iCare ILLUME AI-assisted diabetic retinopathy screening

Screening for diabetic retinopathy

Currently, it is estimated that one in five diabetics have diabetic retinopathy (DR). Negative demographic changes mean that potentially vision-threatening pathologies will be present in ever younger diabetic patients as well as in ever larger numbers of diabetic adults.

Without screening, DR often goes undiagnosed until vision changes, sometimes irreversible, occur in the later stages of the disease. Diabetics themselves often have no subjective symptoms of DR, in part because initial signs in the early stages of the disease may only be intermittent.

To slow the progression of DR, lifestyle and diet changes are important but the primary motivation for screening is that there are now very effective treatment options for preventing or significantly slowing vision loss. The treatments include laser photocoagulation and intravitreal injections. The rate of DR progression may be rapid, so timely intervention is vital.

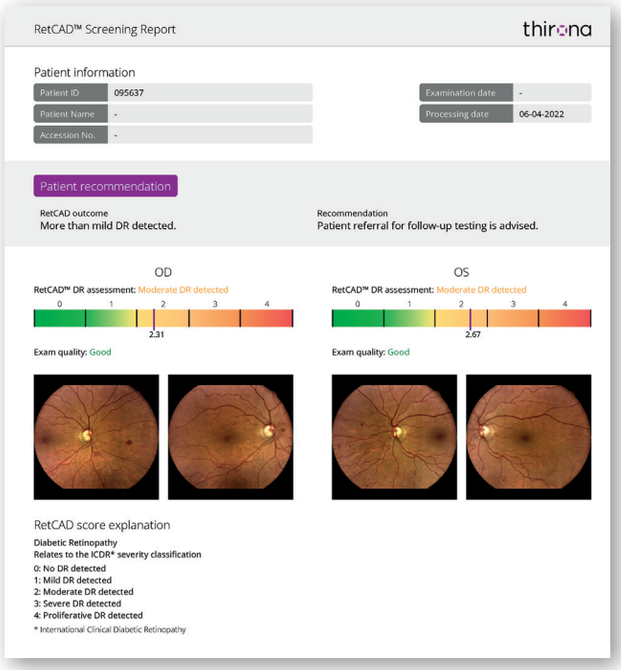

Figure 1. Example of patient screening report after automated analysis by AI, as displayed in ILLUME. The report is in printable format and stored for later retrieval.

Regular screening for DR is essential

Regular screenings are essential for patients diagnosed with diabetes, especially in patients with type 1 diabetes. Many national associations recommend a goal of annual DR examinations for patients with either type 1 or type 2 diabetes. However, few countries have national screening programs in place. As a result, coverage falls short of these goals. In large EU countries, for example, coverage varies from a low of 11% (Italy) to 68% (France and Germany) of the affected population.

Historically, the main reason for sub-optimal screening coverage has been a lack of resources, especially the limited availability of trained ophthalmologists for the traditional direct or indirect ophthalmoscopy or slit lamp biomicroscopic examination. The introduction of easy-to-use color fundus cameras and, where adopted, telemedicine for remote image reading by experts have helped, but not solved the resource problem. Adding artificial intelligence (AI) in the initial DR screening phase promises to vastly increase both the efficiency and effectiveness of screening programs. Researchers have suggested that with AI-assisted screening for referable DR, existing ophthalmologist resources could easily accommodate the expected demand for screening, worldwide.

Medical applications of artificial intelligence (AI) solutions have been most successful when designed for use early in the care continuum, are easy to implement and offer radical improvements in cost or time for health care providers. In screening for DR, AI is used for initial disease triage, requires minimal effort from the user while vastly reduces the expense and time resources needed for manual image reading. In addition, screening by AI offers a real-time, anytime and anywhere service. Screening for DR is therefore an ideal clinical application for AI.

Diagnosing DR

The latest ophthalmic imaging devices allow for capturing the information needed to reliably detect potentially vision-threatening vascular changes in the retina. Fundus cameras offer high resolution images of the critical retinal regions completely non-invasively. Imaging takes just a few minutes and patients normally need no preparation, such as pupil-dilating eyedrops, and they can resume their normal activities straightaway.

The iCare DRSplus TrueColor confocal fundus imaging system represents the latest generation of office/practice devices – it can take a high-quality, 45° x 40° field of view image of the retina even when the subject has ocular media opacities, such as cataract, and with pupil diameter as small as 2.5 mm without pupil dilation.

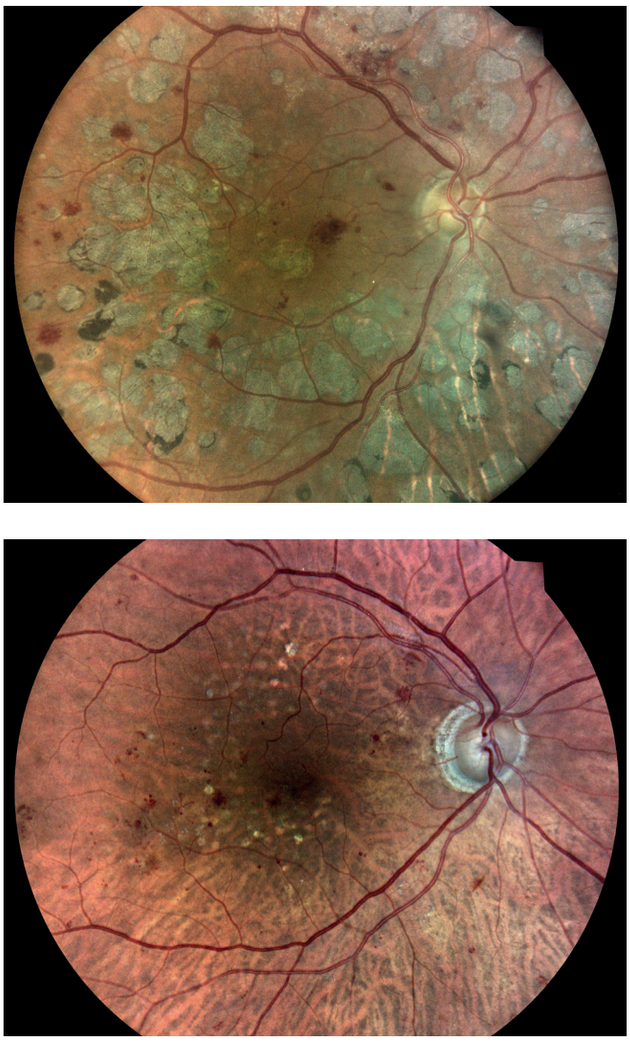

Figure 2. TrueColor fundus images from the iCare DRSplus fundus imaging system revealing signs of diabetic retinopathy.

Grading DR

There are a number of grading systems in use globally; all have in common a grade of no retinopathy, background retinopathy, a stage of preproliferative DR and proliferative DR.

Background retinopathy is generally characterized by arterial micro aneurysms, visibly present in only part of the retina. Preproliferative DR (NPDR) is the early stage of disease progression when blood vessels in the retina leak. Leaking can be seen as fluid, hemorrhage or lipids in the retina and these blood vessels close over time causing ischemia. Proliferative DR (PDR) is the stage when new, abnormal blood vessels grow in response to local ischemia (neovascularization). These vessels, in turn can easily leak into the vitreous, causing tractional changes to the surface of the retina. At this late stage, patients themselves notice their vison deteriorating. Grading according to the International Clinical Diabetic Retinopathy (ICDR) severity scale is shown in the table below.

Grade	Clinical features	Category
0	No abnormalities	No apparent Retinopathy
1	Presence of microaneurysm(s) only	Mild NPDR
2	More than just microaneurysm(s) but less than grade 3	Moderate NPDR
3	Any of: >20 intra-retinal hemorrhages in each quadrant; definitive venous beading in >2 quadrants; Intraretinal microvascular abnormalities in >1 quadrants; Definite venous beading (in >2 quadrants), or no signs of proliferative retinopathy	Severe NPDR
4	One or more of the following: neovascularization, and/or vitreous or preretinal hemor-rhages.	Proliferative DR

Table 1. Grading according to the International Clinical Diabetic Retinopathy (ICDR) severity scale.

The iCare ILLUME solution

The iCare ILLUME is a turn-key DR screening solution for iCare DRSplus TrueColor fundus imaging system users. iCare ILLUME has been designed to be reliable, easy to implement and simple to use. Fundus images, one macula-centered and one nasal (centered on the optic disk), are uploaded from the iCare DRSplus camera to an iCare cloud-based computer server for storage and communication. The AI engine for scoring the images is also hosted in the cloud. The patient's fundus images are automatically analyzed for DR and the results presented on the user's PC screen within minutes.

iCare ILLUME uses RetCAD artificial intelligence software

The iCare ILLUME screening solution uses RetCAD*, developed by Thirona, for automated diagnostics. RetCAD AI is based on convolutional neural networks, a state-of-the-art technique in machine learning used in medical imaging for its ability to jointly learn discriminative features and classify large data sets.

RetCAD algorithms first calculate a quality index and normalize each acquired fundus image prior to AI analysis. Images judged to be of insufficient quality are not processed further and can be automatically flagged to the operator for repeat imaging.

From a patient's fundus images, RetCAD outputs a score for the level of DR detected in each eye. The score for the patient is then the higher score of the two eyes. The scores are presented as a number in the range from 0 to 5, covering the ICDR range. Unlike a human reader scoring whole numbers, RetCAD gives a score to two decimal places, e.g., 2.31. This level of detail can help the human grader to make their own interpretation of the images. For better engagement with the patient, the numerical DR result is also presented on a green—red color "traffic light" background.

RetCAD algorithms also produce heatmaps of the imaged retina indicating possibly abnormal areas for human expert review and further interpretation. The heat maps are digitally processed, contrast-enhanced images of the fundus. One heat map is the original fundus image filtered to highlight any lesions appearing bright on the image, such as exudates, while the other heat map is the image filtered to highlight the lesions appearing red, such as microaneurysms and hemorrhages. The heat maps can help explain the automated DR score to the operator and any expert reader, as well as serving as a readily understandable visuals for better patient communication.

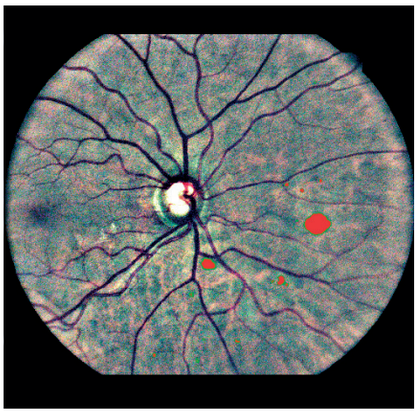

Figure 3.
RetCAD heatmap example indicating red lesions.

Evaluation of RetCAD performance

In its development, the RetCAD AI software was trained on a large color fundus image data set, comparing regions extracted from images of both normal and abnormal retinas. The RetCAD software released has been evaluated on multiple expert-graded fundus image datasets (none of which had been used to train the RetCAD software). The images in these datasets had been independently acquired by researchers using several brands of color fundus cameras at various angles and resolutions. In performance evaluations, the numerical scoring of the RetCAD software is directly compared with the grading of the same fundus images by human expert readers, considered the gold standard for the grading of DR.

Sensitivity and specificity

The usefulness or accuracy of diagnostic tests, including software, are universally described in terms of sensitivity and specificity. Sensitivity is the proportion

* iCare has partnered with Netherlands-based Thirona B.V. to allow the use of RetCAD DR software for iCare ILLUME. RetCAD is a class IIa CE 0344-certified medical device software product that uses deep learning to analyze color fundus images for the presence of DR. RetCAD is available with a software module for scoring DR, as well as a module for Age-related Macular Degeneration (AMD) and a module for Glaucoma (GLC).

of identified positives out of all positives in a sample (the highest possible result being 100%). Specificity is the proportion of negatives that have been correctly labelled as negative (labelling all negatives correctly would give a result of 100%). Correctness is determined by the results from a gold-standard comparator, generally believed to be as close to perfection as possible. In DR, the comparator is the grading of images by the consensus opinion of expert human readers.

There is an intrinsic trade-off between sensitivity and specificity. AI software applications inherently allow for a threshold level to be set to optimize performance for practical clinical use. Sensitivity is typically set such that a very high proportion of positive (abnormal) cases are detected while keeping the number of false positives (images labeled by AI as abnormal but actually normal) low and manageable for the application. Setting a relatively low threshold value for the software would result in higher sensitivity (e.g., identifying all referable DR cases), but at the cost of a lower specificity (patients needlessly referred to experts). Correspondingly, a relatively high threshold value for the software results in higher specificity (very few needless referrals), but at the cost of a lower sensitivity (missing some patients with referable DR).

This sensitivity vs. specificity trade-off is best visualized with a ROC-curve, where the area under the curve (AUC or Az) is a calculation of the software's performance. As a single indicator, with the AUC result closest to 1 usually representing the best performance, the AUC result can be a useful numerical tool to readily compare the performance of different softwares.

RetCAD evaluation by Messidor datasets

In RetCAD white paper, a summary of the results of evaluation by the dataset are presented. The Messidor-2 database is a publicly available set of 1748 color fundus images (45° field), with each image having been graded for the presence of referable DR (defined as more than background retinopathy). The Messidor-2 dataset comprises DR examinations from 874 patients, with one macula-centered image per eye. All patients in the database were graded by three medical experts individually, and also graded according to the experts' consensus. The consensus found 190 patients had referable DR and 684 patients did not have referable DR.

Assigning the highest DR score of the two fundus images to be the patient-level score for DR, RetCAD software achieved an Az value of 0.981 for the identification of patients with referable DR using the Messidor-2 images. The performance of RetCAD for automated detection of DR compares favorably with the skills of expert human readers as well as the consensus of multiple readers. RetCAD also compare extremely favorably with the results of evaluations of other AI software for DR screening, including FDA-cleared solutions.

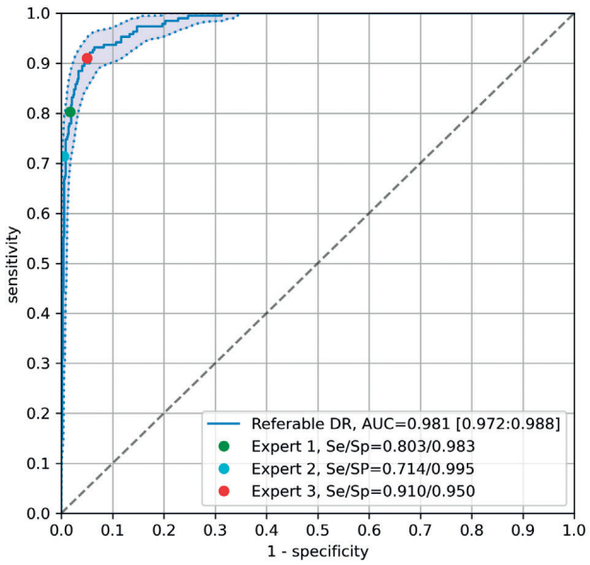

Figure 4. ROC curve of the results of using RetCAD v. 2 software on the Messidor-2 fundus image dataset, with 190 positive and 684 negative patients with referable DR. RetCAD achieved an AUC/Az value of 0.981 for identifying patients with referable DR. Source: Thirona, White paper (2020).

Real-world evaluation of RetCAD for DR screening

RetCAD has also been evaluated for differentiation between non-referable and referable diabetic patients with DR for in real clinical settings (V Sánchez et al.), at the Ophthalmology Department, Ramón y Cajal University Hospital (IRYCIS), Madrid, Spain.

In this 2019 study, 3189 diabetic patients attending a regular screening program had their fundus images scored by RetCAD AI as well as human experts. All the patients had macula-centered images taken using a 45o field of view fundus camera. All readable cases (6325) were graded by human experts using the ICDR severity scale, showing a low prevalence of referable DR (ICDR severity grades 2—4) of 1.5% in this study group.

All images were uploaded to RetCAD and automatically scored for severity of DR. RetCAD scored 274 of the cases as referable DR. After reading by one human expert and adjudication by a second expert reader, 231 of these 274 cases were graded as referable DR. True positives by RetCAD AI were 231 out of a total of 237 cases. Six cases scored by RetCAD as non-referable DR were graded by the human experts as referable DR; in other words there were six false negatives by RetCAD AI scoring.

In this study group, using AI alone for screening triage would have resulted in 274 reading tasks for human experts. Considering that without RetCAD AI

triage, there would have been 6325 reading tasks for the experts, this result suggests a workload reduction of 96%. At the same time, 6/237 cases with referable DR would have been erroneously scored as mild, non-referable DR.

This study also indicated the real-world variability in human reader skills, as reader one, with five years of experience, graded 86 of the 274 images (scored as referable DR by RetCAD) also as referable, whereas grader two, with three years of experience, graded a total of 150 of the same 274 images as referable DR.

In this real world study, the sensitivity of the RetCAD software for identifying referable DR was 90.53% and specificity was 97.13%, with an AUC value of 0.988 [0.981:0.993] when comparing to the grader with 5 years of experience. The researchers concluded that RetCAD correctly identified the vast majority of referable DR cases while missing almost no true cases of severe retinopathy (6/6325 images) and that RetCAD AI may be used for screening triage for referable DR in a diabetic population with a workload reduction of 96%.

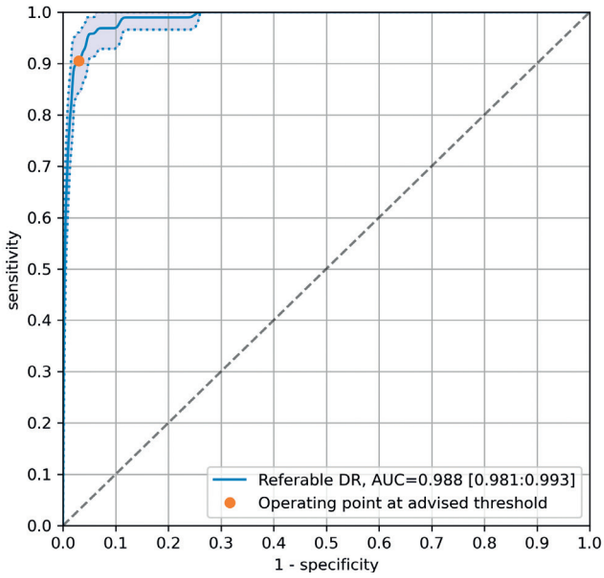

Figure 5. ROC curve of the results using RetCAD for the detection of referable DR versus non-referable DR, the operating threshold with a cut-off with the standard RetCAD cut-off has been added (orange dot). RetCAD had an AUC of 0.988. Source: V Sánchez et al. Performance of a deep learning system for detection of referable diabetic retinopathy (2022).

Evaluation of RetCAD using iCare DRSplus fundus imaging system

iCare has also commissioned from Thirona an evaluation of the performance of RetCAD using a dual image, both eye protocol with the iCare DRSplus fundus imaging system as the source of the images. In a study group of 521 diabetes patients, 2111 fundus images were acquired using an iCare DRSplus TrueColor confocal fundus imaging system and input to RetCAD v2.0.1 for scoring. By protocol, at least two images per eye were taken, with at least one central (centered on the fovea pit) and one nasal (centered approx. 19° nasally to the foveal pit). The highest score from all a patient's images was used for scoring the patient-level DR.

The reference DR severity level was set by an NHS certified grader. Separately, all the images were independently graded by three experts. Expert 1 had over nine years of experience, while experts 2 and 3 each had over three years of experience. Resolving the four-stage NHS England severity scale with the five-stage ICDR severity scale was achieved by combining the scores for both ICDR stages 2 and 3 (moderate and severe NPDR) and treating the sum as equivalent to the NHS pre-proliferative stage, R2.

The score thresholds used by RetCAD to correspond to the ICDR severity scale 0—4 grades and the equivalent NHS England severity classification (R0—R4) grades are shown in the following table. The RetCAD scores indicating AI-judged referable grades of DR are in bold.

RetCAD score	ICDR scale	NHS England classification
0-1.00	0 none	R0 no retinopathy
1.00-2.00	1 mild	R1 background retinopathy
2.00-3.00	**2 moderate**	**R2 pre-proliferative retinopathy**
3.00-4.00	**3 severe non-proliferative**	**R2 pre-proliferative retinopathy**
4.00-5.00	**4 proliferative**	**R3 proliferative retinopathy**

Table 2. RetCAD DR scoring ranges vs. grading according to the ICDR severity scale and NHS England classification of DR.

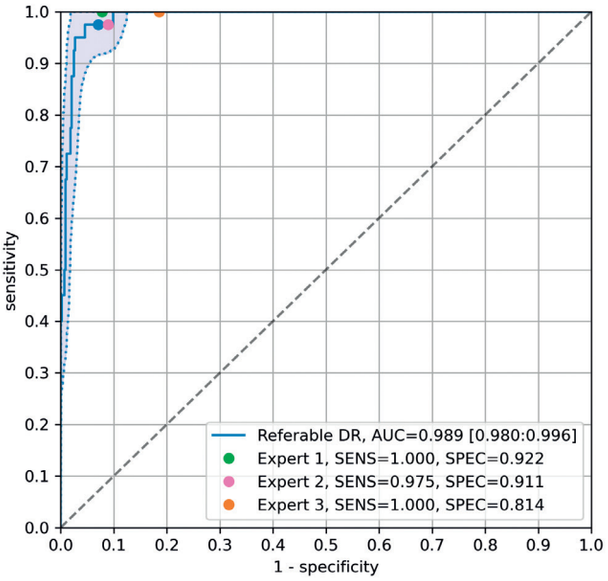

Figure 6a. ROC curve from a dataset (n=476) captured using the iCare DRSplus input to RetCAD v. 2.0.1 software. The device-software combination achieved an AUC/Az value of 0.989 for identifying patients with referable DR. Source: Thirona/iCare (2022)

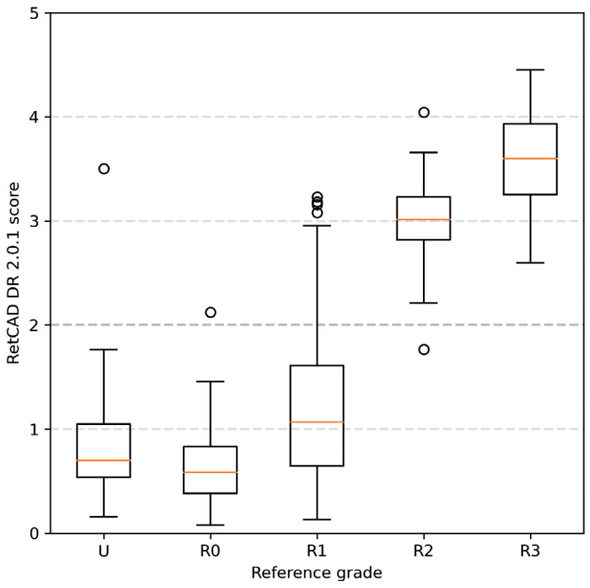

Figure 6b. Boxplot of RetCAD scores versus patient-level results following the NHS England expert classification of DR severity grades (U = ungradable by experts). Source: Thirona/iCare (2022).

Results of evaluation of iCare DRSplus image set at the patient level

The RetCAD threshold score of 2.0 for referable DR, which represents the lower bound of NHS grade R2, is shown here as the blue dot. In the analysis for the ROC curve (blue), patients graded R0 and R1 are classed as non-referable, while patients graded R2 and R3 are classed as referable. Ungradable patient images were excluded. For the detection of referable DR at the patient level, the sensitivity of RetCAD was 97.5% and the specificity was 92.9% with an overall area under the curve (AUC) of 0.989. Importantly, RetCAD achieved 100 percent sensitivity for vision-threatening DR (NHS R3 - Proliferative Retinopathy) with iCare DRSplus camera images, see Figure 6b boxplot of results.

Conclusion of the evaluation

This study showed that the negative predictive value (NPV) of RetCAD AI software using iCare DRSplus TrueColor confocal fundus images was excellent. Mark van Grinsven, Head of development RetCAD at Thirona stated, “RetCAD works very well on the iCare DRSplus image data, achieving high sensitivity and specificity values. Both patient- and eye-level analysis show acceptable performance with AUC values of >0.98. For vision-threatening DR, the sensitivity is 100%, meaning no vision threatening patients/eyes are missed by the software”.

Using the iCare DRSplus and iCare ILLUME in practice

For each eye, the DRSplus operator captures two fundus images, one image macula-centered and the other nasal centered. Once the four images have been uploaded, the AI software returns its automated assessment of DR, calibrated to ICDR severity scale grades, with an automated referral and follow up recommendation. Note that whereas a human reader will grade a patient with an ICDR severity score of 0, 1, 2, 3 or 4, RetCAD AI calculates a sliding numerical score (0.00—5.00), to two decimal places. This additional detail can offer the operator more insight for their referral advice to the patient

The automated analysis of the images is performed in real-time, and the results are typically reported within a minute to the operator. The patient’s report including the result of the AI analysis is viewed from a standard computer browser. No software installation is required. The report is stored in iCare ILLUME and can also be stored locally, added to the patient’s EHR or printed using the existing browser/computer functionality.

The original fundus images, together with enhanced heat map images and the AI-based scoring are produced as an easy-to-read A4 format.

iCare ILLUME solution diagram

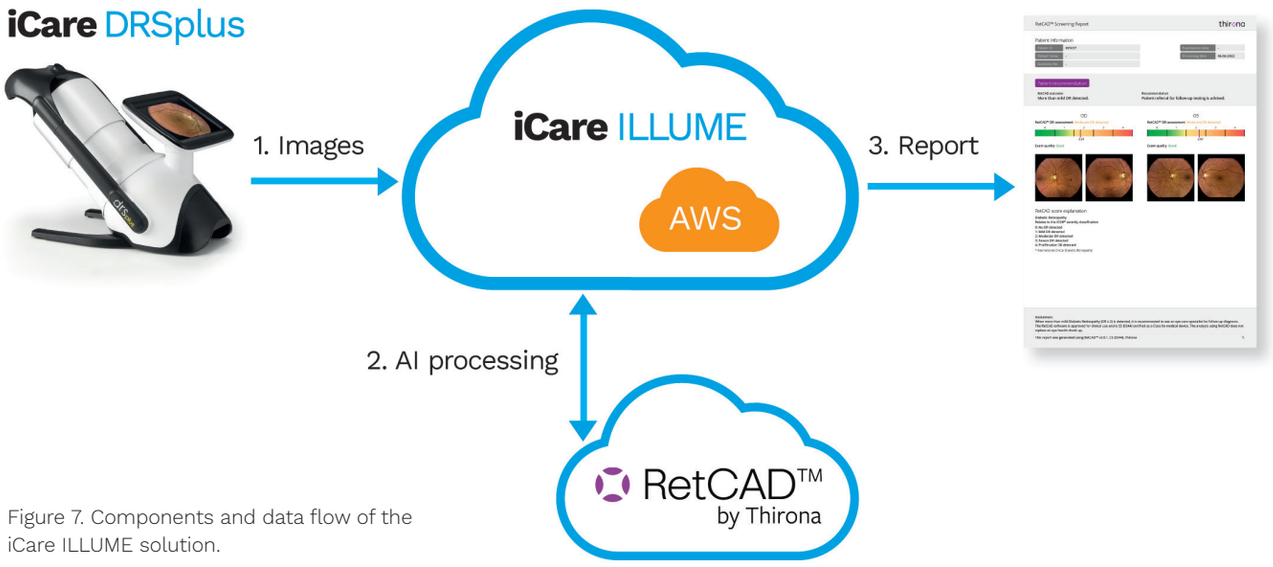

Figure 7. Components and data flow of the iCare ILLUME solution.

If images are ungradable (e.g., due to poor eye fixation), the operator is notified in real-time, permitting the operator to retake the fundus images.

Data communication, security and patient confidentiality

The fundus images are uploaded to the cloud-based iCare ILLUME screening application. The iCare ILLUME application is hosted in a secure and GDPR-compliant, manner region-specificAmazon Web Services (AWS) data center. All image-related patient identification data are pseudonymized prior to being transmitted to the cloud-based RetCAD AI software. The transmission of data by iCare ILLUME uses secure cryptographic protocols (HTTP over TLS 1.2).

Summary

Using the iCare DRSplus TrueColor fundus imaging system together with RetCAD AI, the iCare ILLUME solution has been shown to have excellent sensitivity and specificity for the detection of referable DR. Studies have shown that the AI behind iCare ILLUME to be at least as good as human reading for finding referable DR. Furthermore, iCare ILLUME has the advantage of offering a consistent diagnostic service quality, available at all times. Although, like human experts, iCare ILLUME may miss the occasional referable case, in real-world situations the use of AI has, however, been shown to significantly improve the detection of sight-threatening DR compared to the skill a single expert reader. The iCare ILLUME is a secure and easy-to-use solution that adds the power of AI diagnostics to iCare DRSplus confocal fundus imaging systems.

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Sánchez-Gutiérrez V et al. Performance of a deep learning system for detection of referable diabetic retinopathy in real clinical settings, arXiv:2205.05554, May 2022

Regulatory notices

RetCAD™ is a Class IIa CE (0344) and TGA certified software product using artificial intelligence for analysis of color fundus images for the presence of Diabetic Retinopathy, Age-related Macular Degeneration and glaucoma. The intended use of RetCAD is to assist eye care providers in early diagnosis and grading of the vision threatening diseases. Fundus image analysis by RetCAD is not intended to be a substitute for an eye health check. RetCAD is a trademark of Thirona B.V.

iCare DRSplus™ is a CE (0123) marked confocal fundus imaging system. The iCare DRSplus is intended for the acquisition of color images of the retina without the use of a mydriatic agent.

iCare ILLUME™ is the trademark for a software application that has no intended medical purposes, and as such it's not a medical device. iCare ILLUME is not available in all regions.

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iCare World Australia
Level 9, 276 Flinders Street
Melbourne Victoria 3000,
Australia
Ph. +61 3 85927079
infoAU@icare-world.com

Centervue S.p.A.
Via San Marco 9H
35129 Padova, Italy
Ph. +39 049 501 8399
info@icare-world.com

Icare Finland Oy
Äyritie 22
01510 Vantaa, Finland
Ph. +358 9 8775 1150
info@icare-world.com

Icare USA, Inc.
4700 Falls of Neuse Rd. Ste 245
Raleigh, NC. 27609
Ph. +1 888.422.7313
Fax +1 877.477.5485
infoUSA@icare-world.com

www.icare-world.com

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