UK National
Screening Committee

Automated grading to replace level 1 graders in the Diabetic Eye Screening Programme

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

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Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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List of abbreviations

AI	Artificial Intelligence
ARIAS	Automated Retinal Image Analysis System
AUC	Area Under The [ROC] Curve
CE	Conformité Européenne
CI	Confidence Interval
CEA	Cost Effectiveness Analysis
CNN	Convolutional Neural Networks
CUA	Cost Utility Analysis
DESP	Diabetic Eye Screening Programme
DL	Deep Learning
DM	Diabetes Mellitus
DMO	Diabetic Macular Oedema
DR	Diabetic Retinopathy
DSS	Decision Support System
EDESP	English Diabetic Eye Screening Programme
ETDRS	Early Treatment of Diabetic Retinopathy Study [severity scale]
F&T	Flow And Timing
FDA	Food and Drug Administration
ICDR	International Clinical Diabetic Retinopathy [severity scale]
ICER	Incremental Cost Effectiveness Ratio
IT	Index Test
ML	Machine Learning
mtmDR	More-than-mild Diabetic Retinopathy
NN	Neural Networks
NPV	Negative Predictive Value
OCT	Optical Coherence Tomography
PPV	Positive Predictive Value
PDR	Proliferative Diabetic Retinopathy
QALY	Quality Adjusted Life Year
rDR	Referable Diabetic Retinopathy
ROC	Receiver Operating Characteristics [curve]
RS	Reference Standard
RoB	Risk Of Bias
SE	Sensitivity
SDESP	Scottish Diabetic Eye Screening Programme
SiDRP	Singapore National Diabetic Retinopathy Screening Program
SP	Specificity
SpDESP	Spanish Diabetic Eye Screening Programme
vtDR	Vision-threatening Diabetic Retinopathy
WHO	World Health Organization

Plain English summary

Diabetes can cause eye problems called diabetic retinopathy. If left untreated, it can get worse and lead to sight loss. Diabetic retinopathy is one of the leading causes of blindness in the working-age population in the UK.

Eye screening tests can detect eye problems before they affect sight. In the UK, all patients with diabetes aged 12 and over are invited to attend the UK Diabetic Eye Screening Programme (DESP) once a year. During the visit, health professionals take images of each eye. Then, trained professionals called level 1 graders study all images. More experienced (level 2) graders study images of patients with suspected diabetic retinopathy. If there is disagreement between level 1 and level 2 graders, level 3 graders make a final decision. Patients without diabetic retinopathy can return for another screen after 12 months. Patients with diabetic retinopathy need to have further assessment and treatment.

Currently, the DESP is under a lot of pressure. The number of people with diabetes continues to increase and there is a shortage of trained professionals. There are artificial intelligence (AI) systems that can study the images. So, it has been suggested that AI systems could replace level 1 graders. Such systems have already been implemented in Scotland and Portugal.

The UK National Screening Committee has not looked at the evidence on the use of AI in the English DESP before. Therefore, it is not currently recommended.

This review looked for evidence to see whether:

- AI systems are accurate enough to identify cases of diabetic retinopathy
- the replacement of level 1 graders with AI systems provides better health and value for money
- there is any evidence on social and ethical aspects of using AI systems in screening programmes.

The results from the review indicate that:

- some AI systems are accurate enough to do the initial reading of images, but only 3 systems have been evaluated in good quality studies conducted in the UK
- a system called iGradingM is implemented in Scotland and there is evidence that its performance is good; however, we could not find much evidence on experience with its implementation and use
- there is some evidence that using the above AI systems for initial screening of images provides better value for money, but the analyses need updating as new information and new versions of the systems are now available
- the evidence on social and ethical aspects of using AI systems in screening programmes should be assessed further.

In conclusion, further research is needed before implementing AI in the English DESP.

Executive summary

Purpose of the review

The purpose of this review is to provide a reference point for a discussion on the major modification proposal to the English Diabetic Eye Screening Programme (DESP) which involves the replacement of level 1 graders with automation of grading using Automated Retinal Image Analysis Systems (ARIAS) to triage patients into low and high-risk cases. This is achieved by identifying and synthesising research evidence on the accuracy, clinical and cost-effectiveness of ARIAS, and studies and review/opinion papers addressing the social and ethical implications of the implementation of Artificial Intelligence (AI) technology in screening programmes.

Background

Diabetic eye disease is the most common microvascular complication of diabetes. The microvasculopathy can lead to visual dysfunction by causing diabetic retinopathy and maculopathy and increases the risk of developing cataracts and glaucoma. Sight-threatening diabetic retinopathy is one of the leading causes of blindness in the working-age population in the UK. It is caused by the damage to the blood vessels that nourish the retina, which may result in areas of ischaemia and dysfunction, and may trigger the aberrant response of new vessels growing into the vitreous cavity (proliferative retinopathy) that can cause haemorrhage and scarring of the retina. Patients with severe levels of diabetic retinopathy are reported to have poorer quality of life and reduced levels of physical, emotional, and social well-being, and they utilize more health care resources. Diabetic maculopathy is caused by the leakage of fluid in the macula, which is the part of the eye responsible for detailed vision such as reading and face recognition.

In the UK all people with type 1 and type 2 diabetes (excluding women who have only gestational diabetes) aged 12 or over are invited to the national screening programme for diabetic eye disease every year. The aim of the screening programme is to reduce the risk of vision loss for people with diabetes mellitus through the early detection of retinopathy or maculopathy during its common asymptomatic stage, and provide them with appropriate monitoring and treatment, as patients often do not present until advanced complications when treatment outcomes are less favourable and costs are higher.

There are some variations in the screening protocols and grading schemes used in the DESPs across the UK nations. The English DESP (EDESP) involves taking two-field 45° colour fundus photographs using pupil dilation (mydriasis) that are manually assessed by human graders. These photographs are graded as follows, in order of progression:

- no retinopathy (R0)
- background retinopathy (R1)
- pre-proliferative retinopathy (R2)
- proliferative retinopathy (R3; R3A (active); R3S (treated and stable))
- no maculopathy (M0)
- maculopathy (M1) - early maculopathy (does not require treatment) or clinically significant macular oedema (requires treatment).

Patients that are graded R0M0, or R1M0 in the more severely graded eye are invited to return for rescreen after 12 months. Patients graded R2 or those who have early maculopathy (M1) are referred to either the Hospital Eye Service (HES) or Digital Surveillance (DS) clinic where they are kept under surveillance and screened more frequently (every 3-6 months) to monitor the progression of diabetic retinopathy or maculopathy. DS clinics or HES may interface with Optical Coherence Tomography (OCT) assessment to detect maculopathy which could not be diagnosed using non-stereoscopic fundus photography. Patients graded R3A or those who have clinically significant macular oedema (M1) are referred to HES where they receive treatment which involves laser photocoagulation or injections of anti–vascular endothelial growth factor drugs. If digital images are not clear enough to allow the image of the retina to be graded, then a second test using a method called slit lamp biomicroscopy will be required.

The EDESP grading pathway includes multi-level manual grading systems. All fundus photographs are reviewed by level 1 graders. Level 2 graders review fundus photographs of patients who were graded as R1, R2, R3, and M1 by level 1 graders. Level 2 graders also review all ungradable photographs, as determined by level 1 graders, and 10% of photographs which were graded as R0 by level 1 graders for quality control. Discrepancies between level 1 and level 2 graders are reviewed by level 3 graders.

DESPs are labour intensive and for the EDESP to cope with the increasing burden of diabetes, the UK NSC received a proposal to modify the programme by replacing level 1 graders with ARIASs to triage patients into low and high-risk cases. The proposal suggested that the detection of diabetic eye disease through ARIASs would reduce the need for human graders, thus reduce the cost of screening.

ARIASs have been used for level 1 grading in the DESPs of Scotland and Portugal and are now considered for clinical use in other countries, such as the USA, the Netherlands, Singapore, Korea, Spain, Thailand and India. The systems used in Scotland (iGradingM) and Portugal (RetmarkerSR) are based on traditional Machine Learning (ML) algorithms which extract from the images pre-specified ‘hand-crafted’ features, such as microaneurysms, and use the information to classify patients into those who have ‘any disease’ (images sent for human grading) and ‘no disease’ (routine recall). Both programmes have quality assurance systems that monitor the performance of ARIAS.

Most of the recently developed systems use Deep Learning (DL) algorithms that do not depend on pre-specified features. Instead, they use raw data to build up features that allow better classification of the images as determined by the reference standard.

Focus of the review

The aim of the current review is to identify and synthesise the evidence on the major modification proposal to the EDESP which involves the replacement of level 1 graders with an ARIAS to triage patients into low and high-risk cases. However, the UK NSC will consider the evidence reviewed here in the context of the whole UK. The review aimed to answer the following questions:

Question 1 (rapid review, criteria 4 & 5): What is the diagnostic accuracy of the ARIASs at detecting diabetic eye disease in patients with diabetes mellitus? (The term ‘diagnostic accuracy’ does not imply that the system is used to diagnose diabetic retinopathy or any other condition; the only use of ARIASs investigated in the current review is as a first line screening test designed to identify patients with ‘no disease’ or ‘non-referable disease’, as part of a multi-level screening programme, such as the EDESP).

Question 2 (rapid review, criteria 11 & 12): What is the clinical impact of DESPs using an ARIAS for level 1 grading compared with DESPs with fully manual grading?

Question 3 (evidence map, criterion 14): What is the cost-effectiveness of replacing level 1 manual graders with an ARIAS in DESPs compared with DESPs with manual level 1 grading?

Question 4 (evidence map, criterion 12): What are the social and ethical implications of implementing artificial intelligence (AI)-based tools in screening programmes and would it be acceptable to health professionals and the public?

Two methodologies were used: Question 1 and 2 were addressed with a rapid review whereas questions 3 and 4 with an evidence map. For questions 1 to 3 we prioritised UK-based studies and studies conducted in similar settings; studies evaluating commercially available and CE-marked/FDA-approved ARIASs; we also prioritised RCTs and prospective cohort studies. For question 4, all primary studies evaluating the social and ethical impact of AI-based technology in medical screening programmes or similar settings were included; we also included, but reported separately, all review and opinion papers that appeared to be relevant to this question based on the information provided in their abstracts.

Two separate searches were carried out from January 2000 to June 2020. The first one addressed questions 1-3 (accuracy, effectiveness and cost-effectiveness). The second search addressed question 4 (social and ethical aspects of AI in screening programmes). We also searched the reference lists of included studies and other publications and, if necessary, contacted authors and manufacturers to request further information.

Findings and gaps in the evidence of this review

Ninety two studies were judged to be relevant to at least one question and included in the review; of those 3 studies addressed more than one question. We identified:

- 56 studies relevant to question 1 (accuracy of ARIASs; rapid review), of which 28 studies met one or more of the prioritisation criteria detailed above and were included in the narrative synthesis
- 2 studies relevant to question 2 (effectiveness of ARIASs; rapid review)
- 5 studies (9 publications) relevant to question 3 (health economic evaluation of ARIASs; evidence map)
- 57 studies relevant to question 4 (social and ethical impact of ARIASs; evidence map), of which 19 were primary studies and 38 were review and opinion papers.

Question 1 (accuracy of ARIASs; rapid review):
Fifty six studies were judged to be relevant to question 1 of which 28 studies evaluating 10 ARIASs were prioritised for inclusion in the narrative synthesis. Sixteen studies evaluated 7 DL-based systems: EyeArt v2.1 (n=5 studies), EyeGrader (n=1), IDx-DR v2 (n=4), Google AI (n=2), RedCAD (n=1), SELENA (n= 2) and VUNO (n=1). Further 12 studies evaluated ARIASs based on traditional ML algorithms: iGradingM (n=7), RetmarkerSR (n=4), RetinaLyze (n=2) and EyeArt v1 (two versions of EyeArt were included: an earlier ML-based version and the current DL-based version). One study compared the performance of 3 systems: EyeArt v1, iGradingM and RetmarkerSR).

DL-based ARIASs
Only 2 of the DL studies, both evaluating EyeArt v2.1, were conducted in the UK: Heydon 2020 which was a large prospective multi-centre study and Olivera-Barrios 2020 which was a retrospective study comparing the performance of EyeArt v2.1 when used with the EDESP photographic protocol and an alternative widefield platform. Only EyeArt v2.1 and IDx-DR v2 were evaluated in prospective clinical studies: Heydon 2020 (UK), Lim 2019 (USA) and Liu 2020 (USA) evaluated EyeArt v2.1, and Abramoff 2018 (USA) and van der Heijden 2018 (the Netherlands) evaluated IDx-DR v2. By ‘prospective study’ we mean that data collection was planned before the index test and reference standard were performed (see the definition in the STARD checklist[1]). None of the prospective clinical studies compared the performance of alternative ARIASs in the same cohort of patients.

[1] https://www.equator-network.org/reporting-guidelines/stard/

The number of participants ranged from 96 to >30 000. There was considerable variation across studies in terms of selection and characteristics of the included participants; prevalence and spectrum of diabetic retinopathy; setting; screening pathway and protocol, reference standard, grading scheme and handling of ungradable images. All these sources of variation are likely to affect the performance of ARIASs, especially when the system is evaluated away from the setting in which it was developed and initially evaluated. Some of these factors were investigated in the included studies or other publications and the results are summarised and reported in the review.

Most of the studies were considered to be at high or unclear risk of bias in at least one of the QUADAS-2 domains. The main issues concerned the selection of patients (only 3 studies were considered at low risk of bias), the reference standard (as the reference grading did not involve a panel of ophthalmologists or retinal specialists or the final grade from a multi-level screening programme with established training and quality assurance protocols) and the exclusion of ungradable images. Since we could not determine whether the mix of patients in non-UK studies was similar to that in the UK DESP in all significant ways, we graded all such studies ‘unclear’ for applicability concerns unless the sample was clearly different from the patients see in the UK; in addition, 7 studies were graded ‘high’ or ‘unclear’ for applicability concerns in the Index Test domain as the photographic protocol differed from those used in the UK DESPs.

Across all studies, sensitivity for referable diabetic retinopathy was consistently >90%. There were 3 exceptions, all relating to the IDx-DR v2 system: Abramoff 2018 (USA) reported 87.2% (95% CI, 81.8–91.2%) sensitivity when stereoscopic widefield fundus photography was used as a reference standard and 85.9% (95%% CI, 82.5%–88.7%) when the latter was combined with OCT; Verbraak 2019 (the Netherlands) reported sensitivity of 79.4% (95% CI 66.5–87.9) due to the presence of a single isolated haemorrhage or cotton wool spot (but no microaneurysms) in the 13 false negative results; and van der Heijden 2018 (the Netherlands) reported considerable difference in sensitivities when ICDR and EURODIAB criteria were applied.

The picture was similar when considering the results for sight-threatening or vision-threatening diabetic retinopathy. Most studies reported sensitivity of around or more than 95% including Abramoff 2018 (IDx-DR) against both reference standards (‘4W-D’ and ‘4W-D & OCT’). The prospective pivotal study evaluating EyeArt v2.1 against a ‘4W-D’ photographic protocol reported variable sensitivities ranging from 78.6% to 100% (reported separately for different cohorts and settings, with wide CIs due to the small samples sizes of the individual cohorts). Another exception was van der Heijden 2018 (IDx-DR v2, the Netherlands) who reported sensitivity of 64% (36%–86%) using the EURODIAB criteria and 62% (32%–85%) using the ICDR criteria. The reason for these very different results was unclear from the paper.

The specificity ranged considerably, from 54.0% (95% CI, 53.4% to 54.5%) for R0M0 & R1M0 in Heydon 2020 (UK; EyeArt v2.1) to >95% in some studies, which reflects the inclusion/exclusion of ungradable images and other sources of variation. The relatively low specificity in Heydon 2020 is most likely due to the fact that all images that would normally be sent for manual grading were fed to the ARIAS and included in the analysis. The two studies that used 4W-D protocol in the reference standard reported much higher specificities. Lim 2019 (USA; EyeArt v2.1) reported specificity of 86.5% (95% CI, 84.3% - 88.7%) when ‘dilation-if-ungradable’ protocol was used and 86.0% (95% CI, 83.7% - 88.4%) for ‘no dilation’. Abramoff 2018 (USA; IDx-DR v2) reported specificity of 90.7% (95% CI, 88.3–92.7%) against the reference standard of 4W-D and 90.7% (95% CI, 86.8%–93.5%) against ‘4W-D + OCT’, which remained unaffected (89.8%) in the sensitivity analysis when ungradable images were included.
Finally, van der Heijden 2018 (IDx-DR) reported that specificity was comparable (86% and 84%, respectively) when using the ICDR and EURODIAB criteria.

Of all included studies evaluating DL-based ARIASs, we considered only Heydon 2020 to be of sufficient quality and to allow direct generalisation to the EDESP. It included a cohort of 30 405 consecutive patient episodes from 3 current EDESP centres. For referable disease (M1, R2, R3) sensitivity was 95.7% (95%CI 94.8% to 96.5%); specificity (for the combination of R0M0 and R1M0) was 54.0% (95%CI 53.4% to 54.5%); the detection rate for R2 was 100% (95%CI 98.7% to 100%) and for R3 100% (95%CI 97.9% to 100%); and the system was able to identify 89.4% (95%CI 87.0% to 91.5%) of the images classified as ‘ungradable’ by human graders. The accuracy was similar across the 3 centres. The study was rated ‘low’ for risk of bias and applicability concerns in all QUADAS-2 domains. No subgroup analysis was reported in the paper, but the authors very kindly provided additional information which is included in the report (personal communication).

ML-based ARIASs

Of the 4 ML-based ARIASs, RetinaLyze was evaluated in 2 small studies at high risk of bias. The most recent study was published in 2008 and was conducted in the UK. The manufacturer confirmed that this was the most recent evaluation and that the system has not been upgraded since then. Of the 4 studies evaluating RetmarkerSR only the most recent one, Tufail 2016, was conducted in the UK and was judged to be at low risk of bias. The sensitivity for referable diabetic retinopathy was 85.0% (95% CI 83.6%-86.2%), the specificity for R0M0 & R1M0 was 47.7% (95% CI 47% to 48.5%); and the sensitivity for proliferative diabetic retinopathy was 97.9% (95% CI 94.9%-99.1%). However, this may not be the most recent version of the software as the manufacturer stated that they had been upgrading the system (personal communication). The other 3 studies were conducted in Portugal; one of these studies reported internal quality assessment data from the Portuguese DESP according to which there were only 11 false negative cases out of 3 287 cases included in quality assessment (which translates into 0.3% of quality control cases and 0.02% of all screened patients).

iGradingM has been in use in the SDESP since 2011. Prior to its implementation it had been evaluated in 3 large SDESP cohorts one of which was prospectively recruited. The reported sensitivities were consistently >90% for referable diabetic retinopathy and approached 100% for sight-threating disease. The specificity was around 67% in two studies while the rest reported detection rate for individual grades that will translate into similar results. One study published only as a conference abstract reported the results from an internal quality assessment from the SDESP; sensitivity was comparable to that in previous studies but specificity was lower: sensitivity 97%, specificity 38% and false negative rate ranging from 0 to 0.6% (13). It was also reported that the number of episodes handled by the programme had increased by 20.3% in the period from 2010 to 2015 and in the observed 6-month period in 2015, 58.1% of all episodes were passed on to the autograder. iGradingM failed to read disc-centred images when evaluated in the EDESP in Tufail 2016, but the results reported by Goatman 2011 who compared the EDESP and

SDESP photographic protocols, were in line with those reported in the Scottish evaluations. According to Tufail and colleagues the discrepant results could be explained with pre-processing of the images in Goatman 2011 (personal communication).
In the comparative HTA assessment conducted by Tufail et al, EyeArt v1 achieved the highest sensitivity for both referable diabetic retinopathy and proliferative diabetic retinopathy, but 80% of the patients with ‘no disease’ were classified as ‘referrals’. The RetmarkerSR had much lower sensitivity for referable diabetic retinopathy, but for proliferative disease the sensitivity was comparable to that of EyeArt v1; also, a much higher proportion of patients with ‘no disease’ or those with non-referable diabetic retinopathy were classified as ‘no referral’. The accuracy of EyeArt v1 was not affected by ethnicity, sex or camera type, but sensitivity was marginally lower with increasing patient age. The accuracy of RetmarkerSR appeared to vary with patient age, ethnicity and camera type.

ARIAS compared to human graders
We included 4 studies that compared ARIASs to human graders not involved in the reference grading: 3 evaluated DL-based ARIASs (Google AI, SELENA and RetCAD) and one evaluated iGradingM. The study evaluating iGradingM was the only prospective evaluation and the only study conducted in the UK (Scotland). None of the studies were considered to be at high risk of bias with respect to comparative accuracy, but had some methodological issues that applied equally to ARIAS and human graders. On the whole, DL-based ARIASs had higher sensitivities and lower specificities compared to human graders. The study evaluating iGradingM in the SDESP reported that the system had sensitivity of 90.5% (95%CI 89.3–91.6) and specificity of 67.4% (95%CI 66.0–68.8) for referable diabetic retinopathy. In comparison, the sensitivity of manual grading was 86.5% (95%CI 85.1–87.8) and the specificity 95.3% (95%CI 94.6–95.9). iGradingM and human graders misclassified as normal 240 and 341 patients with diabetic retinopathy, respectively, and the difference was statistically significant ($p<0.001$); of those with M1, R2, M2, R3 or R4, iGradingM and human graders classified 7/330 and 3/330, respectively, as ‘no retinopathy’ but the difference was not statistically significant ($p=0.125$).

Question 2 (effectiveness of ARIAS; rapid review): We did not identify any RCTs comparing DESP with level 1 human graders to DESP with level 1 ARIAS grading in terms of clinical outcomes and other measures of impact. Some accuracy studies reported projected impact, such as workload reduction, but since these outcomes were just a different way of expressing the accuracy estimates, we do not include the results here.

We included 2 prospective cohort studies. Keel 2018 (Australia) investigated the acceptability of ARIAS-based DR screening (n=96) in which the patient is immediately provided with the result, relative to manual grading in which the patient can access the result after 2 weeks. The authors reported that the average time for ARIAS-based screening was 6.9 min (vs 2 weeks with manual grading); 96% of participants were very satisfied or satisfied with the screening and 78% said they preferred ARIAS. However, patients served as their own controls (no proper control group) and the study was judged to be at high risk of bias.

Liu 2020 (USA) investigated whether using ARIAS to make the result from the examination immediately available to patients improves their adherence to follow-up. They reported that in the study cohort (n=180) the adherence rate was 55.4% at 1 year versus historical adherence rate of 18.7% ($P < 0.0001$). However, the study was judged to be at high risk of selection bias; used historical controls; it was not clear if the patients in the historical cohort received the same level of encouragement to attend follow up examination (3 telephone calls and a letter) and, in some cases, the result was provided to the patient with a considerable delay.

Question 3 (cost-effectiveness of ARIAS; evidence map): After excluding all non-UK studies, 5 studies evaluating 3 ML-based systems (EyeArt v1, iGradingM and RetmarkerSR) were included in the evidence map from UK countries. The studies generally found automated grading to be less effective than manual grading, but also less costly. Therefore, many of the results are reported in terms of the additional costs associated with manual grading to gain additional health benefits when compared to automated grading. The HTA conducted by Tufail et al investigated the cost-effectiveness of EyeArt v1 and Retmarker in the EDESP comparing two alternative strategies: 1) ARIAS replacing level 1 graders, and 2) ARIAS acting as a filter prior to level 1 manual grading. They found that both systems are cost-effective with either strategy, but strategy 1) was preferred. Although these studies provide good starting point for further evaluations, they need updating to capture cost-effectiveness over time and to reflect the performance of the new versions of the software.

Question 4 (social and ethical implications; evidence map): Nineteen primary studies and 38 reviews and opinion papers were included in this evidence map after reviewing their abstracts. Five of the primary studies investigated the impact of AI in the context of screening, while the rest had a more general focus (e.g. survey of radiologists) or were conducted in a different healthcare setting (e.g. hospital), but were judged to address relevant questions.

All primary studies were surveys of clinicians (n=9), clinicians and the general public (n=2), the general public (n=2) and patients (n=5). The surveys were conducted in the USA (n=4), UK (n=3), France (n=1), and one each in Australia, China, Europe, Germany, India, Italy, Singapore and Sweden. They investigated a broad range of questions including participants' knowledge, training needs, perceptions, attitudes and satisfaction in relation to AI-based technology. Most of the participants had positive attitudes towards the implementation of AI in healthcare and acknowledged the benefits that such technologies are likely to bring, both in terms of improved patient outcomes and benefits to the healthcare system as a whole. Studies also reported a range of concerns regarding the impact of AI-based technology on clinicians' professional role and identity, clinician-patient relationship, dealing with uncertainty, the impact on clinical decision making, and the need of training and better understanding of AI by healthcare professionals, patients and the general public.

Only one of the review/opinion papers was a systematic review. It looked at the characteristics and usability features of tele-ophthalmology for the elderly population, including AI-based screening (Fatehi 2020).

Recommendations

Based on the synthesis of evidence against the UK NSC criteria, EyeArt v2.1 has consistently high sensitivity, comparable to that of human graders, and could safely be implemented in the EDESP, either as a replacement of level 1 human graders or as a filter before manual grading. It has been shown that the system is cost-effective with either of these strategies, although the analyses need updating to reflect the higher performance of the new version; to capture the long-term impact of the system, and to investigate the effect of using different decision thresholds, ‘disease/no-disease’ vs. ‘referable/non-referable’ disease.

RetmarkerSR (ML-based) also has been shown to have high accuracy (but lower sensitivity than EyeArt v1) and to be cost-effective in the EDESP. Although there is published evidence of its high performance as implemented in the Portuguese DESP, the evidence base is more limited and there is only one UK-based study.

iGradingM has been evaluated in a number of high quality studies in Scotland and there is published evidence of its high performance as implemented in the SDESP. However, the system does not seem to work with the 2-field images and may not be directly implementation in the EDESP. Also, we could not find published evidence on experience with its implementation and use.

There is no direct evidence on the overall impact of ARIAS (including the impact on human graders) but limited evidence from Scotland and Portugal suggest that the risk is low, the performance of ARIAS remains high after implementation, provided robust internal and external quality assurance programme is in place, and the use of ARIAS is likely to increase with time.

Future research:

- Should be done independently from the software developer, in the clinical setting in which the system is meant to be used, under conditions that reflect everyday clinical practice; if possible, they should compare the performance of alternative ARIASs that may have different advantages and disadvantages.
- Should look at outcomes beyond accuracy, such as the actual consequences of false negative and false positive results and the consequences of accidental findings (e.g. missed by ARIAS but referred by human graders).
- They should include a cost-effectiveness evaluation of the system.
- They should investigate the experience and perceptions of healthcare professionals who interact with and/or are directly affected by the ARIAS; the expectations of those who have not yet had this experience (e.g. those in the control arm); the experience

and perceptions of relevant patient groups; and the overall impact on the NHS.

We identified a considerable number of papers looking at the social and ethical aspects of AI implementation in screening programmes. An evidence review of this growing literature will help identify all relevant aspects of the above question, to summarise the existing evidence and identify any gaps that need to be addressed in future research.

Limitations

The following methodological limitations of the review should be acknowledged: only the main electronic databases were searched; searches were limited to records published since 2000, and only including peer-reviewed, English-language journal articles; only 20% of the titles and abstracts were double-screened; papers were excluded after assessment of the volume of published evidence (although prioritisation was based on pre-specified criteria); the definition of one of the signalling questions in QUADAS-2 checklist was changed following a discussion with experts in the field and after the initial grading of studies; as a result some studies were later regraded using the new definition.

High quality evidence on the accuracy of ARIAS in the UK DESPs was found only for 3 systems; given the large number of contextual factors that may affect its performance, generalising the results from studies conducted in other countries is not advisable. No RCTs or prospective cohort studies were found that compare directly DESP with level 1 ARIAS grading vs DESP with level 1 human grading and report outcomes beyond accuracy. The identified health economic evaluations show that the systems are cost-effective but need updating.

Introduction and approach

Background

Target condition

Diabetes
Diabetes Mellitus is a chronic metabolic condition in which the body doesn't make enough insulin (the hormone that regulates blood sugar) or is unable to use it effectively. This results in hyperglycaemia (raised blood sugar) which can lead to serious damage of multiple body systems, especially the nerves and the blood vessels. According to the World Health Organisations (WHO) the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 and continues to rise, especially in low- and middle-income countries. WHO estimates that diabetes was the 7th leading cause of death in 2016 and a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation (3).

In the UK, there were 3.9 million people with diabetes in 2019 and this number is expected to rise to 5.3 million by 2025. Of those, 90% have type 2 diabetes, 8% type 1 diabetes and about 2% have rarer forms of diabetes (4).

Diabetic eye disease
Diabetic eye disease is the most common microvascular complication of diabetes mellitus. The microvasculopathy can lead to visual dysfunction by causing diabetic retinopathy and maculopathy and increases the risk of developing cataracts and glaucoma.

Diabetic retinopathy is caused by damage to the blood vessels that nourish the retina, which is the tissue that lines the inner surface of the eye, surrounding the vitreous cavity. Damage to these capillaries causes closure of the vessels and/or leakage of fluid. These vascular changes may result in areas of ischaemia and dysfunction of the retina which may trigger the aberrant response of new vessels growing into the vitreous cavity (proliferative retinopathy). This, in turn, can cause haemorrhage and scarring of the retina.

Diabetic retinopathy/maculopathy is the second most common cause of blindness in the working-age population in the UK, accounting for 14.4% of all cases in the period 1 April 2009 and 31 March 2010 (the leading cause was hereditary retinal disorders with 20.2%). Although this percentage is still quite high, it is a considerable improvement from the previous period used as a comparator in the study, April 1999 and 31 March 2000, during which diabetic retinopathy/maculopathy was the leading cause of blindness accounting for 17.7% of all cases (5). Worldwide, around 35% of people with diabetes mellitus had some form of diabetic retinopathy and 10% were affected by sight-threatening diabetic retinopathy (6). These estimates will soon be revised in an upcoming systematic review (7).

Diabetic maculopathy is caused by the leakage of fluid in the macula which is the part of the eye responsible for detailed vision, such as reading, counting and face recognition. Clinically significant maculopathy is arbitrarily defined by the presence of retinal thickening or hard exudates within one disc diameter of the fovea (8).

There are several risk factors for diabetic retinopathy and maculopathy including the duration and type of diabetes, the degree of hyperglycaemia, hypertension, hyperlipidaemia and diabetic nephropathy. Patients with severe levels of diabetic retinopathy are reported to have poorer quality of life and reduced levels of physical, emotional, and social well-being, and they utilize more health care resources (9).

Current policy context and previous reviews

Diabetic eye screening programmes in the UK

The UK was the first country to introduce a national screening programme for diabetic eye disease. In England, Scotland and Wales, the Diabetic Eye Screening programme (DESP) has been implemented since 2003 (2), and in Northern Ireland since 2008. The aim of the screening programme is to reduce the risk of vision loss for people with diabetes mellitus through the early detection of retinopathy or maculopathy during its common asymptomatic stage, and provide them with appropriate monitoring and treatment, as patients often do not present until advanced complications when treatment outcomes are less favourable and costs are higher.

The eligible population for these programmes is all people with type 1 and type 2 diabetes aged 12 or over (excluding women who have only gestational diabetes). The differences between the DESPs across the 4 nations are summarised in Table 1.

Table 1 Differences between DESPs across the 4 nations.

Nation	**Scotland**	**England**	**Wales**	**Northern Ireland**
System	Single commissioned National	Multiple individually commissioned Regional	Single commissioned National	Single commissioned National
Software	Single commissioned National system	No National system, 2 suppliers	Single commissioned National system	Single commissioned National system
Automation	Automated primary grading	None	None	None
Images	1-field	2-field	2-field	2-field
Extended Intervals	Yes		Yes	
Added OCT	Yes			

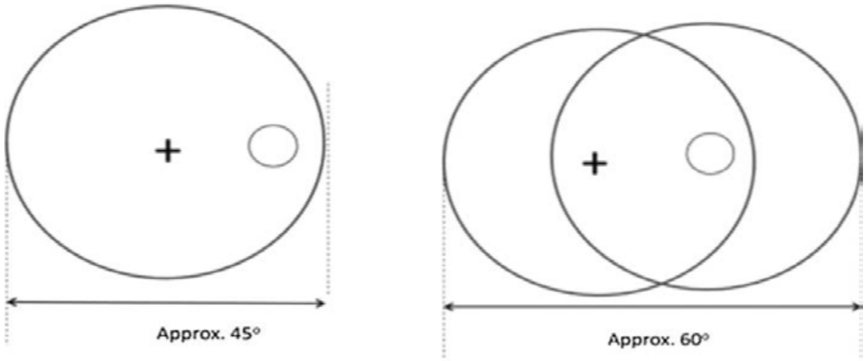
OCT - Optical Coherence Tomography

Generally, fundus photography is used as the screening test for detecting retinopathy. Fundus photography is an ophthalmic imaging technique that shows a magnified and subtle view of the surface of the retina. Two or more photographs may be overlapped to create a wider field of view (Figure 1). Diabetic maculopathy itself cannot easily be identified by non-stereo fundus photography as oedema is transparent and therefore surrogate markers are used (i.e. signs of retinopathy close to the macula). Visual acuity decline may also be used to screen for diabetic macula oedema (DMO) that causes a functional decline. The diagnostic test for DMO is Optical Coherence Tomography (OCT).

The English Diabetic Eye Screening programme (EDESP) involves taking two-field (disc- and macula-centred) 45° colour fundus photographs using pupil dilation (mydriasis) that are manually assessed by human graders. These photographs are graded as follows, in order of progression:

- no retinopathy (R0)

- background retinopathy (R1)
- pre-proliferative retinopathy (R2)
- proliferative retinopathy (R3; R3A (active); R3S (treated and stable))
- no maculopathy (M0)
- maculopathy (M1) - early maculopathy (does not require treatment) or clinically significant macular oedema (requires treatment)



a) One standard 45° fundus image (Scottish Diabetic Eye Screening Programme); b) Two 45° fundus images combined creating 60° field of view (NHS Diabetic Eye Screening programme); adapted from Scanlon 2017 (2)

Figure 1 Photographic fields.

The EDESP screening pathway is depicted in Figure 2 while Figure 3 provides a more detailed picture of the grading part of the pathway. More information about the EDESP can be found in the “*NHS Diabetic Eye Screening Programme Overview of patient pathway, grading pathway, surveillance pathways and referral pathways*” (10).

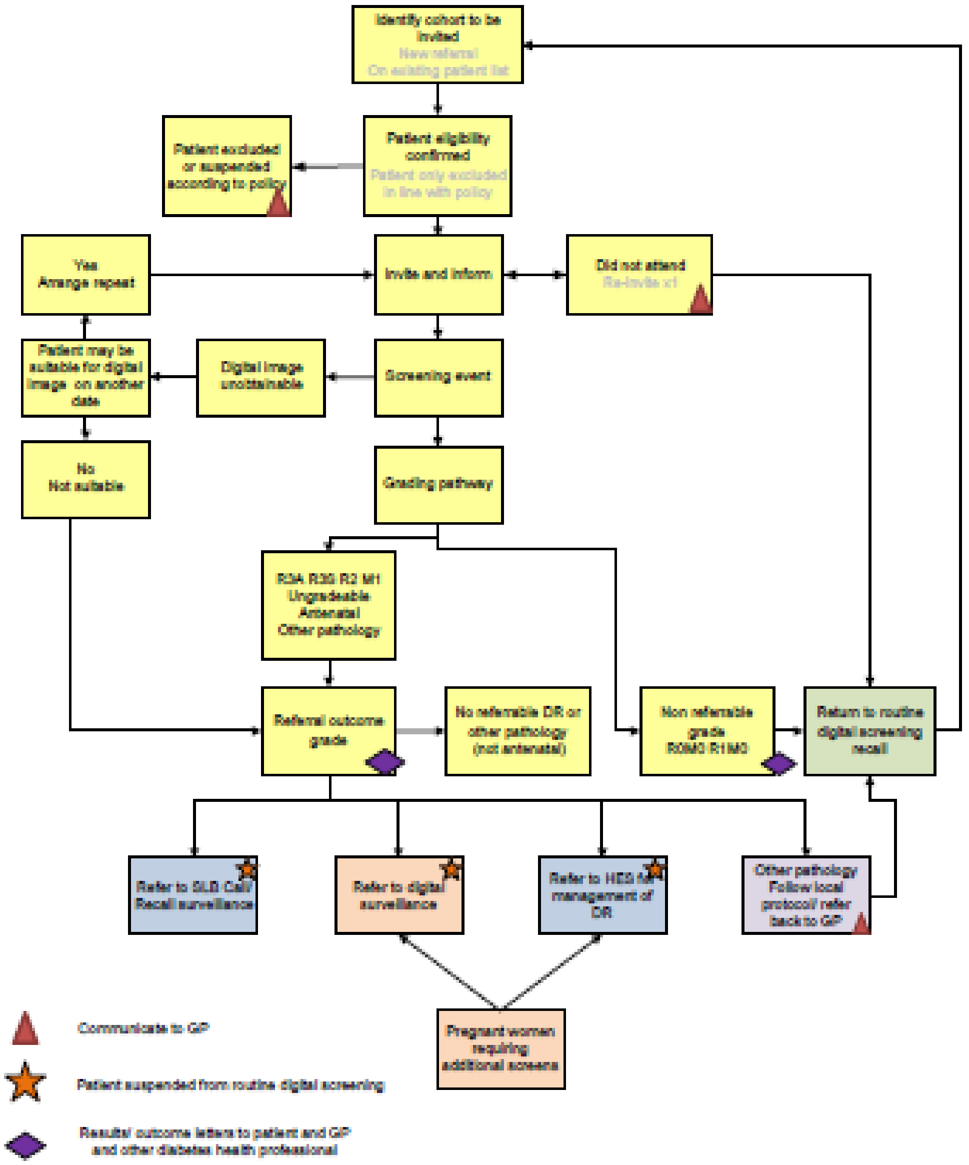

Identify cohort to be invited
New referral
On existing patient list
Patient excluded or suspended according to policy
Patient eligibility confirmed
Patient only excluded in line with policy
Yes
Arrange repeat
Invite and inform
Did not attend
Re-invite x1
Patient may be suitable for digital image on another date
Digital image unobtainable
Screening event
No
Not suitable
Grading pathway
R3A R3S R2 M1
Ungradeable
Antenatal
Other pathology
Referral outcome grade
No referable DR or other pathology (not antenatal)
Non referable grade
R0M0 R1M0
Return to routine digital screening recall
Refer to SLB Call/ Recall surveillance
Refer to digital surveillance
Refer to HES for management of DR
Other pathology
Follow local protocol/ refer back to GP
Pregnant women requiring additional screens
Communicate to GP
Patient suspended from routine digital screening
Results/ outcome letters to patient and GP and other diabetes health professional

Figure 2 Patient pathway in the EDESP (PHE 2017)

Patients who are graded R0M0 or R1M0 in the more severely graded eye are invited to return for rescreen after 12 months. Screening for diabetic eye disease was introduced at annual intervals for pragmatic and administrative reasons. However, the evidence base to support this interval was very limited. In 2016, the UK NSC recommended to extend the screening intervals to 2 years in patients with low risk of developing sight-threatening diabetic eye disease but this recommendation has not yet been implemented within the EDESP (11).

Patients graded R2 or those who have early maculopathy (M1) are referred to either the Hospital Eye Service (HES) or Digital Surveillance (DS) clinic where they are kept under surveillance and screened more frequently (every 3-6 months) to monitor the progression of diabetic retinopathy or maculopathy. DS clinics or HES may interface with OCT assessment to detect maculopathy. The use of OCT is not currently included in the EDESP but can be added if commissioned by the local Clinical Commissioning Groups therefore practices vary across the country.

Patients with active proliferative retinopathy (R3A) or those who have clinically significant macular oedema (M1) are referred to HES for treatment which involves laser photocoagulation or injections of anti–vascular endothelial growth factor drugs (12). If digital images are not clear enough to allow the image of the retina to be graded, then a second test using a method called slit lamp biomicroscopy will be required.

A common grading pathway of fundus photographs is shown in Figure 3. It includes multi-level manual grading systems. All fundus photographs are reviewed by level 1 graders. Level 2 graders review fundus photographs of patients who were graded as R1, R2, R3, and M1 by level 1 graders. Level 2 graders also review all ungradable photographs, as determined by level 1 graders, and 10% of photographs which were graded as R0 by level 1 graders for quality control. Discrepancies between level 1 and level 2 graders are reviewed by level 3 graders. Based on these grades, patients are referred according to the pathway described above.

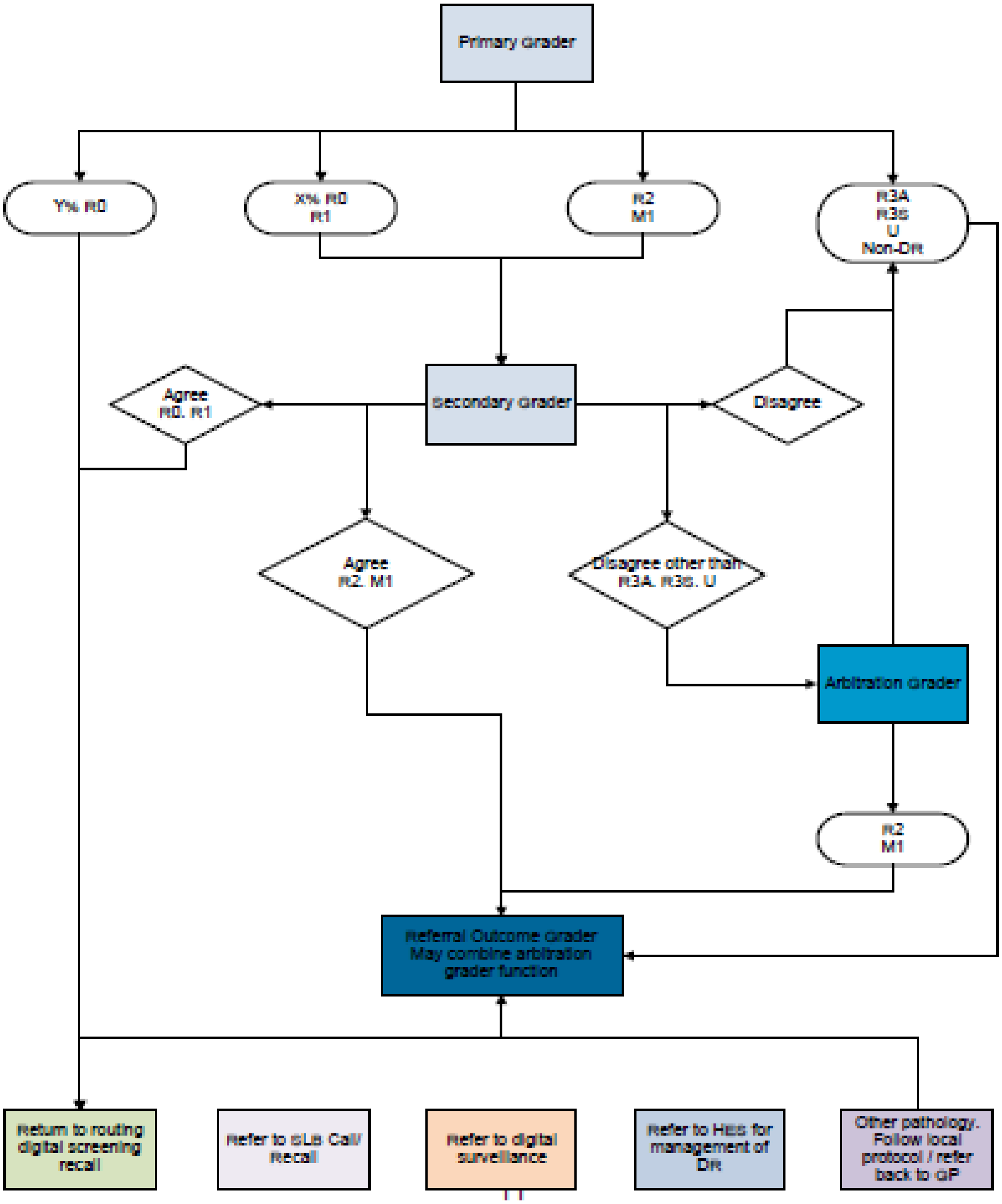


Figure 3 Single common grading pathway in EDESP (PHE 2017)

Proposal for a major modification to the EDESP

DESPs are labour intensive and the number of individuals with diabetes mellitus are projected to escalate in future. For the EDESP to cope with the increasing demand, the UK NSC received a proposal to modify the EDESP by replacing level 1 graders with ARIASs to triage patients into low and high-risk cases. The proposal suggested that incorporating ARIAS in the screening pathway would reduce the need for human graders, thus reducing the cost of screening. An HTA assessment conducted by the research group who made the proposal investigated two different roles of ARIAS in the screening pathway: 1) as a replacement of level 1 graders (Figure 4) and 2) as a screen for all images prior to entering the screening programme (Figure 5). The study found both strategies to be cost-effective, with the replacement of level 1 graders being slightly more cost-effective (1).

ARIASs have been used for level 1 grading in the DESPs of Scotland and Portugal and are now considered for clinical use in other countries, such as the USA, The Netherlands, Singapore, Korea, Spain, Thailand and India. The systems used in Scotland (iGradingM) and Portugal (RetmarkerSR) are based on Machine Learning (ML) algorithms which extract from the images pre-specified 'hand-crafted' features, such as microaneurysms, and use the information to classify patients into 'high risk' (referral) and 'low risk' (routine recall) categories. Most of the recently developed systems use Deep Learning (DL) algorithms that do not depend on pre-specified features; instead, they use raw data to build up features that allow for better classification of the images as determined by the reference standard.

In Scotland, eligible patients undergo acuity testing and non-mydriatic (45º image) fundus photography. The stored images undergo 3 levels of grading. Most of level 1 grading is done by ARIAS, which detects microaneurysms and separates the images with disease from those with no disease. Level 2 graders are either optometrists or nurse practitioners who have the appropriate training. They assign the images with no sight-threatening retinopathy to one of the two outcomes: 1) rescreen in 6 months, or 2) rescreen in 12 months. Images with sings of sight-threatening retinopathy or maculopathy which requires referral to hospital are sent to Level 3 graders. The level 3 graders also undertake internal quality assurance of level 1 and level 2 graders with 500 random images from each grader included yearly for internal quality assurance. In addition, once a year all Scottish graders must participate in external quality assurance which involves grading 100 images over a period of 4 weeks (13).

In Portugal, eligible patients complete a small questionnaire and undergo visual acuity testing and the acquisition of two 45º non-mydriatic fundus images per eye. Images are graded at a central reading centre in two steps: 1) automated analysis using RetmarkerSRSR, and 2) human grading. The software separates images with no signs of diabetic retinopathy from those with signs of disease. It also allows comparison within the same retinal location between different screening visits for the same eye and detects disease progression. Images with signs of pathology/evolution are sent for human grading. In addition to the quality assurance process for human graders, there is quality control protocol for the software. A configurable percentage of the images graded by the algorithm as not requiring human grading are randomly selected and sent to human graders who are blinded to this process (14).

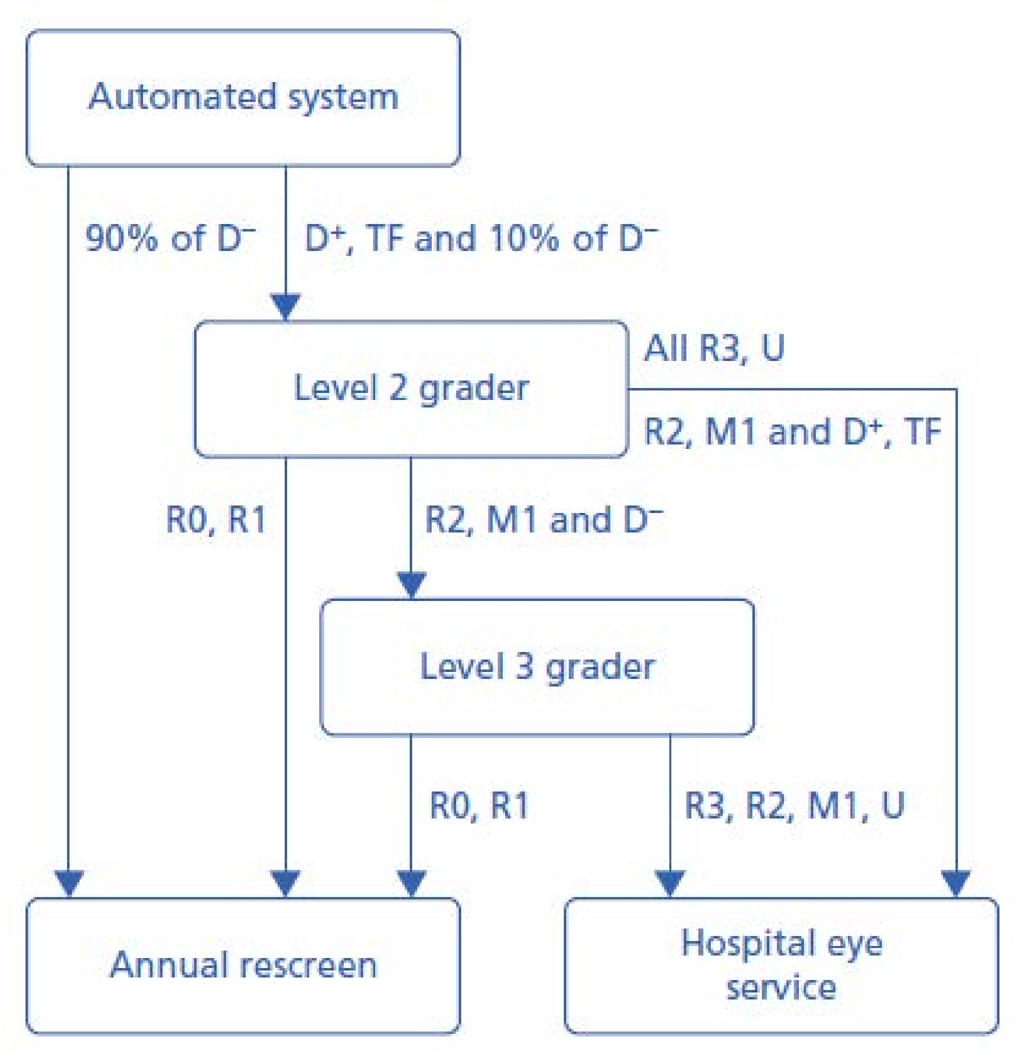


Figure 4 Proposed EDESP modification, replacing level 1 graders with an automated system (Tufail 2016 (1))

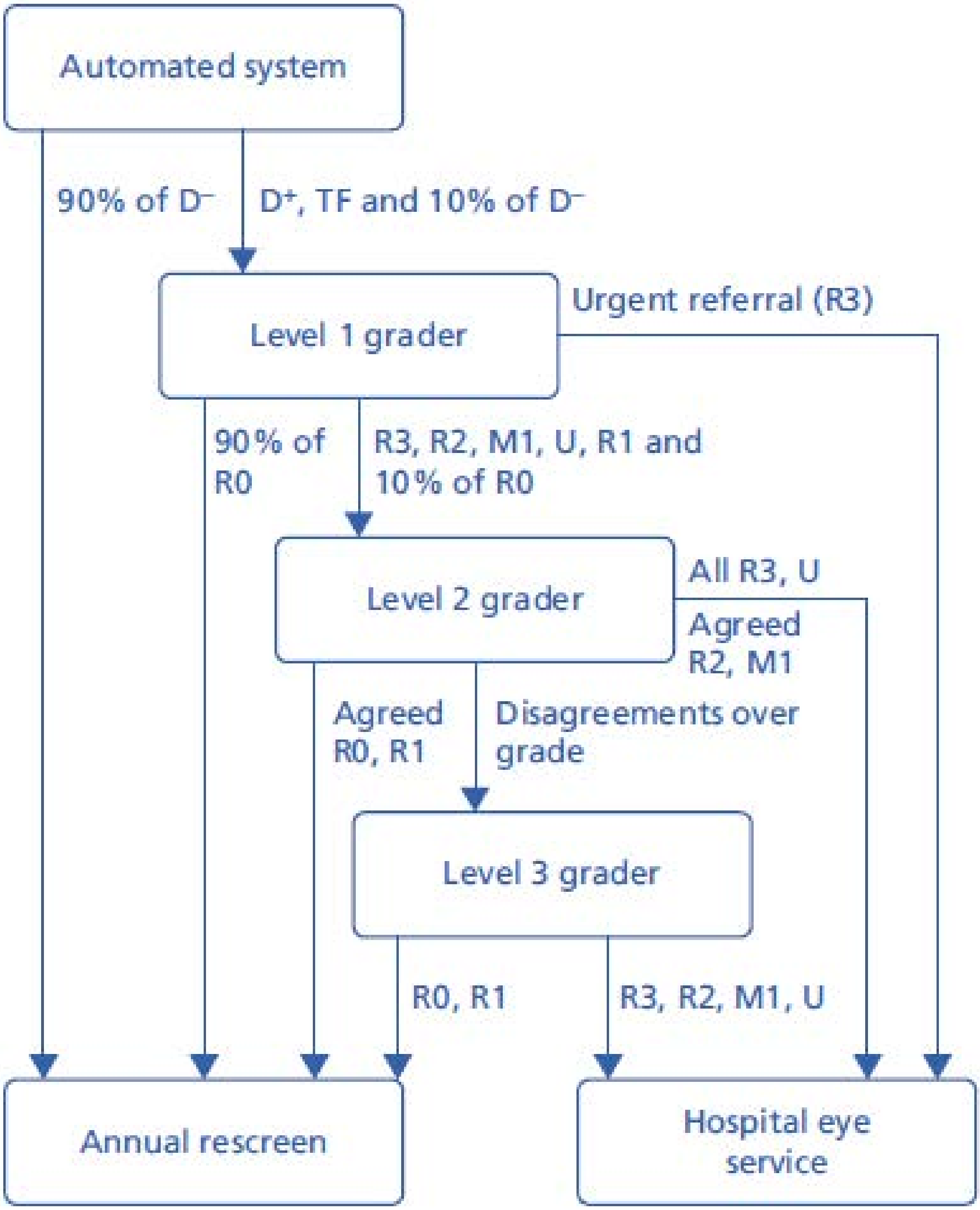


Figure 5 Alternative role of ARIAS investigated in the cost-effectiveness analysis conducted by Tufail 2016 (1)

Objectives

The aim of the current review is to identify and synthesise the evidence on the major modification proposal to the EDESP which involves the replacement of level 1 graders with automation of grading using ARIASs to triage patients into low and high-risk cases. However, the UK NSC will consider the evidence reviewed here in the context of the whole UK. The key questions the review attempts to answer are presented in Table 1 below against the UK NSC screening criteria.

Table 2. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	Question 1: What is the diagnostic accuracy of the automated retinal image analysis systems (ARIASs) at detecting diabetic eye disease in patients with diabetes mellitus?	26
5	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	Question 1	
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (e.g. Down’s syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Question 2: What is the clinical impact of diabetic eye screening programmes with the use of automated retinal image analysis systems (ARIASs) for level 1 grading compared with diabetic eye screening programmes with fully manual grading?	2
12	There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.	Question 2 Question 4: What are the social and ethical implications of implementing artificial intelligence-based tools in screening programmes and would it be acceptable to health professionals and the public?	19 primary studies, 38 reviews / opinion papers
14	The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment	Question 3: What is the cost-effectiveness of replacing level 1 manual graders with an ARIAS in diabetic eye screening programmes compared with diabetic eye screening	5 (UK only)

Criterion	Key questions	Studies Included
against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.	programmes with manual level 1 grading?	

Methods

The current review was conducted by the Exeter Test Group[2] in keeping with the UK NSC evidence review process. Database searches were conducted on 26th June 2020 (the search covering questions 1-3) and 1st and 2nd July 2020 (the search covering question 4) to identify studies relevant to the questions detailed in Table 1. All searches were limited to the period from the beginning of 2000 to the date of the search.

Eligibility for inclusion in the review

The following review process was followed:

1. After removing duplicates, the records identified in the two searches were imported in the EndNote X8.2 (Thomson Reuters) and combined. Each abstract was reviewed against the combined inclusion/exclusion criteria by a single reviewer (ZZ). Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. A second independent reviewer (JP) provided input in cases of uncertainty, and validated 20% of the first reviewer's screening decisions. Any disagreements were resolved by discussion until a consensus was reached.
2. Full-text articles required for the full-text review stage were acquired.
3. Each full-text article was reviewed against the combined inclusion/exclusion criteria by one reviewer (ZZ), who determined whether the article was relevant to one or more of the review questions. A second independent reviewer (JP) provided input in cases of uncertainty, and validated 20% of the first reviewer's screening decisions. Any disagreements were resolved by discussion until a consensus was reached.

Eligibility criteria for each question are presented in Table 2 below.

[2] http://medicine.exeter.ac.uk/testgroup/

Table 2. Inclusion and exclusion criteria for the key questions

Key question	**Inclusion criteria**							**Exclusion criteria**
	Population	**Target condition**	**Intervention**	**Reference Standard**	**Comparator**	**Outcome**	**Study type**	
1. What is the accuracy of ARIAS at detecting diabetic eye disease in patients with DM?	People with type 1 and type 2 DM ≥12 years of age	Referable DR and/or maculopathy (M1, R2, R3) and disease present (R1M0 or worse)	ARIAS	Any	Manual grading, no comparator, head-to-head comparisons of ARIASs	Accuracy measures, overall and at each grade of diabetic retinopathy and maculopathy, where possible	RCTs, prospective or retrospective cohort studies, case-control studies, SRs and meta-analyses	Non-English language, published before 2000, CA, only internal evaluation of ARIAS
2. What is the clinical impact of DESP when level 1 manual grading is replaced by ARIAS?	People with type 1 and type 2 DM ≥12 years of age	N/a	DESP for detection of DR using ARIAS on fundus images for level 1 grading followed by manual grading	N/a	DESP for detection of DR that uses human manual grading on fundus images at all levels	Any clinical utility outcomes	RCTs, cohort studies and SR and meta-analyses of those	Non-English language, published before 2000

3. What is the cost-effectiveness of replacing level 1 manual grading with ARIAS in DESP?	People with type 1 and type 2 DM ≥12 years of age	N/a	DESP for detection of DR using ARIAS on fundus images for level 1 grading followed by manual grading	N/a	DESP for detection of DR that uses human manual grading on fundus images at all levels	Any cost-effectiveness or modelled clinical outcomes	Economic evaluations and reviews of those	Non-English language, published before 2003, non-UK-based evaluations
4. What are the social and ethical implications of implementing AI-based tools in screening programmes?	Health professionals, providers and users of screening programmes, and the general public	Any	Implementation of AI-based tools in any screening programme	N/a	N/a	Social and ethical implications and acceptability	Qualitative studies and opinion and discussion documents	Non-English, published before 2000

AI - Artificial Intelligence, ARIAS - Automated Retinal Image Analysis Systems, CA – Conference Abstract, DESP – Diabetes Eye Screening Programme, DM – Diabetes Mellitus, DR - Diabetic Retinopathy, RCT – Randomised Control Trial, RS - Reference Standard, SR – Systematic Review

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- systematic reviews and meta-analyses: A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2)[‡]
- diagnostic accuracy studies: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Table 35), with additional questions for comparative studies from the pilot version of QUADAS-2C (Table 36); we also categorised studies as prospective or retrospective according to the definition provided in the STARD checklist: "5. Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)"[§]
- interventional non-RCTs: Downs and Black checklist[**]
- RCTs: Cochrane Collaboration's "Risk of Bias" Tool was listed in the protocol but not used in the review as no relevant RCTs were identified.

Databases/sources searched

Two separate search strategies were developed by an information specialist (MR) with experience in healthcare research. The first one covered questions 1-3 (accuracy, effectiveness and cost-effectiveness) combining terms for eye pathology with terms for screening and terms for ARIAS. This search was carried out on MEDLINE (via OvidSp), EMBASE (via OvidSp), the Cochrane Library (CDSR and CENTRAL) and the ClinicalTrials.gov provided by the U.S. National Library of Medicine. We were unable to search the WHO ICTRP trial registry (as stated in our protocol) as the database was not available outside WHO due to the Covid-19 pandemic. The search strategy combined free-text and medical subject headings. The search was limited to the period from the beginning of 2000 to present and was restricted to studies published in English.

The second search aimed to identify studies relevant to question 4 (social and ethical aspects of AI implementation in screening programmes) and combined terms for screening programmes, AI-based tools, and terms relevant to qualitative research, such as experience, perceptions, acceptability or interviews. This search was carried out on MEDLINE (via OvidSp), EMBASE (via OvidSp), CINAHL (via EBSCOhost) and PsycINFO (via OvidSp) and used a combination of free-text and medical subject headings. The search

[‡] https://amstar.ca/
[§] https://www.equator-network.org/reporting-guidelines/stard/
[**] https://bjsm.bmj.com/content/bjsports/52/6/387/DC3/embed/inline-supplementary-material-3.pdf?download=true

was not limited by publication date or language, but only studies published in English since 2000 were considered for inclusion.

We also searched the reference lists of all included studies, systematic reviews and other relevant publications, and emailed authors to check for additional titles (e.g. when a potentially relevant study was recently published as conference abstract). The websites of known ARIAS were also searched and, if necessary, the manufacturer/development team were emailed to request further information.

Results

The search addressing questions 1 to 3 identified 1921 titles of which 544 were excluded as duplicates. The search addressing question 4 yielded 744 titles of which 211 were excluded as duplicates. As the search addressing question 1 to 3 could identify titles relevant to question 4 and vice versa, we combined all unique titles and screened them together. The total number of studies screened at title and abstract level was 1910, of which 397 were selected for full text screening or further assessment (if they related to the evidence map questions). Ultimately, 56 studies were judged to be relevant to question 1 and 28 of them (including two conference abstracts and one FDA approval letter) were prioritised for inclusion in the evidence synthesis; 2 studies were judged to be relevant to question 2; 5 studies (9 publications) to question 3 and 57 studies to question 4; of the latter 19 reported on primary research and 38 were review or opinion papers.

Appendix 2 contains a full PRISMA flow diagram, along with Table 20 which lists all publications included in the review and the questions these publications were identified as being relevant to. Table 22 details the 23 primary studies that met the inclusion criteria for question 1 but were not included in the evidence synthesis (excluded after prioritisation). They were deprioritised because the ARIAS was not commercially available and/or CE-marked or FDA-approved (or we failed to ascertain this); and/or the studies were conducted in populations that are very different from the target population in the UK (e.g. higher prevalence and more severe forms of diabetic retinopathy due to lack of accessible diabetic eye care; or general populations including a large proportion of non-diabetic participants).

We also identified 6 systematic reviews investigating the accuracy of ARIASs that had a similar focus to the current review. Since their inclusion criteria differed from ours, we decided to review the primary studies addressing question 1 rather than to rely on the results from previous systematic reviews. Nevertheless, we summarised the main characteristics and results of these reviews, assessed their methodological quality using the AMSTAR II checklist and report the results in Appendix 5, Table 38 and Table 39; they are included in the total number of 56 studies judged to be relevant to question 1 (Table 20).

Question level synthesis

Criterion 4. There should be a simple, safe, precise and validated screening test. Criterion 5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Question 1 (rapid review) – What is the diagnostic accuracy of the automated retinal image analysis systems (ARIASs) at detecting diabetic eye disease in patients with diabetes mellitus?

Eligibility for inclusion in the review

Studies were included in the review if they met the following inclusion criteria:

- Population: People with type 1 or type 2 DM aged 12 years and over.
- Index tests: ARIAS, alone or in combination with manual grading.
- Comparator: Manual grading, no comparator, head-to-head comparison of ARIASs.
- Outcome measures: Accuracy measures (e.g. sensitivity and specificity), overall and at each grade of diabetic retinopathy and maculopathy, where possible.
- Target condition: Referable diabetic retinopathy and/or maculopathy (e.g. M1, R2, R3) or disease present (R1M0 or higher).
- Reference standard: Any, as defined by the authors.
- Study design: RCTs, prospective or retrospective cohort studies, case-control studies, SRs and meta-analyses (but studies were prioritised by design, see below).

Studies were excluded if:

- They were published in a language other than English, before 2000 or as conference abstracts (we included 2 conference abstracts, Philip 2017 (15) and Lim 2019 (16) and one FDA approval letter (17) which were considered to be of particular importance).
- The algorithm was evaluated in a proportion of the dataset used for development (internal validation). This was a post hoc decision not included in the initial inclusion/exclusion criteria. Although techniques, such as cross-validation, are usually employed to minimise the risk of overfitting, internal validation is more likely to overestimate the performance of the algorithm relative to its performance in clinical practice. We included studies in which the

development and validation datasets came from the same screening programme, but from different patient cohorts.

We prioritised studies for inclusion in the narrative evidence synthesis that evaluated:

- Commercially available ARIASs.
- ARIASs that are CE-marked and/or FDA-approved.
- The latest version of the software.
- ARIAS prospectively.
- ARIAS retrospectively, but in a large dataset derived from consecutive patients attending routine screening within a national screening programme.
- ARIAS in the UK.

The rest of the section is structured as follows: 1) we describe the volume and type of evidence considered to be relevant to this question; 2) we summarise the findings from studies evaluating ARIASs based on DL algorithms; 3) we summarise the findings from studies evaluating ARIASs based on traditional ML algorithms; 4) we discuss studies comparing ARIAS to human graders not involved in the reference grading; and, finally, we discuss the findings from the reviewed accuracy studies and state our conclusions regarding criteria 4 and 5.

Description of the evidence

Fifty six studies were judged to be relevant to question 1. Of those 28 studies were prioritised and included in the narrative synthesis. They evaluated 10 ARIASs: 7 DL-based systems and 4 systems based on traditional ML algorithms (two versions of EyeArt were included: an earlier ML-based version and the current DL-based version). One of the studies, Lim 2019 (16) was published only as a conference abstract including limited information on methods and results; however, a full description of the study and detailed results were included in the FDA approval letter published after our search date, which also contained detailed description of the system, information from a precision study (repeatability and reproducibility) and human factors validation testing (17).

DL-based ARIAS

Sixteen studies in total evaluated 7 DL-based ARIAS: EyeArt v2.1 (n=5 studies), EyeGrader (n=1), IDx-DR v2 (n=4), Google AI (n=2), RedCAD (n=1), SELENA (n= 2) and VUNO (n=1). Son 2020 (18) (VUNO) report accuracy estimates only at the level of individual lesions. However, we decided to include this study as the system is commercially available, CE-marked and approved by the Korea Ministry of Food and Drug Safety; and it uses a slightly different approach in which a wider range of conditions are targeted. The characteristics of the included studies, the results from their methodological quality assessment and the reported accuracy estimates are summarised in Table 3, Table 4 and Table 5, respectively.

Only 2 studies, both evaluating EyeArt v2.1, were conducted in the UK: Heydon 2020 (19) which was a large prospective multi-centre study and Olivera-Barrios 2020 (20) which was a retrospective study comparing the performance of EyeArt v2.1 when used with the EDESP photographic protocol and an alternative widefield platform. The rest of the studies were conducted in the USA (n=5), the Netherlands (n=3), Singapore (n=2, but in the same cohort), and 1 each in Australia, Korea and Spain. Ting 2017 (Singapore) also reported results from 10 additional cohorts, mainly from counties with no established DESPs, in which various reference standards were used. The latter are not included in this section, but a brief summary of the results is provided in Table 27.

Only EyeArt v2.1 and IDx-DR v2 were evaluated in prospective clinical studies: Heydon 2020 (19) (UK), Lim 2019 (16) (USA) and Liu 2020 (21) (USA) evaluated EyeArt v2.1, and Abramoff 2018 (22) (USA) and van der Heijden 2018 (23) (the Netherlands) evaluated IDx-DR v2. We defined study design as 'prospective' or 'retrospective' according to the definition provided in the STARD checklist: "*5. Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)*"[††] None of the prospective clinical studies compared the performance of alternative ARIASs in the same cohort of patients. Three studies compared ARIAS to manual graders not involved in the reference grading: Krause 2018 (24) (Google AI), Ting 2017 (25) (SELENA) and Gonzalez-Gonzalo 2020 (26) (RetCAD) (the results are presented in the section *Studies comparing an ARIAS to human graders not involved in the reference grading* below).

The number of participants ranged from 96 (27) to >30 000 (19). There was considerable variation in study characteristics in terms of:

- Participants: selection (e.g. publicly available datasets providing limited background information, such as MESSIDOR; proprietary datasets collected prospectively or retrospectively, from a single or multiple cohorts, with or without prior selection and enrichment of the sample); demographics (e.g. type and duration of diabetes, racial composition), prevalence and spectrum of retinopathy.
- Screening pathway and protocol: setting (the majority were conducted within a national screening programme and/or primary care setting); photographic protocols (e.g. 1-, 2- or 3-field; use of mydriasis; camera; reimaging in case of technical failure); pre-selection of images (e.g. including only some of the available images per eye), handling of the images determined to be ungradable by the ARIAS

[††] https://www.equator-network.org/wp-content/uploads/2015/03/STARD-2015-checklist.pdf

(included or excluded; reported separately or combined with the referrals), grading scheme (e.g. EDESP, SDESP, ICDR, ETDRS).

- Reference standard: technology (type of fundus photography and photographic protocol, use of OCT to diagnose DMO); background, training and experience of graders; single vs. multiple independent graders; routine manual grading vs. dedicated study graders; method of arriving at the final grade, such as majority voting vs. consensus vs. multi-level grading (e.g. EDESP); handling of ungradable images (as determined by the reference standard).

All these sources of variation are likely to affect the performance of ARIASs, especially when the system is evaluated away from the setting in which it was developed and initially evaluated. Some of these factors have been investigated in the included studies or other publications and their impact on the performance of the systems have been reported. To avoid overwhelming the reader with too much detail, we summarised these sources of variation (and, in some cases, bias) and report them separately in Appendix 5 (*Factors reported to affect the performance of ARIAS*), with references to the respective publications.

The results from the QUADAS-2 assessment of the included studies are presented in Table 4 below. Most of the studies were considered to be at high or unclear risk of bias in the Patient Selection domain as they did not include unselected consecutive patients or failed to report the selection process in sufficient detail. Since we could not determine whether the mix of patients in non-UK studies was similar to that in the UK DESP in all significant ways, we graded such studies 'unclear' for applicability concerns except for studies with clear indication of limited applicability. Most of the studies were judged to be at low risk of bias in the Index Test domain (as the performance of ARIAS was independent from the reference standard or manual graders), but applicability was graded 'unclear' or 'high' in 7 of the studies as the screening protocol differed significantly from the one used in the UK EDESP or no sufficient information was provided in the paper to make such a judgement.

As mentioned earlier, there was considerable variation in the reference standards used across studies (see Appendix 5). We judged studies to be at low risk of bias in the Reference Standard domain if the reference grading involved a panel of experts (ophthalmologists or retinal specialists) blinded to the ARIAS results who independently graded all images and used a pre-specified protocol to resolve disagreements; we also considered studies to be at low risk of bias when the final grade from routine manual grading within a national screening programme (such as EDESP) was used as a reference standard. Initially, the latter criterion also required external arbitration of disagreements between ARIAS and the manual grading. This condition was included because a study conducted in the UK, Tufail 2016 (1), reported some disagreements between the final grades from the EDESP and those from the Doheny Image Reading Centre (USA) where the external arbitration was carried out. However, the disagreements had little impact on the reported accuracy estimates and for most of the results the EDESP graders and the external adjudicators agreed. After discussion with experts in the field, it was agreed that if a national screening programme uses multi-level grading and established training and quality assurance procedures, as in the EDESP, the risk of bias is low and an external arbitration is not necessary. According to these final criteria, 5 studies were judged to be at ‘high’ and another 2 at ‘unclear’ risk of bias in the Reference Standard domain.

However, these results should be interpreted with caution as the above criteria were selected for pragmatic reasons and do not take account of the photographic protocol used as part of the reference standard. In all but 2 studies the reference standard involved the same 1- to 3-field non-stereoscopic fundus photography used in screening. Only Abramoff 2018 (22) (IDx-DR v2) and Lim 2019 (16) (EyeArt v2.1) used a superior reference standard: a widefield stereoscopic retinal imaging protocol (4W-D), that included 4 stereoscopic pairs of digital images per eye, each pair covering 45–60° (equivalent to the area of the retina covered by the modified 7-field stereo protocol); the images were graded by experienced and certified readers at a Fundus Photograph Reading Centre. In Abramoff 2018, 3 readers graded the images independently and used majority voting to arrive at the final grade. In Lim 2019, 2 readers graded the images independently and a third reader adjudicated any disagreements. In Abramoff 2020 the performance of IDx-DR v2 was tested against two reference standards: ‘4W-D fundus imaging only’ and ‘4W-D fundus imaging + OCT’ (for diagnosis of DMO). The variation in the reference standard across studies is likely to affect the reported accuracy estimates and should be taken into consideration when comparing results from different studies.

With regards to the Flow and Timing domain, the main issue was that in some studies images determined as ungradable, either by the ARIAS or by the reference standard, were excluded from the analysis, which could lead to biased accuracy estimates.

Across all studies, sensitivity for referable diabetic retinopathy was consistently >90%. There were 3 exceptions, all relating to the IDx-DR v2 system. Abramoff 2018 (USA) reported 87.2% (95% CI, 81.8–91.2%) sensitivity against the 4W-D reference standard and 85.9% (95%% CI, 82.5%–88.7%) against the composite reference standard of ‘4W-D & OCT’. In both cases the reported sensitivities exceeded the pre-specified goal of >85% sensitivity. Verbraak 2019 (the Netherlands) reported that there were 13 false negative results with a single isolated haemorrhage or cotton wool spot and no microaneurysms, leading to sensitivity of 79.4% (95% CI 66.5–87.9). van der Heijden 2018 (the Netherlands) reported considerable difference in sensitivity when ICDR and EURODIAB criteria were applied, 68% (95% CI: 0.56–0.79) and 91% (95% CI: 0.69–0.98), respectively. The latter also demonstrated that the main source of disagreement was the interpretation of any single haemorrhage as ‘more than microaneurysms alone’ which, following the ICDR criteria, led to the diagnosis of moderate diabetic retinopathy.

The specificity ranged considerably, from 54.0% (95% CI, 53.4% to 54.5%) for R0M0 & R1M0 in Heydon 2020 (UK; EyeArt v2.1) to >95% in some studies, which reflects the inclusion/exclusion of ungradable images and other sources of variation. The relatively low specificity in Heydon 2020 is most likely due to the fact that all images that would normally be sent for manual grading were fed to the ARIAS and included in the analysis.
The two studies that used 4W-D protocol in the reference standard reported much higher specificities. Lim 2019 (USA; EyeArt v2.1) reported specificity of 86.5% (95% CI, 84.3% - 88.7%) when ‘dilation-if-ungradable’ protocol was used and 86.0% (95% CI, 83.7% - 88.4%) for ‘no dilation’. Abramoff 2018 (USA; IDx-DR v2) reported specificity of 90.7% (95% CI, 88.3–92.7%) against the reference standard of 4W-D and 90.7% (95% CI, 86.8%–93.5%) against ‘4W-D + OCT’, which remained unaffected (89.8%) in the sensitivity analysis when ungradable images were included.
Finally, van der Heijden 2018 (IDx-DR) reported that specificity was comparable (86% and 84%, respectively) when using the ICDR and EURODIAB criteria.

The picture was similar when considering the results for vision-threatening diabetic retinopathy. Most studies reported sensitivity of around or more than 95% including Abramoff 2018 (IDx-DR) against both reference standards (‘4W-D’ and ‘4W-D & OCT’).
Lim 2019 (EyeArt v2.1) did not report results for vtDR, but data from the same study provided in the FDA approval letter (17) showed considerable variability, with sensitivity ranging from 78.6% to 100% (reported separately for different cohorts and settings, with wide CIs due to the small samples sizes per cohort). Another exception was van der Heijden 2018 (IDx-DR v2, the Netherlands) who reported sensitivity of 64% (36%–86%) using the EURODIAB criteria and 62% (32%–85%) using the ICDR criteria. The reason for these very different results was unclear from the paper.
Given the considerable number of factors that may affect the performance of ARIASs (discussed earlier), it would be safer to assume that the accuracy of the systems is likely to vary from setting to setting, as illustrated by the studies evaluating IDx-DR v2. Of all included studies evaluating DL-based ARIASs, we considered only Heydon 2020 to be of sufficient quality and to allow direct generalisation of the results to the EDESP. Hence, we provide further details on this study below.

Heydon 2020 (EyeArt v2.1, EDESP)
Heydon 2020 included a cohort of 30 405 consecutive patient episodes from 3 current EDESP centres (North East London [NEL], South East London [SEL] and Gloucestershire) which had slightly different populations in terms of age, sex, ethnicity, uptake of screening

and prevalence of diabetic retinopathy. The software was run in parallel to usual care, without a comparator group. The reference standard was the final outcome from the manual grading at each centre. The study was considered to have no applicability concerns and to be at low risk of bias in all domains.

Particular strengths of Heydon 2020 were that 3 different EDESP centres were involved, allowing for investigation of between-centre performance. Also, all images captured for each eye in the episode were included in the dataset without any editing or selection prior to being processed with the EyeArt v2.1; and none of the poor quality images or those classified as ungradable by human graders were excluded.

For referable disease (M1, R2, R3) sensitivity was 95.7% (95%CI 94.8% to 96.5%) and specificity (for the combination of R0M0 and R1M0) was 54.0% (95%CI 53.4% to 54.5%). The system had sensitivity of 100% (95%CI 98.7% to 100%) for R2 and 100% (95%CI 97.9% to 100%) for R3, and was able to identify 89.4% (95%CI 87.0% to 91.5%) of the images classified as 'ungradable' by human graders. The accuracy was similar across the 3 centres. Although no subgroup analysis was reported in the paper, the authors provided additional information included here verbatim:

"*In Heydon 2020 as all R2 and R3 were test positive it was not possible to investigate any differences with sex/age/ethnic differences in ARIAS performance. Only 17 cases of R1M1 were test negative – hence again in this sample of 30,000 with high sensitivity there is no scope to explore sex/age/ethnic differences in ARIAS performance. For R1M0 and R0M0 there was no difference in ARIAS performance by sex but individuals of older age were more likely to test positive and hence would require manual grading of images. In NEL DESP patients of Black African Caribbean (BAC) ethnicity were more likely than South Asians and Whites to have a test positive ARIAS results for R1 and R0 (49.9% vs 45.7% vs 46.3% respectively) but this equates to a maximum difference 4 percentage points meaning that a slightly higher proportion of BAC would require manual grading after ARIAS. Whereas in SEL patients of South Asian ethnicity were more likely than White or BAC to test positive with ARIAS in presence of R1 or R0 (47.9% vs 51.6% vs 47.1% respectively) and hence require manual grading after ARIAS."* (Heydon et al, personal communication).

The authors estimated that approximately 50% of all screening episodes would require further human grading (which ranged from 47% to 51% across the 3 centres) and will not result in an increased workload for the secondary grader while the workload of the tertiary grader (arbitration) is likely to reduce (19). According to the authors "*The observation that currently 40-50% of level 1 (primary) grading passes to the level 2 (secondary) grader agrees with observation in other NHS DESP centres (ARR Personal communication with* *programme leads at North East London and Gloucestershire DESPs)*” (personal communication).

Table 3 Studies evaluating DL-based ARIASs

Study	Country	Setting	Prospective study*	Compared to humans	N of patients	Photographic protocol	Reference standard
EyeArt v2							
Heydon 2020	UK	EDESP	Yes	No	30 000** (30 405 episodes)	2 fields (EDESP)	The final grade from the EDESP manual grading
Olvera-Barrios 2020	UK	EDESP	No	No	1257	2 fields (EDESP); 100% mydriasis	The final grade from the EDESP manual grading
Lim 2019 and FDA 2020	USA	Primary care and general ophthalmology	Yes	No	893 (1718 eyes***)	2 fields; results reported for no dilation and dilation-if-ungradable	FPRC using 4W-D protocol and independent grading with adjudication
Liu 2020	USA	Primary Care	Yes	No	180	Unclear; no mydriasis	A single fellowship-trained retina specialist (1 out of 5, relation to setting unclear)
Bhaskaranand 2019	USA	EyePACS	No	No	n/a (101 710 episodes)	3 fields; 45.8% mydriasis	EyePACS certified graders (192 assessed externally)
EyeGrader							
Keel 2018	Australia	2 urban endocrinology departments	Yes	Yes (but not reported in detail)	96	1-field; no mydriasis	A single ophthalmologist
IDx-DR							
Abramoff 2018	USA	Primary care	Yes	No	892****	2 fields; 23.6% mydriasis	FPRC using 4W-D protocol and independent grading with adjudication; OCT for DMO
van der Heijden 2018	The Netherlands	Primary care	Yes	No	898	2 fields; mydriasis if needed	3 retinal specialist
Verbraak 2019	The Netherlands	Primary care	No	No	1425	2 fields; mydriasis if needed	2 readers adjudicated by retinal specialist
Shah 2020a	Spain	Primary care	No	No	2680	2 fields; mydriasis if needed	3 ophthalmologists, adjudication by retinal specialist
Google AI							
Krause 2018	USA	EyePACS	No	Yes	998	1 field	3 retinal specialists
Raumviboonsuk 2019	Thailand	Diabetes registry	No	Yes	7517	1 field	Regional graders, subsets adjudicated by retinal specialists
RedCAD							
Gonzalez-Gonzalo 2020	The Netherlands	MESSIDOR 1&2	No	No	1200 + 874	1 field	Dataset ground truth
SELENA							

Study	Country	Setting	Prospective study*	Compared to humans	N of patients	Photographic protocol	Reference standard
Ting 2017	Singapore + other	SiDPR + 10 other	No	Yes	8589*****	2 fields	SIDPR: Single retinal specialist; other cohorts – routine grading
Yip 2020	Singapore	SiDPR	No	No	n/a (455 491 images)	2 fields	As in Ting 2017 (alternative protocols applied to the same cohort)
VUNO							
Son 2020	Korea	IDRiD, e-ophtha	No	No	IDRid: 143, e-ophta: 434	unclear	unclear

*Prospective study design' is defined according the definition provided in the STARD checklist (see p. 36)
**The number of patients (n = 30 000) in Heydon 2020 is given only in the title, but the exact number is not reported in the paper.
***After excluding the images classified as 'ungradable' by the reference standard; the cohort combined sequential enrolment cohort and enrichment permitted cohort; the FDA approval letter reporting on the same study but included only 655 participants; the result of the participants were excluded "better align the analysis population with the proposed intended use population" (p. 4); excluded from the analysis were patients younger than 22 years, patients enrolled at retinal sites and patients with recorded history of DR; there were some discrepancies in the numbers reported in Lim 2019 and in the FDA letter (17).
**** To recruit sufficient numbers of mtmDR participants Abramoff 2018 used an enrichment strategy actively seeking higher risk participants with elevated HbA1c (>9.0%) levels or elevated fasting plasma glucose; the enrichment was independently activated by the statistician while always remaining masked to the ARIAS outputs and the disease levels.
*****The main analysis in Ting 2020 was based on 14 880 patients, of whom 8589 were unique patients (not involved in the development of SELENA); only the results from this sensitivity analysis are included in results reported here.

Publicly available datasets: e-ophta; MESSIDOR – Méthodes d'Évaluation de Systèmes de Segmentation et d'Indexation Dédiées à l'Ophtalmologie Rétinienne; IDRiD - Indian Diabetic Retinopathy Image Dataset
Abbreviations: EDESP – English Dieabetic Eye Screening Programme, DM – Diabetes Mellitus, DMO - Diabetic Macular Oedema, FPRC - Fundus Photograph Reading Centre, OCT – Optical Coherence Tomography, SiDRP - Singapore National Diabetic Retinopathy Screening Program

Table 4 Results from the methodological quality assessment using QUADAS-2 checklist of studies evaluating the accuracy of DL-based ARIASs

ARIAS	Study	PS: RB	PS: A	IT: RB	IT: A	RS: RB	RS: A	F&T: RB
EyeArt v2	Bhaskaranand 2019	🟥 High	🟨	🟨	🟥	🟥	🟩	🟩
	Heydon 2020	🟩 Low	🟩	🟩	🟩	🟩	🟩	🟩
	Liu 2020	🟨 Unclear	🟨	🟩	🟨	🟥	🟩	🟩
	Lim 2019 & DFA 2020	🟥	🟨	🟩	🟨	🟩	🟩	🟨
	Olvera-Barrios 2020	🟥	🟩	🟩	🟩	🟩	🟩	🟩
EyeGrader	Keel 2018	🟥	🟨	🟩	🟨	🟥	🟩	🟩
GoogleAI	Krause 2018	🟨	🟨	🟩	🟩	🟩	🟩	🟥
	Raumviboonsuk 2019	🟨	🟨	🟩	🟩	🟩	🟩	🟥
IDx-DR	Abramoff 2018	🟥	🟨	🟩	🟩	🟩	🟩	🟩
	van der Heijden 2018	🟩	🟨	🟩	🟥	🟩	🟩	🟥
	Verbraak 2019	🟩	🟨	🟩	🟩	🟩	🟩	🟥
	Shah 2020a	🟨	🟨	🟩	🟩	🟩	🟩	🟥
RedCAD	Gonzalez-Gonzalo 2020	🟥	🟥	🟩	🟨	🟨	🟩	🟨
SELENA	Ting 2017*	🟨	🟨	🟩	🟩	🟥	🟩	🟩
	Yip 2020	🟨	🟨	🟩	🟩	🟥	🟩	🟩
VUNO	Son 2020	🟨	🟥	🟨	🟨	🟨	🟨	🟨

* SiDRP dataset only; PS – Patient selection, IT – Index test, RS – Reference standard, F&T – Flow and timing, RB – risk of bias; A – Applicability concerns; Comparative accuracy is incorporated into each domain according to the questions listed in Table 37, e.g. if 'high RB' then the domain is considered 'high RB'

Table 5 Diagnostic accuracy of the included DL-based ARIASs

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR (95% CI)	Accuracy for other grades (95% CI)
EyeArt v2					
Heydon 2020	UK	30 000* (30 405 episodes)	M1, R2, R3, human-graded ungradable (EDESP)	SE 95.7% (94.8% - 96.5%), SP 54.0% (53.4% - 54.5%) for R0M0 & R1M0	68% (67% - 69%) for R0M0 98.3% (97.3% - 98.9%) for R1M1 100% (98.7% - 100%) for R2 100% (97.9% - 100%) for R3 89.4% (87.0% - 91.5%) for ungradable
Olvera-Barrios 2020**	UK	1257	M1, R2, R3, ungradable (EDESP)	SE 90% (81% - 96%)	n/a
Lim 2019 and FDA 2020	USA	893 (1718 eyes***)	Moderate NPDR or higher (ICDR)	Dilation-if-ungradable: SE 95.5% (92.6% - 98.4%) SP 86.5% (84.3% - 88.7%) Gradability 97.5% (96.4% - 98.5%) No dilation: SE 95.5% (92.4% - 98.5%) SP 86.0% (83.7% - 88.4%) Gradability 87.5% (85.4% - 89.7%)	*Images ungradable by ARIAS are included in SE&SP!* vtDR in the sequentially enrolled cohort Primary care (n=45 subjects): SE 100.0% (51.0% - 100%) SP 93.9% (86.5% - 98.8%) Imageability 96.5% (90.6% - 100.0%) Ophthalmology (n=190 subjects): SE 88.9% (60.0% - 100.0%) SP 92.5% (88.7% - 95.6%) Imageability 98.6% (97.0% - 99.7%) vtDR in enrichment permitted cohort Primary care (n=335 subjects): SE 78.6% (58.8% - 95.8%) SP 89.6% (86.6% - 92.4%) Imageability 96.7% (94.8% - 98.5%) Ophthalmology (n=85 subjects): SE 100.0% (51.0% - 100%) SP 87.0% (80.1% - 93.1%) Imageability 97.0% (92.9% - 100.0%)
Liu 2020	USA	180	Moderate or worse DR or inconclusive screening results (ICDR)	SE 100% (92.3% - 100%) SP 65.7% (57.0% - 73.7%) including inconclusive result	n/a (but reported that 29.4% of the results were inconclusive)
Bhaskaranand 2019	USA	n/a (101 710 episodes)	Moderate or severe NPDR, PDR, and/or clinically significant DMO (ERGS, based on the ETDRS)	SE 91.3% (90.9% – 91.7%) SP 91.1% (90.9% – 91.3%) Mydriatic vs. non-mydriatic: SE 93.0% vs 89.6% (no p-value reported) SP 90.4% vs 91.7%	Treatable DR: Mydriatic vs. non-mydriatic SE 98.8% vs 98.0% Other measures:

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR (95% CI)	Accuracy for other grades (95% CI)
					95.4% of the FNs were moderate NPDR and did not meet the general treatment criteria Severe or proliferative DR (potentially treatable): SE 98.5%, the fraction of FNs in the entire cohort was 0.08%
EyeGrader					
Keel 2018	Australia	96	Moderate NPDR or worse and/or DMO (EDESP)	SE 92.3% (no CIs reported) SP 93.7% (unclear if ungradable images were included)	93/96 (96.9%) had a retinal photograph in at least one eye that was gradable for rDR; 10/93 (10.8%) had gradable images in only one eye according to ARIAS
IDx-DR					
Abramoff 2018	USA	892****	mtmDR defined as: ETDRS level ≥ 35, and/or clinically significant DMO (ETDRS)	SE for mtmDR: 87.2% (81.8% – 91.2%) (pre-specified >85%), against 4W-D fundus imaging RS 85.9% (82.5% – 88.7%) against '4W-D + OCT' RS SP for mtmDR (excluding ungradable by the software or the reading centre): 90.7% (88.3% – 92.7%) (pre-specified >82.5%) against 4W-D fundus imaging RS 90.7% (86.8% – 93.5%) against '4W-D + OCT' RS	SE for vtDR: 97.4% (86.2% – 99.9%) against 4W-D fundus imaging RS 92.2% (81.1% – 97.8%) against '4W-D + OCT' RS Sensitivity analysis (worst case scenario including all intention-to-screen patients and using mtmDR as a threshold): SE 80.7% (76.7% – 84.2%) SP 89.8% (85.9% – 92.7%) Ungradable by the software (after excluding the ungradable by the RS): 33/852
van der Heijden 2018	The Netherlands	898	Moderate or vtDR (ICDR and EURODIAB)	EURODIAB criteria: SE 91% (69% – 98%) SP 84% (81% – 86%) ICDR criteria: SE 68% (56%–79%) SP 86% (84%–88%)	vtDR, EURODIAB criteria: SE 64% (36% – 86%) SP 95% (93% – 96%) vtDR, ICDR criteria: SE 62% (32%–85%) SP 95% (93%–96%) 'Ungradable' by ARIAS: 477/1415 (unclear what proportion of those were also rated 'ungradable' by the RS)
Verbraak 2019	The Netherlands	1425	mtmDR and / or DMO (ICDR)	SE 79.4% (66.5–87.9) SP 93.8% (92.1–94.9)	vtDR: SE 100% (77.1–100) SP 97.8% (96.8–98.5)

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR (95% CI)	Accuracy for other grades (95% CI)
				All 13 FNs had a single isolated haemorrhage or cotton wool spot and no microaneurysms	
Shah 2020a	Spain	2680	Moderate or vtDR and/or DMO (ICDR mapped onto the ETDRS)	SE 100% (97%-100%) SP 81.82% (80%-83%) (ungradable images excluded)	vt DR: SE 100% (95%-100%) SP 94.64% (94%-95%) (ungradable images excluded) Ungradable by the ARIAS: 404/3531
Google AI					
Krause 2018	USA	998	Moderate or worse DR or referable DMO (ICDR)	SE 97.1%, SP 92.3% (ungradable images excluded) Referable DMO: SE 94.9%, SP 94.4%	ARIAS classified 4/16 cases of PDR as severe and 2/50 cases of severe DR as moderate
Raumviboonsuk 2019	Thailand	7517	Moderate or worse DR or referable DMO (ICDR)	SE 96.8% (range: 89.3% – 99.3%) SP 95.6% (range: 98.3% – 98.7%) Referable DMO: SE 95.3% (range: 85.9% – 100.0%) SP 98.2% (range: 94.4% – 99.1%) (ungradable images and cases of other retinal diseases excluded for all results)	Severe or worse NPDR and/or DMO: SE 93.6% (range: 85.2%–98.4%) SP 98.2% (range: 94.8%–99.3%) (similar for PDR and/or DMO) 12.6% of all images were classified by ARIAS as 'ungradable'
RedCAD					
Gonzalez-Gonzalo 2020	The Netherlands	Messidor: 1200; Messidor-2: 874	Stage 2 and 3 (Messidor)	Messidor: SE 92.0% (89.1%-95.9%) SP 92.1% (88.7%-95.2%) Messidor-2: SE 92.6% (88.4%-97.4%) SP 93.4% (89.9%-97.2%) (images classified as 'ungradable' by human graders were excluded)	N/a
SELENA					
Ting 2017	Singapore + other	SiDRP: 8589*****	Moderate NPDR or worse and/or DMO and/or ungradable image (ICDR)	SE 89.56% (85.51%-92.58%) SP 83.49% (82.68%-84.27%)	vtDR: SE100% (90.97%-100.0%) SP 81.4% (80.57%-82.22%)
VUNO					
Son 2020	Korea	IDRiD: 143, e-ophta: 434	N/a	Haemorrhage: E-ophtha: SE 89.2% (83.0%–93.7%) SP 91.4% (87.1%–94.7%) IDRiD: SE 88.9% (77.4%–96.6%)	N/a

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR (95% CI)	Accuracy for other grades (95% CI)
				SP 96.6% (90.5%–99.3%) Hard exudate: E-ophtha: SE 93.6% (82.5%–98.7%) SP 97.1% (85.1%–99.9%) IDRiD: SE 92.6% (82.1%-97.9%) SP 100.0% (95.9%–100%) Cotton wool patch: IDRiD: SE 92.3% (74.9%–99.1%) SP 94.0% (88.1%–97.6%)	

Yip 2020 is not included here as it was an exploratory analysis looking at the impact of different technical factors on the performance of SELENA in the same SiDRP cohort investigated in Ting 2017; detailed results are reported in Table 28
Olvera-Barrios 2020 – specificity not reported; the study compared the performance of EyeArt v2 using the standard EDESP photographic protocol vs. EIDON widefield platform

*The number of patients (n = 30 000) in Heydon 2020 is given only in the title, but the exact number is not reported in the paper.

**Olvera-Barrios 2020 – specificity not reported; the study compared the performance of EyeArt v2 using the standard EDESP photographic protocol vs. EIDON widefield platform

***After excluding the images classified as ‘ungradable’ by the reference standard; the study included 2 sequential enrolment cohorts and 2 enrichment permitted cohorts, recruited in primary care and at general ophthalmology clinics, respectively. The accuracy estimates for referable disease are based on Lim 2019 (16) (conference abstract); it is unclear if the sensitivity and specificity estimates include ‘ungradable’ images. The accuracy estimates for vtDR are based on the FDA approval letter (17) reporting only on 655 patients; SE and SP estimates take into consideration ungradable images; the results are reported separately by cohort and setting, hence the small sample sizes and wide confidence intervals.

**** To recruit sufficient numbers of mtmDR participants Abramoff 2018 used an enrichment strategy actively seeking higher risk participants with elevated HbA1c (>9.0%) levels or elevated fasting plasma glucose; the enrichment was independently activated by the statistician while always remaining masked to the ARIAS outputs and the disease levels.

*****The main analysis in Ting 2020 was based on 14 880 patients, of whom 8589 were unique patients (not involved in the development of SELENA); only the results from this sensitivity analysis are included in results reported here.

Publicly available datasets: e-ophta; MESSIDOR – Méthodes d’Évaluation de Systèmes de Segmentation et d’Indexation Dédiées à l’Ophtalmologie Rétinienne; IDRiD - Indian Diabetic Retinopathy Image Dataset

Abbreviations: CI – confidence interval, EDESP – English Diabetic Eye Screening Programme, DM – Diabetes Mellitus, DMO - Diabetic Macular Oedema, DR – Diabetic Retinopathy, ETDRS - Early Treatment of Diabetic Retinopathy Study, ICDR - International Clinical Diabetic Retinopathy severity scale, mtmDR – more than mild DR, OCT – Optical Coherence Tomography, RS – Reference Standard, SE – Sensitivity, SiDRP - Singapore

<table>
<tr><th>Study</th><th>Country</th><th>N of patients</th><th>Definition of referable disease (criteria)</th><th>Accuracy for referable DR (95% CI)</th><th>Accuracy for other grades (95% CI)</th></tr>
<tr><td colspan="6">National Diabetic Retinopathy Screening Program, SP – Specificity, vtDR – vision-threatening DR, 4W-D - : a widefield stereoscopic fundus imaging protocol, that included 4 stereoscopic pairs of digital images per eye, each pair covering 45–60°</td></tr>
</table>

Traditional ML-based ARIAS

The 4 ARIAS based on traditional ML algorithms (non-DL) included iGradingM and its predecessor the Aberdeen system (n = 7 studies), RetmarkerSR (n = 4), RetinaLyze (n = 2) and EyeArt v1 (n=1). The characteristics of the included studies, the results from their methodological quality assessment and the reported accuracy estimates are summarised in Table 6, Table 7 and Table 8; table 9 compares the performance of the 3 ARIASs evaluated in Tufail 2016 (1).

Of the 7 studies evaluating iGradingM, one was conducted in Spain, 4 in Scotland and 2 in England. However, in Tufail 2016 (1) (EDESP) the system failed to read disc-centred images and no valid accuracy results were reported. Only Philip 2007 (28) had a prospective design and compared the performance of the system against human graders not involved in the reference standard grading (discussed in the following section). One of the studies conducted in Scotland, Fleming 2010a (29), included 33 535 consecutive patients from the SDESP and used the programme’s final grade with external adjudication of discrepant results as a reference standard. Also, one of the studies, Philip 2017 (15), reported data from an internal quality assessment of the system in the SDESP. Unfortunately, the results from the latter were reported only in a conference abstract without any methodological details.

All 4 studies evaluating the RetmarkerSR were retrospective. Three were conducted in Portugal and one, Tufail 2016, in England. We contacted the manufacturer to ascertain that no relevant publications have been missed. They also confirmed that the system has been updated (but was still ML-based) and, therefore, the results from older studies may not necessarily reflect the performance of the current version. Also, the accuracy results reported in Rebeiro 2011 (14) were based on data from routine audit within the Portuguese DESP.

Both studies evaluating the accuracy of RetinaLyze were retrospective: Hansen 2004 (30) was conducted in Denmark and Bouhaimed 2008 in Wales (UK) (31). We found 2 more studies evaluating the same system, Larsen 2003 (32) and Larsen 2007 (33), but they used images taken on a 35-mm colour transparency film and later digitalised, and were eventually excluded from the review. We also contacted the manufacturer who confirmed that the most recent study was Bouhaimed 2008 (31) which evaluated the Retinalyze v.1.0.6.1, validated for commercial use.

We also included data from Tufail 2016 (1) (UK) relating to EyeArt v1, despite the fact that the current version (discussed in the previous section) is v2.1 and is DL-based. Since Tufail 2016 is a large, UK-based study of good methodological quality and the only study comparing directly 3 CE-marked and commercially available ARIASs, we believe that such data might be informative and will provide additional evidence.

Overall, the studies evaluating iGradingM were of better methodological quality compared to those evaluating RetmarkerSR and RetinaLyze. Both studies evaluating RetinaLyze were judged to be at high risk of bias in at least one domain (30, 31), while the risk of bias was low for all domains in 3 of the studies evaluating iGradingM (1, 29, 34) and one of the studies evaluating RetmarkerSR (1). Also, since 7/12 studies were conducted in the UK, they were considered to have no applicability concerns. Tufail 2016 was judged to be at low risk of bias and applicability concerns, including the risk of bias related to comparative accuracy (Table 7).

The sensitivity of iGradingM was consistently >90% for referable diabetic retinopathy and approached 100% for higher grades of retinopathy across all included studies. Philip 2007 (SDESP) reported specificity of 67.4% (95%CI 66.0–68.8), Soto Pedre 2015 (Spain) 68.77% (95%CI 67.18–70.36) while the rest of the studies reported detection rate for individual grades that will translate into similar results. The audit data from the SDESP reported by Philip 2017 was in line with the above results but with lower specificity: sensitivity 97%, specificity 38% and false negative rate ranging from 0 to 0.6% (15). As mentioned earlier, iGradingM failed to read disc-centred images in Tufail 2016, but the results reported by Goatman 2011 (34) who evaluated the system in the EDESP and compared the EDESP and SDESP photographic protocols, were in line with those reported in the Scottish evaluations. The authors of Tufail 2016 explained the different results with pre-processing of the images in Goatman 2011 which was not done in their study (personal communication).

The sensitivity of RetmarkerSR for referable diabetic retinopathy was lower in Tufail 2016 (UK) compared to that reported by the development team in Oliveira 2011 (35) (85% vs 96%) while specificity was comparable (around 50%). Rebeiro 2011 (14) reported audit data from the Portuguese DESP suggesting high negative predictive value (only 11 false negatives cases out of 3,287 screened cases, which translates into 0.3% of quality control cases, 0.02% of the total number of patients screened). The sensitivity of RetinaLyze was variable and depended on the specific setting of the algorithm and the use of mydriasis.

In Tufail 2016 (Table 9), EyeArt v1 achieved the highest sensitivity for both referable diabetic retinopathy and proliferative diabetic retinopathy, but 80% of the patients with ‘no disease’ were classified as ‘referrals’. The RetmarkerSR had much lower sensitivity for referable diabetic retinopathy, but for proliferative disease the sensitivity was comparable to that of EyeArt v1; also, a much higher proportion of patients with ‘no disease’ or those with non-referable diabetic retinopathy were classified as ‘no referral’. The accuracy of EyeArt v1 was not affected by ethnicity, sex or camera type, but sensitivity was marginally lower with increasing patient age. The accuracy of RetmarkerSR appeared to vary with patient age, ethnicity and camera type.

Table 6 Studies evaluating traditional ML-based ARIASs

Study	Country	Setting	Prospective study	Compared to humans	N of patients	Photographic protocol	Reference standard
iGradingM							
Philip 2007	UK, Scotland	SDESP	Yes	Yes	6722	1 field; mydriasis if needed	A single grader (clinical research fellow)
Fleming 2010a	UK, Scotland	SDESP	No	No	33 535	1 field; mydriasis if needed	Manual grading + 2 levels of adjudication of all discrepancies
Fleming 2010b	UK, Scotland	SDESP	No	No	7 586	unclear (probably SDESP)	Manual grading + adjudication
Goatman 2011	UK, England	EDESP	No	No	8271	2 fields; 100% mydriasis	Manual grading + 2 levels of adjudication of all discrepancies
Philip 2017 (CA)	UK, Scotland	SDESP	No*	No	Not reported	Not reported but probably 1 field (SDESP)	Not reported
Soto-Pedre 2015	Spain	SpDESP	No	No	5278	1 field; mydriasis if needed	Manual grading
RetmarkerSR							
Oliveira 2011	Portugal	PDESP	No	No	5386 (289)	2 fields; mydriasis if needed	A single ophthalmologist
Ribeiro 2011	Portugal	PDESP	No*	No	3287	2 fields; mydriasis if needed	Manual grading
Figueiredo 2015	Portugal	PDESP	No	No	11 511 (4 datasets)	2 fields; No mydriasis	Manual grading
RetinaLyze							
Bouhaimed 2008	UK, Wales	WDESP	No	No	100	2 fields; 100% mydriasis	Manual grading
Hansen 2004	Denmark	hospital	No	No	83	5 fields; mydriasis used in 1 arm	2 graders adjudicated by a 3rd one
EyeArt v1, RetmarkerSR, iGradingM							
Tufail 2016	UK, England	EDESP	No	No	20258	2 fields; mydriasis if needed	Manual grading with additional arbitration of discrepancies

*Audit of the performance of ARIAS in a national screening programme

Abbreviations: CA - conference abstract, EDESP – English Diabetic Eye Screening Programme, PDESP – Portuguese Diabetic Eye Screening Programme, SDESP – Scottish Diabetic Eye Screening Programme, SpDESP – Spanish Diabetic Eye Screening Programme, WDESP – Welsh Diabetic Eye Screening Programme

Table 7 Results from the methodological quality assessment using QUADAS-2 checklist of studies evaluating the accuracy of traditional ML-based ARIASs

ARIAS	Study	PS: RB	PS: A	IT: RB	IT: A	RS: RB	RS: A	F&T: RB
iGradingM	Fleming 2010a	🟩	🟩	🟩	🟩	🟩	🟩	🟩
	Fleming 2010b	🟥	🟩	🟩	🟩	🟩	🟩	🟩
	Goatman 2011	🟩	🟩	🟩	🟩	🟩	🟩	🟩
	Soto-Pedre 2015	🟩	🟨	🟩	🟩	🟩	🟩	🟥
	Philip 2007	🟩	🟩	🟩	🟩	🟥	🟩	🟩
	Philip 2017*	🟨 Unclear	🟩	🟨	🟩	🟨	🟩	🟨
RetinaLyze	Bouhaimed 2008	🟩 Low	🟩	🟩	🟩	🟩	🟥	🟩
	Hansen 2004	🟥 High	🟨	🟥	🟥	🟩	🟥	🟩
RetmarkerSR	Figueiredo 2015	🟨	🟨	🟨	🟨	🟩	🟨	🟩
	Oliveira 2011	🟥	🟨	🟩	🟩	🟥	🟩	🟩
	Ribeiro 2011	🟩	🟨	🟩	🟩	🟩	🟩	🟩
RetmarkerSR, EyeArt v1, iGradingM**	Tufail 2016	🟩	🟩	🟩	🟩	🟩	🟩	🟩

*Conference abstract;
**iGradingM failed the evaluation.

Abbreviations: PS – Patient selection, IT – Index test, RS – Reference standard, F&T – Flow and timing, RB – risk of bias; A – Applicability concerns; Comparative accuracy is incorporated into each domain according to the questions listed in Table 37, e.g. if ‘high RB’ then the domain is considered ‘high RB’

Table 8 Diagnostic accuracy of the included traditional ML-based ARIASs

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR	Accuracy for other grades
iGradingM					
Philip 2007	UK, Scotland	6722	M1, R2, M2, R3, R4 (SDESP)	SE 90.5% (95%CI 89.3–91.6) SP 67.4% (95%CI 66.0–68.8)	R1 5.9% (95%CI 84.1–87.5) M1 97.4% (95%CI 90.9–99.3) R2 100% (95%CI 67.6–100) M2 97.2% (95%CI 93.6–98.8) R3 100% (95%CI 91.0–100) R4 100% (95%CI 87.9–100) Technical failure 99.8% (95%CI 99.0–100)
Fleming 2010a	UK, Scotland	33 535	M1 and R2 – rescreen in 6 months; M2, R3, R4 – refer to ophthalmology (SDESP)	Not reported	R0 49.6% (95%CI 48.9-50.3) R1 83.9% (95%CI 83.0-84.6) M1 99.2% (95%CI 97.8- 99.7) R2 100% (95%CI 97.9-100) M2 97.3% (95%CI 96.1-98.1) R3 100% (95%CI 98.8- 100) R4 100% (95%CI 98.1-100) Ungradable 99.8% (95%CI 99.5-99.9)
Fleming 2010b	UK, Scotland	7 586	M1, R2, M2, R3, R4 (SDESP)	Adding exudates (EX) and haemorrhages (HM) to microaneurysms (MA) increased SE for detection of rDR from 94.9% (95% CI 93.5 to 96.0) to 96.6% (95.4 to 97.4), (p=0.001), without affecting manual grading workload	MA+EX+HM (similar for MA alone): R0: 36.8 (95%CI 35.3 to 38.3) R1: 79.0 (95%CI 76.9 to 80.9) M1: 92.2 (95%CI 85.3 to 96.0) M2: 95.9 (95%CI 94.0 to 97.2) R2: 100 (95%CI 82.4 to 100) R3: 98.9 (95%CI 96.8 to 99.6) R4: 97.4 (95%CI 94.4 to 98.8) Technical failure: 98.8 (95%CI 97.6 to 99.4)
Goatman 2011*	UK, England	8271	M1, R2, R3 or ungradable (EDESP)	SE (range) 98.3% (MA/BH/EX, 1field) to 99.3% (MA only, 2 fields)	SE for NPDR and PDR was 100% for all strategies; SE for detecting ungradable images ranged from 97.4% to 99.1% across strategies;

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR	Accuracy for other grades
					‘MA+BH+EX’ x 2-field: R0: 60.2% (95%CI 58.8 - 61.5) R1: 94.2% (95%CI 93.1 to 95.1) ‘MA+BH+EX’ x 1-field: R0: 50.7% (95%CI 49.3 – 52.1) R1: 87.6% (95%CI 86.2 – 88.9)
Philip 2017 (CA)	UK, Scotland	N/a	SDESP (assumed)	SE 97%, SP 38%, FNR of 0 to 0.6%	N/a
Soto-Pedre 2015	Spain	5278	Moderate NPDR or more severe DR and/or suspected maculopathy (ICDR)	SE 94.52% (95%CI 92.56–96.49) SP 68.77% (95%CI 67.18–70.36) (ungradable images excluded)	Ungradable patients: 26.16% (n=1374)
Tufail 2016	UK, England	20258	M1, R2, R3 or ungradable (EDESP)	N/a (the system failed the evaluation as it was not able to read disc-centred images)	N/a
RetmarkerSR					
Tufail 2016	UK, England	20258	M1, R2, R3 or ungradable (EDESP)	SE 85.0% (95% CI 83.6%-86.2%) SP 53% (95% CI 52% to 54%) for R0M0 SP 47.7% (95% CI 47% to 48.5%) for R0M0 & R1M0.	Any retinopathy: SE 73.0% (72.0 - 74.0) PDR (R3): SE 97.9% (95% CI 94.9%-99.1%)
Oliveira 2011	Portugal	5386**	NPDR with maculopathy and PDR (Portuguese DESP)	SE 96.1% (CI 95% 94.39–97.89) SP 51.7% (95% CI 50.27–53.07) 2-step algorithm (n=289) SE 95.8% (95% CI 92.8 - 98.4%) SP 63.2% (95% CI 60.8 -65.7%)	Urgent referrals (n=116) 115 classified as ‘having disease’
Ribeiro 2011	Portugal	3287	NPDR with maculopathy and PDR (Portuguese DESP)	Missed only 11 cases (false negatives) out of 3,287 screened cases (0.3% of quality control cases, 0.02% of total patients)	N/a
Figueiredo 2015	Portugal	11 511***	N/a (most likely Portuguese DESP)	Across the 4 datasets: SE ranged from 89.3% to 100% SP ranged from 57.6% to 73%	N/a
EyeArt v1					
Tufail 2016	UK, England	20258	M1, R2, R3 or ungradable (EDESP)	SE 93.8% (95% CI 92.9 - 94.6)	Any retinopathy: SE 94.7% (95% CI 94.2 - 95.2) PDR (R3): SE 99.6% (95% CI 97.0 - 99.9)
RetinaLyze					

Study	Country	N of patients	Definition of referable disease (criteria)	Accuracy for referable DR	Accuracy for other grades
Bouhaimed 2008	UK, Wales	100	Mild NPDR or worse (≥2a according to the Bro Taf Protocol used in the study)	Red lesions: SE 82%, SP 75%, Red & bright lesions: SE 88%, SP 52%, Red & bright lesions (at elevated thresholds in images of good quality): SE 93%, SP 78%	N/a
Hansen 2004	Denmark	83	Moderate NPDR or worse; DMO not graded (ETDRS)	No mydriasis: SE 89.9%, SP 85.7% (11 'ungradable' eyes and 1 patient with AMD excluded from analysis) Mydriasis: SE 97.0%, SP 75.0%	For moderate NPDR or more severe DR: SE 100% for images captured both with and without pupil dilation

*Compared 4 screening strategies: 1- or 2-field photographs x 'MA' or 'MA/BH/EX'; the 2-field protocol was the standard EDESP protocol
** 289 included in the second step of the algorithm
***4 datasets combined

Abbreviations: BH – blot haemorrhage, DESP – Diabetic Eye Screening Programme, DMO – Diabetic Macular Oedema, DR – Diabetic Retinopathy, EDESP – English Diabetic Eye Screening Programme, EX – exudate, FNR – False Negative Rate, HM – haemorrhage, MA – microaneurysm, NPDR – Non-proliferative Diabetic Retinopathy, PDR – Proliferative Diabetic Retinopathy, rDR – Referable Diabetic Retinopathy, RS – Reference Standard, SDESP – Scottish Diabetic Eye Screening Programme, SE – Sensitivity, SP – Specificity

Table 9 Summary of the results from Tufail 2016 which compared directly 3 ARIASs ('ungradable' images included)

ARIAS	Sensitivity for rDR (95%CI)	Sensitivity for pDR (95%CI)	Sensitivity for any DR (95% CI)	Specificity (95%CI) [equivalent to detection rate of R0&M0&R1M0]	Detection rate for R0M0
EyeArt v1 (preDL)	93.8% (92.9%-94.6%)	99.6% (97.0%-99.9%)	94.7% (94.2% - 95.2%)	15.8% (15.3%-16.4%)	20%
RetmarkerSRSR	85.0% (83.6%-86.2%)	97.9% (94.9%-99.1%)	73.0% (72.0 % - 74.0%)	34.7% (34.0%-35.4%)	53%
iGradingM	Failed the evaluation as all disc-centred images were classified as 'ungradable'				

CI – confidence interval, DL- deep learning, rDR – referable diabetic retinopathy, pDR – proliferative diabetic retinopathy

Studies comparing an ARIAS to human graders not involved in the reference grading

Table 9 summarises the characteristics and results from studies in which an ARIAS was compared to human graders not involved in the reference standard grading. We included 4 such studies: 3 evaluated DL-based ARIASs (Google AI, SELENA and RetCAD) and one evaluated an ARIAS based on traditional ML (iGradingM). The study evaluating iGradingM was the only prospective evaluation and the only study conducted in the UK (Scotland).

None of the studies were considered to be at high risk of bias with respect to comparative accuracy while the other limitations, which applied equally to ARIAS and human graders, have already been reported in the previous sections (see Table 4 and Table 7). On the whole, DL-based ARIASs had higher sensitivities and lower specificities compared to human graders. However, only Ting 2017 (25) reported the statistical significance of these differences (Table 9). Given the differences between DESPs, even in a single country such as the UK (see Table 1), the results from these 3 studies may not be generalizable beyond the settings in which they were conducted.

Therefore, only the results from Philip 2007 (28), the only prospective study evaluating a traditional ML-based ARIAS, are directly relevant to the current review. The study included 6722 consecutive patients from the SDESP and compared the performance of iGradingM against that of 3 human graders from the programme who also performed the photography. The comparison was only at ‘level 1 grading’ and did not compare the performance of the SDESP as a whole (i.e. SDESP with manual grading at level 1 vs SDESP with ARIAS at level 1). As per the SDESP protocol, the images were 45^o 1-field (macula-centred) and pupil dilation was used if necessary. The study was judged to be at low risk of bias except for the Reference Standard domain which was graded as ‘high risk’ because the reference grading was done by a single grader (clinical research fellow).

For referable diabetic retinopathy, iGradingM had sensitivity of 90.5% (95%CI 89.3–91.6) and specificity of 67.4% (95%CI 66.0–68.8). In comparison, the sensitivity of manual grading was 86.5% (95%CI 85.1–87.8) and the specificity 95.3% (95%CI 94.6–95.9). iGradingM and human graders misclassified as normal 240 and 341 patients with diabetic retinopathy, respectively, and the difference was statistically significant (p<0.001); of those with M1, R2, M2, R3 or R4, iGradingM and human graders classified 7/330 and 3/330, respectively, as ‘no retinopathy’ but the difference was not statistically significant (p=0.125).

Table 10 Studies comparing directly the accuracy of the ARIAS and human graders not involved in the reference standard grading

ARIAS: study and country	1. Study design 2. Dataset 3. RS	Comparator	Accuracy of human graders	Accuracy of ARIAS
Google AI: Krause 2018, USA	1. Retrospective cohort study, 2. EyePACS-2: 1958 images from 998 unique individuals 3. Consensus by 3 retinal specialists	3 ophthalmologists, individually and as a majority decision	Accuracy for rDR: Ophthalmologists' majority decision: SE 83.8% SP 98.1% Individual ophthalmologists (range): SE 74.9% to 76.4%, SP 97.5% to 99.1% Accuracy for referable DME: Ophthalmologists' majority decision: SE 83.3% SP 99.0% Individual ophthalmologists (range): SE 62.7% to 86.4%, SP 98.6% to 99.1%	Accuracy for rDR: SE 97.1% SP 92.3% Accuracy for referable DME: SE 94.9% SP 94.4% No statistical comparison reported
RetCAD: Gonzalez-Gonzalo 2020, Spain, The Netherlands	1. Retrospective cohort study 2. Messidor (n=1200) 3. Dataset's ground truth	2 graders, a general ophthalmologist and a retinal specialist, with 4 and 20 years of DR screening experience, respectively	Accuracy for rDR: HG1 SE 79.6% (95%CI 74.8-84.8) SP 97.7% (95%CI 96.0-99.2) HG2 SE 69.0% (95%CI 62.9-74.7) SP 99.1% (95%CI 97.9-100.0)	Accuracy for rDR SE 92.0% (95%CI 89.1-95.9) SP 92.1% (95%CI 88.7-95.2) No statistical comparison reported
Selena: Ting 2017, Singapore and others	1. Retrospective cohort study 2. 8589 unique patients (excl. those used in the development) 3. A single retinal specialist with >5 years experience	2 trained senior nonmedical professional graders with >5 years experience currently employed in the SIDRP	Accuracy for rDR: SE 84.84% (95%CI 81.28-88.51) SP 98.55% (95%CI 98.27-98.79) Accuracy for vtDR: SE 89.74% (95%CI 74.77-96.27) SP 99.09% (95%CI 98.86-99.27)	Accuracy for rDR: SE 89.56% (95%CI 85.51- 92.58), p=0.04 SP 83.49% (95%CI 82.68-84.27), p<0.001 Accuracy for vtDR: SE 100% 100 (95%CI 90.97-100), p=0.04 SP 81.4% (95%CI 80.57-82.22), p<0.001
iGradingM/Aberdeen system: Philip 2007, UK	1. Prospective cohort study 2. 14 406 images from 6722 consecutive patients from the SDESP	3 retinal screeners who also performed the photography	Technical failures: SE 93.7% (95%CI 91.3–95.4) SP 99.0% (95%CI 98.7–99.2) Accuracy for rDR:	Technical failures: SE 99.5% (95%CI 98.4–99.8) SP 84.4% (95%CI 83.5–85.3) Accuracy for rDR:

	3. A single clinical research fellow		SE 86.5% (95%CI 85.1–87.8) SP 95.3% (95%CI 94.6–95.9) N of patients misclassified as normal: 341 N of patients with M1, R2, M2, R3 or R4 graded as 'no retinopathy': 3/330	SE 90.5% (95%CI 89.3–91.6) SP 67.4% (95%CI 66.0–68.8) N of patients misclassified as normal: 240, p<0.001 N of patients with M1, R2, M2, R3 or R4 graded as 'no retinopathy': 7/330, p=0.125
Abbreviations: CI – confidence interval, DR – Diabetic Retinopathy, HG1 – Human Grader 1, HG2 – Human Grader 2, rDR – Referable Diabetic Retinopathy, RS – Reference Standard, SE – Sensitivity, SDESP – Scottish Diabetic Eye Screening Programme, SP – Specificity, vtDR – Vision-threatening Diabetic Retinopathy				

Discussion of findings

There is sufficient evidence from high quality diagnostic accuracy studies that the DL-based system EyeArt v2.1 has sensitivity of around 90%, comparable to that of human graders, and could be safely implemented in the EDESP as a replacement of level 1 human graders or as a filter before level 1 human grading, as suggested in Tufail 2016 (1). The system has been evaluated in multiple studies including a prospective pivotal study that informed the FDA approval (16, 17) and a large UK-based prospective multicentre study, Heydon 2020 (19), that evaluated the performance of the system in realistic EDESP conditions (19). In addition, an earlier version of the system, EyeArt v1, was evaluated by Tufail et al in an EDESP cohort and showed similar sensitivity (1). Particular strengths of Heydon 2020 are that:

- The study included a large consecutively recruited representative cohort with pre-specified sample size based on Tufail 2016 (1).
- There was no selection or editing of the images prior to their processing with EyeArt v2.1 and all images that would normally be sent for manual grading were included.
- The performance of EyeArt v2.1 was shown to be robust across the 3 EDESP sites which varied in a number of ways including mean age and racial composition of the cohorts. Additional subgroup data provided by the authors as well as data from Tufail 2016 (EyeArt v1) show that patient characteristics, such as race and age, and technical factors, such as camera type, have little or no impact on the accuracy of the system.

Depending on whether the system is used to screen out patients with no disease or to differentiate between ‘referable’ and ‘non-referable’ cases, the specificity and the respective workload reduction that could be expected will vary, and is likely to have an impact on the cost-effectiveness of the system.

There is high quality evidence for acceptable sensitivity of two ML-based systems, iGradingM in the SDESP and RetmarkerSR in the EDESP. Both ARIASs are currently used in Scotland and Portugal, respectively, and there is some published evidence that their sensitivity remains high after implementation. However, iGradingM may not be able to work with the EDESP photographic protocol without some additional pre-processing of the images; and the evidence for the performance of RetmarkerSR in the EDESP comes from a single study (1).

We found no high quality studies reporting on the accuracy of the other ARIASs in the UK DESPs. Systems using similar protocols and evaluated in high quality studies in similar settings outside the UK, and especially those evaluated *independently* from the software developer, could be expected to have comparable accuracy in the UK. However, given the large number of contextual factors that could affect the performance of these systems (see

Appendix 5), generalising the results from studies conducted in other countries should be avoided and used only in the initial selection of candidate ARIASs. The selected systems should be evaluated in the DESP in which they are intended to be used.

The evidence on the comparative accuracy of alternative ARIASs is also limited. We identified only one study, Tufail 2016 (1), which compared directly the performance of 3 ML-based ARIASs in a clinical cohort of consecutive participants. Unfortunately, the results from this study may not be applicable to the new versions of the software. Given the considerable clinical heterogeneity across studies, indirect (between-study) comparisons are unlikely to produce valid results and, therefore, the question about the comparative accuracy of ARIASs need to be investigated in future studies.

We did not find any studies that compared the overall performance of DESP with level 1 human graders versus DESP with level 1 ARIAS grading. The comparisons between ARIAS and human graders were limited to level 1 grading, with manual grading often included in the reference standard. The overall impact of replacing level 1 graders with ARIAS was inferred from the accuracy estimates and there was no direct evidence of the actual impact that such replacement may have (including the impact on human behaviour).

One journal article from 2014 reported accuracy data from an internal quality assessment of RetmarkerSR in the Portuguese DESP (14) and one conference abstract from 2017 reported accuracy and usage data for the autograder in the SDESP (which we assumed to be iGradingM, although the system was not explicitly named) (15). Data on the impact that these systems, which have been in used for almost 10 years, on the overall performance of the respective DESPs could be very helpful for future research and policy decisions, and could point to the range of questions that should be considered before the implementation of ARIASs. As mentioned above, the audit data from Scotland indicates that the sensitivity of the system, as observed in the internal quality assessment, was similar to that reported from previous evaluations, while the specificity was at the lower end of the continuum (sensitivity of 97%, specificity of 38% and false negative rate of 0 to 0.6%). The number of episodes handled by the programme had increased by 20.3% in the period from 2010 to 2015 and, in the observed 6-month period in 2015, 58.1% of all episodes were passed on to the autograder (15).

Summary of Findings Relevant to Criteria 4 and 5: Criterion met.

There is sufficient evidence from high quality diagnostic accuracy studies that the DL-based system EyeArt v2.1 has sensitivity of around 90%, comparable to that of human graders, and could be safely implemented in the EDESP as a replacement of level 1 human graders or as a filter before level 1 human grading, as suggested in Tufail 2016 (1). There is also high quality evidence for the acceptable accuracy of iGradingM in the SDESP and RetmarkerSR in the EDESP (although the latter is limited to a single study). Both systems are currently implemented in Scotland and Portugal and there is some published evidence of their 'real life' performance.

There is no high quality evidence for the accuracy of the other ARIASs in the UK DESPs. Given the large number of factors that could affect the performance of these systems and the considerable clinical heterogeneity across studies: 1) the results from studies conducted in other countries should be used only for the initial selection of candidate systems; high quality *independent* evaluations should be prioritised; 2) indirect (between-study) comparison of alternative ARIASs is unlikely to lead to valid results and the comparative accuracy of alternative systems should be assessed directly (in the same study) or in the same cohort under similar, pre-specified conditions.

Criterion 11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an “informed choice” (such as Down’s syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Question 2 (rapid review) – What is the clinical impact of diabetic eye screening programmes with the use of automated retinal image analysis systems (ARIAS) for level 1 grading compared with diabetic eye screening programmes with fully manual grading?

Eligibility for inclusion in the review

Studies were included in the review if they met the following inclusion criteria:

- Population: People with type 1 or type 2 DM aged 12 years and over.
- Intervention: A DESP for the detection of DR and/or maculopathy that uses ARIAS on fundus photographs for level 1 grading followed by manual grading for level 2 and 3.
- Comparator: A DESP for the detection of DR and/or maculopathy that uses human manual grading on fundus photographs for level 1 and all other levels of grading.
- Outcome measures: Any clinical utility outcomes, including clinically significant outcomes and patient management and practical implications outcomes.
- Study design: RCTs, prospective and retrospective cohort studies, and systematic reviews and meta-analyses of these.
- Publication date and language: Studies had to be published in English after 2002.

Description of the evidence

We did not identify any RCTs that investigated the above question. We included 2 prospective cohort studies, both at high risk of bias and of limited applicability (Table 10 and Table 32). Some accuracy studies reported projected impact in terms of workload reduction and other outcomes, but these were non-comparative retrospective cohort studies and the reported outcomes (e.g. workload reduction) were inferred from the reported accuracy estimates.

Table 11 Studies evaluating the impact of implementing ARIAS in a DESP

Study & country	**ARIAS**	**Study design and PICO**	**Outcomes**	**Risk of bias (checklist)**
Keel 2018 (27), Australia	EyeGrader^{TM} (DL-based)	Prospective cohort study, within-patient control: P: 96 patients attending 2 endocrinology departments I: ARIAS-based DR screening providing immediate result to patients C: human grading with results available online in 2 weeks Outcomes: Satisfaction and preference based on a questionnaire, mean assessment time ARIAS-based screening	Mean assessment time for ARIAS-based screening was 6.9 min 96% very satisfied or satisfied 78% preferred ARIAS	High risk of bias: convenience sample, no control group, within-subjects comparison with ARIAS results always provided to the participant first
Liu 2020 (21), USA	EyeArt 2.0 (DL-based)	Prospective cohort study, historical control: P: 180 patients with type 1 or 2 diabetes (≥18 old) at a primary care centre for low-income patients (from January 1, 2018 through August 31, 2018) I: ARIAS-based DR screening C: Historical adherence rate of consecutive adult patients with diabetes seen over a period of 9 months (July 1, 2016, and March 31, 2017), from the same primary care clinic	Among patients referred for a follow-up exam, the adherence rate was 55.4% at 1 year vs. historical adherence rate of 18.7% ($P < 0.0001$). No false negative results were found. 17 patients had additional pathologic features that required evaluation earlier than recommended by ARIAS (as identified by human graders: 9 with grade 1 to 2 hypertensive retinopathy, 2 with AMD, 7 were glaucoma suspects, and 1 with nonspecific chorioretinal scarring.	High risk of bias: possible selection bias; historical controls; patients in the ARIAS cohort received 3 telephone calls and a letter to encourage them to attend; unclear if the same level of encouragement was used in the historical control; 42 patients received their results within 2-weeks of the index test (which could serve as another reminder)

Discussion of findings

Results of the studies are summarised in Table 10 including key methodological issues identified in the quality assessment (reported in full in Table 32). Keel 2018 (Australia) compared the time taken and the acceptability of ARIAS-based DR screening in which the patient is immediately provided with the result, relative to manual grading in which the patient can access the result after 2 weeks. However, there was no control group, i.e. patients served as their own controls, and the study was judged to be at high risk of bias. Liu 2020 (USA) investigated whether using ARIAS to make the result from the examination immediately available to the patient improves adherence to follow-up. However, the study was judged to be at high risk of selection bias; used historical controls and in some cases the result was provided to the patient with considerable delay.

Summary of Findings Relevant to Criterion 11: Criterion not met.[7]

We did not identify any relevant RCTs or high quality prospective cohort studies comparing DESP with level 1 manual grading to DESP with level 1 ARIAS grading in terms of clinical outcomes and overall impact. The two prospective cohort studies included here did not include concurrent comparator groups; were judged to be at high risk of bias; and their results may not generalise to the UK DESP. Future studies should start by clarifying the range of relevant clinical outcomes and other impact measures to be investigated by involving all relevant stakeholders. Large prospective trials may not be feasible and alternative study designs should be explored.

[7] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Question 3 (evidence map) – What is the cost-effectiveness of replacing level 1 manual graders with automated retinal image systems (ARIAS) in diabetic eye screening programmes compared with diabetic eye screening programmes with manual level 1 grading?

Eligibility for inclusion in the review

Studies were included in the review if they met the following inclusion criteria:

- Population: People with type 1 or type 2 DM aged 12 years and over
- Intervention: A DESP for the detection of DR and/or maculopathy that uses ARIAS on fundus photographs for level 1 grading followed by manual grading for level 2 and 3
- Comparator: A DESP for the detection of DR and/or maculopathy that uses human manual grading on fundus photographs for level 1 and all other levels of grading
- Outcome measures: Any cost-effectiveness or modelled clinical outcomes, e.g. NNS, NNT, proportion of appropriate screening outcome (true positive or true negative correctly identified), interval retinopathy or maculopathy, loss of vision, proportion of vision loss prevented, number/proportion of different grades of retinopathy and maculopathy detected (including ungradable), incidental findings
- Country in which the study was conducted: UK (non-UK studies were excluded)
- Study design: Economic evaluations (any type) and reviews of these.
- Publication date and language: Studies have to be published in English after 2002.

Summary of findings

Eighteen references were identified from title/abstract screening as potentially relevant to the evidence map. Nine of these were subsequently excluded: one conference abstract did not report an evaluation of ARIAS (Harding 2019), 3 were review/opinion papers (Scanlon

2019, Sosale 2019, Dismuke 2020) and 6 were not set in the UK (Ballreich 2016, Australia; Fuller 2019, US; Xie 2019 and 2020, Singapore; Andreasen and Kjellberg 2008, Denmark).

The 9 included references report on 5 different evaluations: one reporting separate results for England and Scotland (Olsen 2013, Prescott 2014), one based in England (Tufail 2016 and 2017, Liew 2014, Egan 2016), two based in Scotland (Scotland 2007 and 2010) and one described as based in the UK (Bhaskaranand 2016).

The evaluations generally find automated grading to be less costly than manual grading, but less effective. Therefore, many of the results are reported in terms of the additional costs associated with manual grading to gain additional health benefits when compared to automated grading.

Olson 2013 (36) and Prescott 2014 (37) use data from centres in England and Scotland to compare fully automated grading to the English and Scottish manual grading systems (and a further strategy based on the English system). The focus of the study was the presence of maculopathy in a cohort of patients already diagnosed with diabetic retinopathy. The authors use a Markov microsimulation model with a 20 year time horizon, with costs from year 2009/2010 to conduct a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). In terms of both cost per cases detected and cost per QALYs (after 20 years), Olsen and Prescott estimate that the fully automated system (iGradingM, Medalytix Ltd) dominates the English manual grading system (it is cheaper and more effective). To correct for sampling bias in the Scottish dataset used, the authors adjusted the frequency of different features to reflect expected frequency within a screening programme. They then estimated that the fully adjusted strategy cost an additional £900 per case detected compared to the Scottish manual system. The fully automated system was estimated to cost £113 more than the Scottish manual system and provide incremental QALYs of 0.0005, thus the fully automated system had an ICER of £222,210 compared to the Scottish system.

Tufail 2016 (1) and Tufail 2017 (38) estimate the cost-effectiveness of RetmarkerSR and EyeArt v1 (both ML-based) as replacements for initial human grading (strategy 1) and as filters prior to primary human grading (strategy 2). They use a decision tree model, with a 1-year time horizon and costs from 2013/2014. It is assumed that manual grading is implemented as in the Homerton University Hospital, London. For both ARIASs and strategies, automated grading is estimated to be less costly, but less effective, than manual grading. However, since the overall performance is driven down by the relatively high false positive error rate (while the systems are comparable to manual grading in picking up cases with disease), both systems and strategies are cost-effective and could reduce the requirement for manual grading. For strategy 1 and strategy 2, the reduced cost (relative to manual grading) per appropriate outcome missed by the software was £4.51 and £2.80 with EyeArt and £11.81 and £9.71 with RetmarkerSR, respectively. Appropriate outcomes were defined as either disease present [M1, R2, R3, and U] or absent [R0, R1] which agreed with human graders.

Bhaskaranand 2016 (39) report in a conference abstract the incremental costs for the use of EyeArt v1 (non-DL) compared to fully manual grading strategies (defined to be similar to that in the UK NHS DESP). They conclude that EyeArt v1 could lead to significant cost savings.

Scotland 2007 (40) report a CEA to compare first level manual grading in the Scottish DESP with an automated system (a version of iGradingM). They use a decision tree approach to model the number of referable cases detected and appropriate screening outcomes, alongside costs. Scotland 2007 report that automated grading was estimated to identify 50 fewer cases, but save £201,600 per year compared to manual grading. They conclude that automated grading is likely to be cost-effective due to similar effectiveness, but lower costs, compared to manual grading.

Using data from three centres in Scotland, Scotland 2010 (41) compare the automated grading system described in Scotland 2007 to an improved automated grading system (a version of iGradingM), and to manual grading. They take the model used by Scotland 2007, and extrapolate this to allow consideration of the consequences of any missed referable cases. Scotland 2010 estimate that the improved automated grading system performs better than the original automated system, but misses 123 referable cases when compared to manual grading. However, the improved automated grading system is estimated to be less costly than manual grading (by £212 695). They also estimate that given manual grading is more effective, to gain an additional QALY using the manual grading rather than the improved automated system, the additional cost is £25,676 to £267,115 depending on the probability of the improved automated system missing true proliferative cases. The authors, therefore, conclude that the improved automated system is likely to be cost-effective compared to manual grading.
Further details on the studies, as reported in the abstracts, are given in Table 33.
Those studies that attempt to capture cost-effectiveness over time are preferred. Those where the outcome is cost per case detected will not capture the longer-term impacts of correct/incorrect identification.

In summary, we identified 5 studies (one published only as an abstract) that evaluated the cost-effectiveness of 3 ARIASs–EyeArt v1, RetmarkerSR and iGradingM–all based on traditional ML algorithms. The studies show that ARIASs are less effective but less costly compared to manual grading and could lead to considerable savings. The performance is driven down by the relatively high false positive error rate while the systems are comparable to human graders in picking up cases with disease. Although these studies provide good starting point for further evaluations, they need updating to capture cost-effectiveness over time and to reflect the performance of the new versions of the software.

Criterion 12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

Question 4 (evidence map) – What are the social and ethical implications of implementing AI-based tools in screening programmes and would it be acceptable to health professionals and the public?

Eligibility for inclusion in the review

Studies were included in the review if they met the following inclusion criteria:

- Population: Health professionals, providers and users of screening programmes, and the general public.
- Intervention: Implementation of AI-based tools in any screening programme.
- Outcome measures: Social implications (e.g. public's opinion on the use of AI in their clinical management), ethical implications (e.g. data privacy, involvement of third party i.e. developers of ARIASs) and acceptability.
- Study design: Qualitative studies (e.g. surveys, interviews, clinical audits and service evaluation reports); relevant opinion/discussion papers.
- Publication date and language: Studies have to be published in English since 2000.

Summary of findings

Eighty three titles were selected at title/abstract level for further inspection. Of those, 19 primary studies (Table 34) and 38 reviews and opinion papers (Table 35) were considered to be potentially relevant and included in the evidence map. Five of the primary studies investigated the impact of AI in the context of screening (27, 42-45) while the rest had a more general focus (e.g. radiologists' attitudes towards AI) or investigated the issues in a different setting (e.g. clinicians perceptions of a ML-based early warning system to predict severe sepsis and septic shock (46)). The reason to include this latter group of studies was that the investigated issues (e.g. clinicians' trust in AI technology) were judged to be relevant to screening, even though the study was not conducted in this setting.

All primary studies were surveys of clinicians (n=9), clinicians and the general public (n=2), the general public (n=2) and patients (n=5). Clinicians were radiologists in 7 of the studies and psychiatrists, physicians and healthcare professionals, respectively, in the other 3. One of the surveys was aimed at directors of screening programmes, but no further information was given in the abstract. The patients were adults participating in DESPs (n=3), neurosurgery patients and their families (n=1) and women participating in a breast cancer screening programme (n=1). The surveys were conducted in USA (n=4), UK (n=3), France (n=1), and one each in Australia, China, Europe, Germany, India, Italy, Singapore and Sweden.

The surveys investigated a broad range of questions including participants' knowledge, training needs, perceptions, attitudes and satisfaction in relation to AI-based technology. Most of the participants had positive attitudes towards the implementation of AI in healthcare and acknowledged the benefits that such technologies are likely to have both in terms of improved patient outcomes and benefits to the healthcare system as a whole. Studies also reported a range of concerns regarding the impact of AI-based technology on clinicians' professional role and identity, clinician-patient relationship, dealing with uncertainty, the impact on clinical decision making, and the need for training and better understanding of AI by healthcare professionals, patients and the general public.

Of the reviews and opinion papers, Fatehi 2020 was a systematic review of the characteristics and usability features of tele-ophthalmology for the elderly population, including AI-based screening (47); Carter 2020 was a non-systematic review of the ethical legal and social implications of AI implementation in breast cancer care (48) and Larson 2020 was a theoretical paper in which the authors proposed an ethical framework for using and sharing clinical data for the development of AI applications (49). The rest of the papers were non-systematic reviews and editorials many of which focused specifically on the implementation of ARIASs in DESPs or ophthalmology in general Table 35.

In summary, there is a rapidly growing volume of evidence on the social and ethical aspects of AI in screening and healthcare. An evidence review is warranted and would help identify the range of relevant topics, summarise the existing evidence and identify gaps that need further investigation. However, a traditional evidence review limited to screening may not be the most appropriate approach; instead, we suggest that methods, such as realist synthesis, are employed to make use of evidence from related settings (e.g. healthcare and other areas) that deal with similar issues and generate evidence transferable to screening.

Review summary

Conclusions and implications for policy

Despite the large number of publications on AI algorithms designed to detect and grade diabetic eye disease, only a few ARIASs have been evaluated in large clinical studies that provide reliable data on their accuracy in clinical practice. Given the large number of contextual factors that could affect the performance of these systems, the results from such studies should not be generalised beyond the setting in which they were conducted. They could be used to inform the initial selection of candidate ARIASs which then should be evaluated in the setting in which they are to be implemented. Also, indirect (between-study) comparisons of alternative ARIASs are unlikely to produce valid results.

This means that out of the 10 ARIASs included in this review, we have applicable high quality evidence for 3 systems: EyeArt v2.1 (DL), iGradingM (ML) and RetmarkerSR (ML). Evidence from multiple studies show that EyeArt has consistently high sensitivity (~90%) comparable to that of human graders and could be used as an initial screen in the EDESP. Although most of the studies focused on referable disease, the EDESP-based evaluations report that the sensitivity of the system remains high (>90%) for 'disease/no disease', 'referable/non-referable disease' and approaches 100% for more severe forms of diabetic retinopathy (1, 19, 38). The large prospective study conducted by Heydon et al shows that the sensitivity of the most recent version of the software, EyeArt v2.1, remains high when evaluated in realistic conditions and the performance of the system is stable across different EDESP sites. Although there is no direct evidence about the overall impact that the implementation of EyeArt could have on the EDESP, Heydon et al estimated that using referable disease as a threshold, approximately 50% of all screening episodes would require further human grading and this will not result in an increased workload for the secondary grader while the workload of the tertiary grader (arbitration) is likely to reduce (19). The HTA conducted by Tufail et al also showed that implementing the system either as a replacement of level 1 graders or as a filter prior to manual grading is cost-effective. Given that the new version of the system evaluated in Heydon 2020 has comparable sensitivity and higher specificity, its implementation could lead to even greater savings than those reported by Tufail et al (1, 19, 38).

There is also high quality evidence of the performance of iGradingM in the SDESP including data from an internal quality assurance assessment published in 2017 (15). The latter shows that the system is safe to use in clinical practice with sensitivity of 97%, comparable to that in the published evaluations, and a false negative rate of 0 to 0.6%. The study also shows that the use of the system had increased over time and in the observed 6-

month period in 2015, 58.1% of all screening episodes in the SDESP were passed on to the autograder. However, iGradingM may not work with the EDESP photographic protocol without additional pre-processing of the images (1).
Another ML-based system, RetmarkerSR, has also been evaluated in a high quality study in the EDESP (1). Although it had lower sensitivity compared to EyeArt v1, the sensitivity was still acceptable (85%) and it had higher specificity and overall performance, and was cost-effective with either of the strategies evaluated by Tufail et al (1). An internal quality assurance study from the Portuguese DESP, where the system is currently in use, shows that the system is safe to use in clinical practice, with 0.3% false negative cases of all quality control cases and 0.02% of the total number of patients screened (14).

Only one study, Tufail 2016 (1) reported on the comparative accuracy of alternative ARIASs, RetmarkerSR and EyeArt v1, and the results may not be applicable to the new versions of the software. Only 4 studies compared the accuracy of ARIASs to that of human graders not involved in the reference grading. Overall, ARIASs had higher or similar sensitivity to that of manual grading but lower specificity. However, the results are likely to vary with the background and experience of human graders and may not be transferable from one setting to another.

We did not find any relevant RCTs or prospective cohort studies comparing DESP with level 1 manual grading to DESP with level 1 ARIAS grading in terms of clinical outcomes or other impact measures. We included 2 prospective cohort studies conducted in the USA and Australia, and evaluating EyeArt v2 and EyeGrader, respectively; they looked at the impact of ARIAS screening in primary care on the patient satisfaction using within-subject controls (Australia) and adherence to follow up examination using historical controls (USA). Both studies were considered to be at high risk of bias and their results are not directly applicable to the UK DESP.

Three ML-based ARIASs were evaluated in the UK-based health economic studies included in the review: iGradingM, RetmarkerSR and EyeArt v1. Overall, the studies found that ARIASs are less effective but also less costly compared to manual grading. Their overall performance was driven down by the high false positive rate while their sensitivity was comparable to that of human graders. Given that the current DL-based systems have higher specificity, the implementation of ARIAS as an initial screen could result in even greater savings that those reported in the studies. Tufail et al also showed that while using ARIAS as a filter prior to level 1 human grading is still cost-effective, the strategy where level 1 human graders are replaced by ARIAS could lead to greater savings. Another factor that may affect the cost-effectiveness of the systems is the decision threshold selected: to screen out disease-negative cases or to differentiate between referable and non-referable disease.

We identified a considerable number of surveys looking at the perceptions, attitudes, concerns and educational needs of healthcare professionals and patients with respect the implementation of AI-based technology in screening programmes (n=5) and related healthcare settings. We also identified a growing number of opinion and review papers addressing the social and ethical aspects of AI implementation in screening programmes. An evidence review of this growing literature will help identify all relevant aspects of the above question, to summarise the existing evidence and identify any gaps that need to be addressed in future research.

Future research

Future evaluations of ARIAS:

- Should be done independently from the software developer, in the clinical setting in which the system is meant to be used, under conditions that reflect everyday clinical practice; if possible, they should compare the performance of alternative ARIASs that may have different advantages and disadvantages.
- Should look at outcomes beyond accuracy, such as the actual consequences of false negative and false positive results and the consequences of accidental findings (e.g. missed by ARIAS but referred by human graders).
- They should include a cost-effectiveness evaluation of the system.
- They should investigate the experience and perceptions of healthcare professionals who interact with and/or are directly affected by the ARIAS; the expectations of those who have not yet had this experience (e.g. those in the control arm); the experience and perceptions of relevant patient groups; and the overall impact on the NHS.

There is a wide range of methodological questions that require further discussion and investigation. These concern:

- The design of evaluations of ARIASs to inform their implementation. For instance: What are the most relevant clinical outcomes that such evaluations should investigate and report (e.g. are diabetic retinopathy grades sufficient or patients should be followed up to investigate the actual consequences of different accuracy outcomes)? What is the optimal reference standard, in terms of technology and process by which the final outcome is produced? What is the best feasible way to investigate the comparative accuracy and overall impact of ARIAS vs human graders within a DESP? What aspects other than accuracy should be investigated?
- AI software is constantly evolving and this is one of its strengths. What is the best way to manage and monitor this, to make sure that the next version is safe, reliable and at least as effective as the previous one? Should the performance of ARIAS, once implemented, be monitored in the same way as DESP with human graders is

monitored or different process is required? What is the experience with this in Scotland and Portugal?

- The tasks that ARIASs should be able to perform. For instance: Should they be looking at diabetic retinopathy/maculopathy alone, or should be able to identify a broader spectrum of lesions and conditions (e.g. glaucoma and age-related degenerative maculopathy, which some ARIASs have been designed to identify)? Should they be able to incorporate other information into the final decision, such as information from the previous visit(s) (e.g. RetmarkerSR) and other demographic and clinical data (as some systems not included here have been designed to do)?
- How the impact of ARIAS on healthcare professionals, patients and the NHS as a whole should be investigated? So far, most of the studies are in the form of surveys asking general questions with little regard of respondents' experience and interaction with AI. Can we learn from the experience in other areas of AI research, outside screening, to design more informative and reliable studies of the impact of AI?

Limitations

The following methodological limitations of the review should be acknowledged: only the main electronic databases were searched; searches were limited to records published since 2000, and only including peer-reviewed, English-language journal articles; only 20% of the titles and abstracts were double-screened; papers were excluded after assessment of the volume of published evidence (although prioritisation was based on pre-specified criteria); the definition of one of the signalling questions in QUADAS-2 checklist was changed following a discussion with experts in the field and after the initial grading of studies; as a result some studies were later regraded using the new definition.

High quality evidence on the accuracy of ARIAS in the UK DESPs was found only for 3 systems; given the large number of contextual factors that may affect its performance, generalising the results from studies conducted in other countries is not advisable. No RCTs or prospective cohort studies were found that compare directly DESP with level 1 ARIAS grading vs DESP with level 1 human grading and report outcomes beyond accuracy. The identified health economic evaluations show that the systems are cost-effective but need updating.

Appendix 1 — Search strategy

Electronic databases

Two separate strategies were developed. The first strategy aimed to identify studies related to questions 1 to 3 (accuracy, effectiveness and cost-effectiveness of ARIAS in DESP) while the second search strategy aimed to identify studies relevant to question 4 (ethical and social aspects of the implementation of AI in screening programmes). The two strategies are detailed in the next section while details of the searches are provided in Table 2. Results were imported into EndNote X8.2 (Thomson Reuters) and de-duplicated.

Table 12. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search	Hits
Searches covering question 1-3				
MEDLINE(R) ALL 1946 to June 25, 2020	Ovid SP	26/06/2020	2000 – 25 June 2020	991
EMBASE 1974 to 2020 June 25 Date limited to 2000-current	Ovid SP	26/06/2020	2000 – 25 June 2020	894
Cochrane Database of Systematic Reviews (CDSR)	Wiley Online	26/06/2020	Inception to present	0
Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	26/06/2020	Inception to present	27
ICTRP	Not available at present			N/A
Clinicaltrials.gov		26/06/2020	Inception to present	9
Total 1912 titles plus 9 clinical trials Duplicates: 544 For title and abstract screening: 1377				
Searches covering question 4				
Ovid MEDLINE(R) ALL 1946 to June 30, 2020	Ovid SP	01/07/2020	1946 to present	253
Embase 1974 to 2020 June 30	Ovid SP	01/07/2020	1974 to present	346
APA PsycInfo 1806 to June Week 5 2020	Ovid SP	01/07/2020	1806 to present	42
CINHAL		02/07/2020	Inception to present	103
Total: 744 Duplicates: 211 For title and abstract screening: 533				

Search Terms

Search terms included in the strategy covering questions 1 to 3

Search terms included combinations of free text and subject headings grouped into the following categories:

- disease area: Eye disease, retinopathy, eye pathology, maculopathy, diabetic eye, diabetic macular, retinal fundus
- index test: Diagnostic techniques, ophthalmological; diagnosis, computer assisted, sensitivity and specificity, diagnostic test, diagnostic accuracy, diagnostic performance, screening, imaging, reference standard, artificial intelligence, deep learning, neural network, automated retinal image analysis system, automated grading, automated level, ARIAS, iGradingM, EyeArt, IDx-DR, DR-RACS, RetinaLyze, RetmarkerSR, Singapore Eye Lesion Analyzer, RetinaVue, TRIAD network

Search terms for Ovid MEDLINE(R) ALL are shown in Table 3, and search terms for Embase are shown in Table 4.

Table 13. Search strategy for Ovid MEDLINE(R) ALL <1946 to June 25, 2020>

N	Terms (N of hits)
1	exp eye diseases/ (563274)
2	retinopathy.ti,ab. (43575)
3	eye pathology.ti,ab. (319)
4	maculopathy.ti,ab. (4228)
5	diabetic eye.ti,ab. (732)
6	diabetic macular.ti,ab. (4004)
7	retinal fundus.ti,ab. (315)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (578122)
9	exp Diagnostic Techniques, Ophthalmological/ (169047)
10	exp Diagnosis, Computer-Assisted/ (83108)
11	"Sensitivity and Specificity"/ (346232)
12	diagnostic test*.ti,ab. (46123)
13	diagnostic accuracy.ti,ab. (43812)
14	diagnostic performance.ti,ab. (16194)
15	screening.ti,ab. (520833)
16	imaging.ti,ab. (798701)
17	(Sensitivity or specificity).ti,ab. (1033830)
18	reference standard.ab. (14139)
19	optical coherence tomography.ti,ab. (35177)
20	or/9-19 (2600413)
21	exp Artificial Intelligence/ (96870)
22	artificial intelligence.ti,ab. (6988)
23	deep learning.ti,ab. (8539)
24	neural network*.ti,ab. (48131)
25	automated retinal image analysis system.ti,ab. (2)

26	automated grading.ti,ab. (72)
27	automated level.ti,ab. (8)
28	(automated adj (tool* or technique* or identification or detection)).ti,ab. (4376)
29	ARIAS.ti,ab. (299)
30	iGradingM.ti,ab. (2)
31	EyeArt.ti,ab. (5)
32	IDx-DR.ti,ab. (6)
33	DR-RACS.ti,ab. (0)
34	RetinaLyze.ti,ab. (1)
35	RetmarkerSR DR.ti,ab. (0)
36	Singapore Eye Lesion Analyzer.ti,ab. (0)
37	RetinaVue.ti,ab. (0)
38	TRIAD network.ti,ab. (0)
39	or/21-38 (135626)
40	8 and 20 and 39 (1048)
41	limit 40 to yr="2000 -Current" (991)

Table 14. Search strategy for Embase <1974 to 2020 June 25>

N	Terms (N of hits)
1	exp eye disease/di [Diagnosis] (136263)
2	retinopathy.ti,ab. (59510)
3	eye pathology.ti,ab. (375)
4	maculopathy.ti,ab. (5348)
5	diabetic eye.ti,ab. (1103)
6	diabetic macular.ti,ab. (5986)
7	retinal fundus.ti,ab. (479)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (194744)
9	exp computer assisted diagnosis/ (1112353)
10	exp "sensitivity and specificity"/ (359564)
11	diagnostic test*.ti,ab. (64444)
12	diagnostic accuracy.ti,ab. (63870)
13	diagnostic performance.ti,ab. (23087)
14	screening.ti,ab. (729183)
15	imaging.ti,ab. (1108924)
16	(Sensitivity or specificity).ti,ab. (1302252)
17	reference standard.ab. (19637)
18	optical coherence tomography.ti,ab. (47622)
19	or/9-18 (3902148)
20	exp Artificial Intelligence/ (39401)
21	artificial intelligence.ti,ab. (9221)
22	deep learning.ti,ab. (10678)
23	neural network*.ti,ab. (59173)
24	automated retinal image analysis system.ti,ab. (4)
25	automated grading.ti,ab. (121)

26	automated level.ti,ab. (7)
27	(automated adj (tool* or technique* or identification or detection)).ti,ab. (5773)
28	ARIAS.ti,ab. (413)
29	iGradingM.ti,ab. (3)
30	EyeArt.ti,ab. (20)
31	IDx-DR.ti,ab. (13)
32	DR-RACS.ti,ab. (1)
33	RetinaLyze.ti,ab. (4)
34	RetmarkerSR DR.ti,ab. (0)
35	Singapore Eye Lesion Analyzer.ti,ab. (0)
36	RetinaVue.ti,ab. (6)
37	TRIAD network.ti,ab. (0)
38	or/20-37 (105880)
39	8 and 19 and 38 (917)
40	limit 39 to yr="2000 -Current" (894)

Table 15. Search strategy for the Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Eye Diseases] explode all trees	18741
#2	retinopathy:ti,ab	4616
#3	eye pathology:ti,ab	314
#4	maculopathy:ti,ab	316
#5	diabetic eye:ti,ab	1426
#6	diabetic macular:ti,ab	2327
#7	retinal fundus:ti,ab	874
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	23185
#9	MeSH descriptor: [Diagnostic Techniques, Ophthalmological] explode all trees	7678
#10	MeSH descriptor: [Diagnosis, Computer-Assisted] explode all trees	1871
#11	MeSH descriptor: [Sensitivity and Specificity] explode all trees	15181
#12	"diagnostic test*":ti,ab	1124
#13	"diagnostic accuracy":ti,ab	2512
#14	"diagnostic performance":ti,ab	742
#15	screening:ti,ab	48626
#16	imaging:ti,ab	32475
#17	(Sensitivity or specificity):ti,ab	46522
#18	"reference standard":ab	850
#19	"optical coherence tomography":ti,ab	2959
#20	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19	139933
#21	MeSH descriptor: [Artificial Intelligence] explode all trees	968
#22	"artificial intelligence":ti,ab	229
#23	"deep learning":ti,ab	229

#24	"neural network*":ti,ab	521
#25	"automated retinal image analysis system":ti,ab	0
#26	"automated grading":ti,ab	1
#27	"automated level":ti,ab	1
#28	(automated NEXT (tool* or technique* or identification or detection)):ti,ab	115
#29	ARIAS:ti,ab	23
#30	iGradingM:ti,ab	0
#31	EyeArt:ti,ab	1
#32	IDx-DR:ti,ab	0
#33	DR-RACS:ti,ab	0
#34	RetinaLyze:ti,ab	0
#35	RetmarkerSR:ti,ab	3
#36	"Singapore Eye Lesion Analyzer":ti,ab	0
#37	RetinaVue:ti,ab	2
#38	"TRIAD network":ti,ab	0
#39	#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38	1841
#40	#8 and #20 and #39	27

Table 16. Search strategy for the Clinical trials database

Terms	Search Results*	Entire Database**
Synonyms		
Eye Diseases	9 studies	9,594 studies
diseases of the eye	--	20 studies
Disorder of eye	--	1 studies
Disorders of the globe	--	1 studies
Eye Disorders	--	47 studies
oculopathy	--	2 studies
ophthalmic disorders	--	1 studies
Ophthalmological disorder	--	9 studies
ophthalmopathy	--	93 studies
Diseases	9 studies	274,158 studies
Disorders	2 studies	98,155 studies
condition	1 studies	39,071 studies
Eye	9 studies	16,012 studies
Ocular	2 studies	4,860 studies
ophthalmic	2 studies	2,545 studies
Oculus	1 studies	207 studies
Optic	1 studies	1,457 studies
Eyeball structure	--	1 studies
Orbital region	--	10 studies
Diabetic Retinopathy	9 studies	547 studies
Retinopathy diabetic	--	1 studies
Retinopathy	9 studies	2,972 studies

Retinal Disease	9 studies	2,933 studies
retina disorder	--	2 studies
Retinal disorder	--	16 studies
Diabetic	9 studies	4,372 studies
artificial intelligence	9 studies	227 studies
Computational Intelligence	--	1 studies
Machine Intelligence	--	2 studies
intelligence	9 studies	355 studies
artificial	9 studies	1,193 studies
Factitious	--	1 studies
Spurious	--	2 studies

Search terms included in the strategy covering question 4

Search terms included combinations of free text and subject headings grouped into the following categories:

- intervention: Diagnosis, computer assisted; diagnostic test, screening, imaging, artificial intelligence, automation, machine learning
- outcomes: Attitudes, perception, accept, barriers, appropriate, experience, ethical, social
- study design: Qualitative, interview, survey, question

Table 17. Search strategy for Ovid MEDLINE(R) ALL <1946 to June 30, 2020>

N	Terms (N of hits)
1	exp Diagnosis, Computer-Assisted/ (83147)
2	diagnostic test*.ti,ab. (46187)
3	screening.ti,ab. (521711)
4	imaging.ti,ab. (800097)
5	or/1-4 (1393715)
6	exp Artificial Intelligence/ (97028)
7	Automation/ (18051)
8	artificial intelligence.ti,ab. (7049)
9	(automated adj (tool* or technique* or identification or detection or test* or screening)).ti,ab. (5480)
10	automation.ti,ab. (13393)
11	machine learning.ti,ab. (27261)
12	or/6-11 (147104)
13	(attitude* or perception* or acceptab* or barriers or appropriate* or experience*).ti,ab. (2126676)
14	(ethical* or social*).ti,ab. (600302)
15	13 or 14 (2557367)
16	qualitative research/ (55100)

17	(qualitative or interview* or survey* or question*).ti,ab. (1802109)
18	16 or 17 (1807651)
19	5 and 12 and 15 and 18 (253)

Table 18. Search strategy for Embase <1974 to 2020 June 30>

N	Terms (N of hits)
1	exp computer assisted diagnosis/ (1113982)
2	diagnostic test*.ti,ab. (64500)
3	screening.ti,ab. (729884)
4	imaging.ti,ab. (1110040)
5	or/1-4 (2682904)
6	exp artificial intelligence/ (39529)
7	automation/ (57309)
8	artificial intelligence.ti,ab. (9278)
9	(automated adj (tool* or technique* or identification or detection or test* or screening)).ti,ab. (7409)
10	automation.ti,ab. (19034)
11	machine learning.ti,ab. (33905)
12	or/6-11 (141036)
13	(attitude* or perception* or acceptab* or barriers or appropriate* or experience*).ti,ab. (2853491)
14	(ethical* or social*).ti,ab. (751387)
15	13 or 14 (3382481)
16	qualitative research/ (75324)
17	(qualitative or interview* or survey* or question*).ti,ab. (2360248)
18	16 or 17 (2367415)
19	5 and 12 and 15 and 18 (346)

Table 19. Search strategy for PsycINFO <1806 to June Week 5 2020>

N	Terms (N of hits)
1	computer assisted diagnosis/ (1578)
2	diagnostic test*.ti,ab. (3143)
3	screening.ti,ab. (63770)
4	imaging.ti,ab. (73432)
5	or/1-4 (140227)
6	exp artificial intelligence/ (21146)
7	automation/ (2264)
8	artificial intelligence.ti,ab. (3787)
9	(automated adj (tool* or technique* or identification or detection or test* or screening)).ti,ab. (608)
10	automation.ti,ab. (2543)

11	machine learning.ti,ab. (5086)
12	or/6-11 (28041)
13	attitudes/ (26982)
14	(attitude* or perception* or acceptab* or barriers or appropriate* or experience* or views).ti,ab. (1209016)
15	(ethical* or social*).ti,ab. (814078)
16	or/13-15 (1752604)
17	exp qualitative methods/ (15326)
18	(qualitative or interview* or survey* or question* or focus group*).ti,ab. (1091184)
19	17 or 18 (1092960)
20	5 and 12 and 16 and 19 (42)

Table 20. Search strategy for CINAHL

#	Query	Results
S20	S5 AND S12 AND S15 AND S19	103
S19	S16 OR S17 OR S18	793,966
S18	TI (qualitative or interview* or "focus group" or survey or questionnaire*)) OR AB (qualitative or interview* or "focus group" or survey or questionnaire*))	705,051
S17	(MH "Interviews+")	253,066
S16	(MM "Qualitative Studies+")	7,649
S15	S13 OR S14	1,055,374
S14	TI (ethical* or social*) OR AB (ethical* or social*)	332,302
S13	TI (attitude* or perception* or acceptab* or barriers or appropriate* or experience*) OR AB (attitude* or perception* or acceptab* or barriers or appropriate* or experience*)	834,228
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	24,350
S11	TI "machine learning" OR AB "machine learning"	4,822
S10	TI automation OR AB automation	2,915
S9	TI ((automated N2 (tool* or technique* or identification or detection or test* or screening)))	2,603

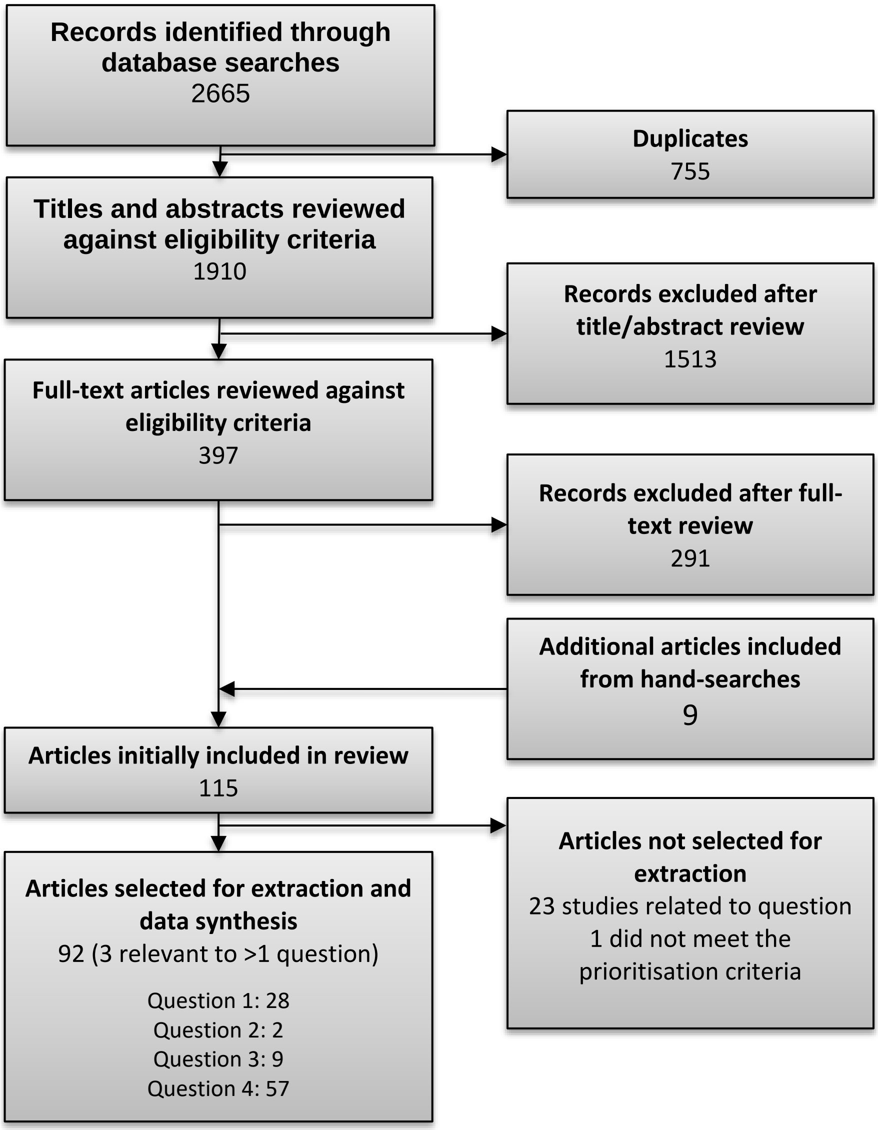
	OR AB ((automated N2 (tool* or technique* or identification or detection or test* or screening)))	
S8	TI "artificial intelligence" OR AB "artificial intelligence"	2,606
S7	(MM "Automation+")	9,478
S6	(MM "Artificial Intelligence+")	11,742
S5	S1 OR S2 OR S3 OR S4	904,632
S4	TI imaging OR AB imaging	168,567
S3	TI screening OR AB screening	141,479
S2	TI "diagnostic test*" OR AB "diagnostic test*"	11,898
S1	(MM "Diagnosis+")	725,110

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 3 summarises the volume of publications included and excluded at each stage of the review. 91 publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 6 Summary of publications included and excluded at each stage of the review


Records identified through database searches
2665
Duplicates
755
Titles and abstracts reviewed against eligibility criteria
1910
Records excluded after title/abstract review
1513
Full-text articles reviewed against eligibility criteria
397
Records excluded after full-text review
291
Additional articles included from hand-searches
9
Articles initially included in review
115
Articles not selected for extraction
23 studies related to question 1 did not meet the prioritisation criteria
Articles selected for extraction and data synthesis
92 (3 relevant to >1 question)
Question 1: 28
Question 2: 2
Question 3: 9
Question 4: 57

Publications included after review of full-text articles

Studies were prioritised for extraction and data synthesis. It was planned *a priori* that the following approach would be taken to prioritise studies for extraction:

1. For all questions, UK-based studies were prioritised. In the absence or minimal volume of such studies, those from comparable countries were prioritised next.
2. Systematic reviews and meta-analyses were considered the highest quality of evidence. Following this, study designs were prioritised for questions 1 and 2 in the following (descending) order: RCTs, prospective cohort studies, retrospective cohort studies.
3. In addition, studies reporting on the accuracy of ARIAS (question 1) were prioritised:
   a. If they evaluated commercially available ARIAS
   b. If they evaluated ARAIS that are CE-marked and/or FDA approved
   c. If they evaluated the latest version of the software.

Table 21 Publications included after review of full-text articles and the questions they address

Study	Q1: Accuracy	Q2: Effectiveness	Q3: Cost-effectiveness	Q4: Social and ethical impact: Primary studies	Q4: Social and ethical impact: Review and opinion papers
Abramoff 2010	No	No	No	No	Yes
Abramoff 2018	Yes	No	No	No	No
Abramoff 2020	No	No	No	No	Yes
Alexander 2020	No	No	No	Yes	No
Anonymous 2018	No	No	No	No	Yes
Anonymous 2019	No	No	No	No	Yes
Balyen 2019	No	No	No	No	Yes
Berens 2020	No	No	No	No	Yes
Bhaskaranand 2016 (CA)	No	No	Yes	No	No
Bhaskaranand 2019	Yes	No	No	No	No
Bouhaimed 2008	Yes	No	No	No	No
Bourla 2018	No	No	No	Yes	No
Broome 2020	No	No	No	No	Yes
Carter 2020	No	No	No	No	Yes
Channa 2020	No	No	No	No	Yes
Chee 2018	No	No	No	No	Yes
Coppola 2020	No	No	No	Yes	No
Egan 2016	No	No	Yes	No	No
ESR 2019	No	No	No	Yes	No
Fatehi 2020	No	No	No	No	Yes
FDA 2020 (approval letter)	Yes	No	No	No	No
Figueiredo 2015	Yes	No	No	No	No
Fleming 2010a	Yes	No	No	No	No

Fleming 2010b	Yes	No	No	No	No
Francolini 2020	No	No	No	No	Yes
Ginestra 2019	No	No	No	Yes	No
Goatman 2011	Yes	No	No	No	No
Gonzalez-Gonzalo 2020	Yes	No	No	No	No
Gorges 2020 (CA)	No	No	No	Yes	No
Graham 2019	No	No	No	No	Yes
Halamka 2019	No	No	No	No	Yes
Hamilton 2002	No	No	No	Yes	No
Hansen 2004	Yes	No	No	No	No
Heydon 2020	Yes	No	No	No	No
Islam 2020 (SR)	Yes	No	No	No	No
Jheng 2020	No	No	No	No	Yes
Jonmarker 2019	No	No	No	Yes	No
Jungmann 2020	No	No	No	Yes	No
Kapoor 2019	No	No	No	No	Yes
Kapoor 2019	No	No	No	No	Yes
Keel 2018	No	Yes	No	Yes	No
Keskinbora 2020	No	No	No	No	Yes
Koh 2019 (CA)	No	No	No	Yes	No
Krause 2018	Yes	No	No	No	No
Larson 2020	No	No	No	No	Yes
Li 2018	Yes	No	No	No	No
Liew 2014	No	No	Yes	No	No
Liew 2019	No	No	No	No	Yes
Lim 2019 (CA)	Yes	No	No	No	No
Liu 2020	Yes	Yes	No	No	No
Meyer 2020	No	No	No	Yes	No
Nadarzynski 2019	No	No	No	Yes	No
Nagendran 2020 (SR)	Yes	No	No	No	No
Nielsen 2019 (SR)	Yes	No	No	No	No
Norgaard 2017 (SR)	Yes	No	No	No	No
O'Connor 2019	No	No	No	No	Yes
Oliveira 2011	Yes	No	No	No	No
Olsen 2013	No	No	Yes	No	No
Olvera-Barrios 2020	Yes	No	No	No	No
Ooi 2019	No	No	No	Yes	No
Ooms 2019 (CA)	No	No	No	Yes	No
Padhy 2019	No	No	No	No	Yes
Palmisciano 2020	No	No	No	Yes	No
Patel 2007	No	No	No	No	Yes
Paul 2006	No	No	No	Yes	No
Philip 2007	Yes	No	No	No	No

Philip 2017	Yes	No	No	No	No
Prescott 2014	No	No	Yes	No	No
Rahimy 2018	No	No	No	No	Yes
Rajalakshmi 2020	No	No	No	No	Yes
Raumviboonsuk 2019	Yes	No	No	No	No
Ribeiro 2011	Yes	No	No	No	No
Ruamviboonsuk 2020	No	No	No	No	Yes
Scotland 2007	No	No	Yes	No	No
Scotland 2010	No	No	Yes	No	No
Scott 2019	No	No	No	No	Yes
Shaban-Nejad 2018	No	No	No	No	Yes
Shah 2020a	Yes	No	No	No	No
Simoes 2019 (SR)	Yes	No	No	No	No
Sivaprasad 2020	No	No	No	No	Yes
Son 2020	Yes	No	No	No	No
Sosale 2019	No	No	No	No	Yes
Soto-Pedre 2015	Yes	No	No	No	No
Stolte 2020	No	No	No	No	Yes
Ting 2017	Yes	No	No	No	No
Ting 2019	No	No	No	No	Yes
Ting 2019	No	No	No	No	Yes
Ting 2020	No	No	No	No	Yes
Tufail 2016	Yes	No	Yes	No	No
Tufail 2017	Yes	No	Yes	No	No
van der Heijden 2018	Yes	No	No	No	No
Verbraak 2019	Yes	No	No	No	No
Vollmer 2020	No	No	No	No	Yes
Wang 2012	No	No	No	No	Yes
Waymel 2019	No	No	No	Yes	No
Wong 2019	No	No	No	No	Yes
Wong 2020	No	No	No	No	Yes
Xiang 2020	No	No	No	Yes	No
Yip 2020	Yes	No	No	No	No

Publications excluded after review of full-text articles

Of the 397 publications included after the review of titles and abstracts, 278 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 11.

Table 22 Publications excluded after review of full text articles

Reference	Reason for exclusion
Abbas Q, Fondon I, Sarmiento A, Jimenez S, Alemany P. Automatic recognition of severity level for diagnosis of diabetic retinopathy using deep visual features. Med Biol Eng Comput. 2017;55(11):1959-74.	algorithm in development*
Abramoff MD, Niemeijer M, Suttorp-Schulten MS, Viergever MA, Russell SR, van Ginneken B. Evaluation of a system for automatic detection of diabetic retinopathy from color fundus photographs in a large population of patients with diabetes. Diabetes Care. 2008;31(2):193-8.	Review**
Abramoff MD, Niemeijer M, Russell SR. Automated detection of diabetic retinopathy: barriers to translation into clinical practice. Expert Rev Med Devices. 2010;7(2):287-96.	Review
Abramoff MD, Folk JC, Han DP, Walker JD, Williams DF, Russell SR, et al. Automated analysis of retinal images for detection of referable diabetic retinopathy. JAMA Ophthalmology. 2013;131(3):351-7.	Evaluates older non-DL version of the IDx-DR system
Abramoff MD, Leng T, Ting DSW, Rhee K, Horton MB, Brady CJ, et al. Automated and Computer-Assisted Detection, Classification, and Diagnosis of Diabetic Retinopathy. Telemed J E Health. 2020;26(4):544-50.	position paper
Abramoff MD, Tobey D, Char DS. Lessons Learned About Autonomous AI: Finding a Safe, Efficacious, and Ethical Path Through the Development Process. Am J Ophthalmol. 2020;214:134-42.	Review
Acharya UR, Lim CM, Ng EY, Chee C, Tamura T. Computer-based detection of diabetes retinopathy stages using digital fundus images. Proc Inst Mech Eng [H]. 2009;223(5):545-53.	algorithm in development
Acharya UR, Ng EY, Tan JH, Sree SV, Ng KH. An integrated index for the identification of diabetic retinopathy stages using texture parameters. Journal of Medical Systems. 2012;36(3):2011-20.	internal validation only
Acharya UR, Mookiah MRK, Koh JEW, Tan JH, Bhandary SV, Rao AK, et al. Automated diabetic macular edema (DME) grading system using DWT, DCT Features and maculopathy index. Comput Biol Med. 2017;84:59-68.	algorithm in development

Adal KM, Sidibe D, Ali S, Chaum E, Karnowski TP, Meriaudeau F. Automated detection of microaneurysms using scale-adapted blob analysis and semi-supervised learning. Computer Methods and Programs in Biomedicine. 2014;114(1):1-10.	Focus on detection of MA; evaluation at DR level performed on a small subset of the development dataset
Adal KM, van Etten PG, Martinez JP, Rouwen KW, Vermeer KA, van Vliet LJ. An Automated System for the Detection and Classification of Retinal Changes Due to Red Lesions in Longitudinal Fundus Images. IEEE Trans Biomed Eng. 2018;65(6):1382-90.	retinal change detection in images taken at different time points
Ahn JM, Kim S, Ahn KS, Cho SH, Lee KB, Kim US. A deep learning model for the detection of both advanced and early glaucoma using fundus photography. PLoS ONE. 2018;13(11):e0207982.	glaucoma
Akbar S, Akram MU, Sharif M, Tariq A, Yasin UU. Decision Support System for Detection of Papilledema through Fundus Retinal Images. Journal of Medical Systems. 2017;41(4):66.	papilledema
Akram MU, Tariq A, Anjum MA, Javed MY. Automated detection of exudates in colored retinal images for diagnosis of diabetic retinopathy. Appl Opt. 2012;51(20):4858-66.	internal validation only
Akram UM, Khan SA. Automated detection of dark and bright lesions in retinal images for early detection of diabetic retinopathy. Journal of Medical Systems. 2012;36(5):3151-62.	algorithm in development
Akram MU, Tariq A, Khan SA, Javed MY. Automated detection of exudates and macula for grading of diabetic macular edema. Comput Methods Programs Biomed. 2014;114(2):141-52.	algorithm in development
Akram MU, Tariq A, Khalid S, Javed MY, Abbas S, Yasin UU. Glaucoma detection using novel optic disc localization, hybrid feature set and classification techniques. Australas Phys Eng Sci Med. 2015;38(4):643-55.	glaucoma
Akyol K, Sen B, Bayir S. Automatic Detection of Optic Disc in Retinal Image by Using Keypoint Detection, Texture Analysis, and Visual Dictionary Techniques. Comput. 2016;2016:6814791.	algorithm in development
Alam M, Le D, Lim JI, Chan RVP, Yao X. Supervised Machine Learning Based Multi-Task Artificial Intelligence Classification of Retinopathies. Journal of Clinical Medicine. 2019;8(6):18.	OCT***
Al-Jarrah MA, Shatnawi H. Non-proliferative diabetic retinopathy symptoms detection and classification using neural network. J Med Eng Technol. 2017;41(6):498-505.	internal validation only

Alqudah AM. AOCT-NET: a convolutional network automated classification of multiclass retinal diseases using spectral-domain optical coherence tomography images. Med Biol Eng Comput. 2020;58(1):41-53.	OCT
Al-Rawi M, Karajeh H. Genetic algorithm matched filter optimization for automated detection of blood vessels from digital retinal images. Computer Methods and Programs in Biomedicine. 2007;87(3):248-53.	algorithm in development
Amin J, Sharif M, Rehman A, Raza M, Mufti MR. Diabetic retinopathy detection and classification using hybrid feature set. Microsc Res Tech. 2018;81(9):990-6.	algorithm in development
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Narasimha-Iyer H, Can A, Roysam B, Tanenbaum HL, Majerovics A. Integrated analysis of vascular and nonvascular changes from color retinal fundus image sequences. IEEE Trans Biomed Eng. 2007;54(8):1436-45.	change in DR fundus images
Nayak J, Bhat PS, Acharya R, Lim CM, Kagathi M. Automated identification of diabetic retinopathy stages using digital fundus images. Journal of Medical Systems. 2008;32(2):107-15.	internal validation only
Nayak J, Bhat PS, Acharya UR. Automatic identification of diabetic maculopathy stages using fundus images. J Med Eng Technol. 2009;33(2):119-29.	internal validation only
Nguyen PA, Li YC. Artificial Intelligence in Clinical Implications. Computer Methods and Programs in Biomedicine. 2018;166:A1.	Review
Nidhi MT, Gunaseelan K. Efficient ranking of diabetic retinopathy and glaucoma using echo state neural network and radial basis function (RBF). Journal of Medical Imaging and Health Informatics. 2016;6(3):869-74.	internal validation only
Niemeijer M, van Ginneken B, Russell SR, Suttorp-Schulten MS, Abramoff MD. Automated detection and differentiation of drusen, exudates, and cotton-wool spots in digital color fundus photographs for diabetic retinopathy diagnosis. Invest Ophthalmol Vis Sci. 2007;48(5):2260-7.	internal validation only
Noronha K, Acharya UR, Nayak KP, Kamath S, Bhandary SV. Decision support system for diabetic retinopathy using discrete wavelet transform. Proc Inst Mech Eng [H]. 2013;227(3):251-61.	internal validation only
O'Connor AM, Tsafnat G, Thomas J, Glasziou P, Gilbert SB, Hutton B. A question of trust: can we build an evidence base to gain trust in systematic review automation technologies? Syst. 2019;8(1):143.	Review
Ogunyemi O, Moran E, Daskivich LP, George S, Teklehaimanot S, Ilapakurthi R, et al. Autonomy versus automation: Perceptions of nonmydriatic camera choice for teleretinal screening in an urban safety net clinic. Telemedicine and e-Health. 2013;19(8):591-6.	different purpose
Ordonez PF, Cepeda CM, Garrido J, Chakravarty S. Classification of images based on small local features: a case applied to microaneurysms in fundus retina images. Journal of Medical Imaging. 2017;4(4):041309.	External evaluation only at the level of lesions

Osareh A, Mirmehdi M, Thomas B, Markham R. Automated identification of diabetic retinal exudates in digital colour images. British Journal of Ophthalmology. 2003;87(10):1220-3.	internal validation only
Osareh A, Shadgar B, Markham R. A computational-intelligence-based approach for detection of exudates in diabetic retinopathy images. IEEE Trans Inf Technol Biomed. 2009;13(4):535-45.	internal validation only
Padhy SK, Takkar B, Chawla R, Kumar A. Artificial intelligence in diabetic retinopathy: A natural step to the future. Indian J Ophthalmol. 2019;67(7):1004-9.	Review
Pan X, Jin K, Cao J, Liu Z, Wu J, You K, et al. Multi-label classification of retinal lesions in diabetic retinopathy for automatic analysis of fundus fluorescein angiography based on deep learning. Graefe's Archive for Clinical and Experimental Ophthalmology. 2020;258(4):779-85.	fundus fluorescein angiography
Parekh NU, Bhaskaranand M, Ramachandra C, Bhat S, Solanki K. Explaining an artificial intelligence (AI) system for diabetic retinopathy (DR) screening in primary care. Diabetes Conference: 79th Scientific Sessions of the American Diabetes Association, ADA. 2019;68(Supplement 1).	Review
Patel JL, Goyal RK. Applications of artificial neural networks in medical science. Current Clinical Pharmacology. 2007;2(3):217-26.	Review
Pedrosa M, Silva JM, Matos S, Costa C. SCREEN-DR - Software Architecture for the Diabetic Retinopathy Screening. Studies in Health Technology & Informatics. 2018;247:396-400.	not an accuracy study
Pedrosa M, Silva JM, Silva JF, Matos S, Costa C. SCREEN-DR: Collaborative platform for diabetic retinopathy. International Journal of Medical Informatics. 2018;120:137-46.	not an accuracy study
Pires R, Avila S, Jelinek HF, Wainer J, Valle E, Rocha A. Automatic Diabetic Retinopathy detection using BossaNova representation. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:146-9.	internal validation only
Playout C, Duval R, Cheriet F. A Novel Weakly Supervised Multitask Architecture for Retinal Lesions Segmentation on Fundus Images. IEEE Trans Med Imaging. 2019;38(10):2434-44.	internal validation only
Poly TN, Islam MM, Yang HC, Nguyen PA, Wu CC, Li YJ. Artificial Intelligence in Diabetic Retinopathy: Insights from a Meta-Analysis of Deep Learning. Studies in Health Technology & Informatics. 2019;264:1556-7.	updated systematic review included
Porwal P, Pachade S, Kokare M, Giancardo L, Meriaudeau F. Retinal image analysis for disease screening through local tetra patterns. Comput Biol Med. 2018;102:200-10.	internal validation only

Prakash NB, Hemalakshmi GR, Stella Inba Mary M. Automated grading of diabetic retinopathy stages in fundus images using SVM classifer. Journal of Chemical and Pharmaceutical Research. 2016;8(1):537-41.	internal validation only
Prentasic P, Loncaric S. Weighted ensemble based automatic detection of exudates in fundus photographs. Conf Proc IEEE Eng Med Biol Soc. 2014;2014:138-41.	internal validation only
Prentasic P, Loncaric S. Detection of exudates in fundus photographs using deep neural networks and anatomical landmark detection fusion. Comput Methods Programs Biomed. 2016;137:281-92.	algorithm in development
Punniyamoorthy U, Pushpam I. Remote examination of exudates-impact of macular oedema. Healthc. 2018;5(4):118-23.	internal validation only
Quellec G, Lamard M, Josselin PM, Cazuguel G, Cochener B, Roux C. Detection of lesions in retina photographs based on the wavelet transform. Conf Proc IEEE Eng Med Biol Soc. 2006;2006:2618-21.	algorithm in development
Quellec G, Lamard M, Josselin PM, Cazuguel G, Cochener B, Roux C. Optimal wavelet transform for the detection of microaneurysms in retina photographs. IEEE Trans Med Imaging. 2008;27(9):1230-41.	algorithm in development
Quellec G, Russell SR, Abramoff MD. Optimal filter framework for automated, instantaneous detection of lesions in retinal images. IEEE Trans Med Imaging. 2011;30(2):523-33.	algorithm in development (unclear if independent dataset was used)
Quellec G, Lamard M, Cazuguel G, Bekri L, Daccache W, Roux C, et al. Automated assessment of diabetic retinopathy severity using content-based image retrieval in multimodal fundus photographs. Invest Ophthalmol Vis Sci. 2011;52(11):8342-8.	internal validation only
Quellec G, Lamard M, Abramoff MD, Decenciere E, Lay B, Erginay A, et al. A multiple-instance learning framework for diabetic retinopathy screening. Med Image Anal. 2012;16(6):1228-40.	Algorithm in development
Quellec G, Lamard M, Erginay A, Chabouis A, Massin P, Cochener B, et al. Automatic detection of referral patients due to retinal pathologies through data mining. Med Image Anal. 2016;29:47-64.	Target condition is any pathology that requires referral to an ophthalmologist; uses data mining (not DL) and combines image analysis with contextual data from patient records
Quellec G, Charriere K, Boudi Y, Cochener B, Lamard M. Deep image mining for diabetic retinopathy screening. Med Image Anal. 2017;39:178-93.	Internal validation only

Quellec G, Lamard M, Conze PH, Massin P, Cochener B. Automatic detection of rare pathologies in fundus photographs using few-shot learning. Med Image Anal. 2020;61:101660.	internal validation only
Rahimy E. Deep learning applications in ophthalmology. Current Opinion in Ophthalmology. 2018;29(3):254-60.	Review
Rajalakshmi R. The impact of artificial intelligence in screening for diabetic retinopathy in India. Eye. 2020;34(3):420-1.	Review
Rajesh IS, Arikerie BM, Reshmi BM. A review on automatic identification of fovea in retinal fundus images. International Journal of Medical Engineering and Informatics. 2020;12(2):169-79.	review
Raju M, Pagidimarri V, Barreto R, Kadam A, Kasivajjala V, Aswath A. Development of a Deep Learning Algorithm for Automatic Diagnosis of Diabetic Retinopathy. Studies in Health Technology & Informatics. 2017;245:559-63.	internal validation only
Randive SN, Senapati RK, Rahulkar AD. A self-adaptive optimisation for diabetic retinopathy detection with neural classification. International Journal of Nano and Biomaterials. 2019;8(3-4):204-27.	algorithm in development, seems like an internal validation only
Rasta SH, Nikfarjam S, Javadzadeh A. Detection of retinal capillary nonperfusion in fundus fluorescein angiogram of diabetic retinopathy. Bioimpacts. 2015;5(4):183-90.	fundus fluorescein angiography
Reeves A. ES08.07 System Approach to Screening Management. Journal of Thoracic Oncology. 2019;14 (10 Supplement):S33-S4.	Review
Ren F, Cao P, Li W, Zhao D, Zaiane O. Ensemble based adaptive over-sampling method for imbalanced data learning in computer aided detection of microaneurysm. Comput Med Imaging Graph. 2017;55:54-67.	internal validation only
Ren F, Cao P, Zhao D, Wan C. Diabetic macular edema grading in retinal images using vector quantization and semi-supervised learning. Technol Health Care. 2018;26(S1):389-97.	internal validation only
Reza AW, Eswaran C. A decision support system for automatic screening of non-proliferative diabetic retinopathy. Journal of Medical Systems. 2011;35(1):17-24.	internal validation only
Riaz H, Park J, Choi H, Kim H, Kim J. Deep and Densely Connected Networks for Classification of Diabetic Retinopathy. Diagnostics. 2020;10(1):02.	internal validation only
Rocha A, Carvalho T, Jelinek HF, Goldenstein S, Wainer J. Points of interest and visual dictionaries for automatic retinal lesion detection. IEEE Trans Biomed Eng. 2012;59(8):2244-53.	Algorithm in development
Rogers TW, Gonzalez-Bueno J, Garcia Franco R, Lopez Star E, Mendez Marin D, Vassallo J, et al. Evaluation of an AI system for the detection of diabetic retinopathy	Portable handheld camera

from images captured with a handheld portable fundus camera: the MAILOR AI study. Eye. 2020;07:07.	
Roychowdhury S, Koozekanani DD, Parhi KK. DREAM: diabetic retinopathy analysis using machine learning. IEEE j. 2014;18(5):1717-28.	Non-DL algorithm in development (no real life evaluation)
Roychowdhury S, Koozekanani DD, Parhi KK. Automated detection of neovascularization for proliferative diabetic retinopathy screening. Conf Proc IEEE Eng Med Biol Soc. 2016;2016:1300-3.	internal validation only
Ruamviboonsuk P, Cheung CY, Zhang X, Raman R, Park SJ, Ting DSW. Artificial Intelligence in Ophthalmology: Evolutions in Asia. Asia Pac J Ophthalmol (Phila). 2020;9(2):78-84.	Review
S KS, P A. A Machine Learning Ensemble Classifier for Early Prediction of Diabetic Retinopathy. Journal of Medical Systems. 2017;41(12):201.	internal validation only
Saha SK, Fernando B, Cuadros J, Xiao D, Kanagasingam Y. Automated Quality Assessment of Colour Fundus Images for Diabetic Retinopathy Screening in Telemedicine. Journal of Digital Imaging. 2018;31(6):869-78.	ML to determine image quality as 'accept' or 'reject' during acquisition
Saha SK, Xiao D, Kanagasingam Y. A Novel Method for Correcting Non-uniform/Poor Illumination of Color Fundus Photographs. Journal of Digital Imaging. 2018;31(4):553-61.	Method for adjusting for poor illumination
Sahlsten J, Jaskari J, Kivinen J, Turunen L, Jaanio E, Hietala K, et al. Deep Learning Fundus Image Analysis for Diabetic Retinopathy and Macular Edema Grading. Sci. 2019;9(1):10750.	internal validation only
Saleh E, Blaszczynski J, Moreno A, Valls A, Romero-Aroca P, de la Riva-Fernandez S, et al. Learning ensemble classifiers for diabetic retinopathy assessment. Artificial Intelligence in Medicine. 2018;85:50-63.	internal validation only
Sanchez CI, Garcia M, Mayo A, Lopez MI, Hornero R. Retinal image analysis based on mixture models to detect hard exudates. Med Image Anal. 2009;13(4):650-8.	internal validation only
Sanchez CI, Niemeijer M, Abramoff MD, van Ginneken B. Active learning for an efficient training strategy of computer-aided diagnosis systems: application to diabetic retinopathy screening. Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv. 2010;13(Pt 3):603-10.	internal validation only
Sánchez CI, Niemeijer M, Dumitrescu AV, Suttorp-Schulten MS, Abràmoff MD, van Ginneken B. Evaluation of a computer-aided diagnosis system for diabetic retinopathy screening on public data. Invest Ophthalmol Vis Sci. 2011 Jul 1;52(7):4866-71. doi: 10.1167/iovs.10-6633. PMID: 21527381.	Older non-DL version of the IDx-DR system

Sangeethaa SN, Uma Maheswari P. An Intelligent Model for Blood Vessel Segmentation in Diagnosing DR Using CNN. Journal of Medical Systems. 2018;42(10):175.	internal validation only
Santhi D, Manimegalai D, Parvathi S, Karkuzhali S. Segmentation and classification of bright lesions to diagnose diabetic retinopathy in retinal images. Biomed Tech (Berl). 2016;61(4):443-53.	internal validation only
Savoy M. IDx-DR for Diabetic Retinopathy Screening. Am Fam Physician. 2020;101(5):307-8.	review
Scanlon PH. Update on Screening for Sight-Threatening Diabetic Retinopathy. Ophthalmic Res. 2019;62(4):218-24.	review
Scott IA, Cook D, Coiera EW, Richards B. Machine learning in clinical practice: prospects and pitfalls. Medical Journal of Australia. 2019;211(5):203-5.	Review
Shaban-Nejad A, Michalowski M, Buckeridge DL. Health intelligence: how artificial intelligence transforms population and personalized health. npj digit. 2018;1:53.	Review
Shaban M, Ogur Z, Mahmoud A, Switala A, Shalaby A, Abu Khalifeh H, et al. A convolutional neural network for the screening and staging of diabetic retinopathy. PLoS ONE. 2020;15(6):e0233514.	internal validation only
Sharma P, Nirmala SR, Sarma KK. Classification of retinal images using image processing techniques. Journal of Medical Imaging and Health Informatics. 2013;3(3):341-6.	algorithm in development
Sharma S, Maheshwari S, Shukla A. An intelligible deep convolution neural network based approach for classification of diabetic retinopathy. Bio-Algorithms and Med-Systems. 2018;14 (2) (no pagination)(20180011).	internal validation only
Shuang Y, Di X, Kanagasingam Y. Automatic detection of neovascularization on optic disk region with feature extraction and support vector machine. Conf Proc IEEE Eng Med Biol Soc. 2016;2016:1324-7.	algorithm in development
Shuang Y, Di X, Kanagasingam Y. Exudate detection for diabetic retinopathy with convolutional neural networks. Conf Proc IEEE Eng Med Biol Soc. 2017;2017:1744-7.	algorithm in development
Sim D. Historical perspective of diabetic retinopathy screening in the united kingdom - Where do we go from here? West Indian Medical Journal. 2018;67 (Supplement 1):19.	Review
Singh RK, Gorantla R. DMENet: Diabetic Macular Edema diagnosis using Hierarchical Ensemble of CNNs. PLoS ONE. 2020;15(2):e0220677.	internal validation only
Sinthanayothin C, Boyce JF, Williamson TH, Cook HL, Mensah E, Lal S, et al. Automated detection of diabetic retinopathy on digital fundus images. Diabetic Medicine. 2002;19(2):105-12.	only feature-level accuracy in a small number of images

Sivaprasad S, Raman R, Conroy D, Mohan t, Wittenberg R, Rajalakshmi R, et al. The ORNATE India Project: United Kingdom-India Research Collaboration to tackle visual impairment due to diabetic retinopathy. Eye. 2020;34(7):1279-86.	Review
Sosale AR. Screening for diabetic retinopathy-is the use of artificial intelligence and cost-effective fundus imaging the answer? International Journal of Diabetes in Developing Countries. 2019;39(1).	Review
Srivastava R, Wong DW, Lixin D, Jiang L, Tien Yin W. Red lesion detection in retinal fundus images using Frangi-based filters. Conf Proc IEEE Eng Med Biol Soc. 2015;2015:5663-6.	internal validation only
Stevenson CH, Hong SC, Ogbuehi KC. Development of an artificial intelligence system to classify pathology and clinical features on retinal fundus images. Clin Experiment Ophthalmol. 2019;47(4):484-9.	internal validation only
Stolte S, Fang R. A survey on medical image analysis in diabetic retinopathy. Med Image Anal. 2020;64:101742.	Review
Sumathy B, Poornachandra S. Automated dr and prediction of various related diseases of retinal fundus images. Biomedical Research (India). 2018;2018(Special Issue ArtificialIntelligentTechniquesforBioMedicalSignalProcessingEdition-II):S325-S32.	internal validation only
Tang HL, Goh J, Peto T, Ling BW, Al Turk LI, Hu Y, et al. The reading of components of diabetic retinopathy: an evolutionary approach for filtering normal digital fundus imaging in screening and population based studies. PLoS ONE. 2013;8(7):e66730.	Validation in a collection of images obtained from screening and non-screening settings
Thomas SA, Titus G. Design of a portable retinal imaging module with automatic abnormality detection. Biomedical Signal Processing and Control. 2020;60 (no pagination)(101962).	internal validation only
Ting DSW, Carin L, Abramoff MD. Observations and Lessons Learned From the Artificial Intelligence Studies for Diabetic Retinopathy Screening. JAMA Ophthalmology. 2019;13:13.	Review
Ting DSW, Peng L, Varadarajan AV, Keane PA, Burlina PM, Chiang MF, et al. Deep learning in ophthalmology: The technical and clinical considerations. Prog Retin Eye Res. 2019;72:100759.	Review
Ting DSW, Cheung CY, Nguyen Q, Sabanayagam C, Lim G, Lim ZW, et al. Deep learning in estimating prevalence and systemic risk factors for diabetic retinopathy: a multi-ethnic study. npj digit. 2019;2:24.	overlapping cohorts with Ting 2017
Ting DSW, Pasquale LR, Peng L, Campbell JP, Lee AY, Raman R, et al. Artificial intelligence and deep learning in ophthalmology. British Journal of Ophthalmology. 2019;103(2):167.	review

Ting DSJ, Foo VH, Yang LWY, Sia JT, Ang M, Lin H, et al. Artificial intelligence for anterior segment diseases: Emerging applications in ophthalmology. British Journal of Ophthalmology. 2020;12:12.	Review
Tobin KW, Chaum E, Govindasamy VP, Karnowski TP. Detection of anatomic structures in human retinal imagery. IEEE Trans Med Imaging. 2007;26(12):1729-39.	algorithm in development
Tobin KW, Abramoff MD, Chaum E, Giancardo L, Govindasamy V, Karnowski TP, et al. Using a patient image archive to diagnose retinopathy. Conf Proc IEEE Eng Med Biol Soc. 2008;2008:5441-4.	algorithm in development
Torok Z, Peto T, Csosz E, Tukacs E, Molnar AM, Berta A, et al. Combined Methods for Diabetic Retinopathy Screening, Using Retina Photographs and Tear Fluid Proteomics Biomarkers. J Diabetes Res. 2015;2015:623619.	internal validation only
Tsai CL, Madore B, Leotta MJ, Sofka M, Yang G, Majerovics A, et al. Automated retinal image analysis over the internet. IEEE Trans Inf Technol Biomed. 2008;12(4):480-7.	not a screening algorithm
Tufail A, Rudisill C, Egan C, Kapetanakis VV, Salas-Vega S, Owen CG, et al. Automated Diabetic Retinopathy Image Assessment Software: Diagnostic Accuracy and Cost-Effectiveness Compared with Human Graders. Ophthalmology. 2017;124(3):343-51.	full HTA report already included
Ullah H, Saba T, Islam N, Abbas N, Rehman A, Mehmood Z, et al. An ensemble classification of exudates in color fundus images using an evolutionary algorithm based optimal features selection. Microsc Res Tech. 2019;82(4):361-72.	algorithm in development
Umadevi KS, Jeyapriya J. Cascaded neural network based automated detection of diabetic retinopathy. Indian Journal of Public Health Research and Development. 2017;8(4):1322-8.	algorithm in development
Valverde C, Garcia M, Hornero R, Lopez-Galvez MI. Automated detection of diabetic retinopathy in retinal images. Indian J Ophthalmol. 2016;64(1):26-32.	Review
van Grinsven MJ, van Ginneken B, Hoyng CB, Theelen T, Sanchez CI. Fast Convolutional Neural Network Training Using Selective Data Sampling: Application to Hemorrhage Detection in Color Fundus Images. IEEE Trans Med Imaging. 2016;35(5):1273-84.	Evaluation at the level of lesions only
Venkatesan R, Chandakkar P, Li B, Li HK. Classification of diabetic retinopathy images using multi-class multiple-instance learning based on color correlogram features. Conf Proc IEEE Eng Med Biol Soc. 2012;2012:1462-5.	internal validation only
Verbraak FD, Schmidt-Erfurth U, Grzybowski A, Abramoff M, Schlingemann R. Is automated screening for diabetic retinopathy indeed not yet ready as stated by Grauslund et al.? Acta Ophthalmologica. 2020;98(2):e257-e8.	Review

Vidal-Alaball J, Royo Fibla D, Zapata MA, Marin-Gomez FX, Solans Fernandez O. Artificial Intelligence for the Detection of Diabetic Retinopathy in Primary Care: Protocol for Algorithm Development. JMIR Res Protoc. 2019;8(2):e12539.	protocol for algorithm development
Vijayabaskar J, Rajeswari D, Vaithiyanathan V. To detect diabetic retinopathy in fundus enhanced retina images using effective ROI segmentation and kirch's templates. International Journal of Pharmacy and Technology. 2016;8(4):23240-52.	algorithm in development, no info on validation
Vijayalakshmi R, Selvarajan S. A decision support system for detecting the stages of diabetic retinopathy by using fundus images. Journal of Pure and Applied Microbiology. 2015;9(Special Edition):65-70.	unable to obtain full text
Vollmer S, Mateen BA, Bohner G, Kiraly FJ, Ghani R, Jonsson P, et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. The BMJ. 2020;368 (no pagination)(l6927).	Review
Wang S, Summers RM. Machine learning and radiology. Med Image Anal. 2012;16(5):933-51.	Review
Wang S, Yin Y, Cao G, Wei B, Zheng Y, Yang G. Hierarchical retinal blood vessel segmentation based on feature and ensemble learning. Neurocomputing. 2015;149(PB):708-17.	Focus on blood vessel segmentation
Wang S, Tang HL, Al Turk LI, Hu Y, Sanei S, Saleh GM, et al. Localizing Microaneurysms in Fundus Images Through Singular Spectrum Analysis. IEEE Trans Biomed Eng. 2017;64(5):990-1002.	No evaluation at DR level; only at the level of lesions
Wang K, Jayadev C, Nittala MG, Velaga SB, Ramachandra CA, Bhaskaranand M, et al. Automated detection of diabetic retinopathy lesions on ultrawidefield pseudocolour images. Acta Ophthalmol (Oxf). 2018;96(2):e168-e73.	ultra-widefield pseudocolor images
Wang R, Chen B, Meng D, Wang L. Weakly Supervised Lesion Detection From Fundus Images. IEEE Trans Med Imaging. 2019;38(6):1501-12.	algorithm in development
Wang H, Yuan G, Zhao X, Peng L, Wang Z, He Y, et al. Hard exudate detection based on deep model learned information and multi-feature joint representation for diabetic retinopathy screening. Comput Methods Programs Biomed. 2020;191:105398.	Focus on detection of exudates, no DR level evaluation
Welikala RA, Dehmeshki J, Hoppe A, Tah V, Mann S, Williamson TH, et al. Automated detection of proliferative diabetic retinopathy using a modified line operator and dual classification. Comput Methods Programs Biomed. 2014;114(3):247-61.	internal validation only
Welikala RA, Fraz MM, Dehmeshki J, Hoppe A, Tah V, Mann S, et al. Genetic algorithm based feature selection combined with dual classification for the	internal validation only

automated detection of proliferative diabetic retinopathy. Comput Med Imaging Graph. 2015;43:64-77.	
Wong TY, Sabanayagam C. The War on Diabetic Retinopathy: Where Are We Now? Asia Pac J Ophthalmol (Phila). 2019;8(6):448-56.	Review
Wong TY. Artificial intelligence in ophthalmology: Concepts, progress, challenges and myths synopsis. Clinical and Experimental Ophthalmology. 2019;47 (Supplement 1):15-6.	Review
Wong TY, Sabanayagam C. Strategies to Tackle the Global Burden of Diabetic Retinopathy: From Epidemiology to Artificial Intelligence. Ophthalmologica. 2020;243(1):9-20.	Review
Xu L, Luo S. Optimal algorithm for automatic detection of microaneurysms based on receiver operating characteristic curve. J Biomed Opt. 2010;15(6):065004.	algorithm in development
Xu K, Feng D, Mi H. Deep Convolutional Neural Network-Based Early Automated Detection of Diabetic Retinopathy Using Fundus Image. Molecules (Basel). 2017;22(12):23.	internal validation only
Yao L, Zhong Y, Wu J, Zhang G, Chen L, Guan P, et al. Multivariable Logistic Regression And Back Propagation Artificial Neural Network To Predict Diabetic Retinopathy. Diabetes Metab Syndr Obes. 2019;12:1943-51.	not image analysis
Yedururi S, Katabathina VS, Jo NH, Rachamallu M, Prasad S, Marcal L. Machine learning and artificial intelligence in oncologic imaging: Potential barriers and solutions, abdominal imagers' perspective. Cancer Imaging Conference: 19th Meeting and Annual of the International Cancer Imaging Society Italy. 2019;19(Supplement 1).	Review
You Z, Hu X, Shi K. Will artificial intelligence replace ophthalmologist in diabetic retinopathy screening? Biomedical Research (India). 2017;28(15):6920.	Review
Yun WL, Mookiah MRK, Koh JEW. Automated detection of proliferative diabetic retinopathy using brownian motion features. Journal of Medical Imaging and Health Informatics. 2014;4(2):250-4.	internal validation only
Zaki WMDW, Zulkifley MA, Hussain A, Halim WHWA, Mustafa NBA, Ting LS. Diabetic retinopathy assessment: Towards an automated system. Biomedical Signal Processing and Control. 2016;24:72-82.	Review
Zapata MA, Royo-Fibla D, Font O, Vela JI, Marcantonio I, Moya-Sanchez EU, et al. Artificial Intelligence to Identify Retinal Fundus Images, Quality Validation, Laterality Evaluation, Macular Degeneration, and Suspected Glaucoma. Clinical Ophthalmology. 2020;14:419-29.	not retinopathy (different target condition)
Zhang L, Feng S, Duan G, Li Y, Liu G. Detection of Microaneurysms in Fundus Images Based on an Attention Mechanism. Genes (Basel). 2019;10(10):17.	internal validation only

Zheng R, Liu L, Zhang S, Zheng C, Bunyak F, Xu R, et al. Detection of exudates in fundus photographs with imbalanced learning using conditional generative adversarial network. Biomedical Optics Express. 2018;9(10):4863-78.	Focus on exudate detection, no DR level evaluation
Zhou W, Wu C, Chen D, Wang Z, Yi Y, Du W. Automated Detection of Red Lesions Using Superpixel Multichannel Multifeature. Comput. 2017;2017:9854825.	internal validation only
Zhou K, Gu Z, Liu W, Luo W, Cheng J, Gao S, et al. Multi-Cell Multi-Task Convolutional Neural Networks for Diabetic Retinopathy Grading. Conf Proc IEEE Eng Med Biol Soc. 2018;2018:2724-7.	internal validation only
Zutis K, Trucco E, Hubschman JP, Reed D, Shah S, van Hemert J. Towards automatic detection of abnormal retinal capillaries in ultra-widefield-of-view retinal angiographic exams. Conf Proc IEEE Eng Med Biol Soc. 2013;2013:7372-5.	ultra-widefield-of-view exam; target condition: abnormal retinal capillaries

*Algorithm in development – early development of an algorithm or papers in which it appeared that no external validation has been performed but it was not completely clear from the paper to be classified as ‘internal validation only’; due to limited resources, we were unable to investigate this further
**Review – non-systematic review of the literature
***OCT – the index test was Optical Coherence Tomography
DL – Deep Learning, ML – traditional (non-DL) Machine Learning, DR – diabetic retinopathy

Table 23 Studies meeting the inclusion criteria for question 1 but excluded after prioritisation

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
Abramoff 2016, USA, France	IDx-DR X2.1 (DL)	rDR: moderate NPDR or worse and/or macular oedema (modified ICDR)	Messidor-2	As per dataset	SE 96.8% (95% CI: 93.3%–98.8%), SP 87.0% (95% CI: 84.2%–89.4%), NPV 99.0% (95% CI: 97.8%–99.6%) No cases of severe NPDR, PDR, or ME were missed. SE was not statistically different from published IDP SE which had a CI of 94.4% to 99.3%, SP was significantly better than the published IDP SP CI of 55.7% to 63.0%.	Older version of IDx-DR

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
Araujo 2020, Portugal	DR|GRADUATE (DL-based)	R0 - R4	multiple	as per dataset	quadratic-weighted Cohen's kappa (κ) between 0.71 and 0.84 was achieved in five different datasets	
Bellemo 2019, Zambia	SELENA	Moderate non-proliferative diabetic retinopathy (NPDR) or worse, DME and ungradable images (UK National Health Service)	Prospective cohort study	UNCLEAR! if the reference standard was 1) or 2) 1) Nurses and imaging technicians of non-medical background from Kitwe Central Hospital. Images graded separately for DR&DME 2) Re-graded in Singapore using ICDRSS	rDR: AUC 0.973 (95% CI 0.969–0.978), SE 92.25% (95% CI 90.10%–94.12%), SP 89.04% (95% CI 87.85%–90.28%) Of the referable eyes: SE 99·42% (99·15–99·68) for vtDR SE 97·19% (96·61–97·77) for DME Comparable performance in patients stratified by age, sex, and HbA1c	Deprioritised country (population different from that in the UK in terms of access to diabetes care and diabetic eye screening)
Bhaskaranand 2016, USA and elsewhere	EyeArt v2	ICDR	EyePACS	Human graders (no further detail)	SE 90.0% (95% CI: 88.0%-92.0%) SP 63.2% (95% CI: 61.7%-64.6%) AUC 0.879 (95% CI: 0.865-0.893).	
Gargeya 2017, USA	DL-based	No DR vs any sign of DR	MESSIDOR 2 and E-Ophtha	as per dataset	AUC 0.94 AND 0.95 for MESSIDOR 2 and E-Ophtha	
Gulshan 2016, USA and India	Google AI (DL)	Moderate or worse DR or referable DME (ICDR)	EyePACS-1, Messidor-2	A simple majority decision of US board-certified ophthalmologists, EyePACS-1 (n = 8) and Messidor-2 (n = 7)	All-cause referable predictions in EyePACS-1 (including ungradable images) 1) At high SP operating point: SE 90.7% (95%CI,89.2%-92.1%), SP 93.8% (95% CI, 93.2%-94.4%) 2) At high SE operating point: SE 96.7% (95% CI,	Older version of Google AI; retrospective evaluation

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
					95.7%-97.5%), SP 84.0% (95% CI, 83.1%85.0%) 3) Severe or worse DR only: SE 84.0% (75.3, 90.6), SP 98.8% (98.5, 99.0) on EyePACS-1; SE 87.8% (73.4, 96.0), SP 98.2% (97.4, 98.9) on Messidor-2 4) Maculopathy only: SE 90.8% (86.1, 94.3), SP 98.7% (98.4, 99.0) on EyePACS-1; SE 90.4% (81.9, 94.8), SP 98.8% (98.1, 99.3) on Messidor-2 5) Ungradable images on EyePACS-1: SE 93.9%, SP 90.9% On EyePACS-1 mean agreement for rDR among ophthalmologists was 77.7% (SD, 16.3%), complete agreement 19.6%; for non-referable images, mean agreement 97.4% (SD, 7.3%), complete agreement 85.6% On Messidor-2 the respective values were 82.4% (SD,16.9%), 37.8%, rDR, 96.3% (SD, 9.9%) and 85.1%; The accuracy in mydriatic and non-mydriatic images was similar	
Gulshan 2019, India	Google AI	Moderate or worse DR or referable DME (ICDR)	Prospective cohort study (compared to human graders)	Adjudication by a panel of 3 retinal specialists	Site 1: Trained grader: SE 75.5%, SP 94.2%, Retinal specialist: SE 89.8%, SP 83.5%, Model: SE 88.9%, SP 92.2% Site 2: Trained grader: SE 84.2%, SP 98.6%	Deprioritised country (population different from that in the UK in terms of access to diabetes care and diabetic eye screening)

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
					Retinal specialist: SE 73.4%, SP 98.7% Model: SE 92.1% (90.1 – 93.8), SP 95.2 (94.2 -96.1) the results were similar for referable DME; the new model had AUC of 0.986 vs 0.974 for the old one	
Harangi 2019, Hungary	DL-based	5-class DR, 3-class DME	ISBI 2018 data	as per dataset	total accuracy 90.07% for the 5-class DR challenge, and 96.85% for the 3-class DME one, respectively	
He 2020, China	Airdoc, Beijing, China (DL-based)	ICDR	889 diabetic patients at community hospital	2 ophthalmologists, independently	For DR: SE 90.79% (95% CI 86.4–94.1), SP 98.5% (95% CI 97.8–99.0) and AUC 0.946 (95% CI 0.935–0.956), respectively. For RDR, SE 91.18% (95% CI 86.4–94.7), SP 98.79% (95% CI 98.1–99.3) and AUC 0.950 (95% CI 0.939–0.960),	
Kanagasingam 2018, Australia	DL-based	DR vs no DR; severity of DR based on ICDR; identification of specific pathologies, e.g. MA, exudates; image quality	real-life study, 386 images from 193 patients in primary care	ophthalmologist	This is pilot study. Of the 193 patients (93 [48%] female; mean [SD] age, 55 [17] years [range, 18-87 years]), the AI system judged 17 as having diabetic retinopathy of sufficient severity to require referral. The system correctly identified 2 patients with true disease and misclassified 15 as having disease (false-positives). The resulting specificity was 92%(95% CI, 87%-96%), and the positive predictive value was 12%(95% CI, 8%-18%). Many false-positives were	

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
					driven by inadequate image quality (eg, dirty lens) and sheen reflections.	
Leibig 2017, Germany	DL-based	R1 or worse; R2 or worse	Messidor	as per dataset	Depending on network capacity and task/dataset difficulty, we surpass 85% sensitivity and 80% specificity as recommended by the NHS when referring 0−20% of the most uncertain decisions for further inspection.	
Li 2018, China, Australia, Singapore	EyeGrader (DL-based)	EDESP criteria	NIEHS, SiMES, AusDiab	Certified professional senior graders	SE: 89.76% (NIEHS); 93.94% (SiMES), 94.59% (AusDiab); 92.50% (combined) SP: 97.57% (NIEHS); 98.48% (SiMES), 99.17% (AusDiab); 98.52% (combined); no CIs reported	
Liu 2019b, China	WP-CNN (DL-based)	refer/no	STARE	as per dataset	accuracy of 90.84%, AUC of 0.951 and F1-score of 0.934	
Nazir 2019, Pakistan, Korea	Extreme ML vs DL-based and others	both rDR and stage-wise grading	multiple	as per dataset	median accuracy 0.993 at STARE testing set; 0.993 at Review-DB testing set	
Pires 2019, Brazil, USA	DL-based	R0-R4	Messidor-2, DR2	as per dataset	The Neural Network-based classifier yields the best result for testing with DR2 dataset, with an AUC of 96.3% (95% CI: 93.8–98.1%).	
Ramachandran 2018, New Zealand and elsewhere	Visiona (Hong Kong)	New Zealand MoH guidelines	Otago, Messidor	A single grader, checked by an ophthalmologist	Otago: SE 84.6% SP 79.7% AUC 0.901 (0.807–0.995) Messidor: SE 96.0% SP 90.0%	

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
					AUC 0.980 (0.973–0.986)	
Romero 2019, Spain	DL-based	the retinographies were placed into four levels: (1) Level 0 = no DR, (2) Level 1 =mild DR (only microaneurysms), (3) Level 2 = moderate DR (microaneurysms with a minimum of 5 and a maximum of 15 and/or retina hemorrhages inferior to 5), and (4) Level 3 = severe DR or proliferative DR (microaneurysms more than 15 and hemorrhages more than 5 or presence of new vessels elsewhere).	38,339 images randomly selected from the Spain's DESP	four masked senior retina ophthalmologists.	The results of the DLA to detect any-DR were: CWK= 0.886 – 0.004 (95% confidence interval [CI] 0.879–0.894), S = 0.967%, SP = 0.976%, PPV= 0.836%, and NPV = 0.996%. The error type I = 0.024, and the error type II = 0.004. Likewise, the referable-DR results were: CWK= 0.809 (95% CI 0.798–0.819), S = 0.998, SP = 0.968, PPV = 0.701, NPV = 0.928, error type I = 0.032, and error type II = 0.001.	
Roychowdhury 2014, USA	DREAM (non-DL)	DR vs no DR	MESSIDOR	as per dataset	SE 100%, SP 53.16%, AUC 0.904	
Sayres 2019, USA	Google AI	5-point scale (based on ICDR): no DR, mild, moderate, severe and proliferative; Referable DR was defined as moderate or worse DR	EyePACS	Adjudication by 3 fellowship-trained retina specialists	Both forms of assistance increased readers' sensitivity for moderate-or-worse DR: unassisted: mean, 79.4% [95%CI 72.3%-86.5%]; grades only: mean, 87.5% [95% CI, 85.1%-89.9%]; grades plus heatmap: mean, 88.7%	Different focus: comparative evaluation of 3 diagnostic strategies: 1) unassisted human graders (HG); 2) HG provided with ARIAS's grade; 3) HG provided with ARIAS's grade and a heatmap

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
					[95% CI, 84.9%-92.5%] without a corresponding drop in specificity (unassisted: mean, 96.6% [95% CI, 95.9%-97.4%]; grades only: mean, 96.1% [95% CI, 95.5%- 96.7%]; grades plus heatmap: mean, 95.5% [95% CI, 94.8%-96.1%]).	
Shah 2020b, India, Singapore?	DL-based	rDR defined as moderate NPDR or worse	MESSIDOR 1	as per dataset	SE 90.4% and SP 91.0% for any DR; SE 94.7% and SP 97.4% for prompt referral	
Usher 2004, UK	Non-DL	EURODIAB		clinical research fellow	At a setting with 94.8% sensitivity and 52.8% specificity, no cases of sightthreatening retinopathy were missed (retinopathy warranting immediate ophthalmology referral or re-examination sooner than 1 year by National Institute for Clinical Excellence criteria). If the system was implemented at 94.8% sensitivity setting over half the images with no retinopathy would be correctly identified, reducing the need for a human grader to examine images in 1/3 of patients.	
Wang 2020c, China	DeepDR (DL-based)	ICDR: No DR vs DR Present, Mild or less NPDR vs moderate or more NPDR, moderate or less NPDR vs Severe NPDR or	6788 images from local screening programme	Ophthalmologists	For detecting DR, the device had SE 93.50% and SP 77.08%; For moderate or more NPDR output SE 96.57% and SP 78.09%; and SE of the device's severe NPDR or worse output to detect	

Study & country	ARIAS	DR grading	External validation dataset	Reference standard	Accuracy results	Reason for not being prioritised
		worse, Severe NPDR or less versus PDR.			severe NPDR andworse was 98.46% and specificity was 62.15%; and SE of the device's PDR output to detect PDR was 99.16% and SP was 68.75%. The area under the ROC curve were 0.93, 0.96, 0.97and 0.97 respectively. To further verify the usefulness of our software system in the real world, we evaluated the fundus photographs from community screening. A total of 20,000 fundus images were selected, and 7593 photos of poor quality were excluded according to quality standards. The accuracy of staging of the fundus photos was 0.9179. The sensitivity, specificity and area under the curve (AUC) were 80.58%, 95.77% and 0.9327, respectively	
Zago 2020, Brazil, France	DL-based (patch-based approach)	R0 vs R1-R3; R0&R1 vs R2&R3 (rDR)	Messidor, Messidor-2, IDRiD, DDR, Kaggle	as per dataset	It reached AUC 0.912 (95%CI 0.897 - 0.928) and SE 94% (95%CI 92.1% - 95.9%) for DR screening (SP fixed at 50%)	

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 24 Studies reporting on the diagnostic accuracy of EyeArt 2

Study and country	**Study design (comparator)**	**Total number of patients and images included in validation**	**Fundus images**	**Definition of referable disease (criteria)**	**Reference standard**	**QUADAS-2 by domain: RoB/Applica bilty**	**Diagnostic accuracy for referable DR**
Bhaskaran and 2019 (50), USA	The REVERE study: retrospective cohort study (no comparator)	850 908 fundus images from 101 710 patient visits, EyePACS	3-field protocol, plus external eye image; >90% of encounters contained 8 images and 45.8% were mydriatic	Moderate or severe NPDR, PDR, and/or clinically significant macular edema (ERGS, based on the ETDRS)	EyePACS certified graders (trained ophthalmologists and optometrists), plus 192 encounters were regraded by an expert at external grading centre	PS: high/unclear IT: unclearq/high RS: high/low F&T: low	rDR: SE 91.3% (95% CI: 90.9–91.7), SP 91.1% (95% CI: 90.9–91.3), Other measures: 95.4% of the FNs were moderate NPDR and did not meet the general treatment criteria Severe or proliferative DR (potentially treatable): SE 98.5%, the fraction of FNs in the entire cohort was 0.08% Mydriatic vs. non-mydriatic (rDR) SE 93.0% vs 89.6% (no p-value reported) SP 90.4% vs 91.7% Mydriatic vs. non-mydriatic (treatable DR) SE 98.8% vs 98.0%
Heydon 2020 (19), UK (England)	Prospective cohort study (no comparator)	>120 000 images from 30 405 consecutive episodes	EDESP protocol (2 fields 45º images)	M1, R2, R3, human-graded ungradable (EDESP)	EDESP manual grading	PS: low/low IT: low/low RS: high/low F&T: low	Referable / non-referable disease: SE 95.7% (94.8% to 96.5%) for rDR SP 54.0% (53.4% to 54.5%) for R0M0 & R1M0 Detection rate for other grades:

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applica bilty	Diagnostic accuracy for referable DR
		from the EDESP					68% (67% to 69%) for R0M0 98.3% (97.3% to 98.9%) for R1M1 100% (98.7% to 100%) for R2 100% (97.9% to 100%) for R3 89.4% (87.0% to 91.5%) for ungradable Approx. 50% will require human grading (from 47% to 51% across the 3 centres)
Liu 2020 (21), USA	Prospective cohort study (no comparator)	180 patients from a primary care centre	Non -mydriatic fundus photographs	Moderate or worse DR or inconclusive screening results (ICDR)	Grading by 5 fellowship-trained retina specialists	PS: unclear/unclear IT: low/unclear RS: high/low F&T: low	Referable DR (including inconclusive results): SE 100% (92.3%, 100%) SP 65.7% (57.0%, 73.7%) 29.4% inconclusive results
Olvera-Barrios 2020 (20), England	Cross-sectional study (EDESP protocol compared to EIDON widefield platform)	1257 patients	1) 45^{O} 2-field (macula and disc-centred) mydriatic images 2) EIGON: wide-field macula- and disc-centred images	M1, R2, R3, ungradable (EDESP)	Manual grading by the EDESP	PS: high/low IT: low/low RS: low/low F&T: low	Referable DR: EDESP SE 90% (95%CI 81%-96%), EIDON SE 87% (95%CI 77%-93%).

EDESP – English Diabetic Eye Screening Programme, ERGS - EyePACS Retinopathy Grading System, ETDRS - Early Treatment Diabetic Retinopathy Study, NPDR – non-proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy, rDR – referable diabetic retinopathy, vtDR – vision threatening diabetic retinopahty

Table 25 Studies evaluating the accruacy of IDx-DR

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applica bilty	Diagnostic accuracy for referable DR
Abramoff 2018 (22), USA	Prospective cohort study using an enriched dataset (no comparator)	892 patients with DM from 10 primary care practices; 63.4% white; 23.8% had mtmDR	**Index test:** 45º 2 fields (disc- and fovea-centred) images; mydriasis if necessary; 23.6% mydriasis **RS:** The FPRC* using stereo wide-field photography (4W-D stereo protocol), by an FPRC certified photographer; and OCT* for diagnosis of DME;	more than mild DR (mtmDR) defined as: ETDRS level ≥ 35, and/or CSDME	The fundus images were read by 3 experienced readers from the FPRC using majority voting; OCT images were evaluated by experienced readers from FPRC (ETDRS)	PS: high/unclear IT: low/high RS: low/low F&T: low	SE for mtmDR: 87.2% (95% CI, 81.8–91.2%) (pre-specified >85%), against fundus imaging RS 85.9% (95%% CI, 82.5%–88.7%) against 'fundus + OCT' RS SE for vtDR: 97.4% (95% CI 86.2%–99.9%) against fundus imaging RS 92.2% (95% CI 81.1%–97.8%) against 'fundus + OCT' RS SP for mtmDR (excluding ungradable by the software or the reading centre): 90.7% (95% CI, 88.3–92.7%) (pre-specified >82.5%) against funds imaging RS 90.7% (95% CI, 86.8%–93.5%) against 'fundus + OCT' reference standard Ungradable by the software (after excluding the ungradable by the RS): 33/852 Sensitivity analysis (worst case scenario including all intention-to-screen patients and using mtmDR as a threshold): SE 80.7% (95% CI, 76.7%–84.2%) SP 89.8% (95% CI, 85.9%–92.7%) Other: 64.7% of participants completed the protocol of 4 photographs the first time; 5/11 subjects with enlarged optic disc cups, and 13/26 with any drusen or RPE atrophy, received an "mtmDR detected" output. No effect of sex, ethnicity, race, HbA1c, lens status, or site; increased specificity in subjects >65 years old
van der Heijden 2018 (23),	Prospective cohort study	898 patients with type 2	45º 2 fields (one centred on the macula and one	Moderate or vision threatening	3 retinal specialist independen	PS: low/unclear IT: low/high	Referable DR, EURODIAB criteria: SE 91%(95% CI: 0.69–0.98) SP 84% (95% CI: 0.81–0.86)

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy for referable DR
The Netherlands	(no comparator)	diabetes from a primary care centre; EURODIAB: rDR was 2.4% of which 1.6% vtDR; ICDR rDR was 8.1% of which 1.4% vtDR	nasal field according to EURODIAB protocol), no routine mydriasis	DR(ICDR and EURODIAB criteria)	tly graded the images; final decision reached through consensus	RS: low/low F&T: high	PPV 12% (95% CI: 0.08–0.18) NPV 100% (95% CI: 0.99–1.00) Referable DR, ICDR criteria: SE 68% (95% CI: 0.56–0.79) SP 86% (95% CI: 0.84–0.88) PPV 30% (95% CI: 0.24–0.38) NPV 97%(95% CI: 0.95–0.98). Vison threatening DR, EURODIAB criteria: SE 64% (36%–86%) SP 95% (93%–96%) PPV 16% (8%–29%) NPV 99% (99%–100%) Vision threatening DR, ICDR criteria: SE 62% (32%–85%) SP 95% (93%–96%) PPV 14% (7%–27%) NPV 99% (99%–100%) ‘Ungradable’ by ARIAS: 477/1415 (unclear what proportion of those were also rated ‘ungradable’ by the RS) Considerable disagreement between individual graders; 70% of rDR according to ICDR were classified as no rDR by the EURODIAB score
Verbraak 2019 (51), The Netherlands	Retrospective cohort study (no comparator)	1425 patients with type 2 diabetes from 8 primary care sites; around 15% non-Caucasian; 3.9% moderate	45º 2 fields (macula- and disc-centred); mydriasis if necessary	More than mild DR and/ or maculopathy (ICDR)	Two independent experienced readers, with adjudication by a retinal specialist	PS: low/unclear IT: low/low RS: low/low F&T: high	For referable DR: SE 79.4% (95% CI 66.5–87.9) SP 93.8% (95% CI 92.1–94.9) PPV 39.7% (95% CI 33.8–45.8) NPV 98.9% (95% CI 98.2–99.3) All 13 FNs had a single isolated haemorrhage or cotton wool spot and no microaneurysms For vtDR: SE 100% (95% CI 77.1–100) SP 97.8% (95% CI 96.8–98.5) PPV 36.4% (95% CI 28.4–45.2), NPV 100%,

Study and country	**Study design (comparator)**	**Total number of patients and images included in validation**	**Fundus images**	**Definition of referable disease (criteria)**	**Reference standard**	**QUADAS-2 by domain: RoB/Applica bilty**	**Diagnostic accuracy for referable DR**
		DR, 1.1% vtDR					Ungradable by the software (after excluding 'ungradable' by the RS): 132/1425 Interobserver agreement of the graders was 53% (95% CI 43–62) in case of moderate DR and 48% (95% CI 26–68) for vtDR
Shah 2020a (52), Spain	Retrospective cohort study (no comparator)	2680 patients with DM from the primary-care based DR screening programme ; rDR 4.14%, vtDR 2.57%	45º mydriatic images, 2 fields (macula- and disc-centred), no reimaging, mydriasis used in all patients	Moderate or vision threatening DR and/or DME (ICDR mapped onto the ETDRS)	3 ophthalmologists independently graded the images and reached final decision by consensus or by adjudication by a retinal specialist	PS: unclear/unclean IT: low/low RS: low/low F&T: high	Referable DR: SE 100% (95% CI: 97%-100%) SP 81.82% (95% CI: 80%-83%) (ungradable images excluded) Vision threatening DR: SE 100% (95% CI: 95%-100%) SP 94.64% (95% CI: 94%-95%) (ungradable images excluded) Ungradable by the AI: 404/3531 Subgroup analysis: Sex, age over 65, and duration of diabetes >10 years had no significant effect on SE (P > .05/3). For SP there was no significant effect from sex (P > .655), but there was a significant effect of diabetes duration (P < .05/3) and age (P < .05/3): the AI system showed a higher SP in subjects with a diabetes duration below 10 years, 86%, whereas SP for subjects with a diabetes duration over ten years was 71% (P < .0001); and higher SP in subjects younger than 65, 89%, compared to 79% for subjects older than 65 (P < .0001). Efficiency gain was 78.43%
CSDME – clinically significant diabetic macular oedema; FPRC - Fundus Photograph Reading Centre; OCT – Optical Coherence Tomography; RS – reference standard							

Table 26 Studies evaluating the diagnostic accuracy of Google AI

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicability	Diagnostic accuracy for referable DR
Krause 2018 (24), USA	Retrospective cohort study (human graders; Gulshan 2016 version of software)	EyePACS-2: 1958 images from 998 unique individuals	45º primary field, incl. entire optic nerve head and macula	Moderate or worse DR or referable DME (ICDR)	Adjudication by consensus by 3 retinal specialists	PS: unclear/unclear IT: low/low RS: low/low F&T: high	Ungradable images excluded! rDR: SE 97.1%, SP 92.3% Referable DME: SE 94.9%, SP 94.4% ARIAS classified 4 of the 16 cases of proliferative DR as severe and 2 of the 50 cases of severe DR as moderate Reference standard: SE of individual retinal specialists ranged from 74.4% to 82.1%; SP ranged from 99.1% to 99.3%
Raumviboonsuk 2019 (53), Thailand	Retrospective analysis (human graders; using the improved model from Krause 2018)	7517 patients randomly selected from the national registry diabetic patients	45º single-field macula-centred images	Moderate or worse DR or referable DME (ICDR)	Reginal graders with adjudication by retinal specialists in subsets of results (disagreements and agreements)	PS: unclear/unclear IT: low/low RS: low/low F&T: high	Ungradable images and cases of other retinal diseases excluded! rDR: SE 96.8% (range: 89.3%–99.3%) SP 95.6% (range: 98.3%–98.7%) Referable DME: SE 95.3% (range: 85.9%–100.0%) SP 98.2% (range: 94.4%–99.1%) Severe or worse NPDR and/or DME: SE 93.6% (range: 85.2%–98.4%) SP 98.2% (range: 94.8%–99.3%) (and similar for proliferative DR and/or DME); 12.6% of all images were classified by ARIAS as 'ungradable'; in a subset of 2x1000 images (DR and DME) the adjudicators were 2.5 times more likely to agree with the algorithm than regional graders

Table 27 A summary of the study evaluating the diagnostic accuracy of RetCAD v.1.3.0

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy for referable DR
Gonzalez-Gonzalo 2020 (26), The Netherlands, Spain	Retrospective cohort study (no comparator)	Messidor: 1200 images; Messidor-2: 874 images	45º macula-centred; 800 mydriatic and 400 non-mydriatic images	Stage 2 and 3 (Messidor)	Messidor	PS: unclear/high IT: low/high RS: unclear/unclear F&T: unclear	<u>rDR</u> Messidor (n=1200): SE 92.0% (95%CI 89.1-95.9) SP 92.1% (95%CI 88.7-95.2) Messidor-2 (n=874): SE 92.6% (95%CI 88.4-97.4) SP 93.4% (95%CI 89.9-97.2) Images classified as 'ungradable' by human graders are excluded

Table 28 Studies evaluating the diagnostic accuracy of SELENA

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabil ty	Diagnostic accuracy for referable DR
Ting 2017 (25), Singapore & elsewhere	Retrospective cohort study (2 trained senior nonmedical professional graders with >5 years experience currently employed in the SIDRP)	SIDPR: 71,896 retinal images from 14,880 (8589 unique) patients; 10 cohorts (various ethnicities) total of 40,752 images from 10,269 patients)	SIDRP: 2 x 2 fields (macula and disc centred); 10 cohorts: range of retinal cameras were used	Moderate NPDR or worse and/or DME and/or ungradable image (ICDR).	SIDRP: grading by a retinal specialist (>5 years' experience in conducting diabetic retinopathy assessment) 10 cohorts: individual studies' assessment of diabetic retinopathy, based on retinal specialists, general ophthalmologists, trained nonmedical professional graders, or optometrists	For SIDRP only PS: unclear/unclear IT: low/low RS: high/low F&T: low	<u>SIDRP dataset (n=14 880 patients):</u> DLS (rDR): SE 90.5% (95% CI, 87.3%-93.0%) SP 91.6% (95% CI, 91.0%-92.2%). [Pre-set to achieve 90% sensitivity] DLS vs human graders (rDR): SE 90.5% vs 91.1% (P = .68) SP 91.6% vs 99.3% (P < .001) DLS vs human graders (vt DR): SE 100% vs 88.5% (P < .001) SP 91.1% vs 99.6% (P < .001).

							SIDRP dataset (n=8589 unique patients) DLS vs human graders (rDR): SE 89.56% vs 84.84% SP 83.49 vs 98.56% DLS vs human graders (vtDR): SE 100% vs 89.74% SP 81.4% vs 99.09% Range across the 10 cohorts: SE 91.8% to 100% Specificity 73.3% to 92.2% Results for DR, glaucoma and/or AMD are also reported in the paper.

Yip 2020 (54), Singapore (SIDPR, SEED) & USA (AFEDS)	Retrospective cohort study	3 datasets:
		SIDRP: 71,896 original images from 14,880 patients;
		AFEDS: 1403 eyes;
		SEED: 9820 images from 4910 eyes
			Multiple: 45º 1-, 2- and 7-fields compared; different levels of image compression	Moderate non-proliferative DR or worse, including DME (ICDR)	SiDRP and SEED: by an ophthalmologist sub-specializing in retinal diseases, with >5 years experience in assessing DR
					
					AFEDS: concurring assessments from two retinal specialists
						PS: unclear/unclear
						IT: unclear/unclear
						RS: low/low
						F&T: low
							Alternative CNN and computation frameworks had little impact on accuracy.
							Image characteristics had significant effects: AUC dropped progressively from 0.936 (original 350 (KB)) to 0.891 (150 KB). SEs stayed high (83.5 to 90.5%, due to fixed operating point), SPs dropped to 72.4%.
							The number of fields had effects: 2- vs 1-field AUC (0.936 vs 0.908), SE (90.5% vs 89.4%) and SP (91.9% vs 89.4%). 7- field vs 2-field vs 1-field
							AUC (0.949 vs 0.911 vs 0.895), SE (90.0% vs 82.6% vs 78.4%) and SP (86.5% vs 84.4% vs 86.1%).
							Previous cataract surgery vs none: AUC (0.918 vs 0.833), sensitivity (93.4% vs 91.1%), specificity (84.2% vs 76.1%).

Table 29 A summary of the study evaluating the diagnostic accuracy of VUNO Med-Fundus AI

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy for referable DR
Son 2020 (18), Korea	Retrospective cohort study (no comparator)	E-ophtha: 434 images IDRiD: 143 images	n/a	n/a	As per dataset	PS: unclear/unclear IT: unclear/unclear RS: unclear/unclear F&T: unclear	E-ophtha Haemorrhage:* SE 89.2 (83.0 – 93.7) SP 91.4 (87.1 – 94.7) Hard exudate: SE 93.6 (82.5 – 98.7) SP 97.1 (85.1 – 99.9) IDRiD Haemorrhage: SE 88.9 (77.4 – 96.6) SP 96.6 (90.5 – 99.3) Hard exudate: SE 92.6 (82.1-97.9) SP 100.0 (95.9 – 100.0) Cotton wool patch: SE 92.3 (74.9 – 99.1) SP 94.0 (88.1 – 97.6)

*microaneurysms were subsumed to haemorrhages; only diabetic retinopathy lesions included (those related to other eye conditions not extracted)

Table 30 Studies reporting on the diagnostic accuracy of the iGradingM or its predecessor the Aberdeen system

Study and country	Study design (comparator)	Total number of patients (images) and population	Fundus images	Definition of referable disease (criteria); and reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy
Philip 2007, UK (Scotland)	Prospective cohort study (manual screening, 3 retinal screeners who also performed photography)	6722 (14 406) from the SDESP	At least one 45º disc or macula-centred image per eye (dilation used if needed)	M1, R2, M2, R3, R4 (SDESP); A single grader (clinical research fellow)	PS: low/low IT: low/low RS: high/low F&T: low	ARIAS: referral for ‘full disease’ grading SE 90.5% (89.3–91.6) and SP 67.4% (66.0–68.8); Detection rate: R1 5.9% (84.1–87.5); M1 97.4% (90.9–99.3); R2 100% (67.6–100); M2 97.2% (93.6–98.8); R3 100% (91.0–100); R4 100% (87.9–100); technical failure 99.8% (99.0–100)

Study and country	Study design (comparator)	Total number of patients (images) and population	Fundus images	Definition of referable disease (criteria); and reference standard	QUADAS-2 by domain: RoB/Applicab ilty	Diagnostic accuracy
						Manual: referral for ‘full disease’ grading SE 86.5% (85.1–87.8) and SP 95.3% (94.6–95.9); Detection rate: R1 80.9% (78.9–82.7); M1 98.7% (92.9–99.8); R2 100% (67.6–100); M2 99.4% (96.9–99.9); R3 97.4% (86.8–99.5); R4 100% (87.9–100); technical failure 95.7% (93.6–97.1)
Fleming 2010a, UK (Scotland)	Retrospective cohort study (n/a)	33 535 (78 601) from the SDESP	45º macula-centred images (dilation used if needed)	M1 and R2 – rescreen in 6 months; M2, R3, R4 – refer to ophthalmology (SDESP); The screening programme manual grading, with additional 2 levels of arbitration for disagreements	PS: low/low IT: low/low RS: low/low F&T: low	Detection rate: R0 49.6% (48.9 to 50.3), R1 83.9% (83.0 to 84.6), M1 99.2% (97.8 to 99.7), R2 100% (97.9 to 100), M2 97.3% (96.1 to 98.1), R3 100% (98.8 to 100), R4 100% (98.1 to 100), Ungradable 99.8% (99.5 to 99.9) No statistically significant difference between Caucasians, Asians and Afro-Caribbean Outcomes: 12m recall 58.9% (58.3 to 59.4); 6 month recall 99.5% (98.5 to 99.8), refer to ophthalmology 98.1% (97.3 to 98.7), slit-lamp examination 99.8% (99.5 to 99.9)
Fleming 2010b, UK (Scotland)	Retrospective cohort study using an enriched dataset (2 algorithms compared)	7 586 (n/a) from the SDESP	Probably as above (SDESP)	M1, R2, M2, R3, R4 (SDESP); The programme’s final grade and a single grader (one of two clinical research fellows) adjudicated by lead clinician	PS: high/low IT: low/low RS: low/low F&T: low	Adding EX and HM to MA increased SE for detection of rDR from 94.9% (95% CI 93.5 to 96.0) to 96.6% (95.4 to 97.4), (p=0.001), without affecting manual grading workload
Goatman 2011, UK (England)	Retrospective cohort study (4 strategies: ‘MA’ or ‘MA + BH&EX’ on macula or macula & disc fields per eye)	8 271 patient episodes (36 236) from EDESP	Two 45º fields per eye: macula- & disc-centred (mydriasis used in all patients)	M1, R2, R3 or Ungradable (EDESP); Routine grading within the EDESP with additional two levels of arbitration	PS: low/low IT: low/low RS: low/low F&T: low	SE for detecting ungradable images ranged from 97.4% to 99.1%; SE for rDR ranged from 98.3% (MA/BH/EX, single field) to 99.3% (MA only, both fields); SE for pre- and proliferative DR was 100% for all strategies; workload reduction ranged from 26.4% to 38.1%
Soto-Pedre	Retrospective cohort study	5278 (5253) from the Spain	A single 45º macula-centred image	Moderate NPDR or more severe DR and/or suspected	PS: low/unclear IT: low/low	Based on n=3877, ignoring all ungradable results: SE 94.52% [92.56–96.49], SP 68.77%

Study and country	Study design (comparator)	Total number of patients (images) and population	Fundus images	Definition of referable disease (criteria); and reference standard	QUADAS-2 by domain: RoB/Applicab ilty	Diagnostic accuracy
2015, Spain		DR screening programme	(mydriasis used in all patients)	maculopathy (ICDR); Routine manual grading (a single grader)	RS: high/low F&T: high	[67.18–70.36], PPV 34.10% [31.72–36.48], NPV 98.66% [98.17–99.15] Ungradable patients: iGradingM 26.16% (n=1374) vs manual grading 2.03% (n=107), (p < 0.0001).
Philip 2017, UK (Scotland), conference abstract	Audit of the performance of the autograder in the SDESP	2015 EQA round (no further detail provided)	SDESP	SDESP; n/a	Unclear	SE 97%, SP 38%, FNR of 0 to 0.6% during an internal quality assessment

Table 31 Studies reporting on the diagnostic accuracy of RetmarkerSR

Study and country	Study design (comparator)	Total number of patients and images included	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy for referable DR
Oliveira 2011 (35), Portugal	Retrospective cohort study	21 544 images from 5 386 patients; 289 included in the 2-step algorithm evaluation	Two 45º fields: macula- & disc-centred (dilation used if needed)	NPDR with maculopathy and proliferative DR (Portugal screening programme)	A single ophthalmologist	PS: high/unclear IT: low/low RS: high/low F&T: low	SE 96.1% (CI 95% 94.39–97.89) SP 51.7% (95% CI 50.27–53.07) 2-step algorithm (n=289) SE 95.8% (95% CI 92.8 - 98.4%) SP 63.2% (95% CI 60.8 -65.7%) Urgent referrals (n=116) 115 classified as ‘having disease’
Ribeiro 2014 (14), Portugal	Retrospective single-arm audit study including only IT-negatives (indirect comparison	3,287 cases randomly chosen from those classified by the software	Two 45º fields: macula- & disc-centred (dilation	NPDR with maculopathy and proliferative DR (Portugal screening programme)	Human graders from the program blinded to the selection of images	PS: low/unclear IT: low/low RS: high/low F&T: low	RetmarkerSR: Only 11 cases out of the 3,287 cases (0.3% of quality control cases, 0.02% of total patients) were identified by the RS as having referable DR pathology (false negatives)

	with human graders)	as 'no disease'	used if needed)				Human graders (sampling unclear) SE 97.52% SP 98.55%, Inter-grader agreement 96.65%
Figueiredo 2015 (55), Portugal	Retrospective study (unclear if cohort or CC design were used)	4 datasets containing 45 770 fundus images from 11 511 patients	Two 45° fields: macula- & disc-centred, non-mydriatic	Unclear, but most likely as per the Portugal DESP	Human graders at the Diabetic Retinopathy Screening programme	PS: unclear/unclear IT: unclear/unclear RS: high/unclear F&T: low	Across the 4 datasets: SE ranged 89.3% to 100% SP ranged 57.6% to 73%
Tufail 2017 (1), UK	Retrospective cohort study (iGradingM vs. RetmarkerSR vs. EyeArt)	10 2856 images from 20 258 patient episodes	Two 45° image fields: macula- & disc-centred (dilation used if needed)	M1, R2, R3 or Ungradable (EDESP)	Routine screening programme grading, with additional arbitration	PS: low/low IT: low/low RS: low/low F&T: low	SE 85.0% (95% CI 83.6%-86.2%) for referable retinopathy, and 97.9% (95% CI 94.9%-99.1%) for proliferative retinopathy (R3); SP 53% (95% CI 52% to 54%) for R0 & M0 and 47.7% (95% CI 47% to 48.5%) for R0M0 & R1M0. The RetmarkerSR's performance seemed to be marginally influenced by patient's age, ethnicity, and camera type.
CC – case control design, DESP – diabetic eye screening programme, DR – diabetic retinopathy, EDESP – the English diabetic eye screening programme, F&T – flow and timing domain, IT – index test domain, NPDR – non- proliferative diabetic retinopathy, PS – patient selection domain, RS – reference standard domain, SE –sensitivity, SP – specificity							

Table 32 Studies evaluating the diagnostic accuracy of RetinaLyze

Study and country	Study design (comparator)	Total number of patients and images included in validation	Fundus images	Definition of referable disease (criteria)	Reference standard	QUADAS-2 by domain: RoB/Applicabilty	Diagnostic accuracy for referable DR
Hansen 2004, Denmark	Case control study; patients selected according to DR level (use of	83 patients with type 1 or type 2 diabetes	5 overlapping, non-stereoscopic 45° images of each eye; both mydriatic and non-mydriatic images taken	Moderate NPDR or worse (ETDRS); macula oedema not graded	Two independent readers with adjudication of disagreements by a third one	PS: high/unclear IT: high/high RS: low/high F&T: low	For rDR at patient level (accuracy of red lesion detection and quality control combined): No mydriasis: SE 89.9%, SP 85.7% (11 'ungradable' eyes and 1 patient with AMD excluded from analysis) Mydriasis: SE 97.0%, SP 75.0%

	mydriatic vs non-mydriatic images)						For moderate non-proliferative or more severe DR at patient level: SE 100% for images captured both with and without pupil dilation
Bouhaimed 2008, UK (Wales), Kuwait	Retrospective cohort study	458 images from 100 patients attending the Bro Taf screening program of South Wales	45° 2-field macula- and disc-centred images (7 with 30° visual field); mydriasis used in all	Mild NPDR or worse (≥2a according to the Bro Taf Protocol used in the study)	The grade from the programme; each image was evaluated by a team of senior clinician, diabetologist and ophthalmologist	PS: low/low IT: low/low RS: unclear/high F&T: low	Red lesion detection: SE 82%, SP 75%, PPV 41%, NPV 95% Red and bright lesion detection: SE 88%, SP 52%, PPV 28%, NPV 95% Red and bright lesion detection at elevated thresholds in images of good quality: SE 93%, SP 78%, PPV 46%, NPV 98%

Table 33 Methodological quality assessment of the included studies reporting on the clinical effectiveness and impact of ARIASs in DESPs using the Downs and Black checklist (56)

Downs and Black Quality Assessment Checklist	Study	
Question	Keel 2018 (27)	Liu 2020 (21)
Reporting		
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	No (duration of diabetes, previous diagnosis and other risk factors not provided)	Yes
4. Are the interventions of interest clearly described?	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/a (within-subjects comparison)	No
6. Are the main findings of the study clearly described?	Yes (but some data missing, e.g. cross-tabulation of ARIAS and manual grading, to allow for	Yes

	comparative accuracy estimates)	
7. Does the study provide estimates of the random variability in the data for the main outcomes?	No	Yes
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes
9. Have the characteristics of patients lost to follow-up been described?	No	Yes
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	No	Yes
External validity		
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Unclear	Unclear (number of patients invited to participate not reported)
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Unclear
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unclear (but not representative of the UK DESP)	Unclear (but not representative of the UK DESP)
Internal validity – bias		
14. Was an attempt made to blind study subjects to the intervention they have received?	No	Unclear
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	No (unclear if the ophthalmologist who did the reference grading was part of the research team)	Unclear
16. If any of the results of the study were based on "data dredging", was this made clear?	N/a	N/a
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (within-subjects comparison)	Yes
18. Were the statistical tests used to assess the main outcomes appropriate?	N/a (no statistical tests used)	Yes
19. Was compliance with the intervention/s reliable?	Yes	Yes
20. Were the main outcome measures used accurate (valid and reliable)?	Unclear (accuracy was based on a single ophthalmologist's grading)	Unclear (accuracy was based on a single [out of 5] retina specialist's grading)
Internal validity – confounding (selection bias)		
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/a (within-subjects design)	Yes

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N/a (within-subjects design)	No (historical controls)
23. Were study subjects randomised to intervention groups?	No	No
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/a (within-subjects design)	N/a
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N/a (within-subjects design)	No (patients in the ARIAS cohort received 3 telephone calls and a letter to encourage them to attend; unclear if the same level of engagement was used in the historical control)
26. Were losses of patients to follow-up taken into account?	No (loss to follow up reported as % but patient characteristics not reported)	Yes
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N/a (within-subjects design)	Unclear (sample size calculation not reported)

Table 34. Question 3: Evidence map of UK-based health economic evaluations of AI in DESPs

Study	Country	Study type	Objectives	Components of the study	Outcomes	Authors' conclusions
Prescott 2014 & Olsen 2013	England (Birmingham, Liverpool and Oxford) Scotland (Aberdeen, Dundee, Dunfermline, Edinburgh)	CUA Markov microsimulation model (20 years time-horizon, 2009/2010 cost year).	Cost-effectiveness analysis of methods of identifying diabetic macular oedema from retinal photographs including the role of automated grading	P: Retinal screening programmes in England and Scotland I: Fully automated grading (a version of iGradingM) C: three manual grading strategies: English (strategy 1), Scottish (strategy 2), alternative to English manual grading (having similar sensitivity and higher specificity) (strategy 16) O: Costs, cases identified and QALYs	***Vs English manual grading*** Cost per case detected Fully automated strategy dominates strategy 1 (English manual grading): automated is cheaper and identifies more cases. Cost per QALY After 20 years modelled, fully automated strategy dominates strategy 1: fully automated is £97 cheaper and provides incremental QALYs of 0.0001 than English manual grading (strategy 1), ***Vs Scottish manual grading*** *Cost per case detected* Fully automated dominates Scottish manual grading (strategy 2) based on English screening and referral costs. It was estimated to cost £43,000 less and identified 1 more case than the Scottish manual grading system. When patient mix was adjusted to reflect expected frequency within a screening programme, fully adjusted was estimated to cost an additional £900 per case detected compared to the Scottish manual system. Cost per QALY At 20 years, the fully automated system is estimated to cost £113 more than the Scottish manual system and provide incremental	"When applying a ceiling ratio of 30,000 per quality adjusted life years (QALY) gained, Scotland's scheme was preferred. Assuming automated grading could be implemented without increasing grading costs, automation produced a greater number of QALYS for a lower cost than England's scheme, but was not cost effective, at the study's operating point, compared with Scotland's."

					QALYS of 0.0005, thus the fully automated system has an ICER of £222,210 compared to the Scottish system. It is assumed that this analysis is adjusted for patient mix.	
Tufail 2016 & 2017 (Liew 2014 and Egan 2016)	England (London)	CEA Decision tree model (1 year time-horizon, 2013/ 2014 cost year) [from full-text]	Can ARIAS be safely introduced into DR screening pathways to replace human graders	P: patients attending routine annual diabetic eye screening at one London hospital between June 1, 2012, and November 4, 2013. I: RetmarkerSR and EyeArt v1 as a replacement for initial human grading (strategy 1) and as a filter prior to primary human grading (strategy 2) [iGradingM not included in CEA] C: Manual grading O: Cost per appropriate screening outcome (defined as disease present when the reference human grade indicated the presence of potentially sight-threatening retinopathy or technical failure, and disease absent when the reference human grade indicated absence of retinopathy or background retinopathy only	For both ARIAS and strategies, automated is less costly, but less effective than manual grading. **Strategy 1** **Manual vs EyeArt** Incr costs: £101,820 Incr appr outcomes: 14,257 ICER: £7.14 (cost reduction per additional appropriate outcome missed) **Manual vs RetmarkerSR** Incr costs: £167,251 Incr appr outcomes: 8,953 ICER: £18.68 (cost reduction per additional appropriate outcome missed) **Strategy 2** **Manual vs EyeArt** Incr costs: £120,026 Incr appr outcomes: 14,256 ICER: £8.42 (cost reduction per additional appropriate outcome missed) **Manual vs RetmarkerSR** Incr costs: £137, 521 Incr appr outcomes: 8,924 ICER: £15.37 (cost reduction per additional appropriate outcome missed)	"EyeArt v1 and RetmarkerSR 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."
Bhaskaranand 2016 (conference abstract)	UK	CMA Decision tree approach	Comparison of annual population costs	P: UK NHS Diabetic Eye Screening Program I: EyeArt v1	Annual population costs EyeArt: £3,626,974 + £528,000 (=£4,154,974)	Automated DR screening using EyeArt v1 can provide significant

				C: similar to the UK NHS Diabetic Eye Screening Program O: annual population costs	Fully manual grading: £12,000,709 Reported savings using EyeArt v1: £7,627,054	cost savings in DR screening programs
Scotland 2007	Scotland (Grampians)	CEA Decision tree model.	Cost-effectiveness of replacing first level manual grading in the National Screening Programme in Scotland with an automated system	P: diabetic population of Scotland (Grampian region) I: automated system (a version of iGradingM) C: manual grading O: Incr cost per case detected, incr cost per additional appropriate screening outcome	Automated cases detected: 5560 cases (86.9%) Manual cases detected: 5610 cases (87.7%). Incr effects (automated vs manual): -50 cases Cost savings (NHS per year) for automated vs manual: £201,600 Incr cost per additional referable case detected **(manual vs automated)**: £4088 Incr cost per additional appropriate screening outcome **(manual vs automated)**: £1990	"Given that automated grading is less costly and of similar effectiveness, it is likely to be considered a cost-effective alternative to manual grading."
Scotland 2010	Scotland	CEA (and CUA) Decision tree model (same as that used in Scotland 2007).	Assess cost-effectiveness of two automated grading algorithms (as that in Scotland 2007 and an improvement of Scotland 2007) with manual grading	P: three screening centres in Scotland I: Two algorithms (versions of iGradingM). Algorithm (a) is simpler (using image quality assessment and MA/dot haemorrhage (DH) detection) than algorithm (b) (combines image quality assessment with detection algorithms for	Algorithm (b) vs manual grading: Incr effects: -123 referable cases Incr effects: -734 appropriate screening outcomes Incr cost: - £212 695 **ICERs (Manual vs algorithm b - manual more expensive and more effective than algorithm)** Incr cost per referable case: £1727 Incr cost per additional appropriate screening outcome: £289	"Algorithm (b) is more cost-effective than the algorithm based on quality assessment and MA/DH detection. With respect to the value of introducing automated detection systems into screening programmes, automated grading operates within the recommended

			microaneurysms (MA), blot haemorrhages and exudates) C: Manual grading O: Incremental costs per • additional case found, • Appropriate screening outcome QALY gained (using a 20-year extrapolation model to assess impact of any missed referable cases)	The ICER for manual vs algorithm b is between £25,676 and £267,115 per QALY, depending on the probability of algorithm b missing true proliferative cases	national standards in Scotland and is likely to be considered a cost-effective alternative to manual disease/no disease grading.”

Table 35. Question 4: Evidence map of studies investigating the social and ethical implications of implementing AI in screening programmes: Primary studies

Study	Study design and country	Objectives	Components of the study	Outcomes	Authors' conclusions
Alexander 2020	Survey, USA	Survey of US radiologists' workload and use of AI and review of the progress of AI in medical imaging	**P:** Radiologists **I:** n/a **C:** n/a **O:** experience	Not available in the abstract	As AI in medical imaging increasingly proves its worth, it is hard to imagine that AI will not ultimately transform radiology
Bourla 2018	Survey, France	To explore psychiatrists' perspectives on different AI-based assessment techniques through the prism of new CDSS	**P:** Psychiatrists **I:** AI-based CDSS **C:** alternative AI-based CDSS technologies **O:** acceptability	Overall acceptability was moderate (n=515). MRI coupled with ML was considered to be the most useful system, and the connected wristband was considered the least. All the systems were described as risky (410/515, 79.6%). Acceptability was strongly influenced by socio-epidemiological variables	Moderate acceptability, mostly due to lack of knowledge about these new technologies rather than a strong rejection. Strong correspondences between acceptability profiles and professional culture profiles. Many medical, forensics, and ethical issues were raised,

				(professional culture), such as gender, age, and theoretical approach.	including therapeutic relationship, data security, data storage, and privacy risk. It is essential for psychiatrists to receive training and become involved in the development of new technologies.
Coppola 2020	Survey, Italy	A nationwide online survey on AI among radiologist members of the Italian Society of Medical and Interventional Radiology (SIRM)	**P:** Radiologists **I:** AI in radiology **C:** n/a **O:** perceived advantages of AI and overall opinion about AI	1032 radiologists (9.5% of active SIRM members) joined the survey. Perceived AI advantages included a lower diagnostic error rate (750/1027, 73.0%) and optimization of radiologists' work (697/1027, 67.9%). The risk of a poorer professional reputation of radiologists compared with non-radiologists (617/1024, 60.3%), and increased costs and workload due to AI system maintenance and data analysis (399/1024, 39.0%) were seen as potential issues. Most radiologists stated that specific policies should regulate the use of AI (933/1032, 90.4%) and were not afraid of losing their job due to it (917/1032, 88.9%). Overall, 77.0% of respondents (794/1032) were favourable to the adoption of AI, whereas 18.0% (186/1032) were uncertain and 5.0% (52/1032) were unfavourable.	Radiologists had a mostly positive attitude toward the implementation of AI in their working practice. They were not concerned that AI will replace them, but rather that it might diminish their professional reputation.
European Society of Radiology 2019	Survey, Europe	To investigate the expectations about AI in 5-10 years among members of the European Society of Radiology (ESR)	**P:** Radiologists **I:** AI in radiology **C:** n/a **O:** expectations	675 (2.8%) of ESR members completed the survey. AI impact was mostly expected (≥ 30% of responders) on breast, oncologic, thoracic, and neuro imaging, mainly involving mammography, computed tomography, and magnetic resonance. Responders foresee AI impact on: job opportunities (375/675, 56%), 218/375 (58%) expecting	Responders showed a general favourable attitude towards AI

				increase, 157/375 (42%) reduction; reporting workload (504/675, 75%), 256/504 (51%) expecting reduction, 248/504 (49%) increase; radiologist's profile, becoming more clinical (364/675, 54%) and more subspecialised (283/675, 42%). For 374/675 responders (55%) AI-only reports would be not accepted by patients, for 79/675 (12%) accepted, for 222/675 (33%) it is too early to answer. For 275/675 responders (41%) AI will make the radiologist-patient relation more interactive, for 140/675 (21%) more impersonal, for 259/675 (38%) unchanged. If AI allows time saving, radiologists should interact more with clinicians (437/675, 65%) and/or patients (322/675, 48%). For all responders, involvement in AI-projects is welcome, with different roles: supervision (434/675, 64%), task definition (359/675, 53%), image labelling (197/675, 29%). Of 675 responders, 321 (48%) do not currently use AI, 138 (20%) use AI, 205 (30%) are planning to do it. According to 277/675 responders (41%), radiologists will take responsibility for AI outcome, while 277/675 (41%) suggest shared responsibility with other professionals.	
Ginestra 2019	Survey (prospective observational study), USA	To assess clinician perceptions of a ML-based early warning system to predict severe sepsis and septic shock (Early Warning System 2.0)	**P:** Nurses and health care providers dealing with non-ICU admissions **I:** Early Warning System **C:** n/a	Few (24% nurses, 13% providers) identified new clinical findings after responding to the alert. Perceptions of the presence of sepsis at the time of alert were discrepant between nurses (13%) and providers (40%). The majority of clinicians reported no change in	In general, clinical perceptions of Early Warning System 2.0 were poor. Nurses and providers differed in their perceptions of sepsis and alert benefits. These findings highlight the challenges of achieving

			O: change in perception of the patient's risk of sepsis; perceptions of the alert's helpfulness and impact on care	perception of the patient's risk for sepsis (55% nurses, 62% providers). A third of nurses (30%) but few providers (9%) reported the alert changed management. Almost half of the nurses (42%) but less than a fifth of providers (16%) found the alert helpful at 6 hours.	acceptance of predictive and machine learning-based sepsis alerts.
Gorges 2020 (CA)	Survey, N/A	To assess physicians' and general public perceptions on the use of AI to assist medical decision making; in particular, the notion of uncertainty in outcome predictions, and how this might influence treatment decisions	**P:** Physicians and family members **I:** use of AI to assist medical decision making **C:** comparison between the 2 groups and low- and high-risk medical scenarios **O:** perceptions	26 family members and 21 physicians were included in the analysis. Familiarity with AI varied, yet >90% of participants agreed that AI has the potential to improve medical services. Regarding liability for AI-augmented decisions, both families and physicians agreed that the physician was primarily responsible, yet families also assigned responsibility to AI design companies. In **low-risk scenarios**, both groups trusted the AI's suggestion and emphasized patient-physician discussions of results: 92% of families and 95% of physicians would follow the AI's recommendation when positive outcomes [40% vs 20% effectiveness] were predicted; 43% of physicians (vs. 67% of families) reverted to physician judgment when AI risk assessment showed equal effectiveness. **High-risk scenarios** revealed significant differences between the two groups: only 38% of physicians (vs. 69% of families) would follow an AI's suggested intervention if it was against common practice and only 38% of physicians were likely to discuss options with patients.	These surveys suggested that families were accepting of AI-assisted medical decision making. Physicians were more hesitant in trusting AI predictions in the high-risk scenario; this may be in part due to assumed liability favoring a more conservative clinical approach. Results of this survey may inform the development of AI and decision support systems to make these technologies more acceptable to expert and lay users.

				Both groups would consider AI risk metrics when making treatment decisions: 62% of physicians and 88% of families for short-term differences in outcome [44% vs. 66% mortality]; 52% of physicians and 81% for long-term differences [worse immediate mortality, but 20% vs. 50% improved 5-year outcome]. Physicians strongly reverted to physician judgment when AI generated risk assessment showed equal effectiveness: only 5% would follow the AI recommendation, compared with 52% of families.	
Hamilton 2002	Survey, USA	Survey of directors of screening organisations	**P:** Directors of screening organisations **I:** High-throughput screening (HTS) automation **C:** n/a **O:** Perceptions of the current vs. desired state of HTS	Not available in the abstract	Not available in the abstract
Jonmarker 2019	Survey, Sweden	To survey breast cancer screening participants' attitudes towards potential future uses of computerization.	**P:** Women in a breast cancer screening program **I:** Computerization of breast cancer screening **C:** n/a **O:** Attitudes towards potential future uses of computerization	Response rate was 1.3%. Of the submitted surveys, 97.5% were complete; 38% of respondents reported a preference for a computer-only examination. The highest level of confidence was given a computer-only reading followed by a physician reading. Participants with > 12 years of education were more likely to prefer a computer-only reading (odds ratio [OR] 1.655, 95% confidence interval [CI] 1.168-2.344), had a greater trust in letting a computer determine screening intervals and the need for a supplemental MRI (OR	A high level of trust in computerized decision-making was expressed. Higher age was associated with a lower understanding of technology but did not affect attitudes to computerized decision-making. A lower level of education was associated with a lower trust in computerization. This may be valuable knowledge for future studies.

				1.606, 95% CI 1.171-2.202 and OR 1.577, 95% CI 1.107-2.247, respectively). Age was not found to be a significant predictor.	
Jungmann 2020	Survey, Germany	To investigate the attitudes of radiologists, information technology (IT) specialists, and industry representatives on AI and its future impact on radiological work	**P:** Radiologists, IT specialists and industry **I:** AI **C:** comparison between groups **O:** attitudes	The strongest agreement between all respondents occurred with the following: plausibility checks are important to understand the decisions of the AI (93% agreement), validation of AI algorithms is mandatory (91%), and medicine becomes more efficient in the age of AI (86%). In contrast, only 25% of the respondents had confidence in the AI results, and only 17% believed that medicine will become more human through the use of AI. The answers were significantly different between the three professions for four items: relevance for protocol selection in cross-sectional imaging (p=0.034), medical societies should be involved in validation (p=0.028), patients should be informed about the use of AI (p=0.047), and AI should be part of medical education (p=0.026).	Currently, a discrepancy exists between high expectations for the future role of AI and low confidence in the results. This attitude was similar across all three groups. The demand for plausibility checks and the need to prove the usefulness in randomized controlled studies indicate what is needed in future research.
Keel 2018	Survey, Australia	Patient acceptability of a novel AI-based DR screening model within endocrinology outpatient settings	**P:** Adults with DM undergoing DR screening **I:** ARIAS using DL algorithm and real-time reporting of results **C:** Usual practice, results received in 2 weeks **O:** Overall satisfaction and preferred model of care	96 participants were screened for DR and the mean assessment time for automated screening was 6.9 minutes. 96% reported that they were either satisfied or very satisfied with the automated screening model and 78% reported that they preferred the automated model over manual. The sensitivity and specificity of the DLA for correct referral was 92.3% and 93.7%, respectively.	AI-based DR screening in endocrinology outpatient settings appears to be feasible and well accepted by patients.

Koh 2019 (CA)	Survey, UK	To understand the current attitudes and perceptions of radiologists to AI and ML in cancer imaging (online international survey)	**P:** Radiologists **I:** AI and ML in cancer imaging **C:** n/a **O:** attitudes and perceptions	664 responses from radiologists across more than 40 countries, a range of practice backgrounds; > 66% of the responders indicated that the benefits of AI and ML are much bigger or slightly bigger than the risks for cancer imaging; > 86% felt that AI tools would be used in at least some areas of work that would add value to cancer imaging within the next 5 years. The participants had good agreement with the perceived positive effects of utilising AI and ML; but there was more disagreement about the possible negative effects. The responders to the survey indicated the importance of AI in specific areas.	Not available in the abstract.
Meyer 2020	Survey, USA	To examine patients' experiences using an AI-assisted online symptom checker	**P:** Users of the Isabel Symptom Checker [online tool] **I:** Isabel Symptom Checker **C:** n/a **O:** Experiences of symptom checker use, experiences discussing results with physicians, and prior personal history of experiencing a diagnostic error were collected.	329 usable responses obtained. Patients most commonly used the symptom checker to better understand the causes of their symptoms (232/304, 76.3%), followed by for deciding whether to seek care (101/304, 33.2%) or where (eg, primary or urgent care: 63/304, 20.7%), obtaining medical advice without going to a doctor (48/304, 15.8%), and understanding their diagnoses better (39/304, 12.8%). Most patients reported receiving useful information for their health problems (274/304, 90.1%), with half reporting positive health effects (154/302, 51.0%). Most patients perceived it to be useful as a diagnostic tool (253/301, 84.1%), as a tool providing insights leading them closer to correct diagnoses (231/303, 76.2%), and reported they would use it again (278/304, 91.4%).	Despite ongoing concerns about symptom checker accuracy, a large patient-user group perceived an AI-assisted symptom checker as useful for diagnosis. Formal validation studies evaluating symptom checker accuracy and effectiveness in real-world practice could provide additional useful information about their benefit.

				Patients who discussed findings with their physicians (103/213, 48.4%) more often felt physicians were interested (42/103, 40.8%) than not interested in learning about the tool's results (24/103, 23.3%) and more often felt physicians were open (62/103, 60.2%) than not open (21/103, 20.4%) to discussing the results. Compared with patients who had not previously experienced diagnostic errors (missed or delayed diagnoses: 123/304, 40.5%), patients who had previously experienced diagnostic errors (181/304, 59.5%) were more likely to use the symptom checker to determine where they should seek care (15/123, 12.2% vs 48/181, 26.5%; P=.002), but they less often felt that physicians were interested in discussing the tool's results (20/34, 59% vs 22/69, 32%; P=.04).	
Nadarzynski 2019	Survey and semi-structured interviews, UK	To explore participants' willingness to engage with AI-led health chatbots	**P:** General public **I:** AI-based chatbot systems **C:** n/a **O:** Acceptability and perceived utility and trustworthiness	Three broad themes: 'Understanding of chatbots', 'AI hesitancy' and 'Motivations for health chatbots' were identified, outlining concerns about accuracy, cyber-security, and the inability of AI-led services to empathise. The survey showed moderate acceptability (67%), correlated negatively with perceived poorer IT skills OR=0.32 [95% CI: 0.13–0.78] and dislike for talking to computers OR=0.77 [95% CI: 0.60–0.99] as well as positively correlated with perceived utility OR¼ 5.10 [CI95%:3.08–8.43], positive attitude OR=2.71 [95% CI: 1.77–4.16] and perceived	Most internet users would be receptive to using health chatbots, although hesitancy regarding this technology is likely to compromise engagement.

				trustworthiness OR=1.92 [95% CI: 1.13–3.25].	
Ooi 2019	Survey, Singapore	To assess the attitudes and learner needs of radiology residents and faculty radiologists regarding AI and ML in radiology.	**P:** Radiologists **I:** AI and ML **C:** n/a **O:** Attitudes and learner needs	125 respondents (86 male, 39 female; 70 residents, 55 faculty radiologists) completed the questionnaire. The majority agreed that AI/ML will drastically change radiology practice (88.8%) and makes radiology more exciting (76.0%), and most would still choose to specialise in radiology if given a choice (80.0%). 64.8% viewed themselves as novices in their understanding of AI/ML, 76.0% planned to further advance their AI/ML knowledge and 67.2% were keen to get involved in an AI/ML research project. An overwhelming majority (84.8%) believed that AI/ML knowledge should be taught during residency, and most opined that this was as important as imaging physics and clinical skills/knowledge curricula (80.0% and 72.8%, respectively). More than half thought that their residency programme has not adequately implemented AI/ML teaching (59.2%). In subgroup analyses, male and tech-savvy respondents were more involved in AI/ML activities, leading to better technical understanding.	A growing optimism of radiology undergoing technological transformation and AI/ML implementation has led to a strong demand for AI/ML curriculum in residency education
Ooms 2019 (CA)	Survey, USA	To compare experience and perceptions of adults screened by ARIAS and receiving direct specialist contact via tele-presence robot (TR) and usual practice	**P:** Adults screened for DR **I:** ARIAS interfaced with TR **C:** Usual practice **O:** Preferences	A paired t-test did not suggest that those who interacted with the TR had a preference between the TR and a certified reader (4.57 vs 4.79, p=.19). An unequal variances t-test suggested that interacting with the TR increased the likelihood of wanting robots involved in one's healthcare (3.50 vs 2.48, p=.02).	The AI and TR combination presents a novel approach to improving access to ophthalmic care. The TR, having received positive feedback from participants, could facilitate direct interaction with specialists when AI detects DR.

Palmisciano 2020	Survey, UK	To evaluate attitudes of patients and their relatives regarding use of AI in neurosurgery	**P:** Patients and families **I:** AI in neurosurgery **C:** n/a **O:** Attitudes and perceptions	In the first stage, 20 participants responded. Five themes were identified: interpretation of imaging (4/20; 20%), operative planning (5/20; 25%), real-time alert of potential complications (10/20; 50%), partially autonomous surgery (6/20; 30%), and fully autonomous surgery (3/20; 15%). In the second stage, 107 participants responded. Most thought it appropriate and acceptable to use AI for imaging interpretation (76.7%; 66.3%), operative planning (76.7%; 75.8%), real-time alert of potential complications (82.2%; 72.9%), and partially autonomous surgery (58%; 47.7%). Conversely, most did not think that fully autonomous surgery was appropriate (27.1%) or acceptable (17.7%). Demographics did not have a significant influence on perception	Most patients and their relatives believed that AI has a role in neurosurgery and found it acceptable. Notable exceptions were fully autonomous systems, with most wanting the neurosurgeon ultimately to remain in control.
Paul 2006	Survey, India	To assess patient satisfaction levels and factors influencing it during teleophthalmology consultation in India [NN-based ARIAS also mentioned as part of the new technologies]	**P:** Patients **I:** Tele-ophthalmology screening **C:** n/a **O:** Satisfaction with tele-ophthalmology screening	348 respondents in total; 56.4% were males; the mean age of was 50 +/- 17 years. Age ranged from 2 years to 83 years. 44.4% of the respondents were satisfied with teleophthalmology screening (95% CI: 38.58%-49.42%). No association was found between age, gender, education, and occupation, respectively, with satisfaction levels. We found that patients who asked questions during the screening were 2.18 times more likely to be satisfied with teleophthalmology than those who did not (odds ratio [OR] = 2.19, 95% CI 1.37-3.5).	This study highlights sentiments of the rural subjects when they underwent teleophthalmology consultations. This study provides valuable insights about patient's preferences and satisfaction levels with this newer technology
Waymel 2019	Survey, France	To assess the perception, knowledge, wishes	**P:** Radiologists **I:** AI in radiology **C:** n/a	A total of 70 radiology residents and 200 senior radiologists participated in the survey (43.8%	While respondents had the feeling of receiving insufficient previous

		and expectations of a sample of French radiologists towards the rise of artificial intelligence (AI) in radiology	**O:** Perception, knowledge, wishes and expectations	(270/617) response rate). 73.3% (198/270) estimated they had received insufficient previous information on AI; 94.4% (255/270;) would consider attending a generic continuous medical education in this field and 69.3% (187/270) a technically advanced training on AI; 79.3% (214/270) thought that AI will have a positive impact on their future practice. The highest expectations were the lowering of imaging-related medical errors (81%, 219/270), followed by the lowering of the interpretation time of each examination (74.4%, 201/270) and the increase in the time spent with patients (52.2%, 141/270).	information on AI, they are willing to improve their knowledge and technical skills on this field. They share an optimistic view and think that AI will have a positive impact on their future practice. A lower risk of imaging-related medical errors and an increase in the time spent with patients are among their main expectations.
Xiang 2020	Survey, China	To investigate public perceptions of and demands regarding the implementation of medical AI	**P:** General public (including healthcare vs other lines of work) **I:** Implementation of medical AI **C:** n/a **O:** Perceptions and demands	2,780 participants from 22 provinces were enrolled. There was no significant difference between the healthcare workers (54.3% of all participants) and non-healthcare workers in the high proportion (99 %) of participants expressing acceptance of AI (p = 0.8568), but remarkable distributional differences were observed in demands (p<0.001 for both demands for AI assistance and the desire for AI improvements) and perceptions (p<0.001 for safety, validity, trust, and expectations). High levels of receptivity (approximately 100 %), demands (approximately 80 %), and expectations (100 %) were expressed among different age groups. The receptivity of medical AI among the non-healthcare workers was associated with gender, educational qualifications, and demands and perceptions of	The public exhibits a high level of receptivity regarding the implementation of medical AI. There is a strong demand for intelligent assistance in many medical areas, including imaging and pathology departments, outpatient services, and surgery.

AI. There was a very large gap between current availability of and public demands for intelligence services (p<0.001); >90 % of healthcare workers expressed a willingness to devote time to learning about AI and participating in AI research.

Table 36. Question 4: Evidence map of studies investigating the social and ethical implications of implementing AI in screening programmes: Review and opinion papers

Study	Study type	Objectives	Focus of the study
Anonymous 2018	Editorial	Discussion of the emerging role of AI in eye conditions and CVD	AI in eye conditions and CVD
Anonymous 2019	Editorial	Discussion of ML in medicine	ML in medicine
Rajalakshmi 2020	Editorial	ARIAS in DESP in India	ARIAS in DESP
Shaban-Nejad 2018	Editorial	Review of advances of AI in healthcare	AI in healthcare
Sosale 2019	Editorial	AI in DR screening: discussion of its effectiveness and cost-effectiveness	ARIAS in DESP
Sivaprasad 2020	Report	The ORNATE India Project: to build research capacity and capability in India and the UK to tackle global burden of diabetes-related visual impairment.	ARIAS in DESP
Abramoff 2010	Review	To survey the methods, potential benefits and limitations of ARIAS in order to better manage translation into clinical practice	ARIAS in DESP
Abramoff 2020	Review	To perform a literature review of bioethical principles for AI, and derived evaluation rules for autonomous AI, grounded in bioethical principles	AI in healthcare
Balyen 2019	Review	Impact of AI on the early detection and treatment of ophthalmic diseases	AI in ophthalmology
Berens 2020	Review	"This article discusses to what extent the application of AI algorithms can contribute to quality assurance in the field of ophthalmology	AI in ophthalmology
Broome 2020	Review	To review the current status of ML in various aspects of diabetes care (incl. DR screening) and identify key challenges that must be overcome to leverage ML to its full potential.	ML in diabetes
Carter 2020	Review	This paper proceeds in three parts. In part one, the authors consider what AI is, and examples of its development and evaluation for potential use in breast cancer care. In part two, they outline the ethical, legal and social issues of AI. In the final section, they anticipate future directions for AI in breast cancer care and draw some conclusions.	AI in breast cancer care (focus on social, legal and ethical issues)

Channa 2020	Review	Using the example of DR screening to highlight some important aspects to be considered by developers, policymakers, and end users when bringing autonomous AI algorithms into clinical practice.	ARIAS in DESP
Chee 2018	Review	An update and overview of the literature on current telemedicine applications in retina	DL in DR in the context of telemedicine
Fatehi 2020	Systematic review	To investigate the characteristics and usability features of tele-ophthalmology for the elderly population (including AI-based technology)	Tele-ophthalmology for the elderly population
Francolini 2020	Review	Overview of AI and its use in radiotherapy	AI in Radiotherapy
Graham 2019	Review	A review of recent research on AI in healthcare and mental health	AI in healthcare and mental health
Halamka 2019	Review	Review of the role of AI in family medicine using DR and colon cancer as examples	AI and ML in DR and colon cancer
Jheng 2020	Review	To discuss the issues of computing resource consumption and performance of the mobile device-based AI systems, and highlight recent research regarding the feasibility and future potential of application of the mobile device-based AI systems in telemedicine	AI in eye disease screening using smart phones
Kapoor 2019	Review	Review of the application and use of AI in OCT imaging in ophthalmology	AI in OCT in ophtalmology
Kapoor 2019	Review	Review of the role of AI in the diagnosis and management of glaucoma	AI in glaucoma
Keskinbora 2020	Review	To review the developments and potential practices regarding the use of AI in the field of ophthalmology, and the related topic of medical ethics	AI in ophthalmology
Larson 2020	Theoretical paper	The authors propose an ethical framework for using and sharing clinical data for the development of AI applications	AI in healthcare
Liew 2019	Review	Consider 3 core questions relating to AI in radiology, and the barriers to the widespread adoption of AI in radiology and propose solutions and describe a "Centaur" model as a promising avenue for enabling the interfacing between AI and radiologists.	AI in radiology
O'Connor 2019	Review	Discuss the potential reason for the slow adoption of machine learning tools into systematic reviews in healthcare	ML in systematic reviews
Padhy 2019	Review	Review of ARIAS in DESP	ARIAS in DESP
Patel 2007	Review	Review of application of ANN in healthcare	ANN in healthcare
Rahimy 2018	Review	"To describe the emerging applications of DL in ophthalmology	DL in ophtalmology
Ruamviboonsuk 2020	Review	ARIAS in DESP: recent developments and contribution of Asia in DR and other areas	ARIAS in DESP
Scott 2019	Review	Prospects and pitfalls of ML in clinical decision making	ML in clinical decision making
Stolte 2020	Review	Overview of AI in DR including some social/ethical aspects	ARIAS in DESP
Ting 2019	Review	Describes global eye disease burden, unmet needs and common conditions of public health importance for which AI and DL systems may be applicable	AI and DL in eye disease
Ting 2020	Review	Overview of AI in eye disease	AI in eye disease
Vollmer 2020	Review	A proposed framework to inform design, conduct and reporting of AI in healthcare	AI in healthcare

Wang 2012	Review	A short introduction to machine learning and survey its applications in radiology	AI in radiology
Wong 2019	Review	Overview of the field of DR including screening and AI	ARIAS in DESP
Wong 2020	Review	Strategies to Tackle the Global Burden of Diabetic Retinopathy: From Epidemiology to Artificial Intelligence	ARIAS in DESP
Ting 2019	Review	Review of DL applications in ophtalmology	DL in ophtalmology

Appraisal for quality and risk of bias

The results from the methodological quality assessment of the included diagnostic accuracy studies (question 1) is reported in the main text.

Table 37 QUADAS-2 checklist with definitions of the signalling questions

Domain	Signalling questions
Patient selection	1. Was a consecutive or random sample of patients enrolled? Yes, if clear from the paper 2. Was a case-control design avoided? Yes, if clear from the paper 3. Did the study avoid inappropriate exclusions? Yes, if no patients that would normally be included in the EDESP were excluded Risk of bias: Low if all of the above are answered 'yes' Applicability concerns: Low only if the study is conducted in the relevant UK population; Unclear, if conducted in a non-UK population, unless there is a clear indication that the population is different from the target population (e.g. a mixture of diabetic and non-diabetic patients)
Index test	1. Were the index test results interpreted without knowledge of the results of the reference standard? In most cases, this will be 'yes', unless specific reason is given 2. If a threshold was used, was it prespecified? Yes, if clear from the paper Risk of bias: Low, if all of the above are answered 'yes' Applicability concerns: High, if different from the intended EDESP use of the system
Reference standard	1. Is the reference standard likely to correctly classify the target condition? Yes, the reference standard involves a panel of retinal specialists or ophthalmologists or similar experts independently reading the images; Yes, if the final grading from a national screening programme similar to EDESP, which has clear training and quality assurance protocols, is used*; No, if a single grader determines the ground truth, or the final grade from a national screening programme is used without external adjudication 1. Were the reference standard results interpreted without knowledge of the results of the index test? Yes, if clear from the paper Risk of bias: Low, if all of the above are answered 'yes' Applicability concerns: High, if the definition of the target condition is different from the one used in the EDESP (e.g. maculopathy is not included)
Flow and timing	1. Did all patients receive a reference standard? 2. Did all patients receive the same reference standard?

	3. Were all patients included in the analysis? No, if ungradable images have been excluded Risk of bias: Low, if all of the above are answered 'yes'
Additional questions	1. Were the study methods prespecified? 2. Was the study funded/financially supported by the manufacturer or the authors declared conflict of interest? 3. Is the algorithm publically available? 4. Is the output of the model Interpretable and can it be interrogated (visualization of decisions)? 5. Are differential diagnoses and estimates of confidence provided?
*Initially, this criterion also included external adjudication of disagreements between the final manual grading result and the result from ARIAS; however, after discussion with experts we decided to drop the requirement for external adjudication and accept the final grade from an established national screening programme sufficient to ensure low risk of bias provided the programme has clear training and quality assurance protocols.	

Table 38 QUADAS-C checklist: Comparative accuracy*

Domain	Signalling questions
Patient selection	C1.1 Was risk of bias for this domain judged 'low' for all index tests? C1.2 Was the intention for patients either to receive all index tests or to be randomly allocated to index tests? C1.3 If patients were randomized, was the allocation sequence random? C1.4 If patients were randomized, was the allocation sequence concealed until patients were enrolled and assigned to index tests?
Index test	C2.1 Was risk of bias for this domain judged 'low' for all index tests? C2.2 If patients received multiple index tests, were test results interpreted without knowledge of the results of the other index test(s)? C2.3 If patients received multiple index tests, is undergoing one index test unlikely to affect the performance of the other index test(s)? C2.4 Were differences in the conduct or interpretation between the index tests unlikely to advantage one of the tests?
Reference standard	C3.1 Was risk of bias for this domain judged 'low' for all index tests? C3.2 Did the reference standard avoid incorporating any of the index tests?
Flow and timing	C4.1 Was risk of bias for this domain judged 'low' for all index tests? C4.2 Was there an appropriate interval between the index tests? C4.3 Was the same reference standard used for all index tests? C4.4 Are the proportions and reasons for missing data similar across index tests? C4.5 Could the patient flow have introduced bias in the comparison?

*The QUADAS-C tool was applied according to the guidance provided by Bada Yang (b.d.yang@amsterdamumc.nl) and the QUADAS-C group

Appendix 5 – Additional information

A brief description of each ARIAS with a link to the manufacturer's website

iGradingM (traditional ML), no website found

We failed to find the manufacturer website or any information about the most up-to-date version of the system. Tufail 2016 (1) was the most recent study reporting on the system and evaluated iGradingM v 1.1. We assumed that the data reported by Philip 2017(15) (conference abstract) also relates to iGradingM, but the authors did not specify and simply referred to the system as 'the autograder'.

iGradingM was developed by the University of Aberdeen and, during the study, was purchased from the Medalytix Group Ltd, Manchester, UK (which funded Fleming 2010a) by Digital Healthcare, Cambridge, UK, at the initiation of the study, and purchased in turn by EMIS UK, Leeds, UK, after its conclusion (1). The system is designed to remove normal images from manual grading queue by 1) checking the image quality, and 2) detecting early signs of retinopathy by looking for a) microaneurysms only or b) microaneurysms, haemorrhages and exudates (as two alternative modes of operation) (34).

RetmarkerSR (traditional ML), https://www.RetmarkerSR.com/

We contacted the manufacturer who confirmed that: 1) they are not aware of additional titles; 2) the system has been undergong continuous improvement and the results reported in older studies may not reflect the current version of the system; 3) that the software has not been upgraded to DL-based; 4) audit-based reports on the use and performance of the system within the Portuguese DESP are not publicly available as each local authority organises and audits its own screening programme. More detailed description of the system is reported in Tufail 2016 (1).

RetinaLyze (traditional ML), https://www.retinalyze.com/

We contacted the manufacturer who confirmed that: 1) the system has not been upgraded to DL; 2) they are not aware of additional titles; 3) the most recent evaluation is the one reported in Bouhaimed 2008 (31) which evaluated the Retinalyze v.1.0.6.1.

EyeArt v2 (DL): https://www.eyenuk.com/en/products/eyeart/

EyeGrade (DL): Healgoo Interactive Medical Technology Co. Ltd, Guangzhou, China (no valid link found)

IDx-DR v2 (DL): https://dxs.ai/products/idx-dr/idx-dr-overview-2/

Google AI (DL): https://health.google/for-clinicians/ophthalmology/

RedCAD (DL): https://www.delft.care/retcad/

SELENA (DL): https://www.eyris.io/index.cfm

VUNO (DL): https://www.vuno.co/en/

Systematic reviews investigating the accuracy of AI algorithms for detection of diabetic retinopathy

Table 39 Systematic reviews investigating the accuracy of AI algorithms for detection and grading of diabetic retinopathy

Study	Aim	Inclusion and exclusion criteria	Searches	QUADAS-2	Results
Systematic reviews (most criteria for a systematic review met)					
Islam 2020	To investigate the performance of DL algorithms for automated detection of DR in retinal colour fundus photographs	**Inclusion criteria:** 1) published in English and peer- reviewed; 2) provided an outcome of DL algorithms and DR detection; 3) report accuracy; 4) database and number of images reported; 5) definition of DR provided; 6) clearly described DL algorithms and process used in the DR detection. **Exclusion criteria:** Editorials, short reports, traditional methods for detecting DR were excluded	**Databases searched:** EMBASE, PubMed, Google Scholar, Scopus, Web of Science and reference lists **Search period:** 01.01.2000 to 31.03.2019	**High or unclear RoB** PS: 13/23 IT: 0/23 RS: 5/23 F&T: 6/23 **Applicability concerns** PS: 20/23 IT: 0/23 RS: 9/23	**Studies included in the review:** 23 studies (6 with external validation) included in the review **Studies included in meta-analysis:** 20 **Accuracy:** The pooled AUROC was 0.97 (95%CI: 0.95–0.98), SE was 0.83 (95%CI: 0.83–0.83), and SP 0.92 (95%CI: 0.92–0.92); LR+ and LR- were 14.11 (95%CI: 9.91–20.07), and 0.10 (95%CI: 0.07–0.16), respectively **Subgroup analysis:** SE and SP for vision-threating DR was 0.92 (95%CI:0.90–0.94), and 0.91 (95%CI: 0.90–0.92)
Nagendran 2020	To systematically examine the design, reporting standards, RoB, and claims of studies comparing the performance of diagnostic DL algorithms for medical imaging with that of expert clinicians.	**Inclusion criteria:** 1) a peer reviewed scientific report of original research; 2) English language; 3) assessed a DL algorithm applied to a clinical problem in medical imaging; 4) compared algorithm performance with a contemporary human group not involved in establishing the ground truth (RS); 5) at least one human in the group was considered an expert; 6) the aim was to use medical imaging for predicting absolute risk of existing disease or classification into diagnostic groups. **Exclusion criteria**: informal publication types, such as commentaries, letters to the editor, editorials and meeting abstracts.	**Databases:** Medline, Embase, CENTRAL and WHO-ICTRP; manual screening of the reference lists of relevant publications **Search period:** 2010 to June 2019	**PROBAST** used to assess RoB, but results not reported: 5/7 externally validated; 1/7 and 3/7 stated the need of prospective studies in abstract and discussion, respectively; 1/7 recommended clinical use	**Studies included in the review:** 7 of the included 91 studies met our inclusion criteria (of the 91 studies 10 were trial registrations, none of which was relevant, and 81 non-randomised studies); **Studies included in meta-analysis:** n/a **Accuracy:** SE ranged from 86.2% to 97.1% for AI and from 61.1% to 91.2% for clinical experts; sensitivity of AI was higher than that of experts in 4/7 studies (n=7); in the 3 studies for which specificity was reported it ranged from 93.4% to 95.2% for AI and from 95.9% to 98.7% for clinical experts. Two studies reported as a primary measure AUC: 0.936 in the first study and ranging from 0.894 to 0.972 in the second; and one study reported the quadratic weighted kappa: 0.84 for AI and 0.82 for clinical experts. Abramoff 2018 reported SE of 87.2% (95% CI, 81.8–91.2%) and specificity of 90.7% (95% CI, 88.3–92.7%) for AI which were omitted in the review.

Nielsen 2019	To review the diagnostic performance of DL-based algorithms in screening patients with diabetes for DR	**Inclusion criteria:** DTA studies of DL—either a complete algorithm or DL features—to classify full-scale DR in retinal fundus images of patients with diabetes. Studies had to state a grading scale, have a human grader as RS, and provide a performance score for the DL method. No restrictions were made as to the performance score or grading scale, or the profession of the human grader. **Exclusion criteria:** Studies examining only lesions or subcategories of the disease (e.g. mild DR); duplicates, animal studies, reviews, editorials, CA, and unpublished articles.	**Databases:** Medline (via PubMed) and Embase (via OvidSP) and reference lists **Search period:** up to 05.04.2018	**High or unclear RoB** PS: 8/11 IT: 0/11 RS: 1/11 F&T: 2/11 **Applicability concerns** PS: 9/11 IT: 0/11 RS: 6/11	**Studies included in the review:** 11 **Studies included in meta-analysis:** 20 **Accuracy:** 8 studies reported SE of 80.28% to 100.0%; SP of 84.0% to 99.0%; 2 report overall accuracy of 78.7% and 81.0%, respectively; and one study reported AUC of 0.955
Norgaard 2017	To identify studies with methodology and design that are similar to or replicate actual screening scenarios using ARIAS for detection of DR	**Inclusion criteria:** Studies with a realistic screening scenario: (1) The image analysis system must be fully automated and include an image quality assessment and a lesion detection module, and have some form of patient-based output in terms of disease/no-disease or disease level; (2) Data must be based on digital (mydriatic or non-mydriatic) images from consecutively recruited patients with any form of DM who have never been diagnosed with referable DR; (3) Studies must be based on patients from the same cohort and not a selection of different trials	**Databases:** PubMed, Cochrane Library, and Embase; In addition, (1) Review studies identified in database searching were screened for references; (2) Authors with several publications that involved ARIAS were identified, and a search was performed to reveal additional publications; (3) Google search **Search period:** [up to] 21.10.2016	**N/a** Methodological concerns discussed throughout the paper and included: an analysis based on limited number of episodes, accuracy estimates with no CIs and no clear grading scale	**Studies included in the review:** 7 **Studies included in meta-analysis:** n/a **Accuracy:** the detection of DR had high SE (87.0 – 95.2%) but lower SP (49.6 – 68.8%). False-negative results were related to mild DR with a low risk of progression within 1 year. Several studies reported missed cases of DME
Simoes 2019	To evaluate the accuracy of DSS in diagnosing DR	**Inclusion criteria:** DTA studies evaluating the accuracy of DSS in diagnosing DR in patients with DM (both type 1 and 2	**Databases searched:** 10 databases including Medline	**Performed**, but not results reported and unclear if	**Studies included in the review:** 18 **Studies included in the meta-analysis:** 18

		included); the RS had to be fundus examination or funduscopy. **Exclusion criteria:** Other types of diabetes, and studies not reporting sufficient data to allow the reconstruction of the 2x2 table.	via PubMed, Embase, grey literature and reference lists **Search period:** 1970 - 2018	considered in the analysis	**Accuracy:** The pooled SE was 97.7% (95% CI: 97.5%-97.9%) and the pooled SP 90.3% (95% CI: 90.0%-90.6%) **Meta-regression:** Clinical and technological co-factors had no effect on accuracy (no details reported) **Subgroup and sensitivity analysis:** heterogeneity remained high (no details reported)
Wang 2020	To estimate the SE and SP of NN in DR grading	**Included:** Studies evaluating the accuracy of NN to detect referable DR (incl. DME) comparing the IT with ophthalmologists' diagnosis as RS, based on fundus photography without assistance of other medical records, and providing sufficient information for quantitative data synthesis.	**Databases searched:** Medline, Embase, IEEE Xplore, and Cochrane Library **Search period:** up to 23.07.2019	**High or unclear RoB** PS: 13/24 IT: 7/24 RS: 10/24 F&T: 0/24 **Applicability concerns** PS: 0/24 IT: 0/24 RS: 9/24	**Studies included in the review:** 24 **Studies included in meta-analysis:** 24 **Accuracy:** Pooled SE of 91.9% (95% CI: 89.6% to 94.3%) and SP of 91.3% (95% CI: 89.0% to 93.5%). **Subgroup analyses and meta-regression** did not provide any statistically significant findings for the heterogeneous diagnostic accuracy in studies with different image resolutions, sample sizes of training sets, architecture of CNN, or diagnostic criteria.
AI – artificial intelligence, AUC - area under the [ROC] curve, CENTRAL - Cochrane Central Register of Controlled Trials, CI – confidence interval, CNN – convolutional neural networks, DL – deep learning, DME – diabetic macular oedema, DR – diabetic retinopathy, DSS – decision support system, F&T – flow and timing, IT – index test, ML – machine learning, NN – neural networks, PROBAST - prediction model risk of bias assessment tool, RS – reference standard, RoB – risk of bias, SE – sensitivity, SP – specificity, WHO-ICTRP - World Health Organization International Clinical Trials Registry Platform					

Table 40 Quality assessment of the identified systematic reviews

	AMSTAR II Questions															
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Islam 2020	No	n/a	Yes	n/a*	Yes	Yes	Yes	n/a*	Yes	No	Yes	No	No	Yes	n/a*	Yes
Nagendran 2020	No	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	No MA	No MA	Yes	Yes	No MA	No
Nielsen 2019	Yes	No	No	Partial Yes	Yes	NR	Yes	Partial Yes	Yes	No	No MA	No MA	Yes	Yes	No MA	Yes
Norgaard 2017	Yes	No	Yes	No	NR	NR	Yes	Yes	No	No	No MA	No MA	NA	No	No MA	No
Simoes 2019	Yes	No	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes	NR	No
Wang 2020	Yes	No	No	Partial Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes

*We were unable to access the supplementary file.

AMSTAR II Questions:

1. Did the research questions and inclusion criteria for the review include the components of PICO?

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Factors reported to affect the performance of ARIAS

Population

Tufail 2016 (1) reported that the accuracy of EyeArt v1 was not affected by ethnicity and sex, but sensitivity was marginally lower with increasing patient age. The accuracy of RetmarkerSR was affected by patient age and ethnicity. There was considerable variation in the mean age and racial composition of the cohorts across the included studies.

Some studies included only patients with type 2 diabetes (e.g. van der Heijden 2018 (23), but most of the cohorts included both type 1 and type 2 patients. Time since diagnosis and diabetic control are associated with the progression of retinopathy if cohorts vary on these parameters, this is likely to affect the performance of ARIAS.

Tufail 2016 (1) excluded "…patients whose photographs were ungradable at their previous screening episodes, for example because of a known cataract that degraded the quality of retinal photography, were 'technically failed' and underwent slit-lamp biomicroscopy by optometrists in a clinic adjacent to the photographic screening clinic." (p. 7). Variation in the way such patients are handled as well as the fact that in some studies the whole or part of the cohort was screened for the first time (e.g. opportunistic rather than organised screening), could affect the results from the evaluation of ARIAS. Most studies which excluded patients with ungradable images according to the reference grading did not report if this included patients known to have conditions that affect image quality.

Index test

Setting and test operator
The setting and the test operator varied across studies and are likely to affect the results from the evaluation of ARIAS. For instance, in some studies the evaluation was done within a national screening programme (e.g. those conducted in the EDESP) while in other studies it was primary care and the test operator varied from study to study (e.g. a research assistant in van der Heijdan 2018; a technician in Verbraak 2019; many studies did not provide details).

Photographic protocols
There was a significant variation in the fundus photography protocols including (but probably not limited to):

- <u>The number of fields and the area of the retina covered:</u> Studies used 1-field (e.g. SDESP-based studies), 2-field (e.g. EDESP-based studies) or 3-field images (e.g. Bhaskaranand 2019 evaluating EyeArt v2 using the EyePACS protocol). Goatman

2011 (34) showed that iGradingM has slightly better performance when 2-field (EDESP) rather than 1-field (SDESP) images are used. Yip 2020 (54) compared the performance of SELENA using 1-, 2- and 7-field images and showed that the system performed better when the number of fields is increased. Also, in some retrospective studies not all of the images were used (e.g. Krause 2018 (24)).

- Multiple images: Some studies reported that the operator taking the images could decide to take more than the specified number of images, to make sure that images of sufficient quality are available for each eye; in other studies re-imaging was not allowed. Van der Heijden 2018 (23) , who evaluated IDx-DR in primary care, reported that the image quality feedback of the system was underutilized and, as a result, a considerable proportion of the patients were referred due to ungradable images. As the study shows, this could have important implications and the performance of the system could depend on the setting in which is used (e.g. busy primary care vs. dedicated screening programme) and the attitude of those performing the imaging.
- Use of pupil dilation: studies varied according to whether mydriasis was used routinely (e.g. EDESP-based studies, Shah 2020a), not used at all (e.g. Liu 2020) or only when deemed necessary by the test operator; the latter group also varied with regards to the proportion of patients in whom pupil dilation was used.
- Camera type: Tufail 2016 (1) reported that the accuracy of RetmarkerSR was marginally affected by camera type while the accuracy of EyeArt v1 was not.
- Image size: A number of studies showed that image size affects ARIAS performance with larger images (up to a specific threshold) leading to better accuracy (Krause 2018 (24), Yip 2020 (54))
- Cataract surgery: Yip 2020 (54) showed that SELENA achieved higher accuracy in pseudophakic eyes compared to phakic eyes (AUC 0.918 vs 0.833, $p < 0.001$).

Variation in ARIASs

Use of data from previous patient episodes: Some algorithms use data from previous screening episodes to improve the classification of the images from the index visit. An example of such ARIAS is RedmarkerRS which is based on traditional ML and has been implemented in the Portuguese DESP. More information on this approach and examples of DL-based algorithms is provided Stolte 2020 (57).

Algorithms looking for more than one condition: For instance, Son

Comparator

The accuracy of manual grading may vary across different DESP and therefore the comparative accuracy of ARIAS versus human graders may not be generalizable from one DESP to another (see Table 8). Also, there may be variation in the performance human graders across different sites within the same DESP. This means that studies, in which the comparison between ARIAS and manual grading has been done in a single site may not be representative of the whole programme. For instance, Gulshan 2019 (58) reported considerable variation in the performance of manual grading at 2 different sites in India.

Reference standard and target condition

Grading system: Different systems were used across studies. As already discussed with relation to IDx-DR (23), this could affect the reference grading and, from there, the performance of ARIAS.
Graders qualification and experience: The qualification and experience of graders could affect grading but, as demonstrated by Gulshan 2019 (58), the direction of this effect is not always easy to predict.
A screening programme manual grading with or without external adjudication: A number of studies used the local DESP's final grades as the ground truth for the evaluation of ARIAS. In some cases a proportion of the images (e.g. higher grade images, disagreements between the programme and ARIAS) were adjudicated externally. It is difficult to judge the importance of this but, as discussed earlier in relation to Tufail 2016 (1), it is another potential source of heterogeneity across studies.
Method of adjudication: Krause 2018 (24) showed that adjudication by 3 retinal specialists (who first graded all images independently) could lead to different accuracy results depending on whether the final decision was based on majority voting or consensus.
Variation in the technology: As discussed earlier, Abramoff 2018 (22) showed that the performance of IDx-DR differed when the reference standard was stereo wide-field fundus photography (4W-D stereo protocol) and the latter combined was combined with OCT. Also, both reference standards are superior to the standard non-stereo fundus photography used in most of the studies.

Flow and timing

Handling of ungradable images: Studies handled images deemed to be 'ungradable' by the reference graders and/or the system differently. In some studies, all such images were excluded from analysis; in other studies only the images considered to be 'ungradable' by the reference graders were excluded, while those defined as 'ungradable' by the ARIAS but 'gradable' by the reference graders were reported separately, or treated as 'referrals'; and some studies reported separately the agreement between the system and the reference graders in terms of 'ungradable images'. In a number of studies images were excluded because the results from the reference grading were missing.

Appendix 6 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table xx.

Table 41. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	8
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	10
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	20
		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	25
		Method – briefly outline the rapid review methods used.	27
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	27-29
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	30
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		

3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	30, 59
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	59
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	27
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 100 - 116 Quality assessment: 100 - 112
4.2	Additional analyses	Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer.	n/a
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	32
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	33-55
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	47, 51, 53, 55
6.	REVIEW SUMMARY		
6.1	Conclusions and	Do findings indicate whether screening should be recommended?	57

	implications for policy	Is further work warranted? Are there gaps in the evidence highlighted by the review?	
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	58

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[Please if possible use EndNote for references]

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