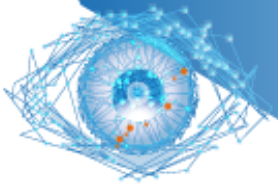

ophtAI

Artificial Intelligence
dedicated to ophthalmology

OphtAI

Scientific Information

February 2024

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1. R&D Partners and organization

OphtAI, is a Joint-Venture between two experts' companies. **Evolucare** and **ADCIS**.

Evolucare is a French leader of Health Information System specialized in Patient Data Management and Healthcare organization

On its own, Evolucare has 30 Years of experience, 300 employees, 4 500 customers, more than 160 000 patients followed-up daily.

ADCIS is a French image analysis expert with a specialization in ophthalmology.

It has 25 Years of experience including collaboration with major companies such as Abbvie, Alcon, Allergan, Novartis, Pfizer…

At the beginning 2022, we finally sealed a years long partnership as Evolucare acquired ADCIS to improve further our image analysis expertise and workflow between our teams, to deliver even more advanced products.

Evolucare, Adcis and OphtAI are since the end of 2023 part of GPI Group, a Europe leader in digital innovation offering software, services and technical solutions to various actors of healthcare systems

GPI has 35 Years of experience and more than 3000 customers worldwide.

Our R&D is done in a common Public & Private Research Department (called ADMIRE) between OphtAI and two major public institutions. Paris Hospital (AP-HP) and INSERM.

Paris Hospital (AP-HP) a network of 41 public hospitals including Lariboisière University Hospital specialized in ophthalmology with its tele ophthalmologic association called ophDiat dedicated to Diabetic Retinopathy screening.

INSERM the French Institute for Medical Research with the Latim its laboratory specialized in Artificial Intelligence.

2. Medical Partners

Pascale Massin – Professor in Ophthalmology – Founder and coordinator of Ophdiat network, AP-HP (Paris Hospitals), President of the Club of the French-Speaking Retina Specialists

« Thanks to Artificial Intelligence, all these extremely sophisticated imaging tools can be used by ophthalmologists who are not specialists of the retina… »

Béatrice Cochener – Professor in Ophthalmology – Head of Ophthalmology at Regional University Hospital of Brest, President of the French Academy of Ophthalmology

« A solution supported by doctors calling for progress.»

Vincent Gualino – Doctor in Ophthalmology – Secretary General of the Club of the French-Speaking Retina Specialists

« AI is not futuristic, it is already in the present »

3. Specificities of our technology

Highest standards
We take health matters seriously, and our device respects ISO 9001, ISO 13485, and is **CE** (N° 38330) and **Santé Canada** (N° 107166) approved Class II Medical Device Software.

Exclusive Database
Our more than 800 000 image worth database was built from the OphDiaT screening Network, which include high level of training and expertise as well as quality insurance, ensuring the best input data to our algorithms. This data is constantly improving and is used to train further versions of our algorithms.

Deep Convolutional Neural Networks
Such systems « learn » to perform task by using examples instead of being programmed with complex rules like “expert systems”.

Such systems are used by some of our competitors, while other use “shallow” CNN, with much less layers, hence ability to discriminate complex data.

Weakly supervised algorithms
Our algorithms were only trained on the final diagnosis, while most of our competitors use fusion of networks specialized in the detection of discrete lesions, hence obtaining strongly supervised algorithms, since they learnt the lesions based on medical diagnosis, while lesion recognition in ours was totally the product of “difference acquisition”, that is, learning what discriminates two categories.

A different approach to grading problem
Most grading solutions are multiclassifiers that output a probability for each class. We took a different approach by combining binary classifiers, hence obtaining a solution which is more easily repurposed and reach higher performances by simplification of each classification problem.

Lesion mapping
Our algorithms were specially trained so that determining the image areas deemed important in their decision is possible, allowing to produce heatmaps of such areas, that are shown to cover actual disease lesions.

Some upcoming algorithms of patented technology include the ability to map different lesions corresponding to different pathology grades with different colors, allowing to distinguish between different pathology signs on a same map, improving the ability for differential diagnosis.

Interpretable results
Our score can be interpreted by comparison to our reference populations, hence allowing to go beyond the abstract sensitivity and specificity performances to apply more specifically to a given score, allowing to determine relative positive/negative predictive values and thus, the certainty of diagnosis. This is not the case of competition, which mostly provide a probability of disease in a monotonous way, not allowing to adapt to various reference populations.

Recommendations
Our results integrate some clinical data and match grading and diagnoses with medically recommended courses of action.

Improved integrations and interoperability
As our solution has been integrated in more and more Ophthalmology Speciality Software and Fundus Camera devices, we have improved interoperability to now be able to manage DICOM images.

Depending on the need, we can also adapt our picture preprocessing to better fit specific devices optical and sensor characteristics to improve further algorithms performances. For example, we have special confocal images preprocessing.

Multiple approaches to disease detection (Circa Mid-2024)
We now have patented three different solutions (and are looking for more!) to solve the screening problem by taking opposite and complimentary approaches to eye disease detection, for the ultimate screening tool.

These will be implemented in our v3 version. Competitors for now are still looking to extend their solutions to more than one to three diseases.

Our solution will be able to detect more than 15 signs and symptoms, as well as generally abnormal eyes, including even rare diseases and covering more than 90% of eye diseases cases.

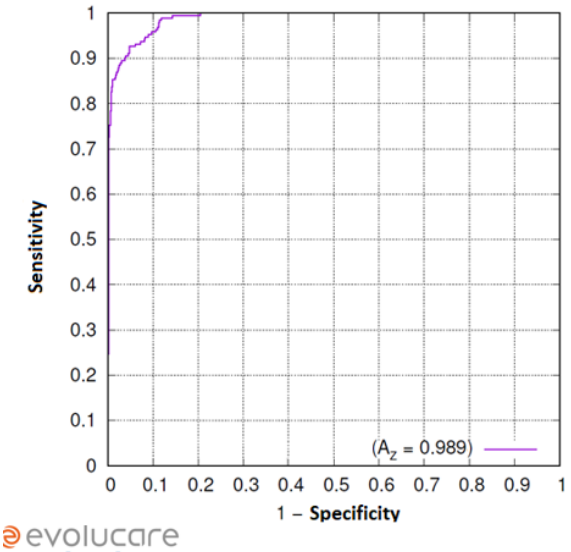
It will be able to assess disease both through general features as well as by direct evaluation of specific symptoms. We have shown improved performances in our assays and are preparing additional clinical trial.

As stated before, lesion mapping will also be improved with multicolored heatmaps, each color being attributed to a specific symptom or signs and if fitting, to matching grades of disease classification.

Functional improvements to extend solution usability for all specialists (End-2024)
We also plan to include image registration functionality to help comparing images from different visits in a same patient, thus allowing to measure pathology evolution.

We are also committed to Include the ability to manage new imaging modalities such as wide field images and OCT.

4. Performances



evolucare labs

Comparison with FDA marked solution

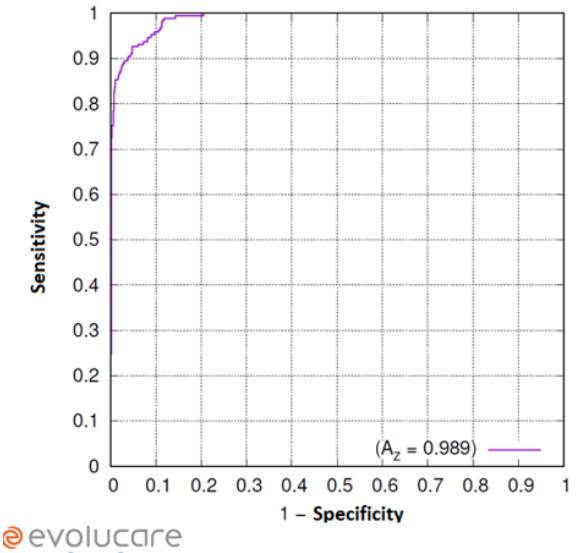
Sensitivity:
For fixed Specificity: 87%
-OphtAI Sensitivity 99%
-X solution Sensitivity 96.9%

False Positive divided by 3

Automated sorting:
Less positive patients sent home with further exam

Quellec G, Charrière K, Boudi Y, Cochener B, Lamard M. *Deep image mining for diabetic retinopathy screening*. Med Image Anal. 2017 Jul;39:178-193.

Quellec, Gwenole & Lamard, Mathieu & Lay, Bruno & Guilcher, Alexandre & Erginay, Ali & Cochener, Béatrice & Massin, Pascale. (2019). Instant automatic diagnosis of diabetic retinopathy.



evolucare labs

Comparison with FDA marked solution

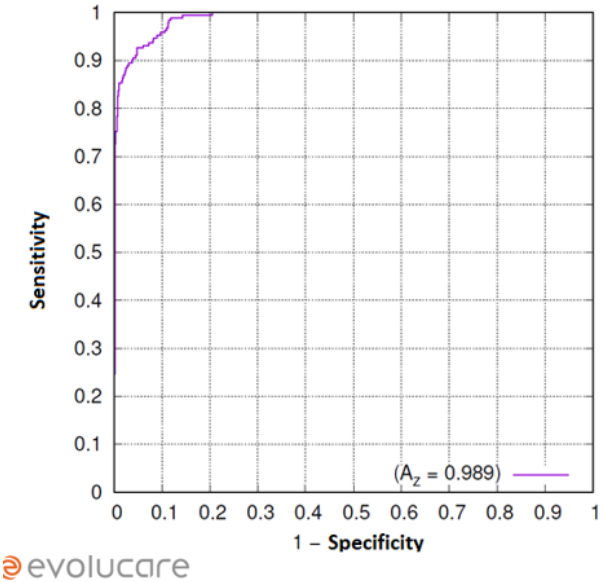
Specificity:
For fixed Sensitivity : 96.8%
-OphtAI Specificity 90,2%
-X Solution Specificity 87%

False Negative Reduction by 25%

Automated sorting:
Less positive patients needlessly sent for further exam

Quellec G, Charrière K, Boudi Y, Cochener B, Lamard M. *Deep image mining for diabetic retinopathy screening*. Med Image Anal. 2017 Jul;39:178-193.

Quellec, Gwenole & Lamard, Mathieu & Lay, Bruno & Guilcher, Alexandre & Erginay, Ali & Cochener, Béatrice & Massin, Pascale. (2019). Instant automatic diagnosis of diabetic retinopathy.



evolucare labs

Comparison with FDA marked solution

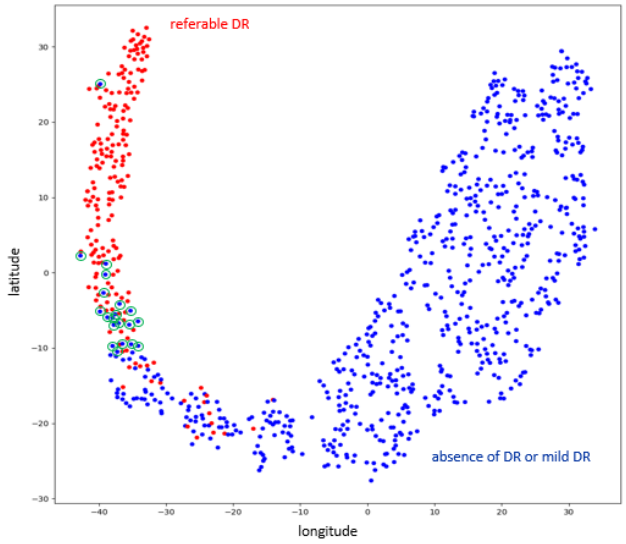
Processing Speed

-OphtAI <3s ; <0.5s GPU
-X : a few minutes

300000 images:
-OphtAI: 10 days
-X solution: 6 months

Quellec G, Charrière K, Boudi Y, Cochener B, Lamard M. *Deep image mining for diabetic retinopathy screening*. Med Image Anal. 2017 Jul;39:178-193.

Quellec, Gwenole & Lamard, Mathieu & Lay, Bruno & Guilcher, Alexandre & Erginay, Ali & Cochener, Béatrice & Massin, Pascale. (2019). Instant automatic diagnosis of diabetic retinopathy.

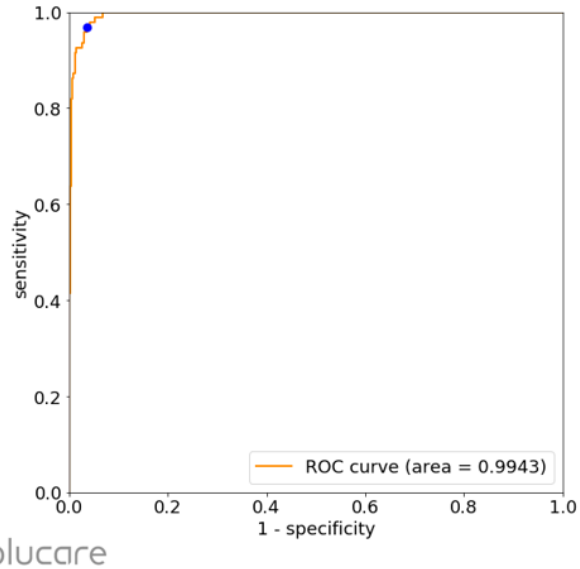


Comparison between AI & human expert

- Each point represent an image from Messidor-2 database in AI perception space (t-SNE representation)
- Couleur match consensus diagnosis by 3 american retina experts

In discordant cases (green circles), a new image interpretation by two retina specialists concurs with AI for 95% of cases

evolucare labs



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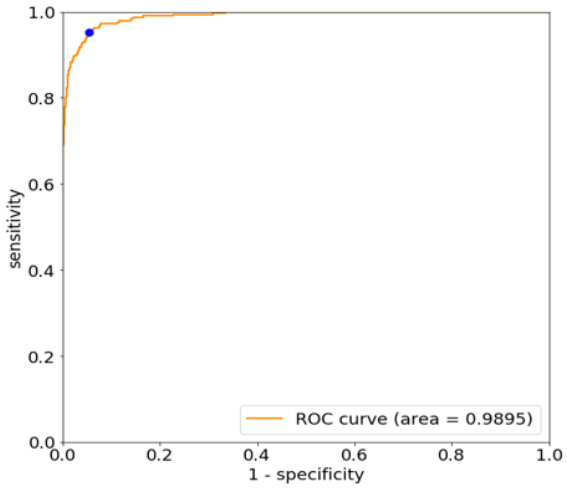
Diabetic Macular Edema

"Receiver Operating Characteristic" (ROC) DME AI Curve
Blue point highlights recommended setting (Sensitivity 96,81%; Specificity 96,34%)



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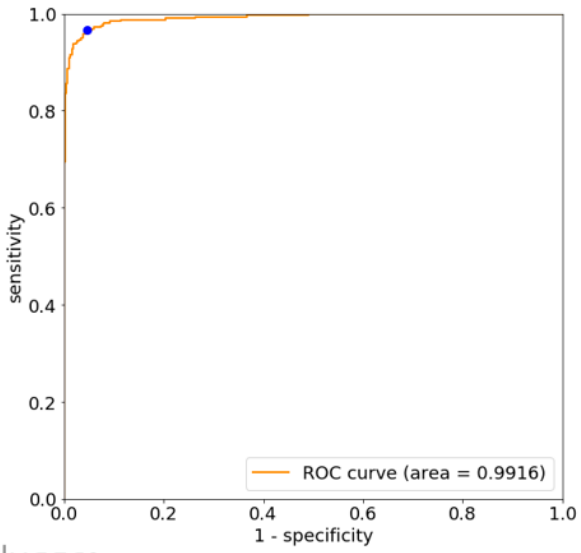
ARM/Drusen

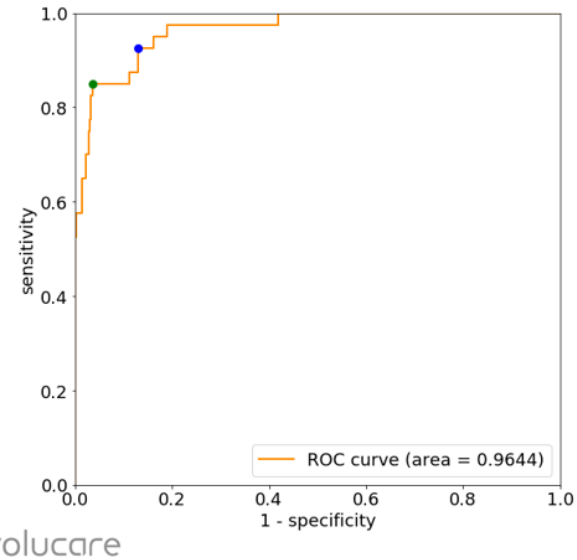
"Receiver Operating Characteristic" (ROC) ARM/Drusen AI Curve
Blue point highlights recommended setting (Sensitivity 95,27%; Specificity 94,58%)



evolucare labs

ARMD

"Receiver Operating Characteristic" (ROC) ARMD AI Curve
Blue point highlights recommended setting
(Sensitivity 96,5%; Specificity 95.4%)



evolucare labs

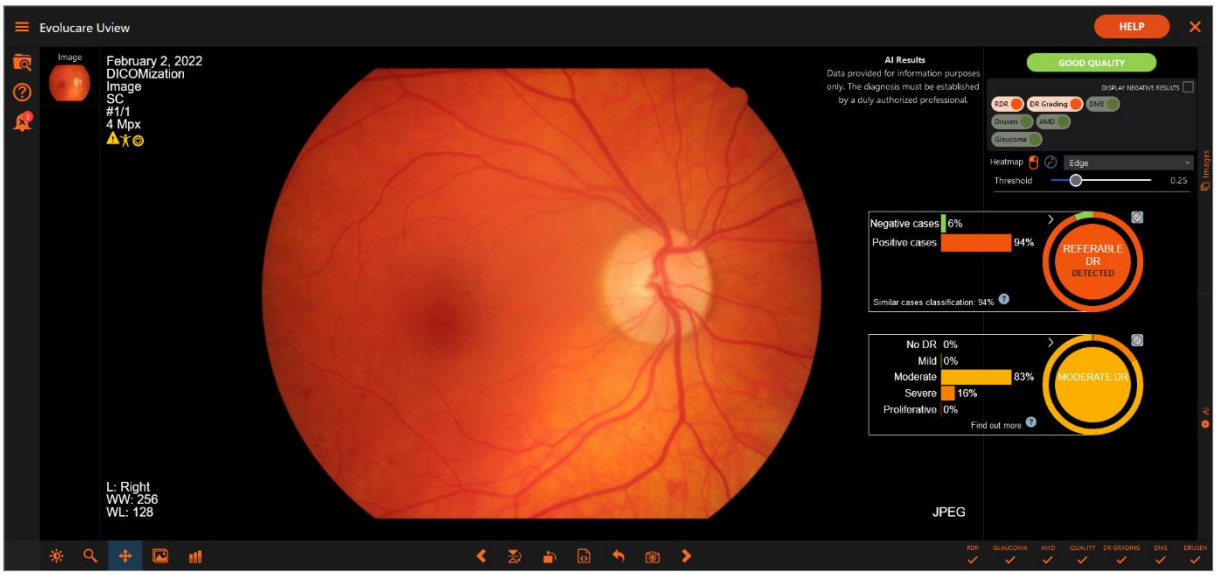
Glaucoma

"Receiver Operating Characteristic" (ROC) Glaucoma AI Curve
Blue point highlights recommended setting
(Sensitivity 92,5%; Specificity 86.4%)
Green point highlights recommended setting
For using Human reader sensitivity level (85 %). Then, human reader specificity is 91 %, for 96,39 % for OphtAI.

5. Explicability Features

As medical diagnosis is complex, engaging matter, it is really important to provide healthcare professionals making decisions with the most comprehensive information, to support their work by helping them make quicker, better and more confident conclusions to improve patient chances against silent, blinding diseases.

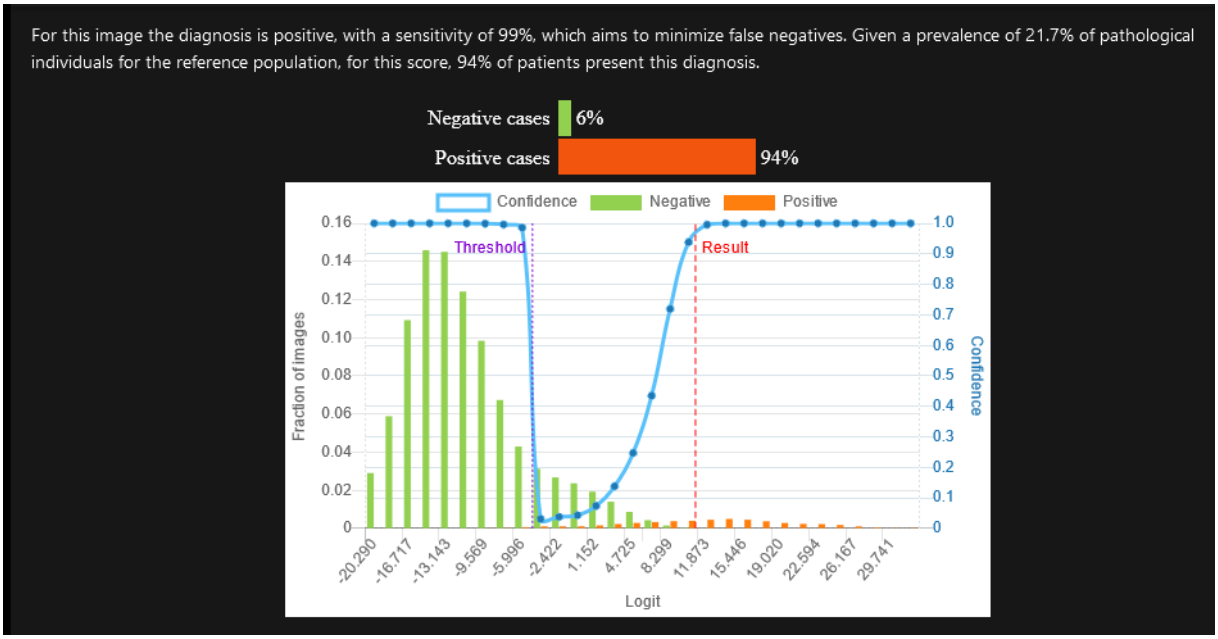
A. Similar Cases Classification



Actual capture of OphtAI User Interface. Histograms on the right-hand panel provides useful information known as “Similar Cases Classification” for each pathology assessment provided.

An advanced explanatory interface can be accessed through the question mark.

It is adapted to each algorithm features and provides extensive information on current diagnosis:



It is processed as a function of image score, depending on given image ratios for each possible ground truth (healthy or ill patients) in a reference database whose image distribution is based on disease prevalence.

For a positive (respectively negative) diagnosis, positive (resp. negative) cases value translates as Positive (respectively Negative) Predictive Value.

Hence, if a patient is referred to an Ophthalmologist (CNN score >= threshold), the positive value equates the probability that this patient actually has such disease. Such probability is low close to the threshold and reaches 100% when getting higher.

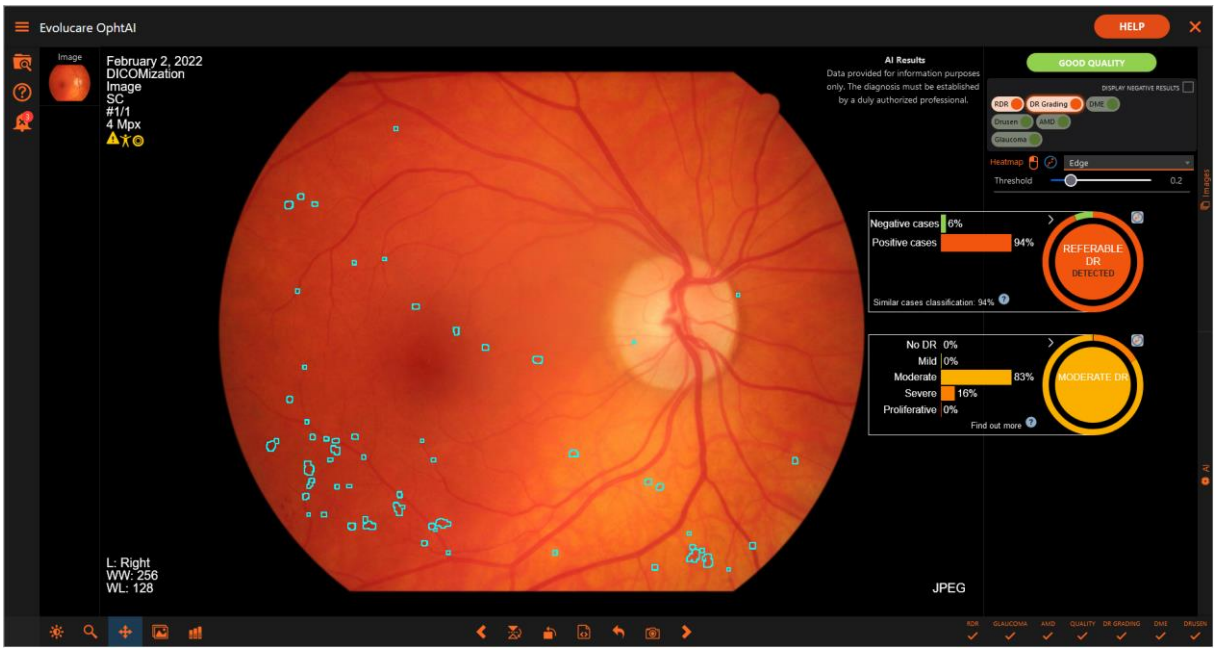
In addition, it provides information on databases used for training, claimed performances, reference reports and publications; as well as comparative scale used for grading of Diabetic Retinopathy.

This helps bringing understanding of the algorithms' workings, answers and performances, thus increasing trust and conjugated "human-AI" performance.

B. Heatmaps

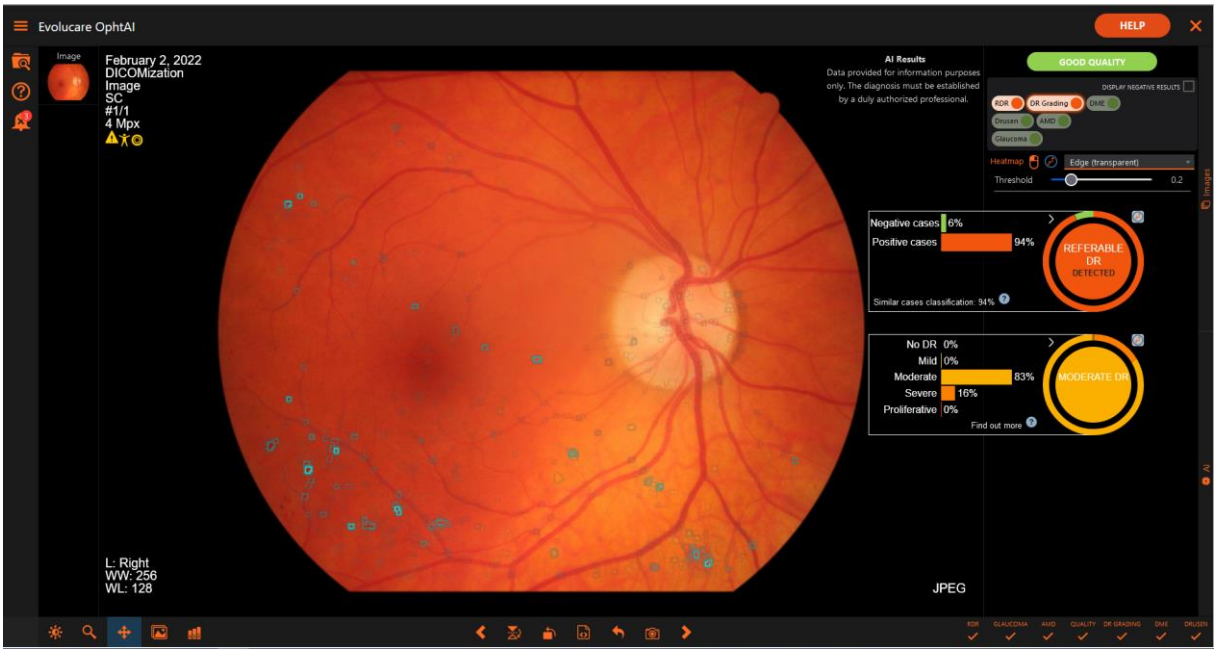
In addition to similar case classification, Heatmaps can be accessed through a mere click on the relevant AI result badge, highlighting even the tiniest lesions, as long as they were deemed important to the diagnosis. This helps explaining the elements associated with diagnosis, as well as validating it.

A threshold may be used to adjust and filter these points, and you may also use different forms of highlighting for increasing visibility and fit your analytic style.



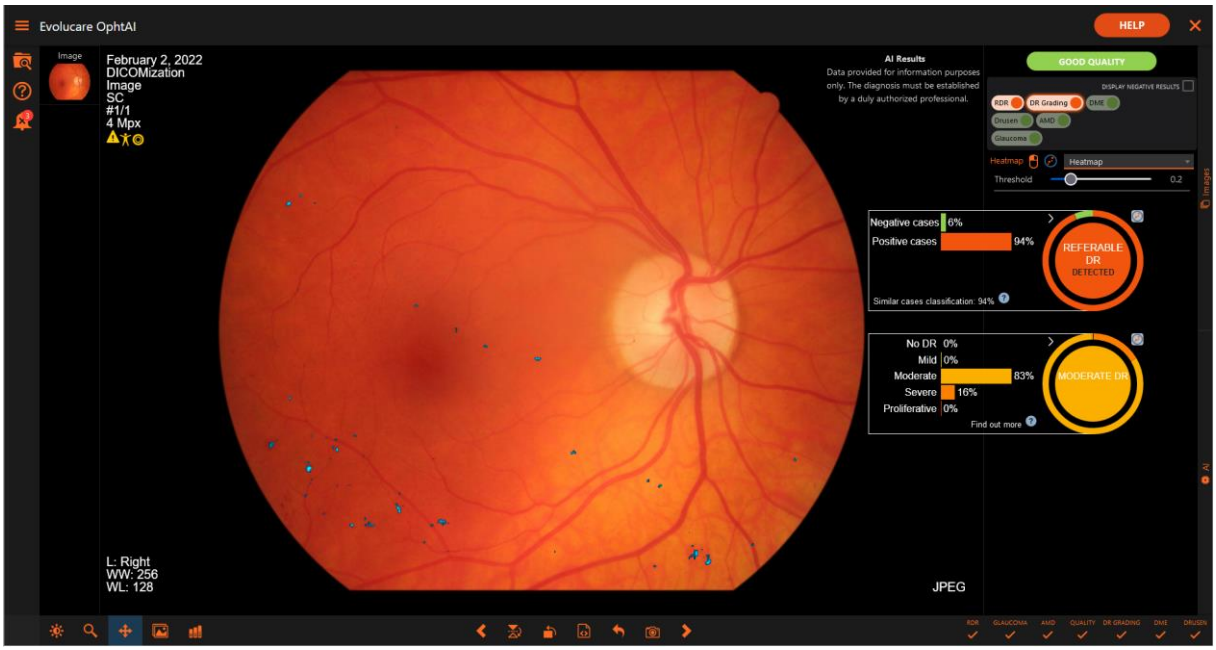
Actual capture of OphtAI User Interface with contour style heatmaps.

These heatmaps surround important fundus areas, past a given importance for the AI assessment threshold, with an opposite color, maximizing contrast and visibility.



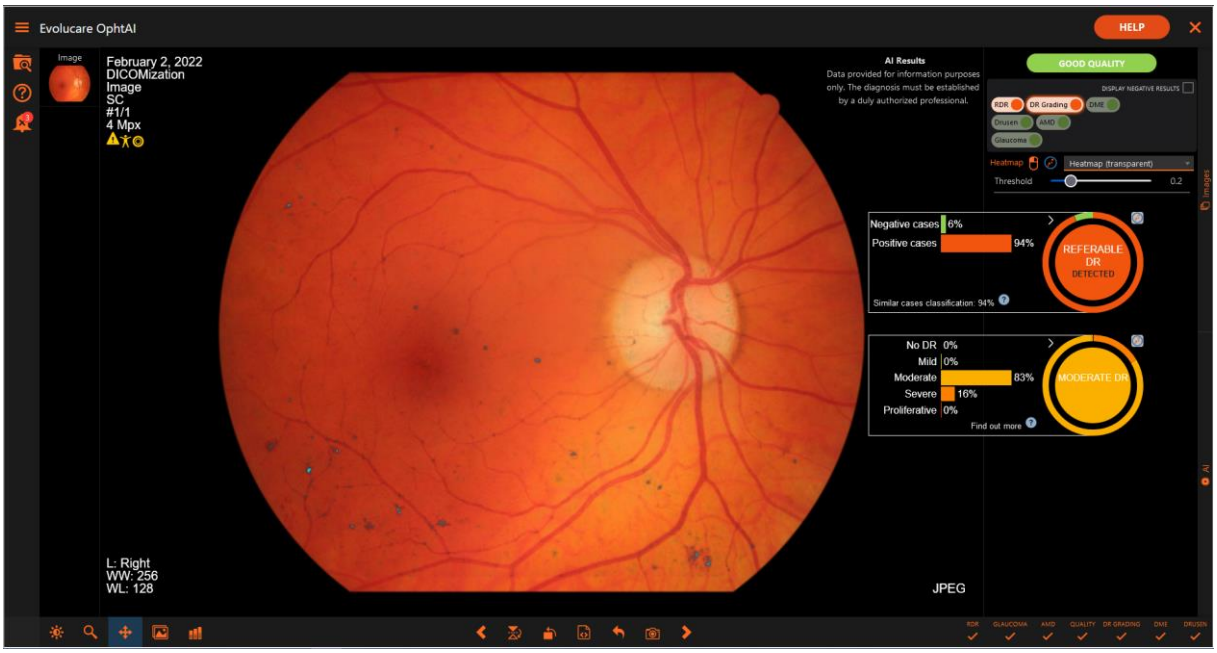
Actual capture of OphtAI User Interface with alpha contour style heatmaps

In addition to contours, these heatmaps include a degree of transparency matching the importance of the fundus area for the AI assessment, both improving further visibility and assessment understanding and validation.



Actual capture of OphtAI User Interface with point style heatmaps.

These heatmaps superpose important fundus areas, past a given importance for the AI assessment threshold, with an opposite color, maximizing contrast and location accuracy.



Actual capture of OphtAI User Interface with alpha point style heatmaps.

In addition to points, these heatmaps include a degree of transparency matching the importance of the fundus area for the AI assessment, both improving further visibility and assessment understanding and validation.

C. Summarized, selected results

In our latest interface, to improve focus and assessment quality, we summarize AI results in the top right-hand corner, displaying only positive results AI badge but allowing to activate suspected disease related AI by a click. In this summary, display is constant, helping to get the same information at the same place, preventing mistakes. In the general AI display, positive AI are classified by order of confidence importance, that is in order of decreasing positive cases classification.

D. Optimized Reference Standards

Our database Diabetic Retinopathy Grading Scale annotation reference has been established especially for screening, and is thus fitting to use for AI telescreening, while some other solutions use more complicated scales as reference, whose standard is based on using more than 2 images/fields per eye, hence not being fitting such use.

To help practitioners with the subtle differences, and explain how some grades would be established, we provided clear information in the solution's interface.

Diabetic disease severity			
Diabetic retinopathy Classification	**Original ICDR scale (from Wilkinson et al., 2003*)**	**Adapted ICDR scale for screening (from Lecleire-Collet, Massin et al., 2007**)**	**Differences**
No apparent retinopathy	No abnormalities	No Diabetic Retinopathy signs	None
Mild nonproliferative diabetic retinopathy	Microaneurysms only	Isolated cotton-wool nodule or retinal hemorrhage, without associated micro-aneurysm OR only micro-aneurysms.	Additional criteria with Isolated cotton-wool nodule or retinal hemorrhage, without associated micro-aneurysm
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe nonproliferative diabetic retinopathy	Stage is more severe than stage 1 but less severe than stage 3	Differences depending on stages 1 and 3
Severe nonproliferative diabetic retinopathy	Any of the following: -More than 20 intraretinal hemorrhages in each of 4 quadrants; -Definite venous beading in 2 quadrants; -Prominent intraretinal microvascular abnormalities in 1 quadrant AND -no signs of proliferative retinopathy	Any of the following: -Intraretinal hemorrhages AND/OR Micro-aneurysms of severity superior or equal to 2A ETDRS standard photography in at least one peripheral field AND/OR venous beading in AND/OR intraretinal microvascular abnormalities of severity superior or equal to 8A ETDRS standard photography in at least one peripheral field AND -no signs of proliferative retinopathy	ICDRS assess signs depending on quadrants, adapter version use fields instead and doesn't count precisely, it compares the retina state to ETDRS references
Proliferative diabetic retinopathy	One or more of the following:neovascularization, vitreous/preretinal hemorrhage	One or more pre-retinal or pre-papillary neovessel ± fibrosis AND/OR proliferative DR complications : vitreous/preretinal hemorrhage, retinal detachment	Additional criteria with fibrosis, and retinal detachment; neovascularization type is precised

Maculopathy classification	**Original ICDR scale (from Wilkinson et al., 2003*)**	**Adapted ICDR scale for screening (from Lecleire-Collet, Massin et al., 2007**)**	**Differences**
No diabetic macular Edema	-	No dry exsudates	Adapted version doesn't consider thickening but locate more precisely lesions, by measuring these in papillary diameter units, instead of just considering "posterior pole". Also, it doesn't distinguish latest two grades
Mild diabetic macular edema	Some retinal thickening or hard exudates in posterior pole but distant from the center of the macula	Few and small sized hard exsudates at more than one papillary diameter from the macula center	
Moderate diabetic macular edema	Retinal thickening or hard exudates approaching the center of the macula but not involving the center	Circinate hard exsudates bigger than one papillar surface at more than one papillary diameter from the macula center	
Severe diabetic macular edema	Retinal thickening or hard exudates involving the center of the macula	Hard exsudates at less than one papillary diameter from the macula center	

E. Recommendations / Course of action

Our solution, to help practitioners, provides recommendations for screening follow-up, based upon 2016 standards for screening and surveillance of ocular complications in people with diabetes, endorsed by the French Speaking Diabetes Society (Société Francophone du Diabète, SFD) and the French Society of Ophthalmologie (Société Française d'Ophtalmologie, SFO).

These are summarised below :

		Non pregnant patient	Pregnant patient
Screening Recommendations	**No Diabetic Retinopathy**	Fundus photography in a year.	Fundus photography in three months.
	Mild Non Proliferative Diabetic Retinopathy	Fundus photography in a year.	Fundus photography in a month.
	Moderate Non Proliferative Diabetic Retinopathy	Patient to be referred without urgency to the ophthalmologist (within 2 months).	Patient to be referred without urgency to the ophthalmologist (within 2 months).
	Severe Non Proliferative Diabetic Retinopathy	Patient to be referred without urgency to the ophthalmologist (within 2 months).	Patient to be referred urgently to the ophthalmologist (within 15 days).
	Proliferative Diabetic Retinopathy	Patient to be referred urgently to the ophthalmologist (within 15 days).	Patient to be referred urgently to the ophthalmologist (within 15 days).
	Diabetic Macular Edema	Patient to be referred without urgency to the ophthalmologist (within 2 months).	Patient to be referred without urgency to the ophthalmologist (within 2 months).
	Non Interpretable	Patient to be referred urgently to the ophthalmologist (within 15 days).	Patient to be referred urgently to the ophthalmologist (within 15 days).
	Glaucoma	Patient to be sent immediately to the ophthalmologist for medical advice, especially since they present functional warning signs (\"tunnel vision\" and scotomas - dark spots perceived by the patient -, whether or not associated with reduced visual acuity; decreased perception of contrasts; discomfort in night vision; difficulty in reading; sensation of dazzling; changes in color vision).	Patient to be sent immediately to the ophthalmologist for medical advice, especially since they present functional warning signs (\"tunnel vision\" and scotomas - dark spots perceived by the patient -, whether or not associated with reduced visual acuity; decreased perception of contrasts; discomfort in night vision; difficulty in reading; sensation of dazzling; changes in color vision).
	ARMD	Patient to be sent immediately to the ophthalmologist for medical advice, especially since they present functional warning signs (distorted perception of straight lines and images, whether or not associated with reduced visual acuity, scotomas - dark spots perceived by the patient -; decreased perception of contrasts; discomfort in night vision; difficulty in reading; sensation of dazzling; changes in color vision).	Patient to be sent immediately to the ophthalmologist for medical advice, especially since they present functional warning signs (distorted perception of straight lines and images, whether or not associated with reduced visual acuity, scotomas - dark spots perceived by the patient -; decreased perception of contrasts; discomfort in night vision; difficulty in reading; sensation of dazzling; changes in color vision).
	MLA/Drusen	*No recommendations*	*No recommendations*

6. Main publications & Patent

2008: OPHDIAT: a telemedical network screening system for diabetic retinopathy in the Ile-de-France: https://doi.org/10.1016/j.diabet.2007.12.006

2008: OPHDIAT: quality-assurance program plan and performance of the network: https://doi.org/10.1016/j.diabet.2008.01.004. PMID: 18424210 https://www.em-consulte.com/article/1169995/ophdiat-c-quality-assurance-programme-plan-and-per https://www.sciencedirect.com/science/article/abs/pii/S1262363608000542?via%3Dihub; https://europepmc.org/article/med/18424210

2009: Benefits of Ophdiat, a telemedical network to screen for diabetic retinopathy: a retrospective study in five reference hospital centers: https://doi.org/10.1016/j.diabet.2008.12.001

2012: Ophdiat(®): five-year experience of a telemedical screening program for diabetic retinopathy in Paris and the surrounding area: https://doi.org/10.1016/j.diabet.2012.05.003

2014: Feedback on a publicly distributed image database: The Messidor database: https://www.researchgate.net/publication/272989606_Feedback_on_a_publicly_distributed_image_database_The_Messidor_database/citation/download

2017: Deep Image Mining for Diabetic Retinopathy Screening: https://arxiv.org/abs/1610.07086

2018: Retinal pathology screening with a multi-image convolutional neural network: https://iovs.arvojournals.org/article.aspx?articleid=2690067

2019: RetinOpTIC - Automatic Evaluation of Diabetic Retinopathy: https://iovs.arvojournals.org/article.aspx?articleid=2744652

2019: Instant automatic diagnosis of diabetic retinopathy: https://arxiv.org/abs/1906.11875

2020: Automatic detection of rare pathologies in fundus photographs using few-shot learning: https://arxiv.org/abs/1907.09449 https://doi.org/10.1016/j.media.2020.101660.

2020: Patent n° PCT/EP2020/062762 "Automatic image analysis method for automatically recognising at least one rare feature"

2020: ExplAIn: Explanatory Artificial Intelligence for Diabetic Retinopathy Diagnosis: https://arxiv.org/pdf/2008.05731.pdf

2021: Ten-year incidence and assessment of safe screening intervals for diabetic retinopathy: the OPHDIAT study: https://doi.org/10.1136/bjophthalmol-2020-316030

2021: Multicenter, Head-to-Head, Real-World Validation Study of Seven Automated Artificial Intelligence Diabetic Retinopathy Screening Systems VETERAN AFFAIRS Contest /AARON Y LEE: OphtAI RD detection shown as most sensitive, cost effective and clinically relevant.

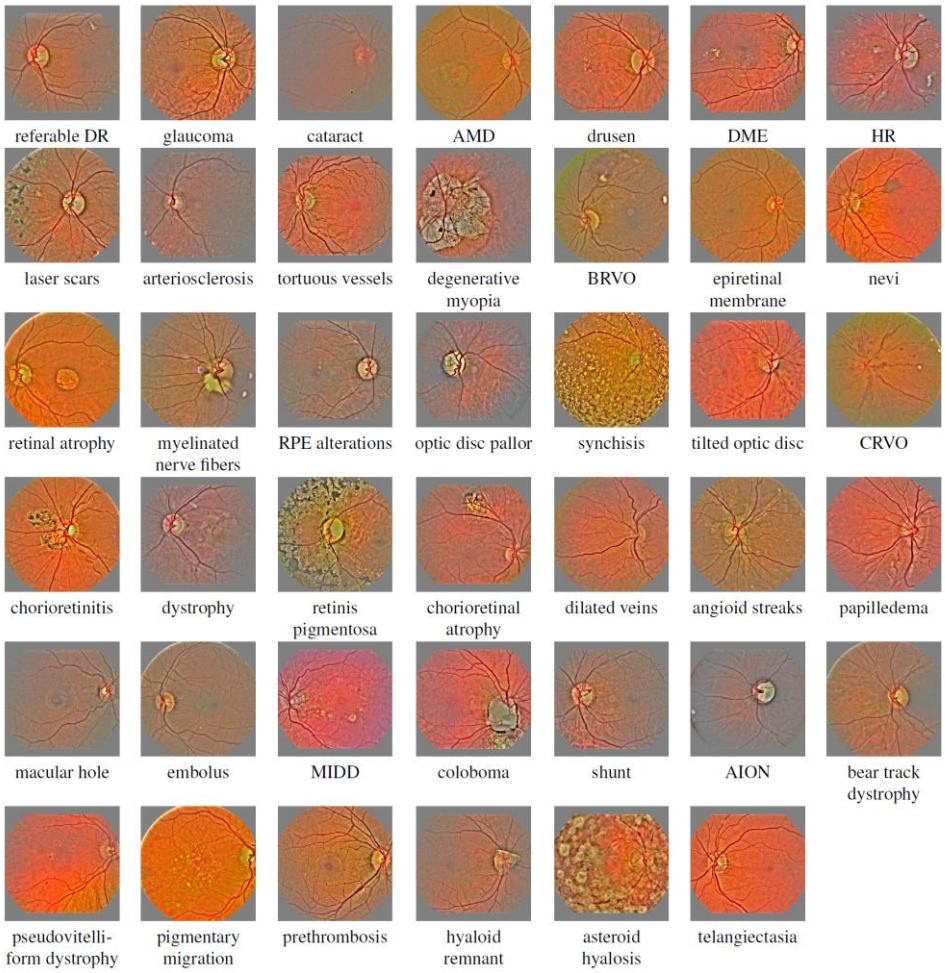
Diabetes Care 2021 Jan; dc201877. https://doi.org/10.2337/dc20-1877

2021: Automatic Screening for Ocular Anomalies Using Fundus Photographs: https://doi.org/10.1097/opx.0000000000001845.

2022: Usage de l'intelligence artificielle en vraie vie dans un protocole RNO (Artificial intelligence in real life as part of eyewear prescription renewal). Roubelat FP, Soler V, Gualino V. Communications orales SFO 2022. https://www.sfo-online.fr/sites/www.sfo-online.fr/files/medias/documents/SFO%202022%20-%20Re%CC%81sume%CC%81s%20communications%20orales%20et%20rapid%20fire.pdf

7. Coming soon 2024

The next version of OphtAI is able to detect general ocular healthiness, and also general anomalies among 37 pathologies or pathologies signs, adding improved algorithms for previously detected diseases:



It will also include specific detectors for the following diseases and signs: