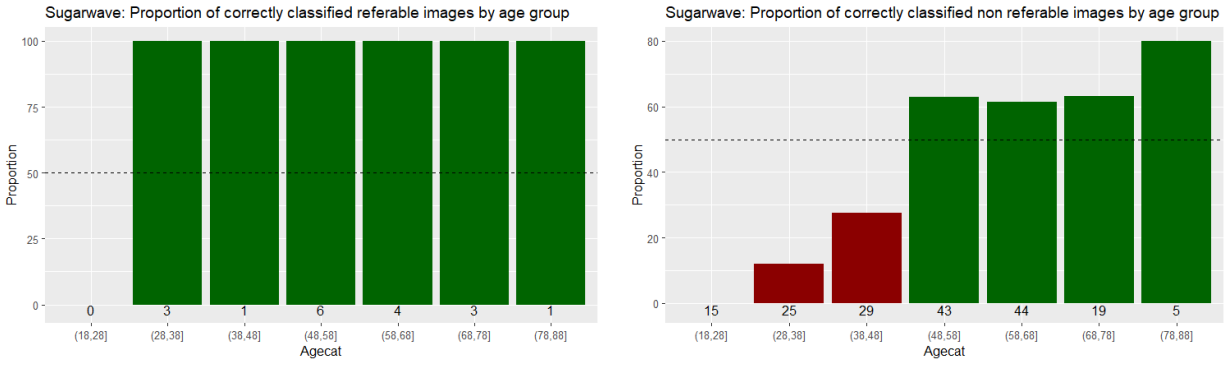


*Figure 9: Accuracy of classification by age group (*SugarwaveAI® system)

As a comparison, the performances of the EyeArt® system appear more uniform across age groups (*Figure 10*).

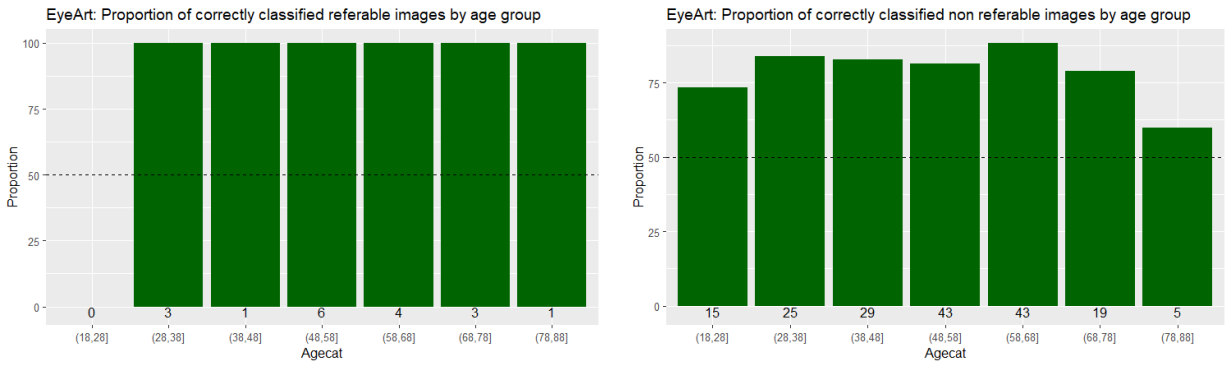


*Figure 10: Accuracy of classification by age group (*EyeArt® system)

Uptake rate

The uptake rate estimates from the study was 85% (95%CI: 80%-90%)

Cost analysis

Figure 11 and Figure 12 compare the performance of the AI-based screening approach (in-practice screening with the EyeArt® System with specialist referral of positive cases) with the traditional screening approaches (where the endocrinologist refers diabetic patients for manual screening to an optometrist/ophthalmologist), both in terms of yield (number of cases detected per 1000 patients) and cost per case detected. Results are shown for different combinations of screening ratios and true DR prevalence in the population.

The AI-based screening program consistently detects more cases that the traditional programs: with additional proportion of cases detected varying from 9% to 19%.

The current system (referral to ophthalmologic evaluation to all patients is, unexpectedly, by far the most expensive, with cost per cases varying form a minimum of 8983 ZAR in high prevalence populations, to more than 20000 ZAR in low-prevalence populations. Conversely, the AI approach produces the lowest cost per case across all hypotheses. Approach B (where the optometrist does the screening and the ophthalmologist only intervenes when the screening reveals signs of DR) has a much lower cost than the current

system, but still compares unfavourably with the AI system, especially in low-prevalence settings.

Figure 13 shows the results of the cost analysis when the AI-based screening is implemented *with the alternative SugarWave®* system.

As expected, given the much lower sensitivity of this alternative system, the cost per case detected increases by an amount between 244 ZAR and 251 ZAR (5.6% to 65%), depending on the DR prevalence in the population. Because of the same high sensitivity, the proportion of cases detected did not change (*Figure 14*).

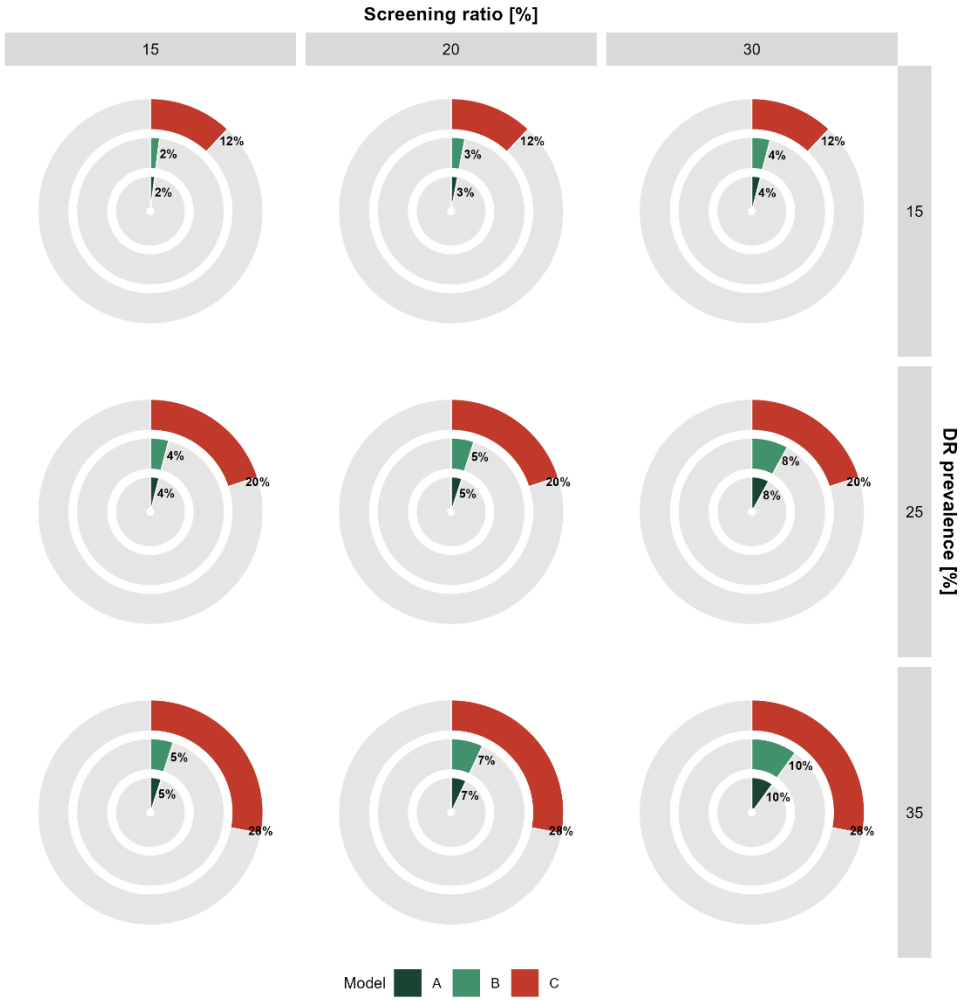


Figure 11: Proportion of cases detected by screening programs A/B (external referral to optometrist/ophthalmologist) and C (in-practice AI screening)
*(*EyeArt® system)

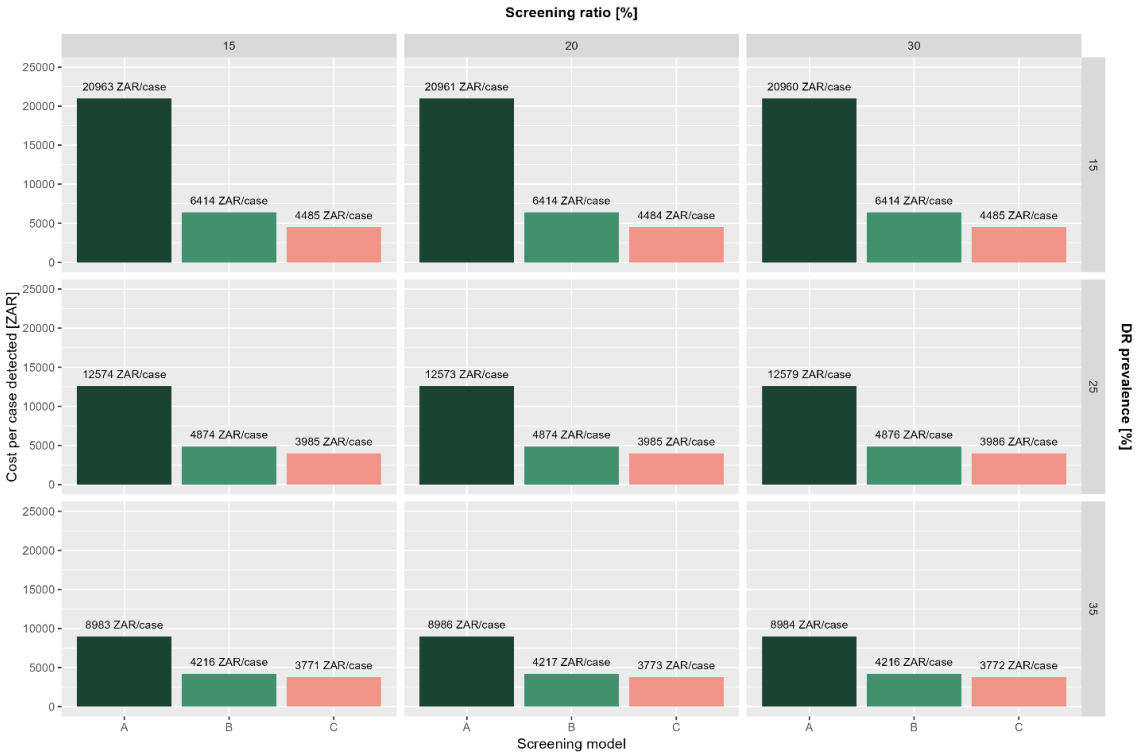


*Figure 12: Cost per case detected by screening programs A,B and C (*EyeArt® system)

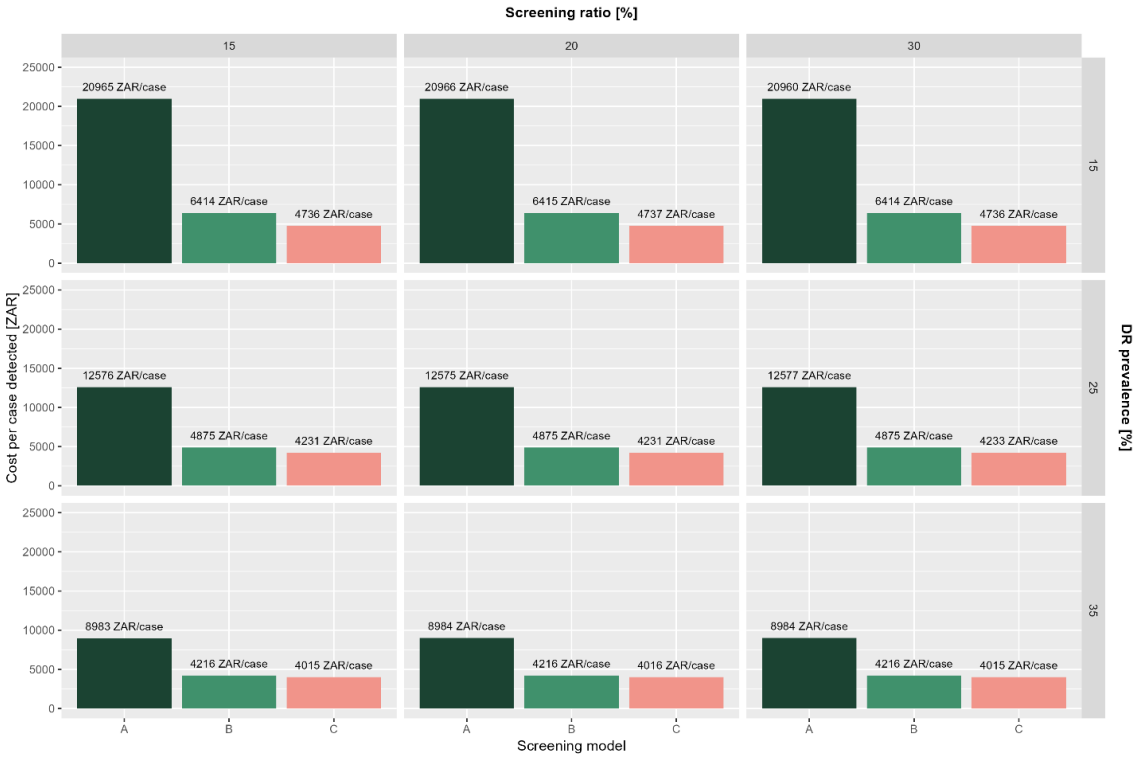


*Figure 13: Cost per case detected by screening programs A,B and C (*SugarWave® system)

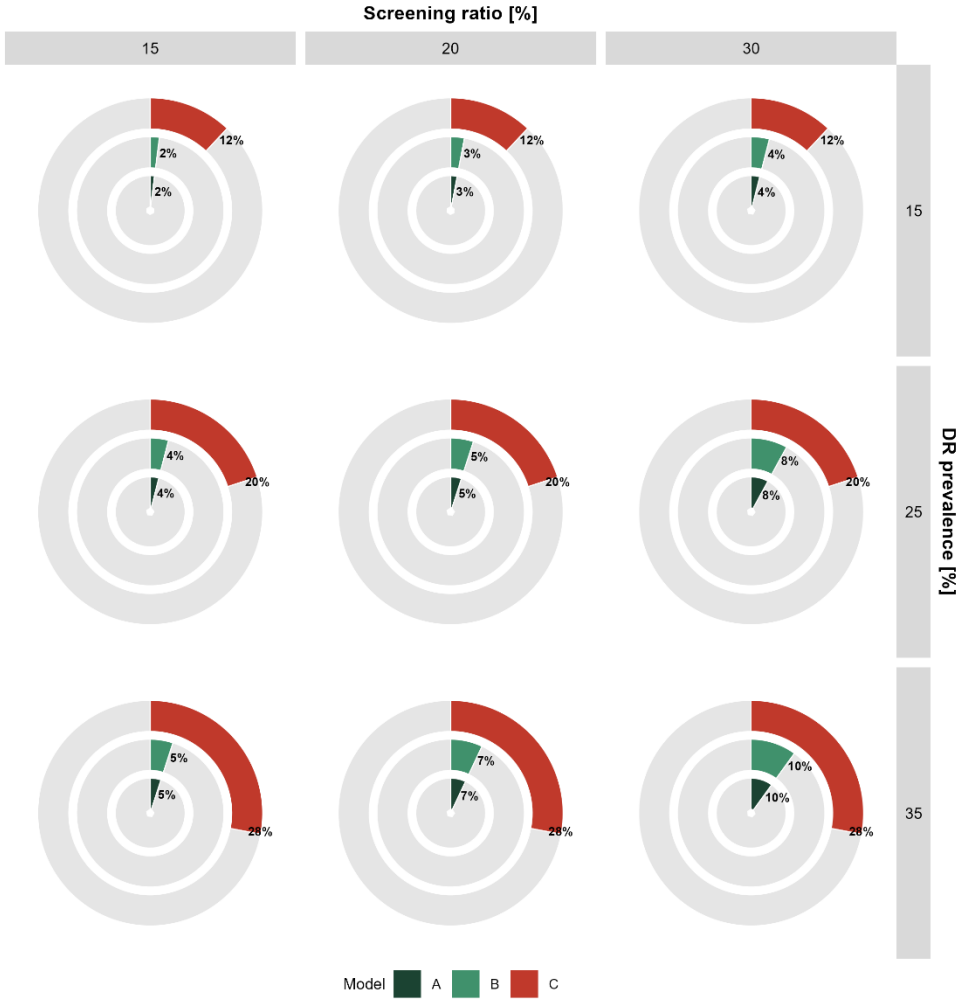


Figure 14: Proportion of cases detected by screening programs A/B (external referral to optometrist/ophthalmologist) and C (in-practice AI screening) (SugarWave® system)

DISCUSSION AND CONCLUSION

This exploratory study evaluated the implementation of an AI-assisted diabetic retinopathy screening programme integrated into routine diabetic care at a specialist endocrinology practice in South Africa. The findings demonstrate that AI-based retinal screening using non-mydriatic fundus photography is feasible in a real-world clinical setting and can achieve high diagnostic performance for identifying referable diabetic retinopathy. The results further suggest that AI-assisted screening may improve the efficiency and cost-effectiveness of diabetic eye care pathways by reducing unnecessary specialist referrals while maintaining a high sensitivity for clinically significant disease.

The prevalence of referable diabetic retinopathy identified by expert ophthalmologic grading in this cohort was 11.8%, with 43.6% of participants showing some degree of diabetic retinopathy and 8.7% presenting with vision-threatening disease. These findings are broadly consistent with international estimates reporting that approximately one-third of diabetic patients exhibit some form of DR, while around 10% develop vision-threatening complications. The relatively high burden of disease observed in this study is unsurprising given the substantial prevalence of cardiovascular and metabolic comorbidities in the sample, including hypertension, obesity, peripheral neuropathy, and kidney disease, all of which are associated with progression of diabetic microvascular complications.

The EyeArt® AI screening system demonstrated excellent sensitivity (95.7%) for detecting referable DR, correctly identifying all but one participant requiring referral. In the context of a screening programme, high sensitivity is essential because missed cases may result in delayed diagnosis and irreversible visual impairment. The very high negative predictive value observed in this study (99.3%) further supports the usefulness of the system as a rule-out tool, allowing patients without evidence of significant disease to avoid unnecessary specialist consultations. These findings are consistent with previous international validation studies reporting high sensitivity and robust screening performance of the EyeArt® platform across different populations and healthcare settings.

Although specificity was lower than sensitivity (84.9%), this level of performance remains acceptable within the context of population screening. The principal consequence of lower specificity is over-referral of patients without clinically significant disease. While this increases the workload at higher levels of care, screening programmes generally prioritise minimising false negatives over reducing false positives. Importantly, the observed specificity of the EyeArt® system remained substantially higher than that of the alternative SugarwaveAI® platform evaluated in this study.

The comparison between the two AI systems highlights the importance of independent local validation before implementation of AI technologies in healthcare settings. Although SugarwaveAI® achieved the same sensitivity as EyeArt®, its markedly lower specificity resulted in excessive false-positive referrals, particularly among younger patients without retinopathy. This overdiagnosis substantially reduced the positive predictive value of the system and negatively affected projected programme costs. These findings demonstrate that similar sensitivity estimates alone are insufficient when evaluating screening technologies; specificity and downstream operational implications must also be considered

carefully. Excessive false-positive referrals may reduce programme efficiency, increase specialist burden, and potentially create unnecessary anxiety for patients.

Agreement between AI grading and expert ophthalmologic assessment ranged from moderate to substantial across different classification systems. The highest agreement was observed for identifying any DR, while agreement for referable and vision-threatening disease was moderate. These findings likely reflect the inherent difficulty in consistently distinguishing between adjacent ICDR severity categories, particularly mild and moderate non-proliferative retinopathy. Some discrepancies may also arise from image quality limitations and the subjective nature of retinal grading, even among trained specialists. Nevertheless, the overall level of agreement observed in this study supports the reliability of AI-assisted grading as a screening approach.

Image gradability was high overall, with very few images deemed ungradable by either the ophthalmologist or the AI system. The small number of inadequate images was primarily attributed to blurring and shadow artefacts, likely related to patient movement or suboptimal image acquisition. These findings suggest that retinal photography can be successfully performed in non-specialist settings after relatively limited staff training. The ability to obtain high-quality retinal images outside ophthalmology clinics is a key advantage of decentralised AI-assisted screening models.

The uptake rate of approximately 85% among patients referred for ophthalmologic evaluation is encouraging and suggests good acceptability of the screening pathway. Integrating retinal screening into routine diabetic care within the endocrinology practice may have reduced barriers to access and improved patient engagement compared with conventional external referral systems. Improved accessibility is particularly important in the South African context, where disparities in specialist healthcare access remain substantial.

The pilot cost analysis provides additional support for the implementation of AI-assisted retinal screening programmes. Across all simulated scenarios, the AI-based screening model achieved lower cost per case detected compared with traditional referral-based pathways. The advantages were especially evident in lower-prevalence settings, where referral of all diabetic patients for specialist screening becomes economically inefficient. The findings suggest that AI-assisted screening may allow more efficient allocation of ophthalmologic resources by limiting specialist consultations to patients most likely to require further management. However, the analysis also demonstrated that programme

costs are highly sensitive to the specificity of the AI system used, reinforcing the importance of selecting appropriately validated technologies.

This study has several limitations that should be acknowledged. First, the study was conducted in a single specialist endocrinology practice, which limits the generalisability of the findings to other healthcare settings or populations. Second, only 57% of eligible screened patients consented to participate, raising the possibility of selection bias. Third, retinal grading was performed by a single ophthalmologist rather than multiple independent graders, preventing assessment of inter-observer variability. Fourth, the cost analysis was preliminary and limited to direct healthcare costs; broader economic impacts such as patient travel costs, productivity losses, and long-term savings from prevention of vision loss were not included. Finally, the cross-sectional nature of the study did not allow assessment of longitudinal outcomes or progression of disease over time.

Despite these limitations, the study provides important real-world evidence supporting the integration of AI-assisted retinal screening into diabetic care pathways in South Africa. The findings demonstrate that AI systems such as EyeArt® can function effectively as high-sensitivity triage tools capable of expanding access to retinal screening while reducing reliance on specialist services. The project also illustrates the feasibility of decentralised screening models involving collaboration between endocrinologists, primary care providers, optometrists, and ophthalmologists.

Future research should focus on larger studies including more diverse patient populations and healthcare environments. Longitudinal studies assessing patient outcomes, adherence to referral recommendations, and progression of retinal disease over time would further strengthen the evidence base. Additional health economic analyses incorporating indirect costs and quality-adjusted life years would also be valuable for informing healthcare policy and reimbursement decisions. Finally, further work is needed to evaluate the integration of AI-assisted retinal screening into public-sector healthcare systems and underserved communities where access to ophthalmologic care remains limited.

In conclusion, this study demonstrates that AI-assisted diabetic retinopathy screening using retinal fundus photography is feasible, accurate, and potentially cost-effective within routine diabetes care. The EyeArt® system achieved excellent sensitivity for identifying referable disease and showed strong potential as a scalable screening solution for improving access to diabetic eye care. AI-assisted screening programmes may contribute substantially to earlier detection of diabetic retinopathy, more efficient use of specialist resources, and

reduction of preventable diabetes-related visual impairment in South Africa and similar settings.

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