Machine learning for ophthalmic image analysis

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OPTIMA
Ophthalmic Image Analysis

MEDICAL UNIVERSITY
OF VIENNA

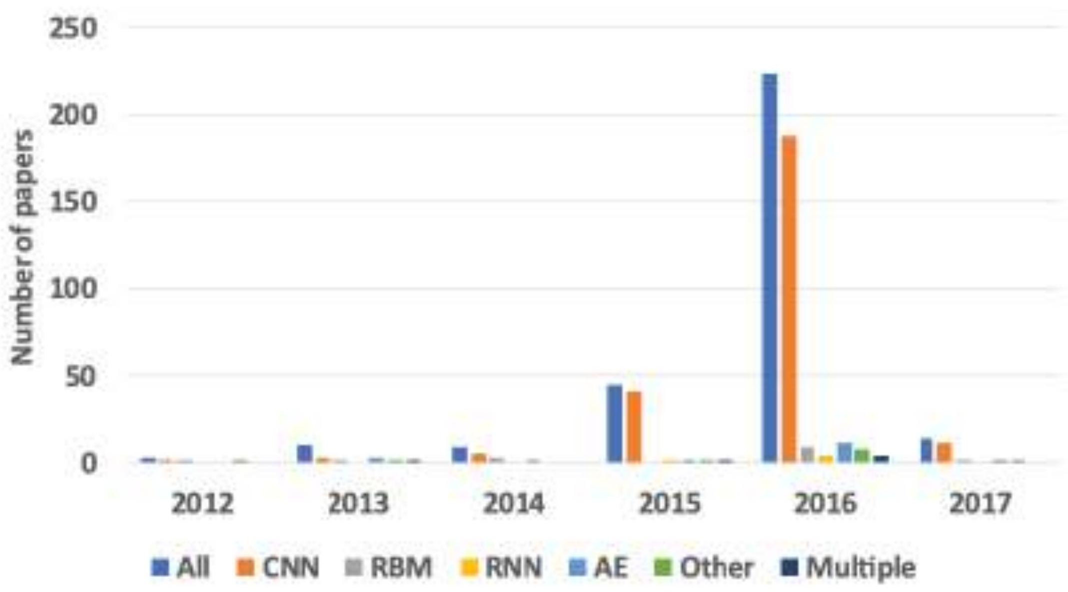
Computer vision

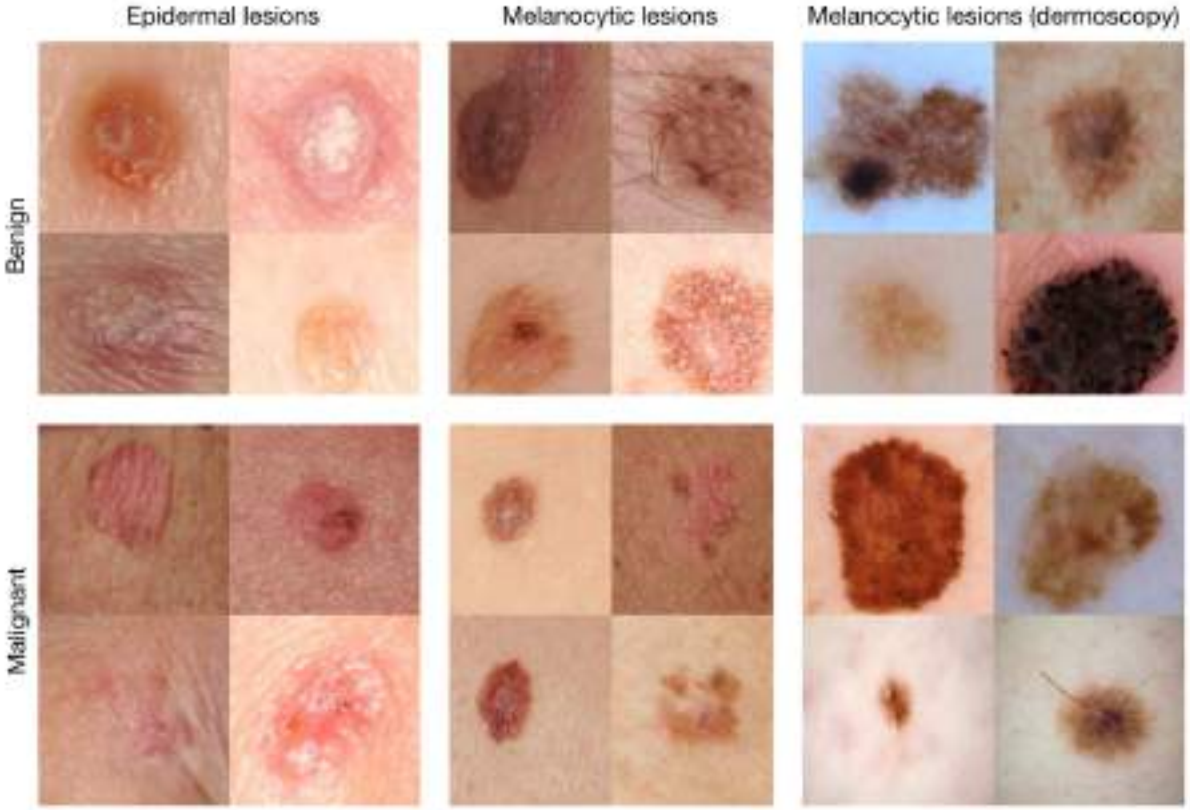
MEDICAL IMAGING

Medicine

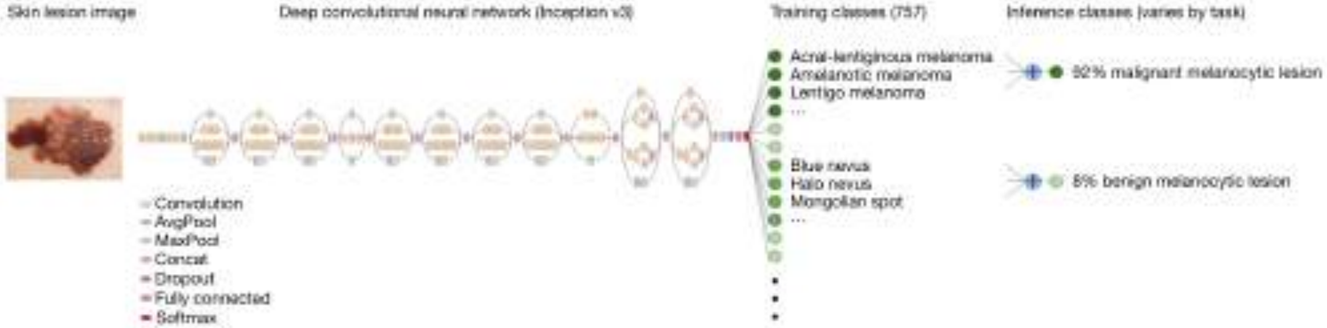
Litjens et al., Feb. 2017, MedIA

“A survey on Deep learning in Medical Image Analysis”





https://cs.stanford.edu/people/esteva/nature/



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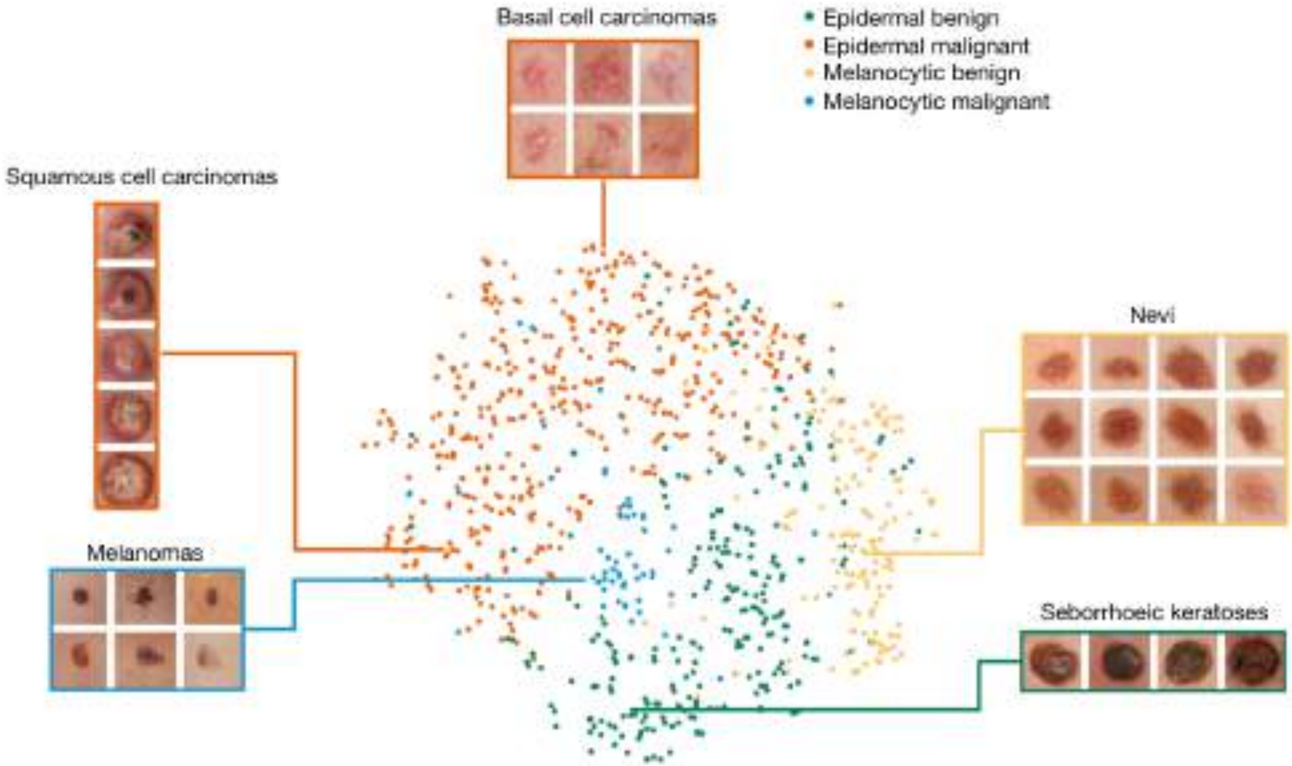


https://cs.stanford.edu/people/esteva/nature/

Original Investigation

FREE

December 12, 2017

Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women With Breast Cancer

Babak Ehteshami Bejnordi, MS[1]; Mitko Veta, PhD[2]; Paul Johannes van Diest, MD, PhD[3]; et al

» Author Affiliations | Article Information

JAMA. 2017;318(22):2199-2210. doi:10.1001/jama.2017.14585

Research

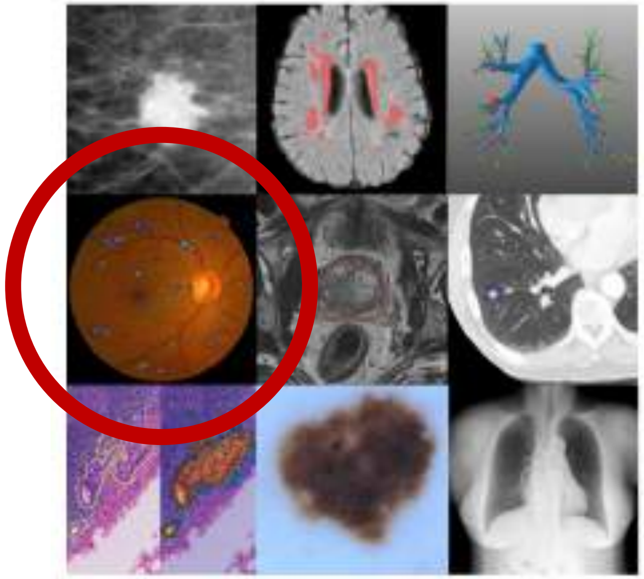
JAMA | Original Investigation | INNOVATIONS IN HEALTH CARE DELIVERY

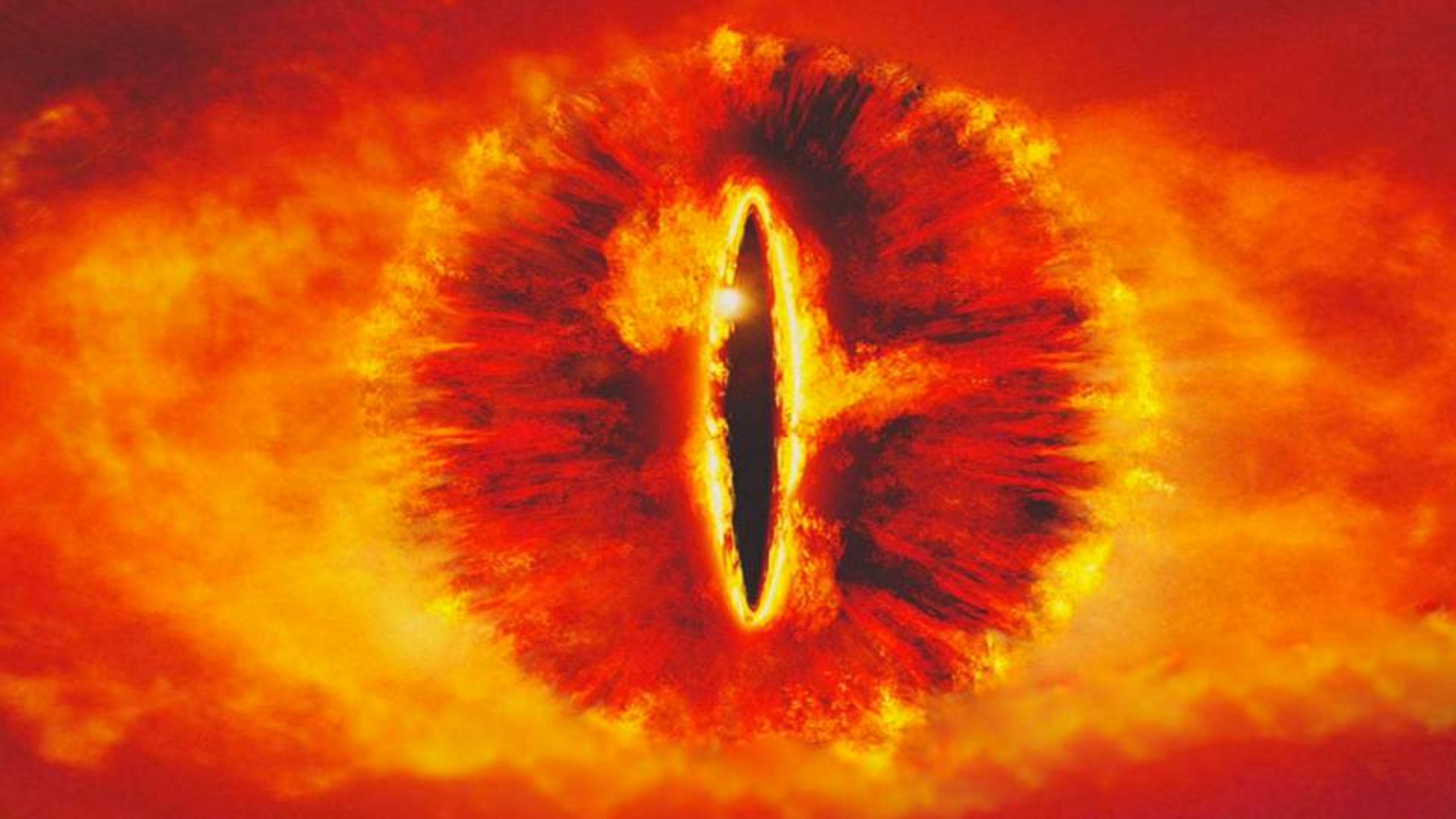
Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Varun Gulshan, PhD; Lily Peng, MD, PhD; Marc Coram, PhD; Martin C. Stumpe, PhD; Derek Wu, BS; Arunachalam Narayanaswamy, PhD; Subhashini Venugopalan, MS; Kasumi Widner, MS; Tom Madams, MEng; Jorge Cuadros, OD, PhD; Ramasamy Kim, OD, DNB; Rajiv Raman, MS, DNB; Philip C. Nelson, BS; Jessica L. Mega, MD, MPH; Dale R. Webster, PhD

Litjens et al., Feb. 2017, MedIA

"A survey on Deep learning in Medical Image Analysis"





What are we going to talk about today?

The eye (and the retina)

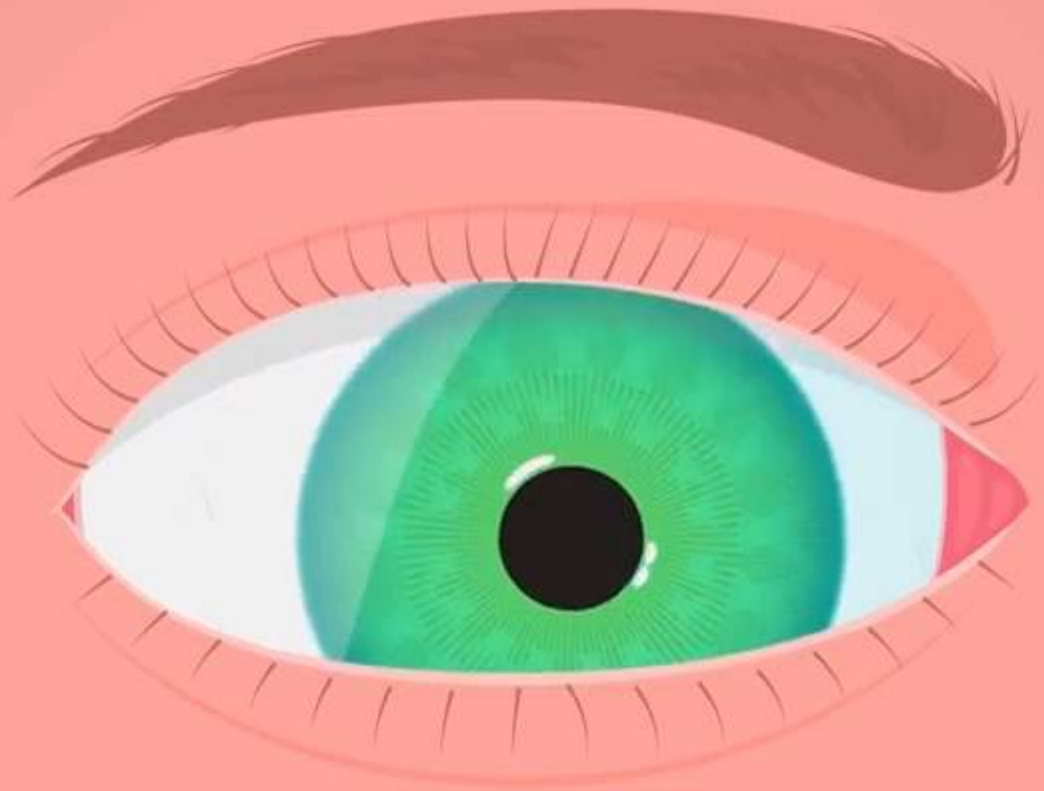
Imaging modalities in ophthalmology

Retinal diseases: AMD, DR, glaucoma

Use cases of machine/deep learning

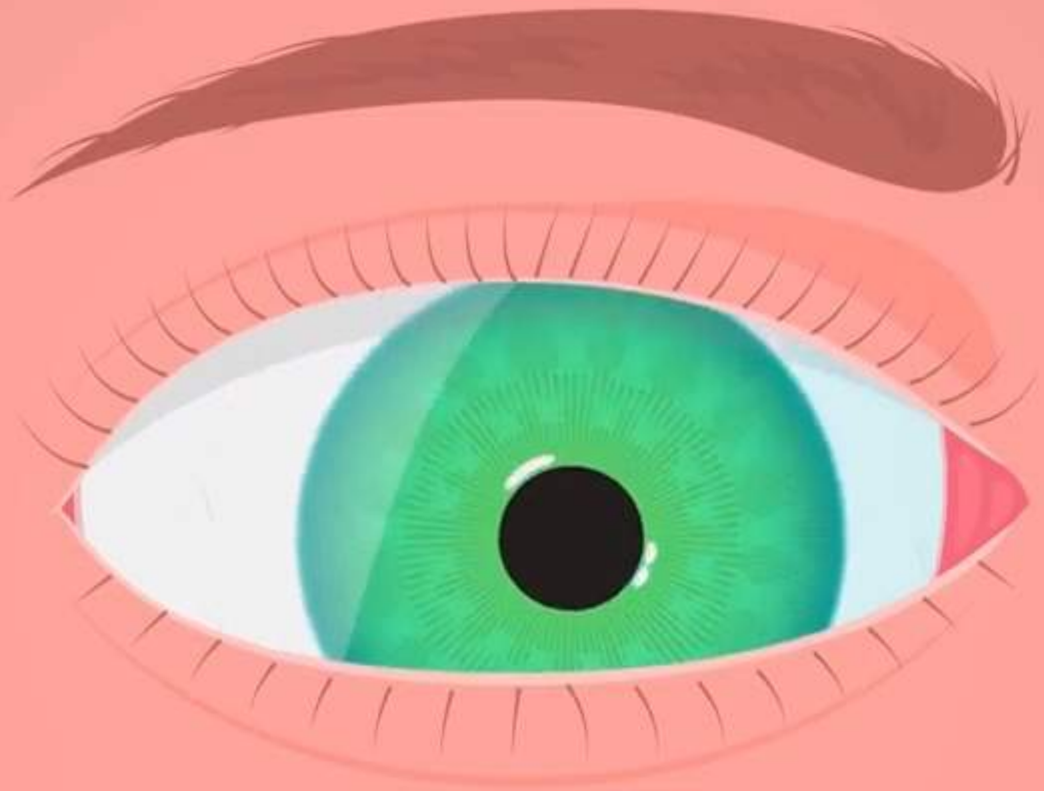
Concluding remarks

Vision



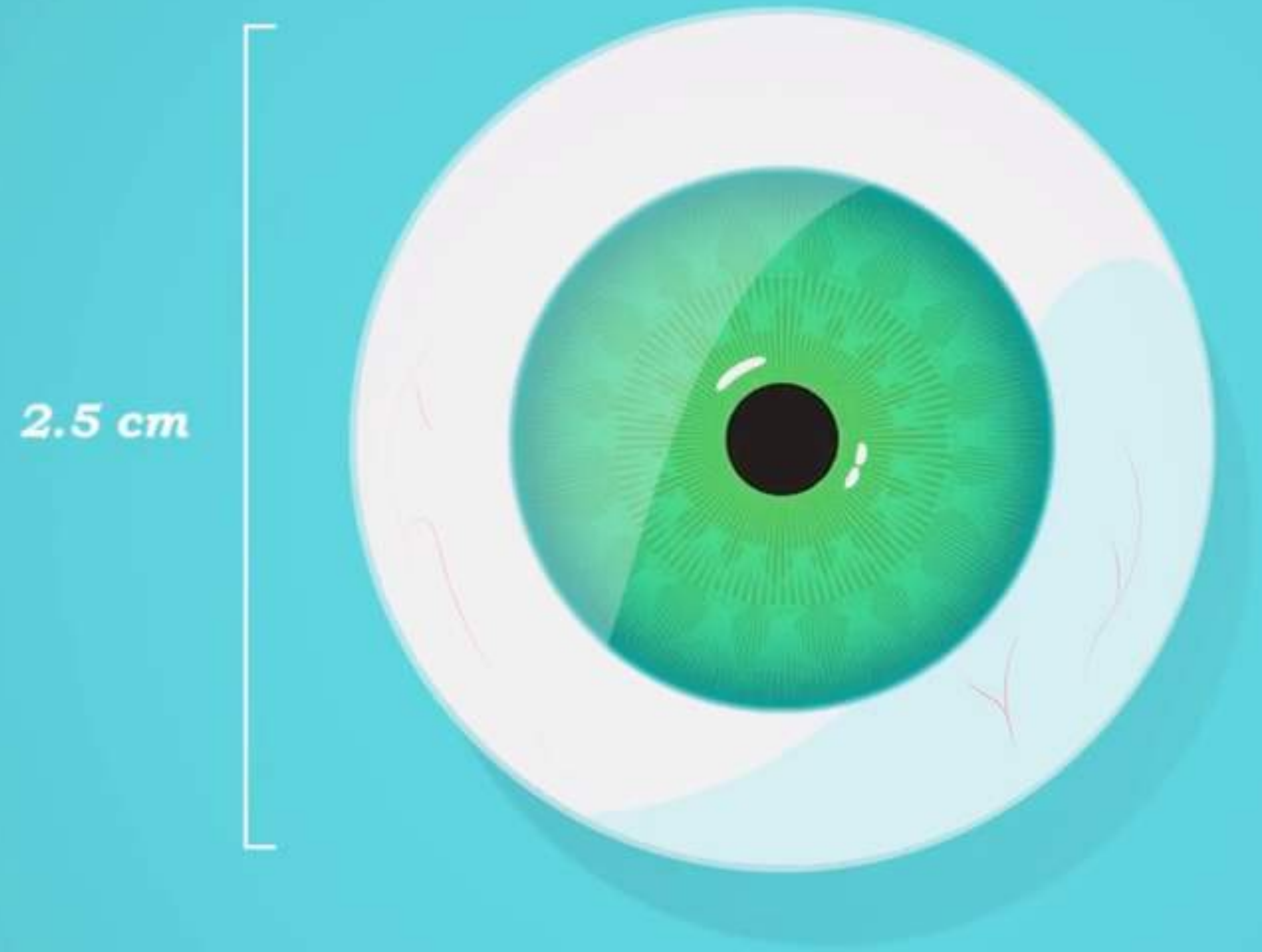
Nearly 70% of all the sensory receptors of the whole body are in the eyes

Vision



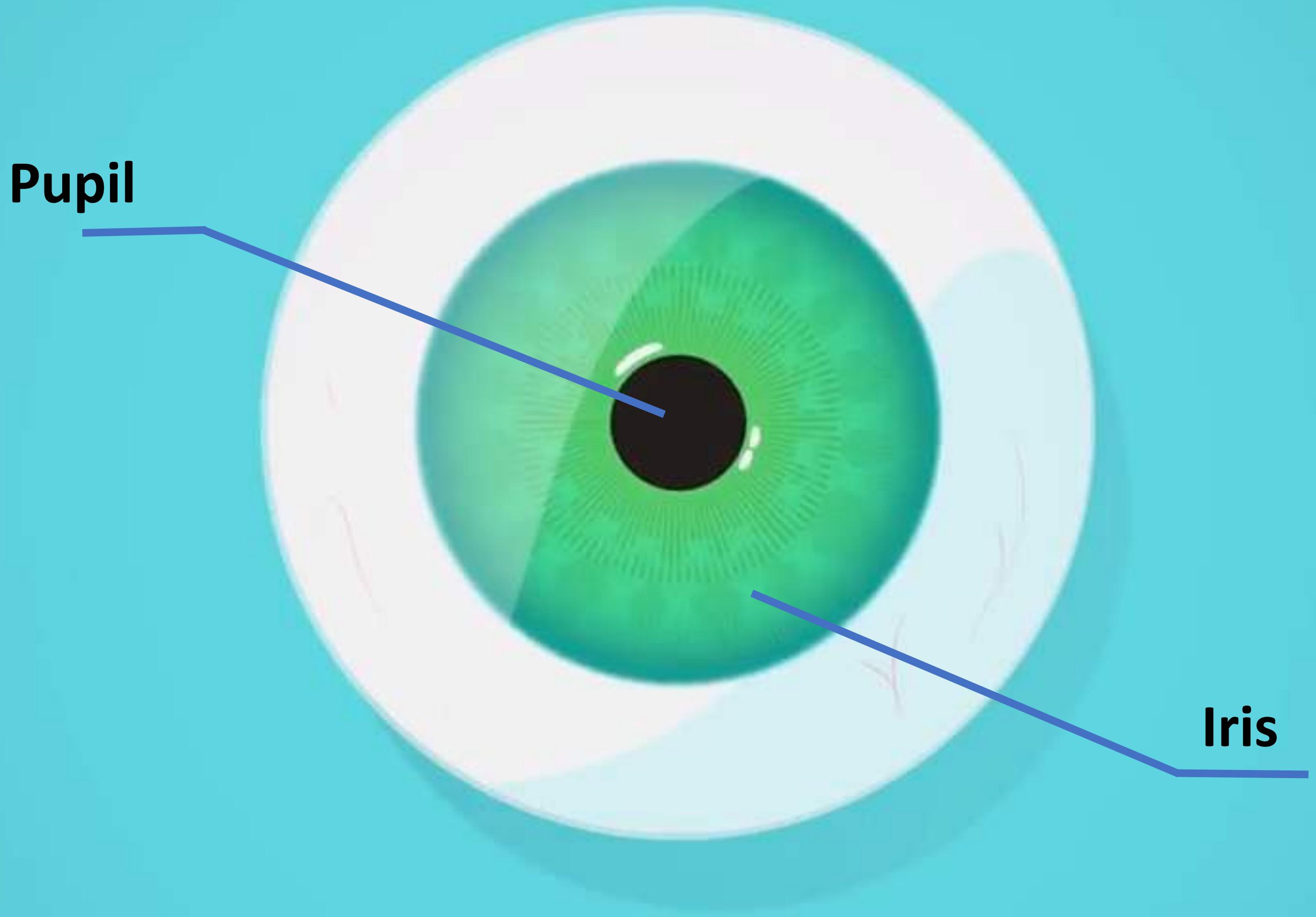
Provided by the complex interaction between the eye and the brain

The eye

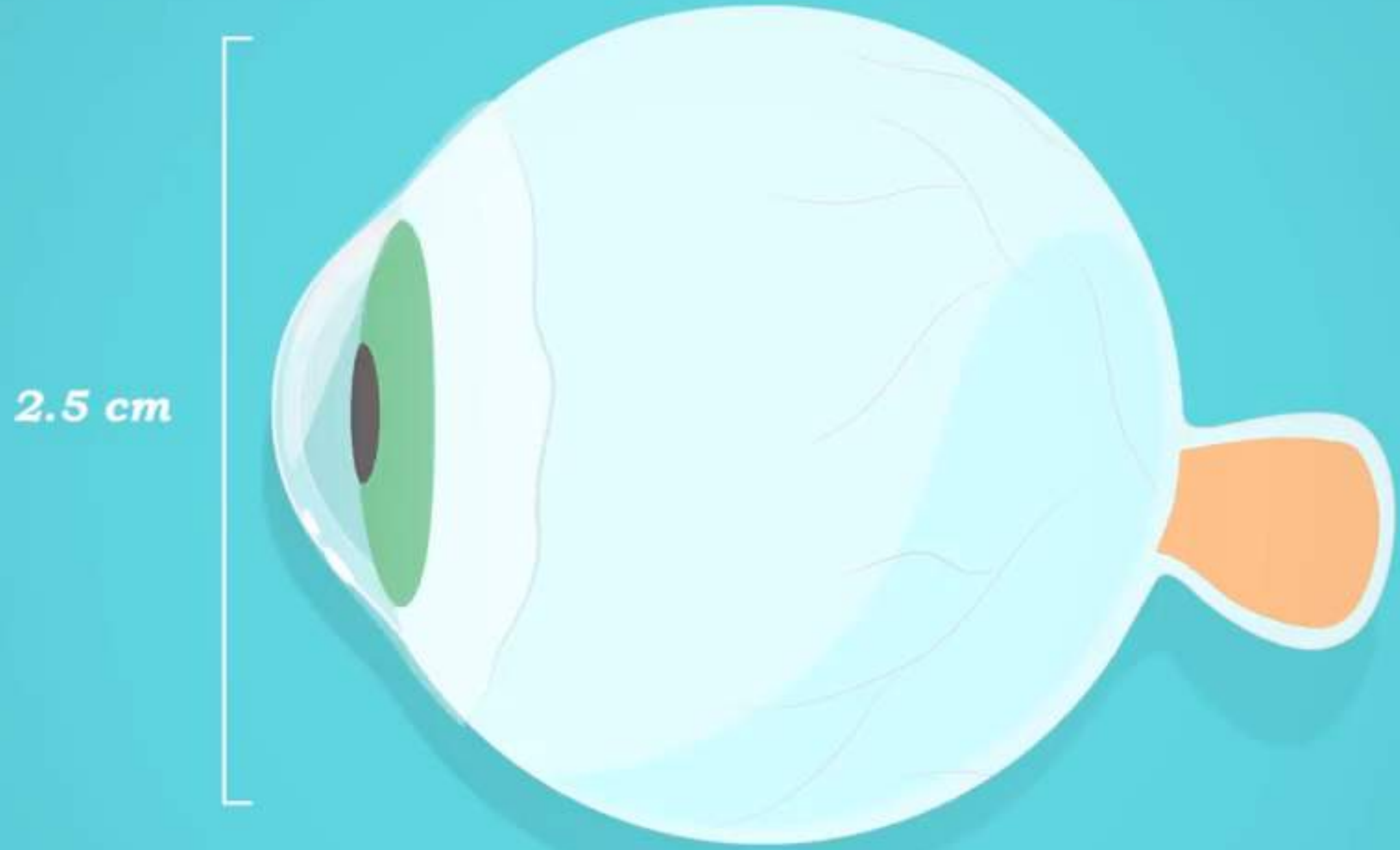


* Average diameter in adults

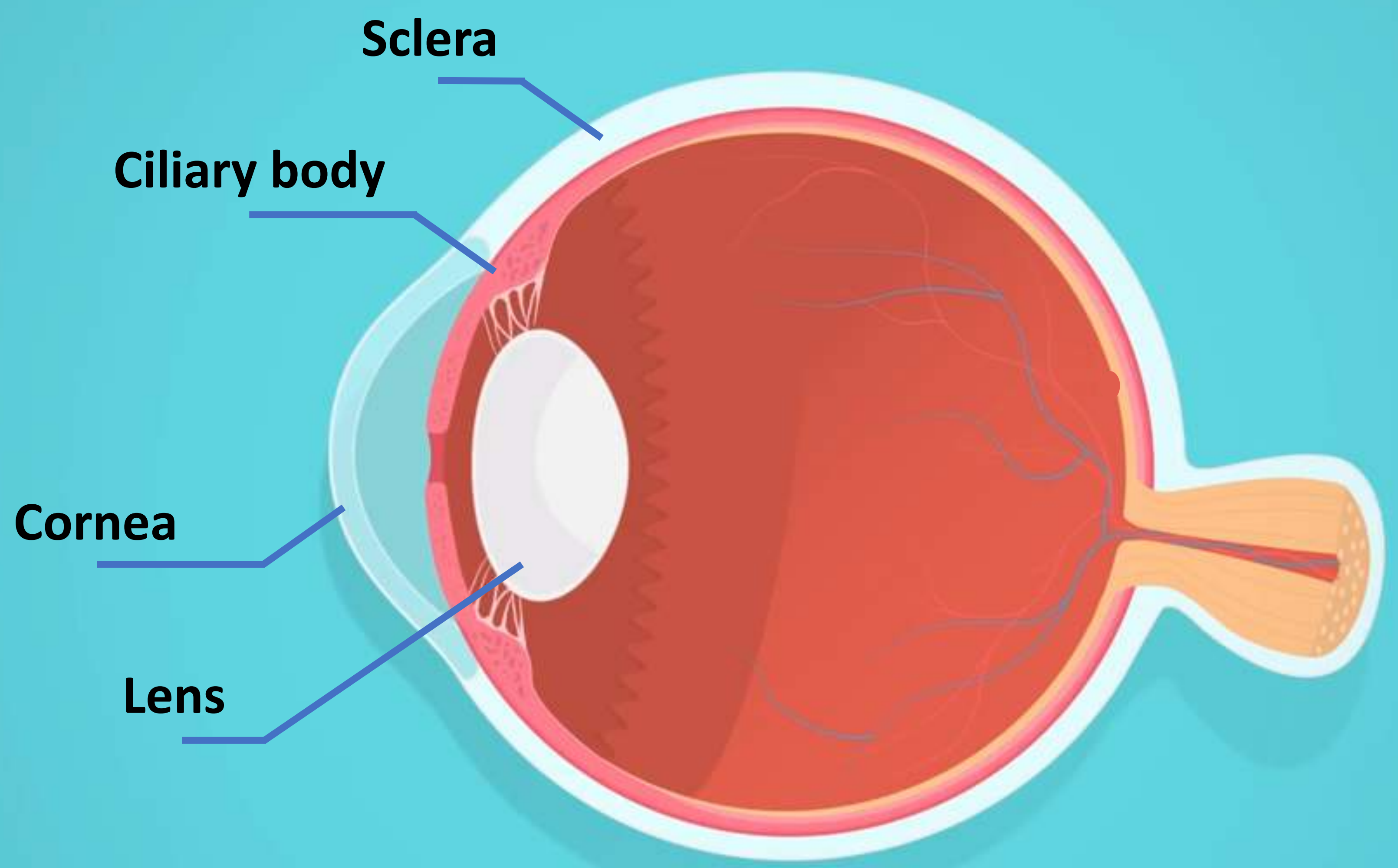
The eye



The eye

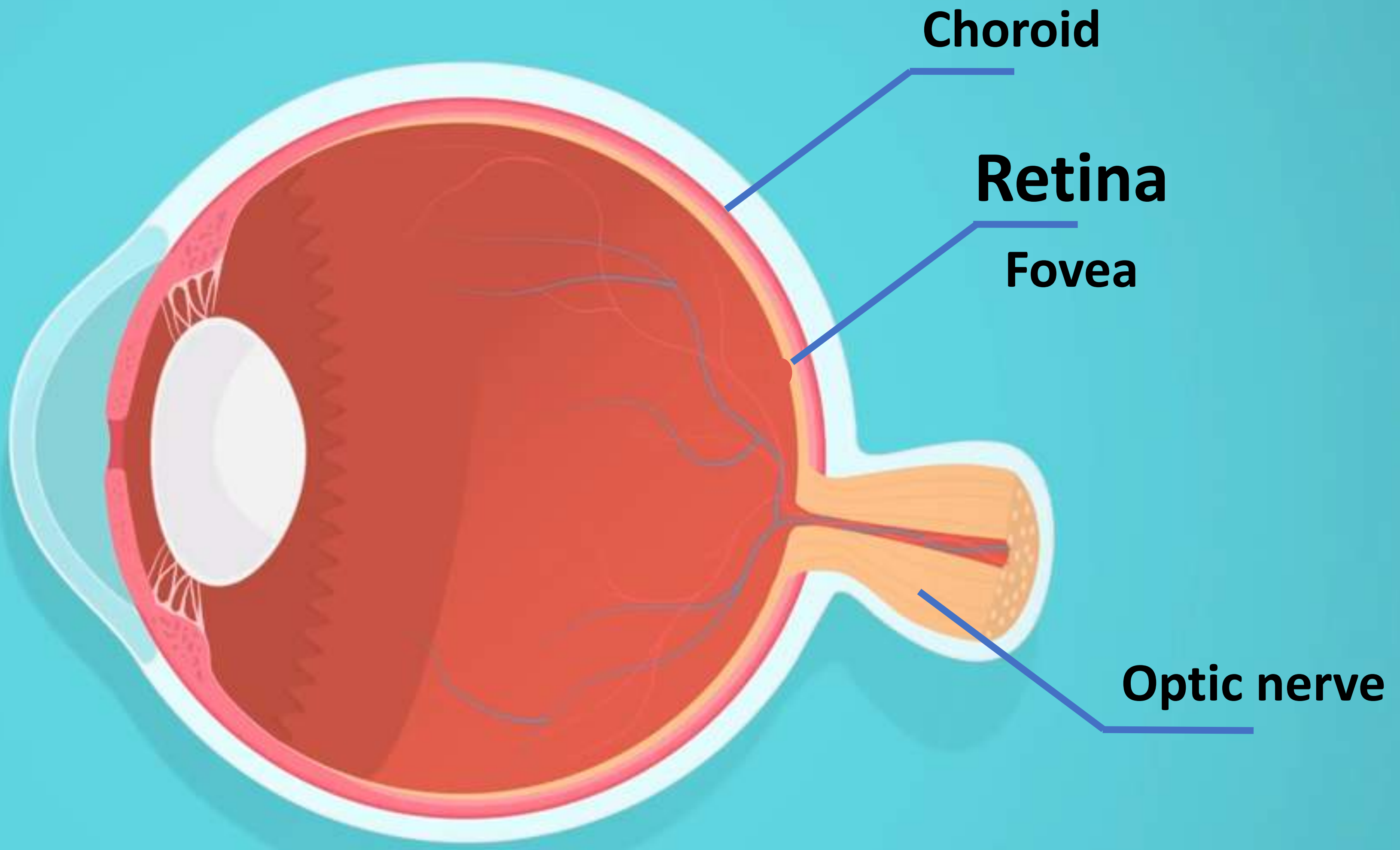


The eye



Anterior chamber

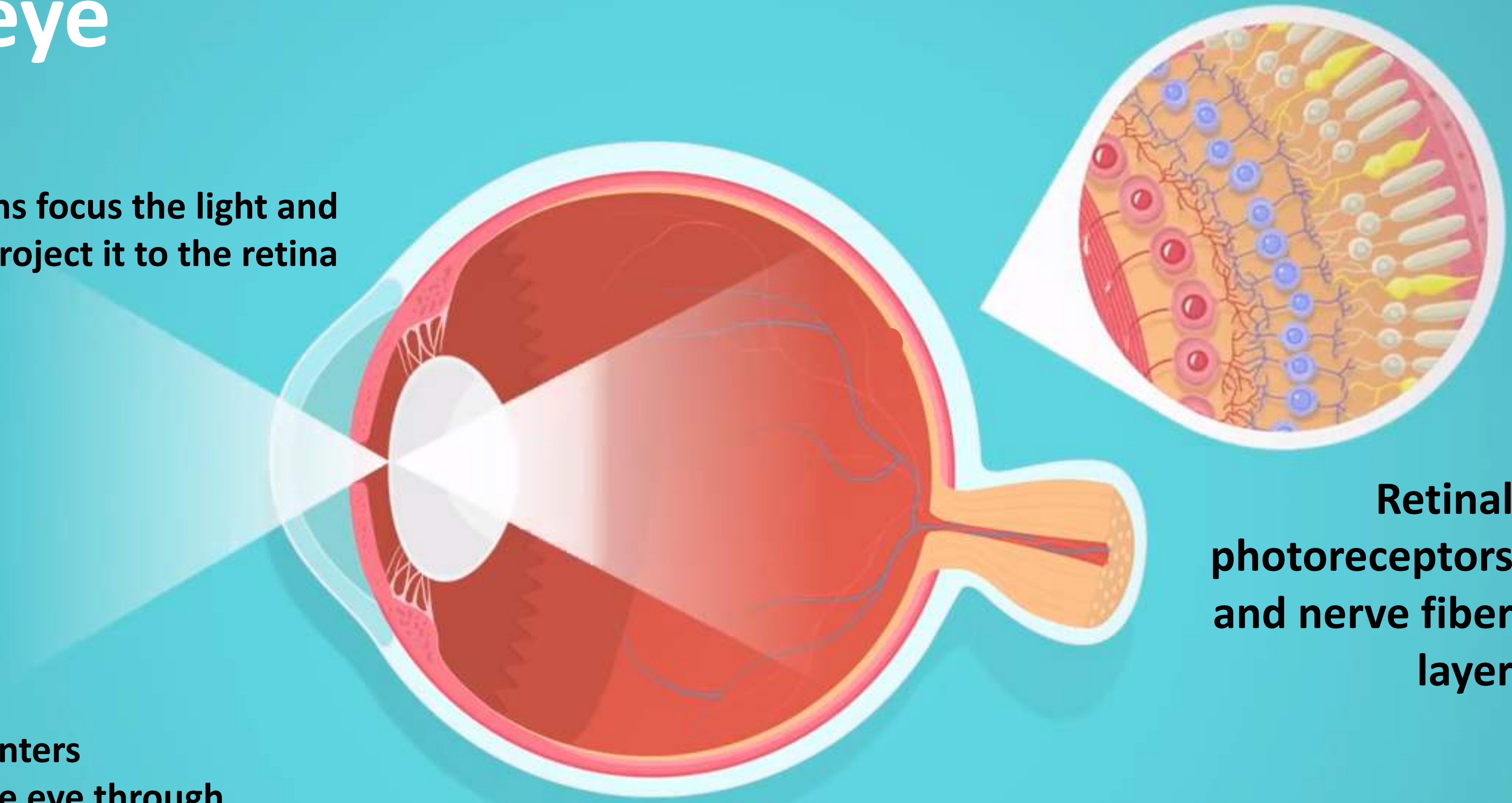
The eye



Posterior chamber

The eye

The lens focus the light and
project it to the retina

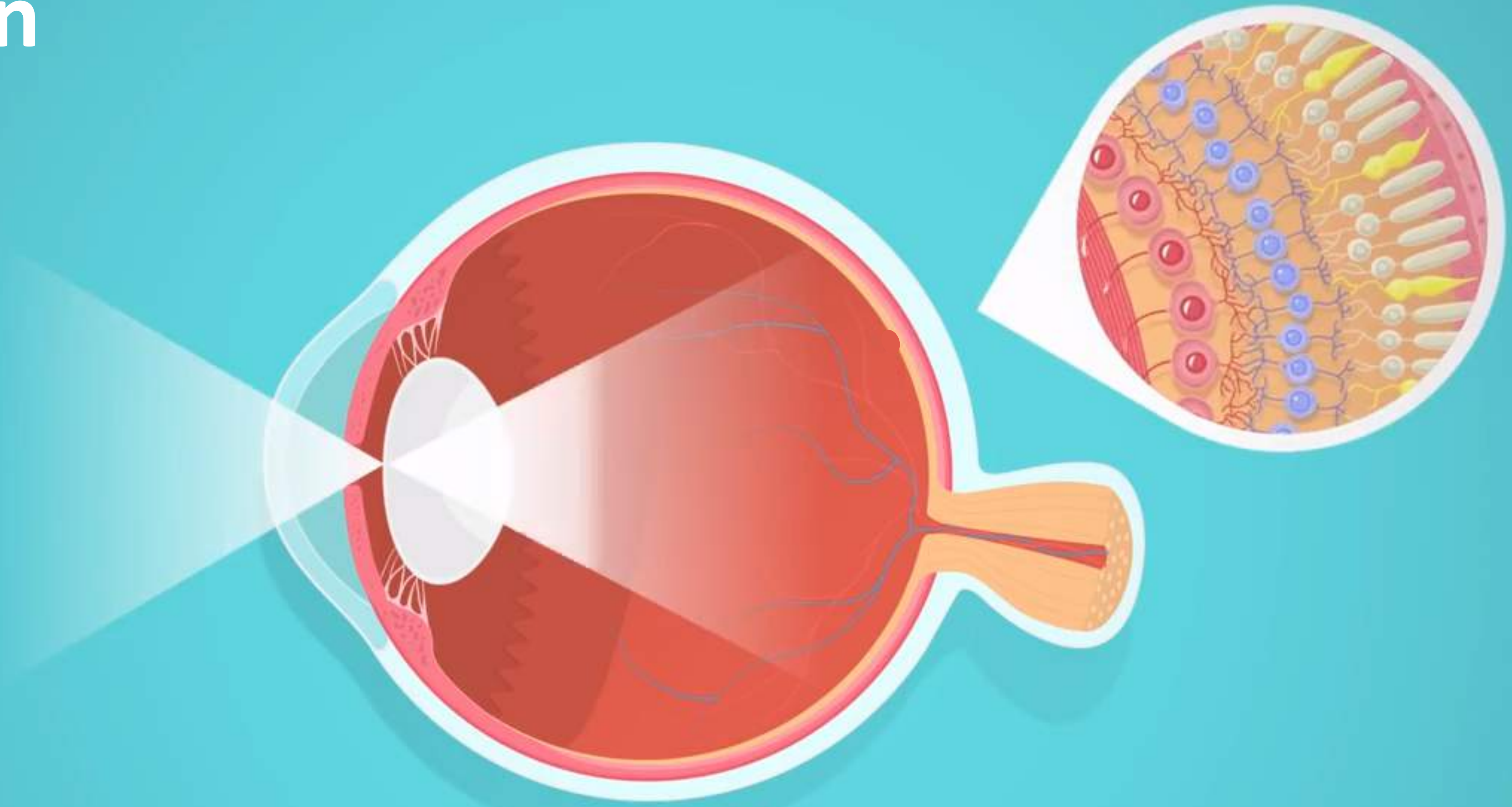


Retinal
photoreceptors
and nerve fiber
layer

Light enters
into the eye through
the cornea and the pupil

The retina

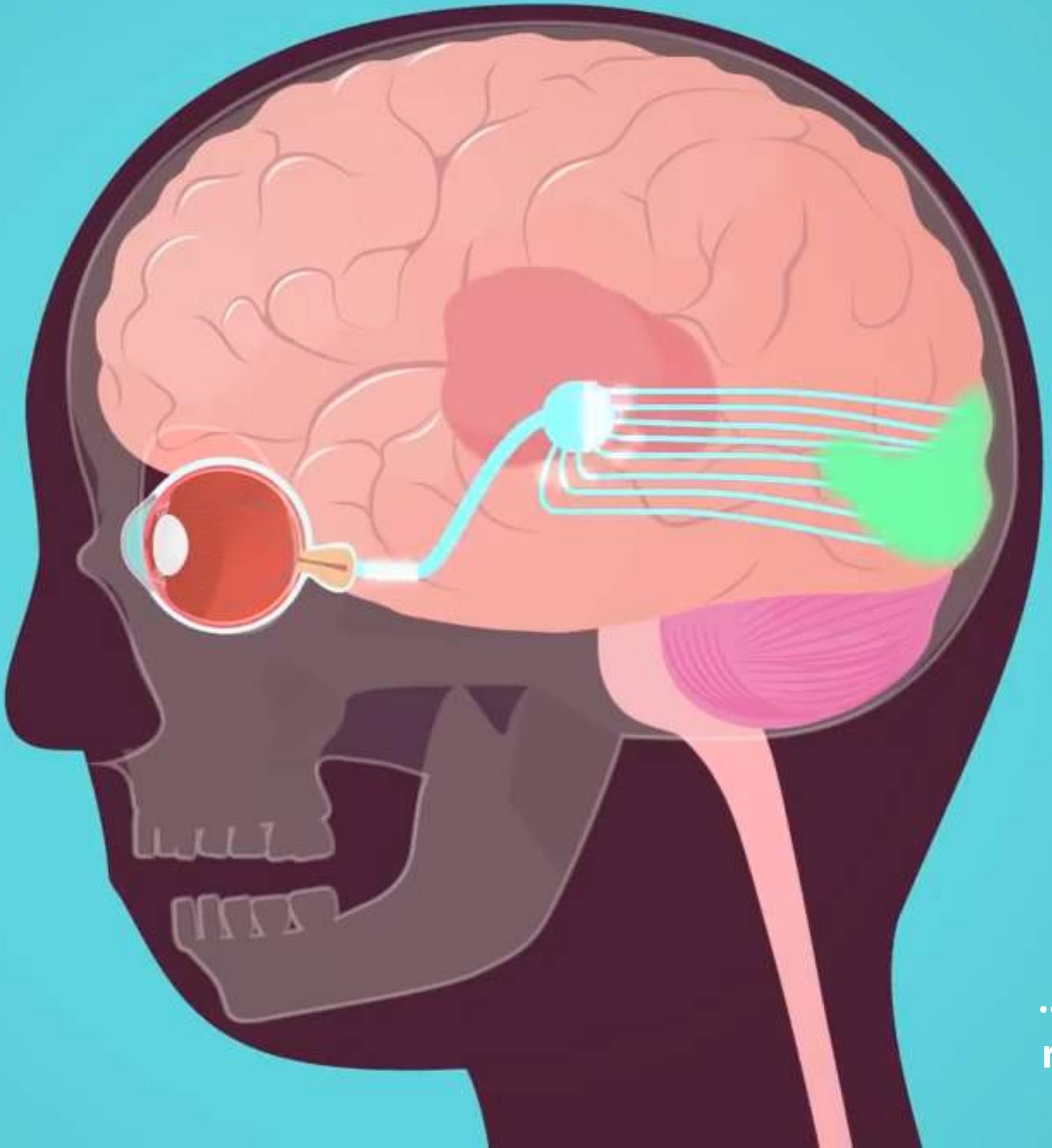
Vision



The neural cells transfer electrical signals through the optic nerve to the brain

Vision

The signals are processed in the brain…



… where the images are rotated and interpreted

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Ophthalmic Imaging

Requires microscopy + imaging technique

Non invasive

Transparency of tissues

- Fundus photography
- Optical Coherence Tomography (OCT)
- OCT-Angiography (OCT-A)

Slit lamp examination
Direct ophthalmology

Ultrasound

Fundus autofluorescence
Scanning Laser Ophthalmocopy

Invasive

Functional behavior

- Dye-based fundus angiography
  - Fluorescein angiography (FA)
  - Indocyanine green angiography (ICGA)

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Invasive
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Fundus photography

2D photography of the inner surface of the eye

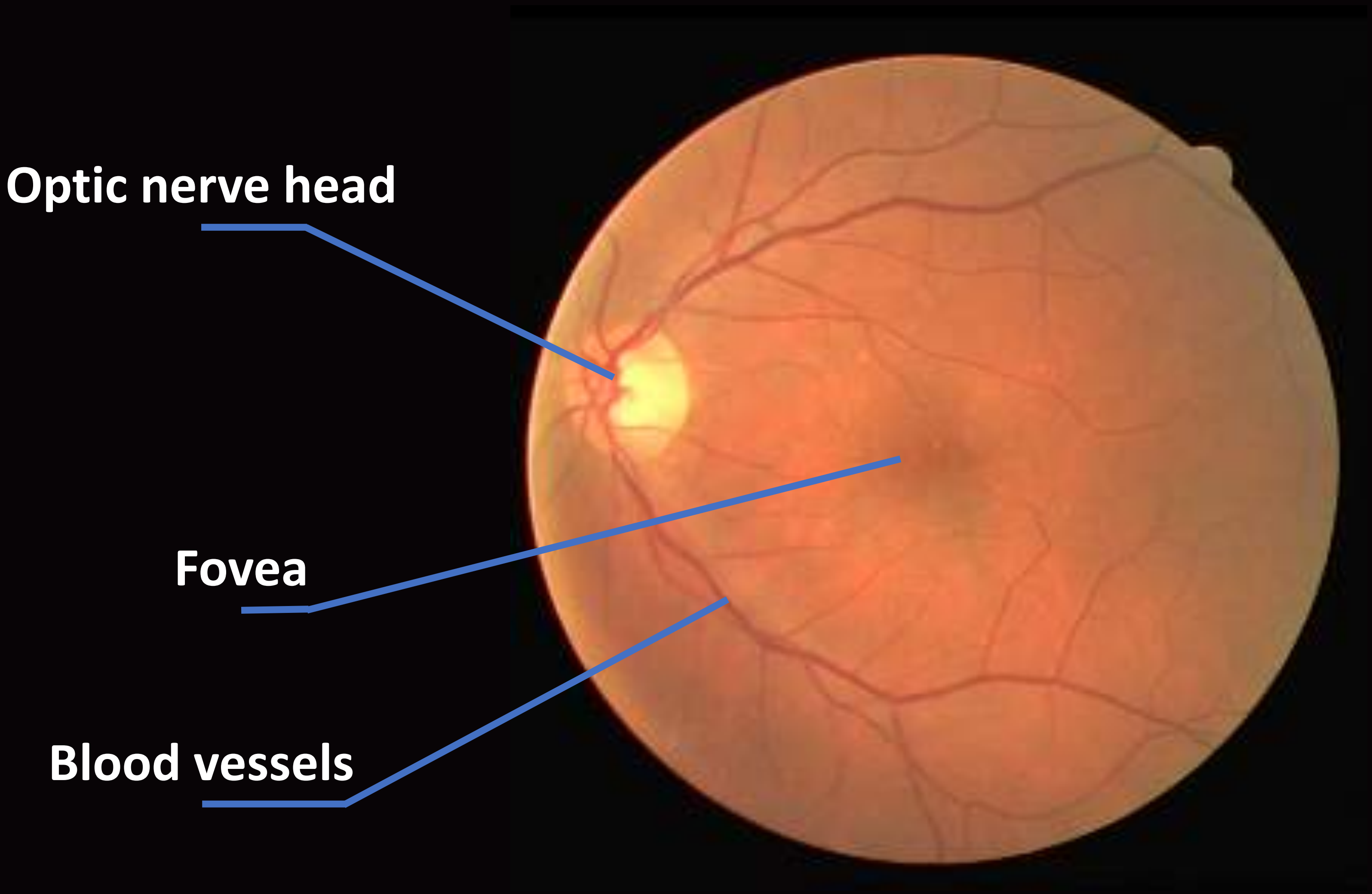
Non-invasive (photograph), fast (seconds), easy and cheap (even with a smartphone!)

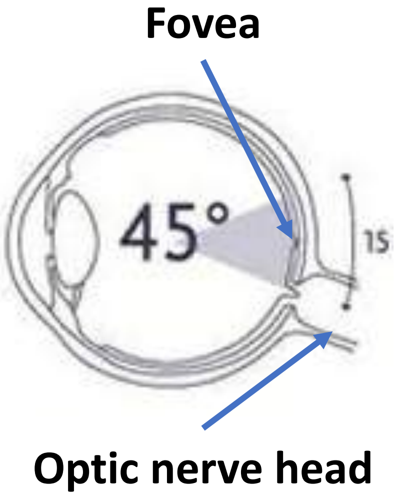
Fundus camera

Standard digital camera
+
Low power microscope

Field of view between 30º and 50º

Fundus photograph





Optical Coherence Tomography

3D imaging technique, close-to microscopy resolution

Non-invasive (no ionizing radiation, just light!), fast (seconds), easy, “cheap” (30k €)

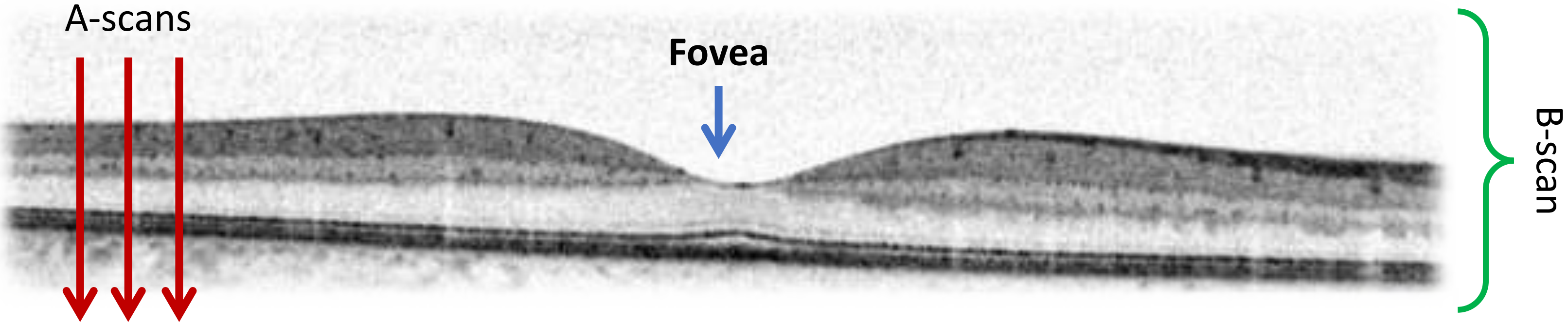
OCT scanner

Based on low coherence interferometry

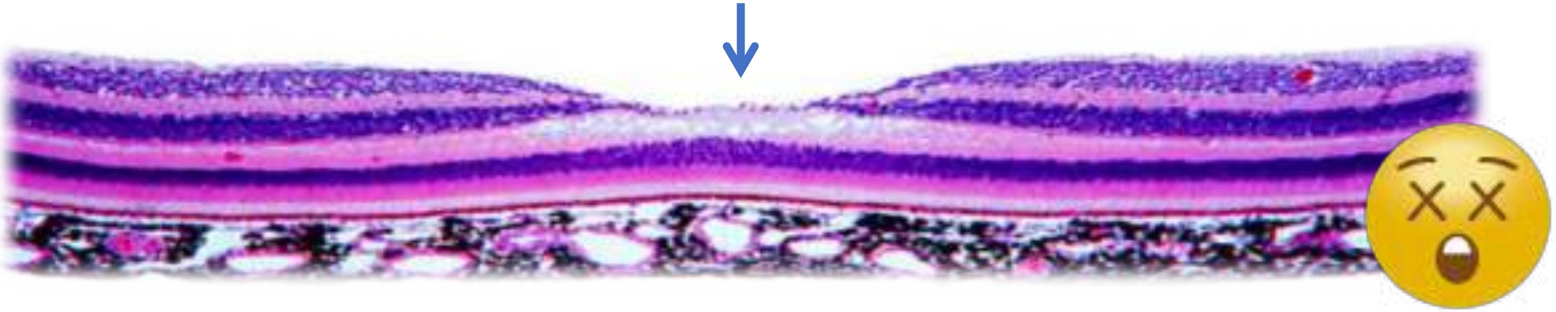
Close to microscopy resolution

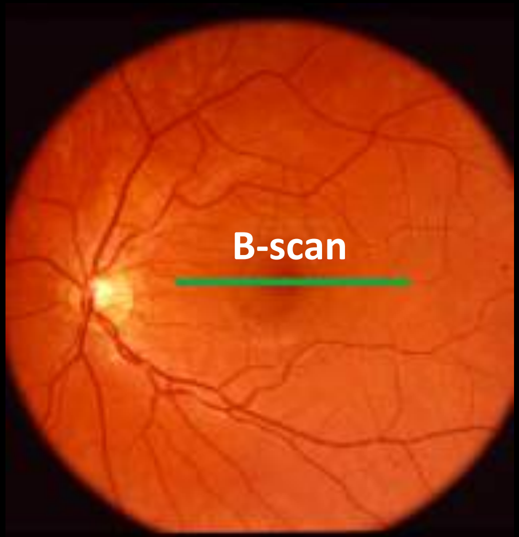
OCT scan

OCT scan (Spectralis)



Histology

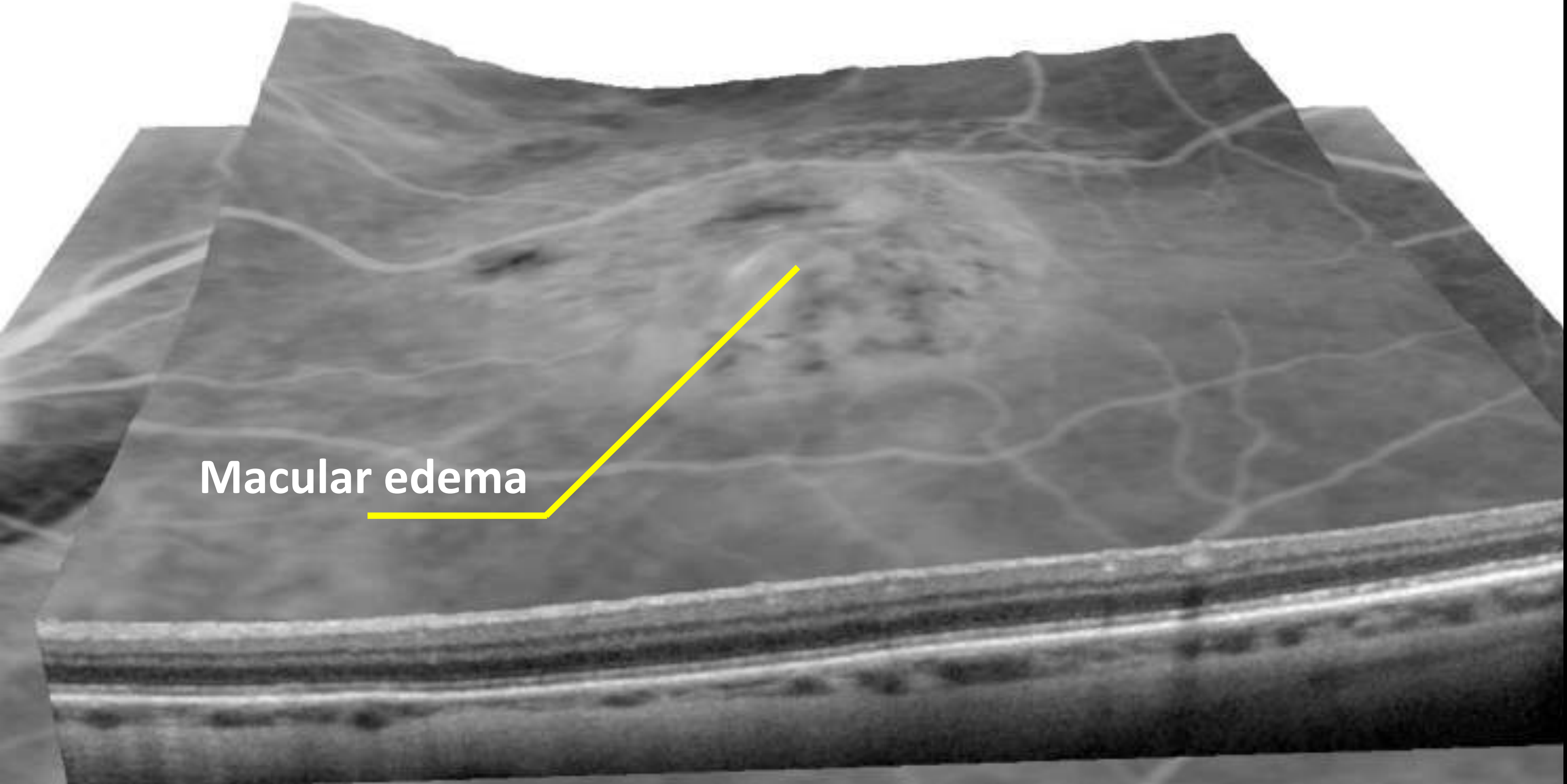


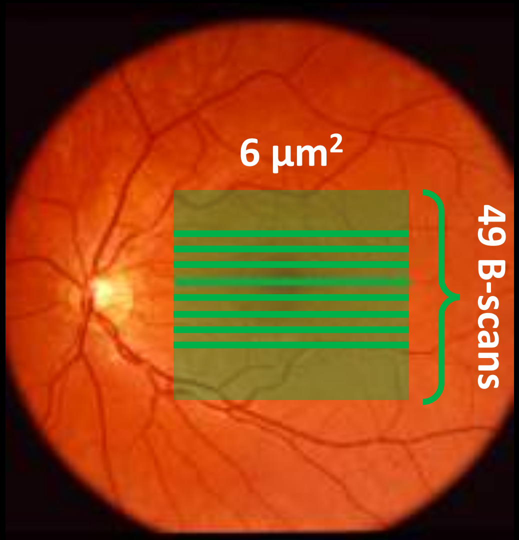


Fundus photograph

OCT scan

OCT scan (Spectralis)





Fundus photograph

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Use cases of machine/deep learning

Concluding remarks?

World Health Organization

285 million people

suffering from visual disorders

BLINDNESS

39 million people

VISUAL IMPAIRMENT

246 million people

World Health Organization

Diabetic retinopathy

Due to the increased prevalence of diabetes

Glaucoma

Difficulties in its early diagnosis

Age-related macular degeneration

Main cause of visual deficiency in industrialized countries

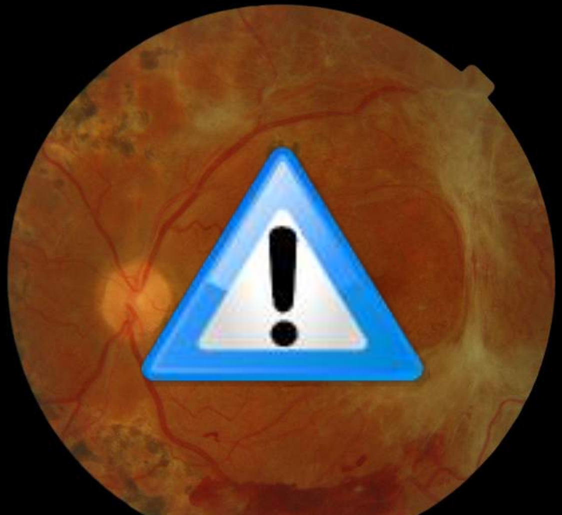
Diabetic retinopathy (DR)

Most common cause of blindness in working age population

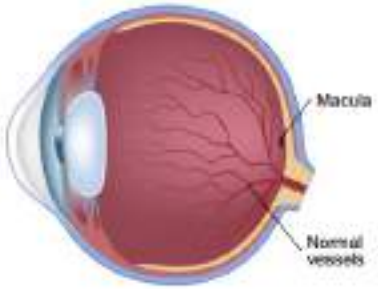
Asymptomatic in its early stages, treatments are less effective when advanced

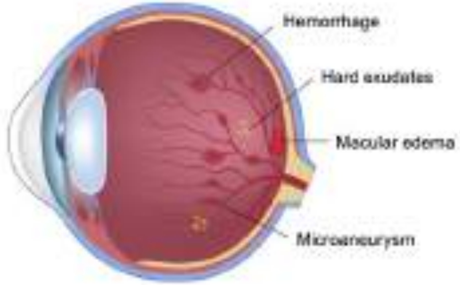
Healthy retina

Non-proliferative DR



Proliferative DR / DME





Diabetic retinopathy (DR)

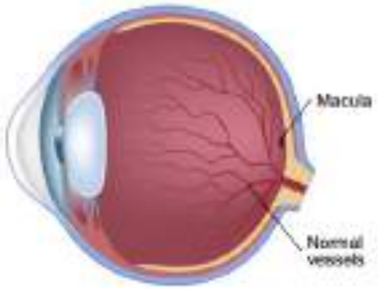
Most common cause of blindness in working age population

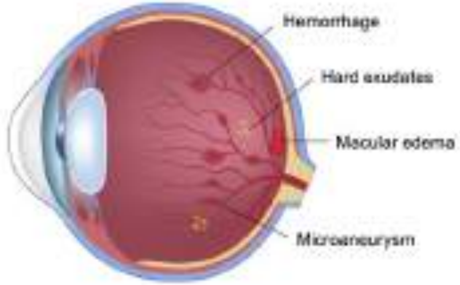
Asymptomatic in its early stages, treatments are less effective when advanced

Healthy retina

Non-proliferative DR

Diabetic Macular Edema





Diabetic retinopathy (DR)

Proliferative Diabetic Retinopathy (PDR)

↓

Vascular proliferation

Preretinal hemorrhage

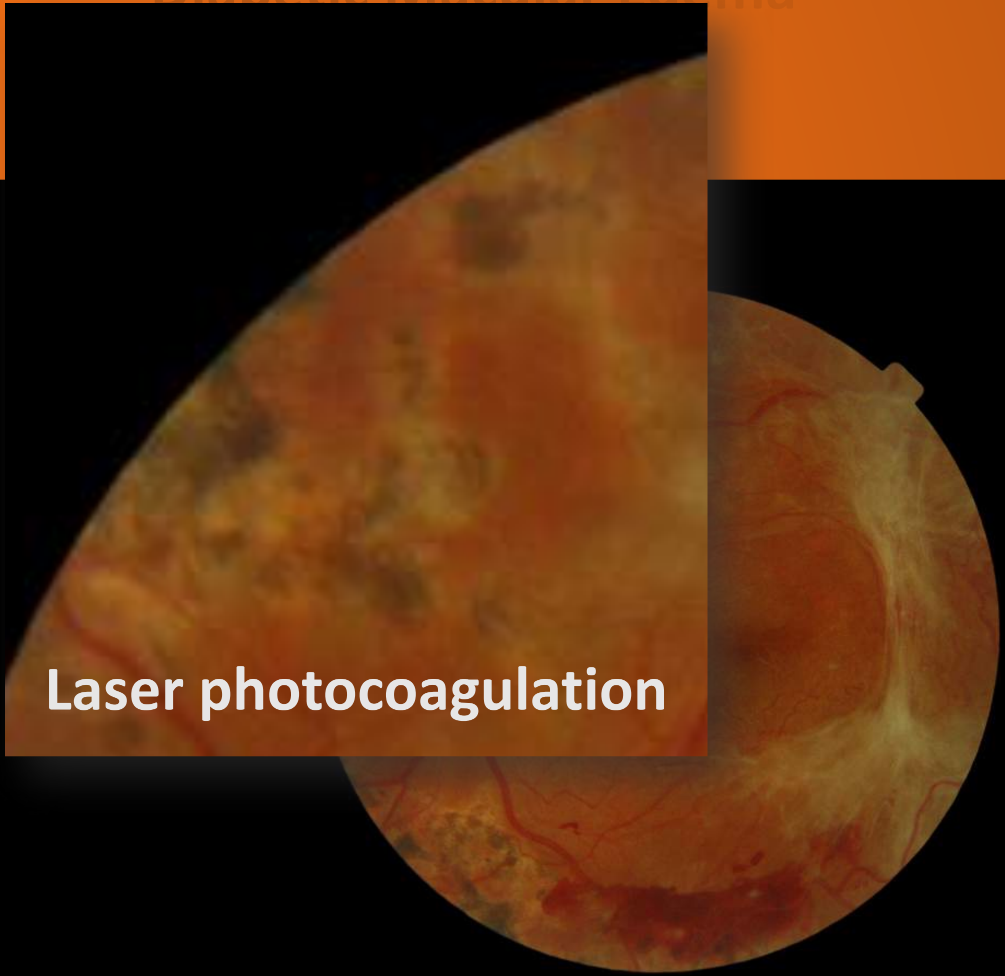
Vitreous hemorrhage

Retinal detachment

↓

Blindness

Diabetic Macular Edema



Diabetic retinopathy (DR)

Proliferative Diabetic Retinopathy (PDR)

macular area

Diabetic Macular Edema (DME)

↓

Capillary loss

Ischemia

Lipid/fluid exudation

Functional loss

↓

Blindness

Diabetic retinopathy

Use cases of machine/deep learning

Early screening

Qualitative feedback

Urgent cases

Segmentation
Blood vessels

Object detection
Red lesions (MA / HE)

Image classification
Early / mild DR

Segmentation
Blood vessels

Image classification
Proliferative DR

Use cases of machine/deep learning in DR

Blood vessel segmentation

Healthy retina

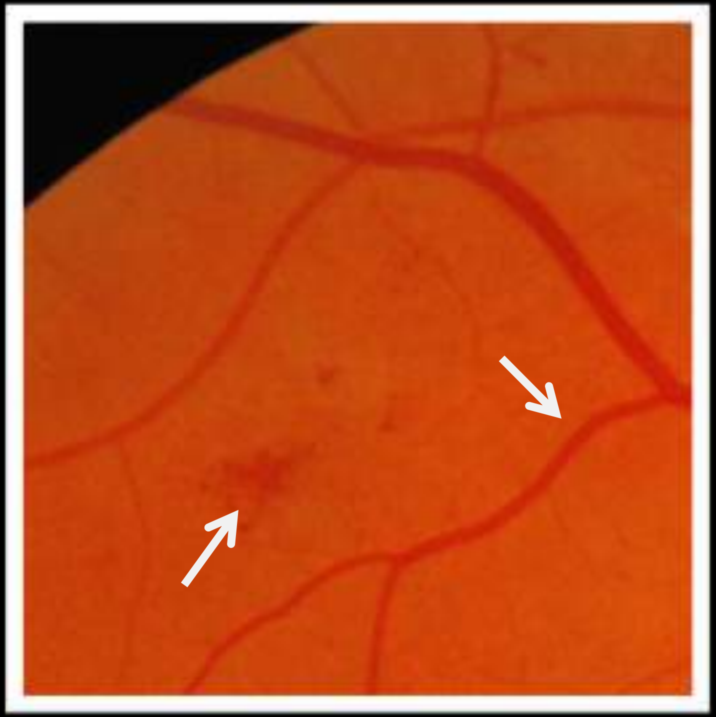
Non-proliferative DR

Proliferative DR

Use cases of machine/deep learning in DR

Blood vessel segmentation

Healthy retina



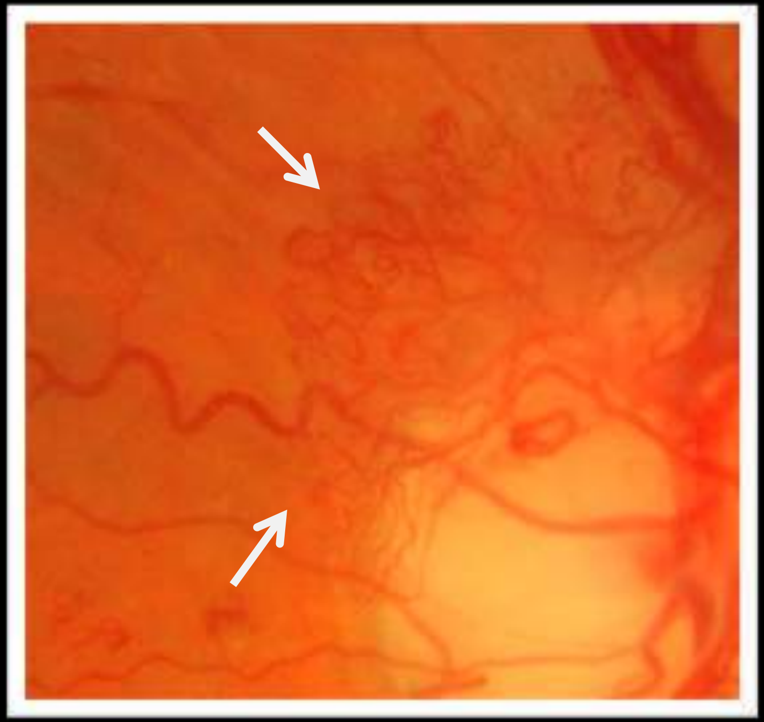
Similar intensities to red lesions

Proliferative DR

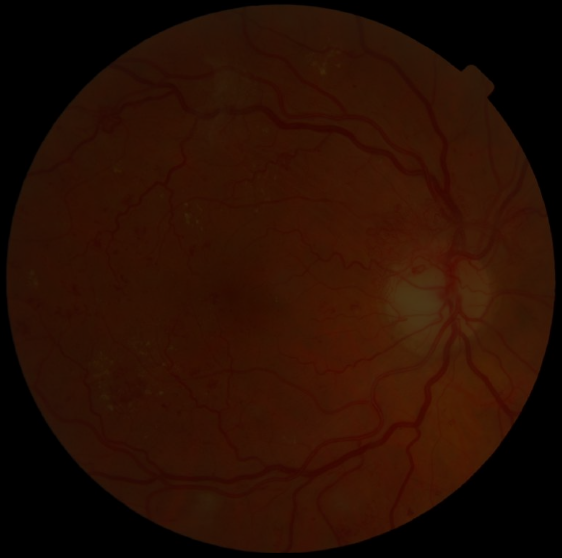
Use cases of machine/deep learning in DR

Blood vessel segmentation

Healthy retina



Neovascularizations

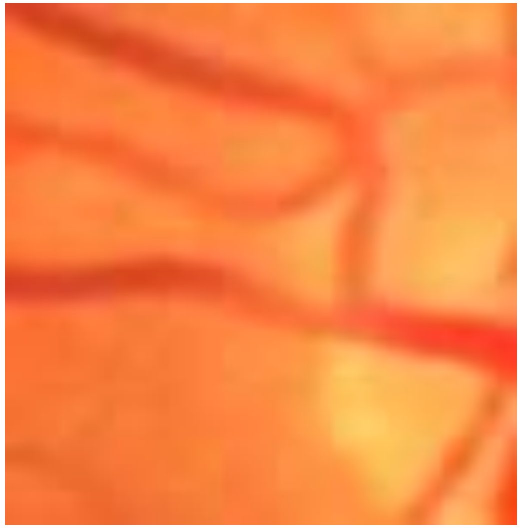


Proliferative DR

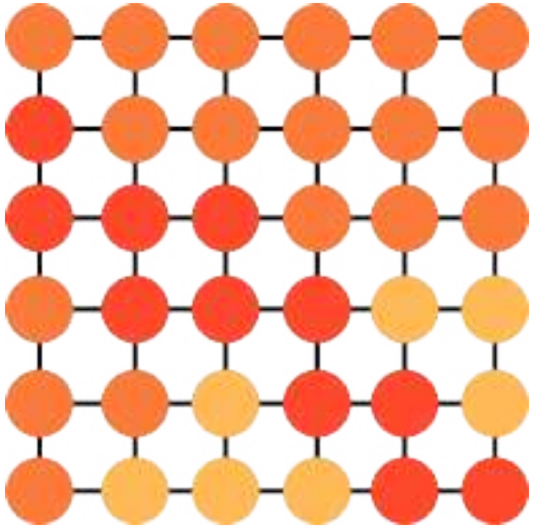
Use cases of machine/deep learning in DR

Blood vessel segmentation

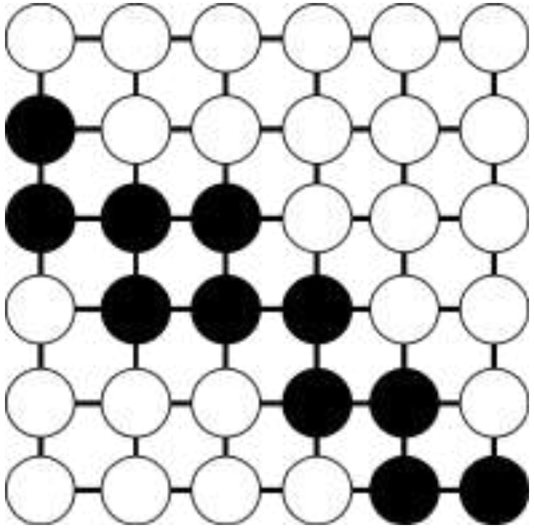
Image I



$E(\mathbf{y}|I)$



Segmentation $\mathbf{y}^*$



$$\mathcal{G} = < \underbrace{\mathcal{V}}_{\text{image pixels}}, \underbrace{\mathcal{E}}_{\text{connectivity rule}} >$$

Use cases of machine/deep learning in DR

Blood vessel segmentation

$$\mathbf{y}^* = \arg\min_{\mathbf{y}\in\mathcal{L}} E(\mathbf{y}|I)$$

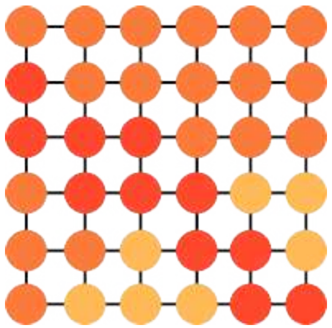
$$E(\mathbf{y}) = \underbrace{\sum_i \psi_u(y_i, \mathbf{x}_i)}_{} + \underbrace{\sum_{(i,j)\in\mathcal{C}_\mathcal{G}} \psi_p(y_i, y_j, \mathbf{f}_i, \mathbf{f}_j)}_{}$$

Unary potentials

Log-likelihood over the labels assignment (classifier based on image features)

Pairwise potentials

Based on interaction between neighbour pixels (according to connectivity rule)



$E(\mathbf{y}|I)$

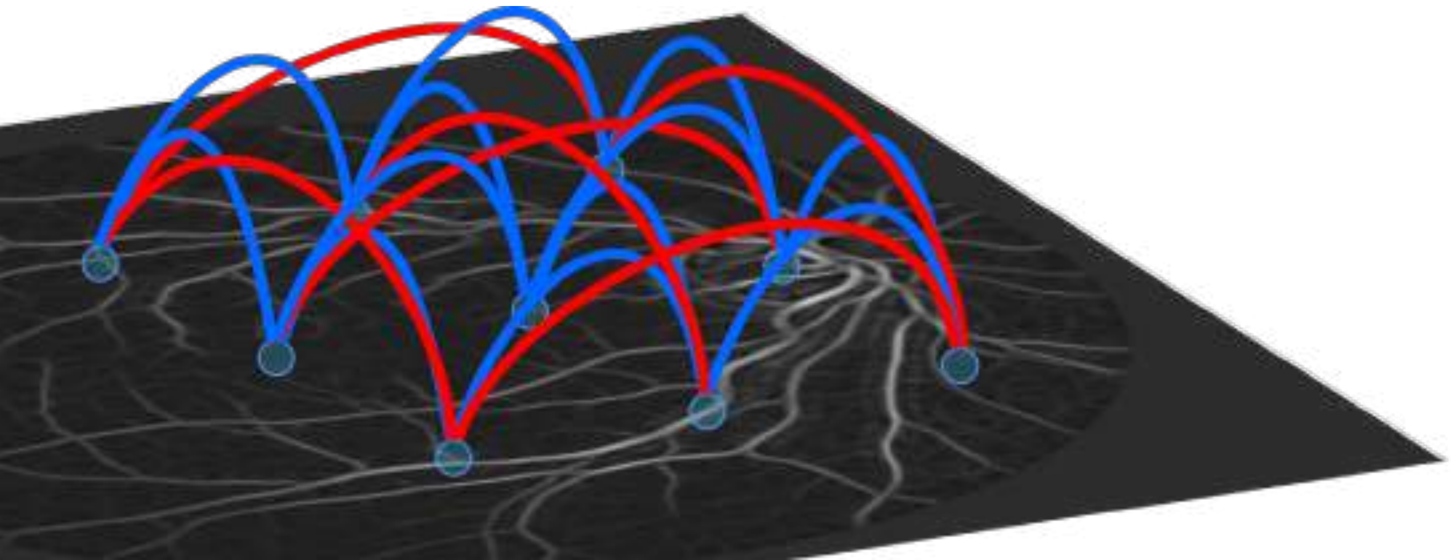
Blood vessel segmentation

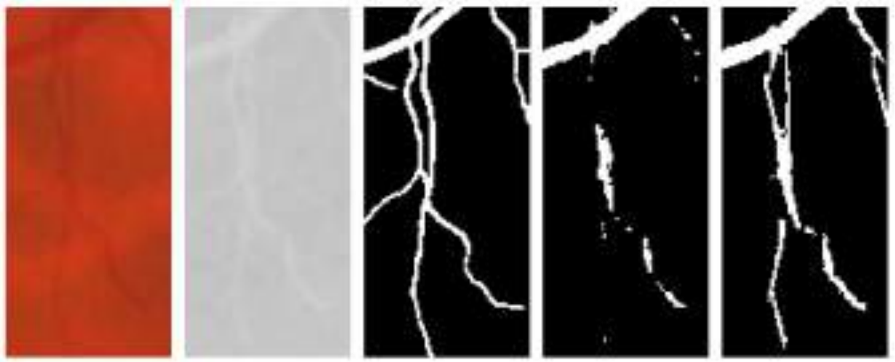
Fully connected Conditional Random Fields (FC-CRFs)

Long range interactions help to better identify thin, elongated structures

Discriminative training based on Structured Output Support Vector Machines (SOSVM)

Structured output learning allows to train FC-CRFs weights for the unary and pairwise potentials



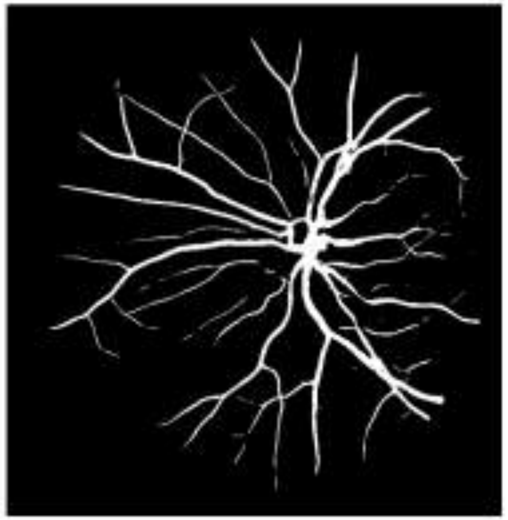


Orlando J.I. & Blaschko M. (2014). *MICCAI*
Orlando J.I. et al. (2017). *IEEE TBME*

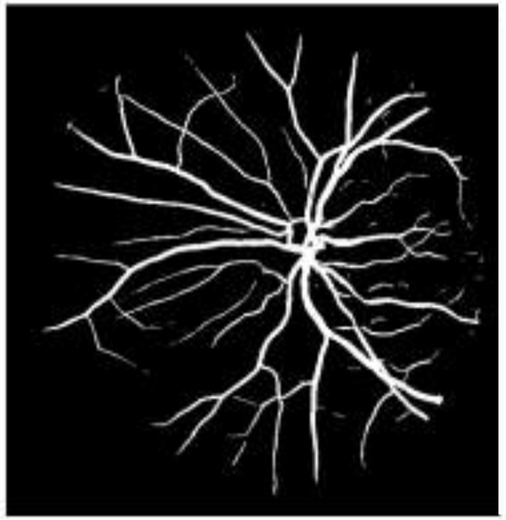
Blood vessel segmentation

Pairwise potentials improve results both qualitatively and quantitatively

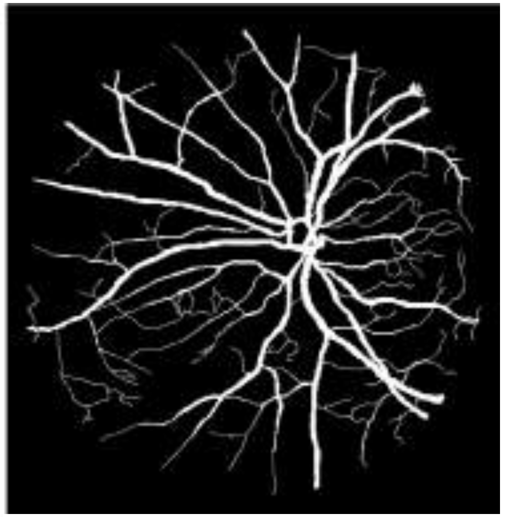
Original image



Unary potentials



FC-CRF



Ground truth

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Use cases of machine/deep learning in DR

Blood vessel segmentation

Pairwise potentials improve results both qualitatively and quantitatively

Unary potentials ***FC-CRF***

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Blood vessel segmentation

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Original image

Unary potentials

FC-CRF

Ground truth

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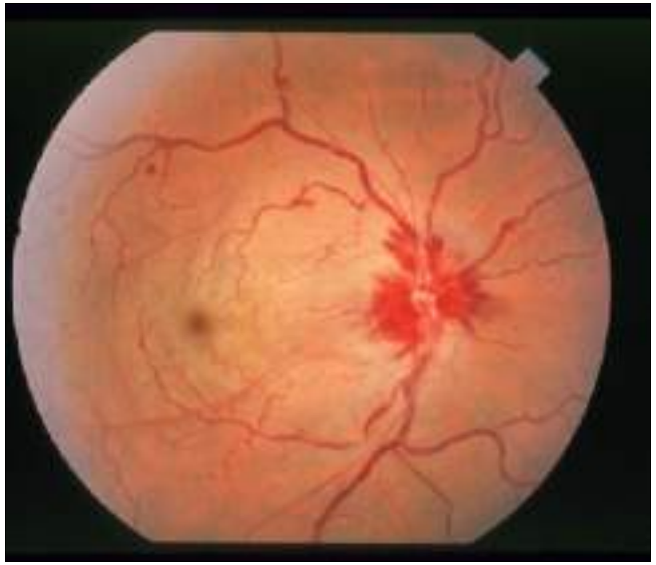
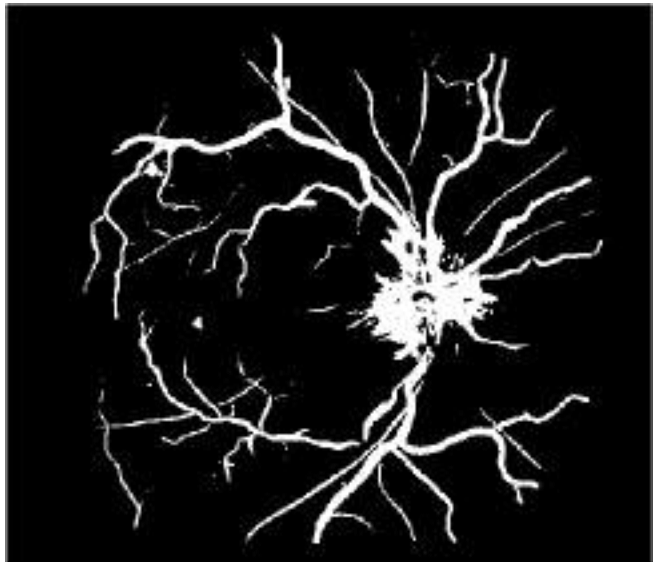
Use cases of machine/deep learning in DR

Blood vessel segmentation

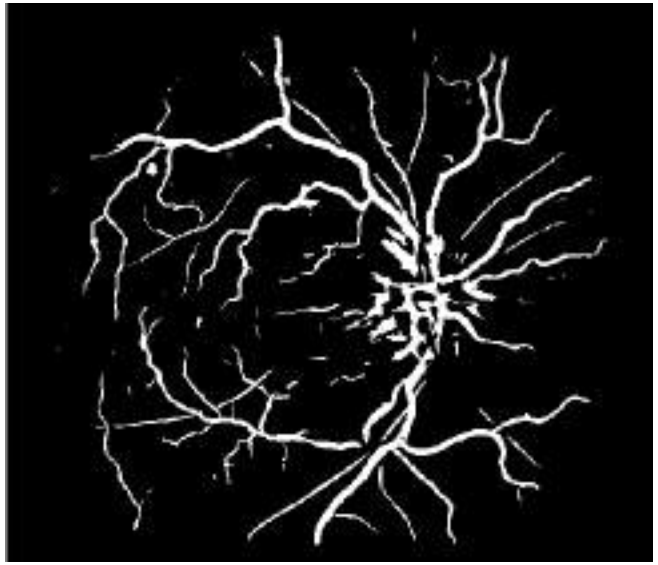
Pairwise potentials allow to identify vascular segments inside ambiguous regions



Original image



Unary potentials



FC-CRF

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Orlando J.I. et al. (2017). *IEEE TBME*

Use cases of machine/deep learning in DR

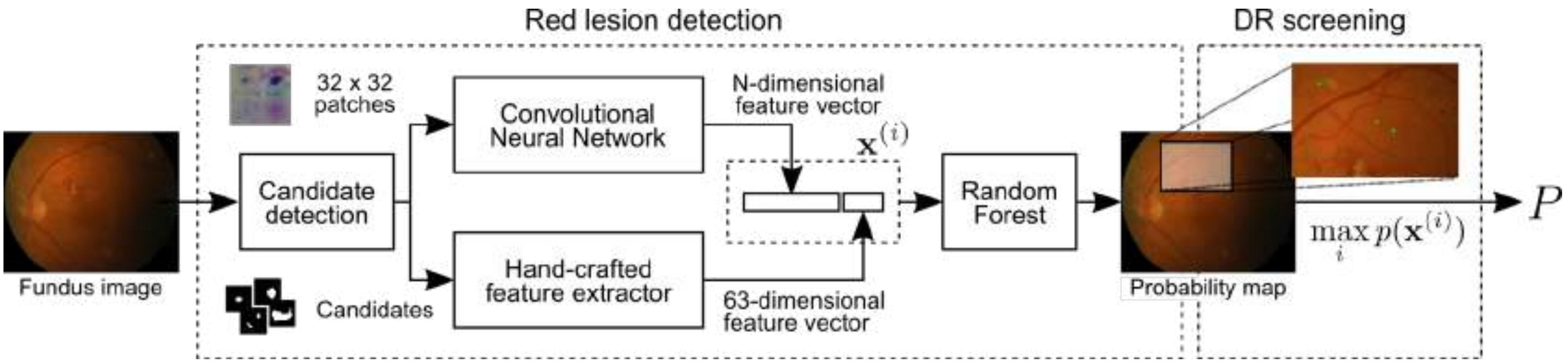
DR screening based on red lesion detection

Earliest signs of DR are subtle and difficult to identify manually

Collecting ground truth data for training DNN is costly and time-consuming

Use cases of machine/deep learning in DR

DR screening based on red lesion detection



Orlando J.I. et al. (2017).
Comput Methods Programs Biomed

Use cases of machine/deep learning in DR

DR screening based on red lesion detection

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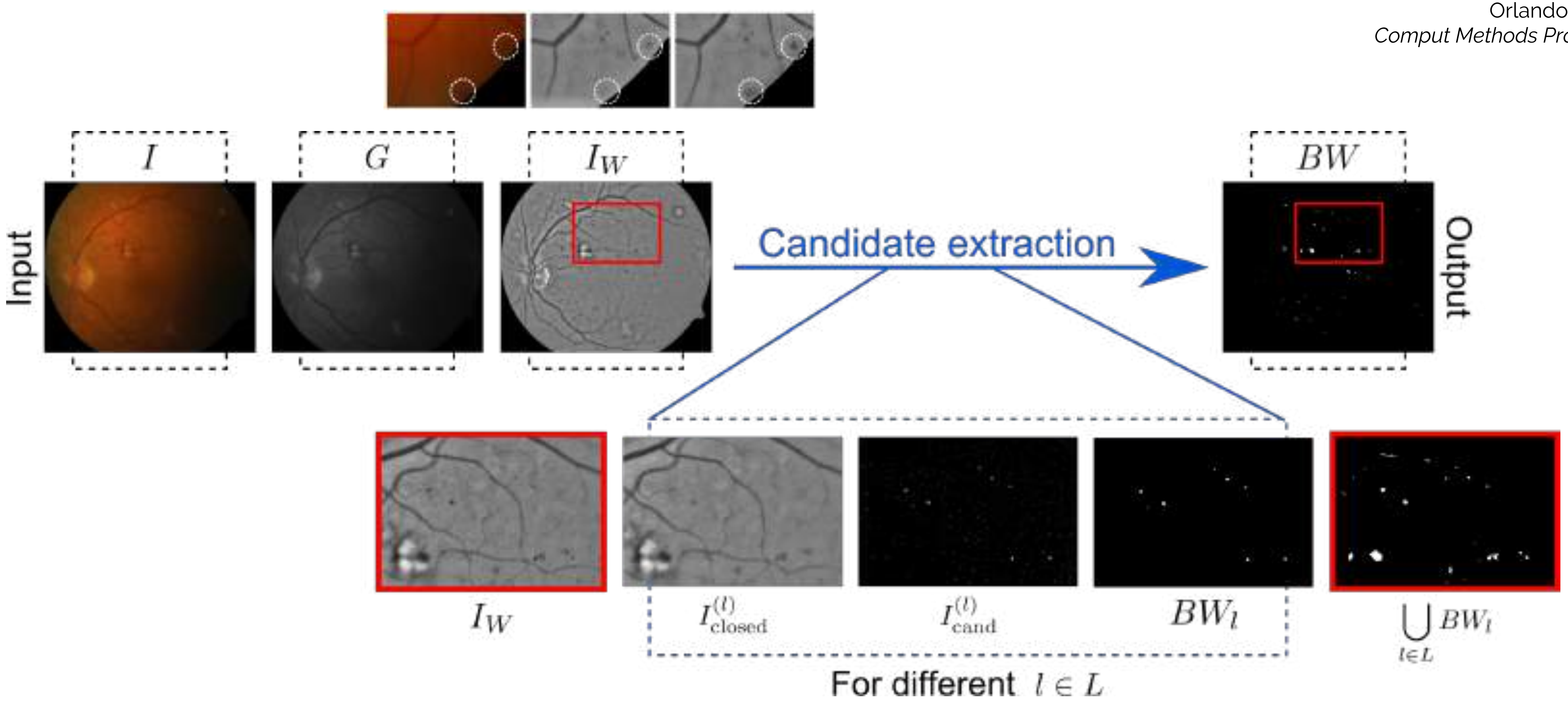


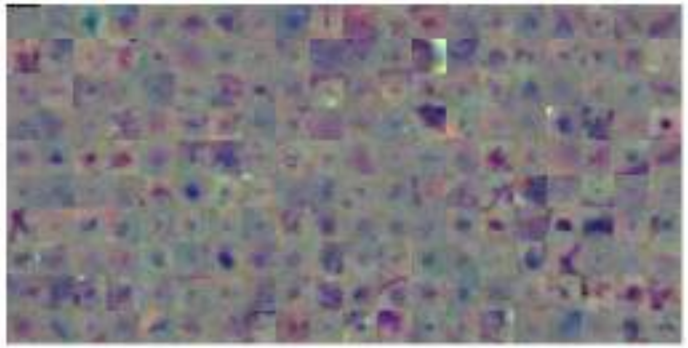
Use cases of machine/deep learning in DR

DR screening based on red lesion detection

Block	Layers	Filter size	Output size
1	conv	$5 \times 5 \times 3$	32
	maxpool	3×3 - stride $= 2$	
	dropout	$p = 0.01$	
2	conv	$5 \times 5 \times 32$	32
	avgpool	3×3 - stride $= 2$	
3	conv	$5 \times 5 \times 32$	64
	avgpool	3×3 - stride $= 2$	
4	conv	$4 \times 4 \times 64$	128
5	fully connected	128	128
6	$\mathcal{L}_\beta(\mathbf{W})$	128	2

$$\mathcal{L}_\beta(\mathbf{W}) = -\beta \sum_{i \in Y_+} \log P(y^{(i)}|X^{(i)};\mathbf{W}) - (1-\beta) \sum_{i \in Y_-} \log P(y^{(i)}|X^{(i)};\mathbf{W}))$$

(a) Non-lesions (false positive candidates)



(b) Lesions (true positive candidates)

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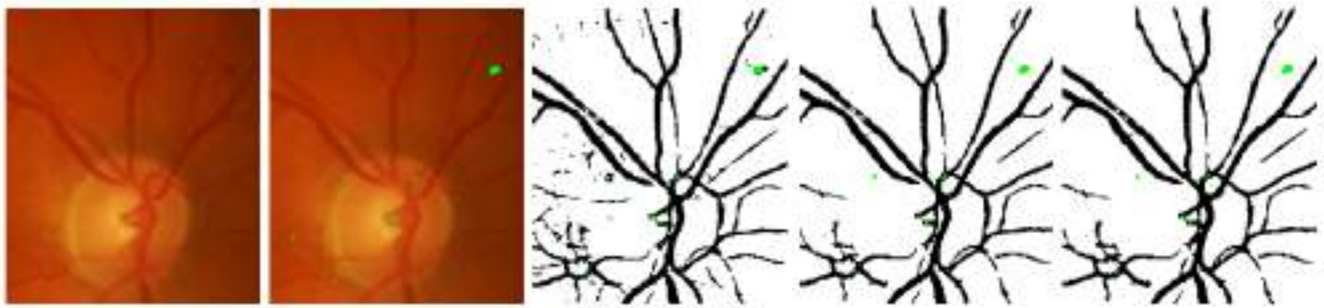
***Feature* based on vessel segmentations**



Intensity based features

Shape features

54-d

9-d

128-d

63-d

CNN features

Hand crafted features

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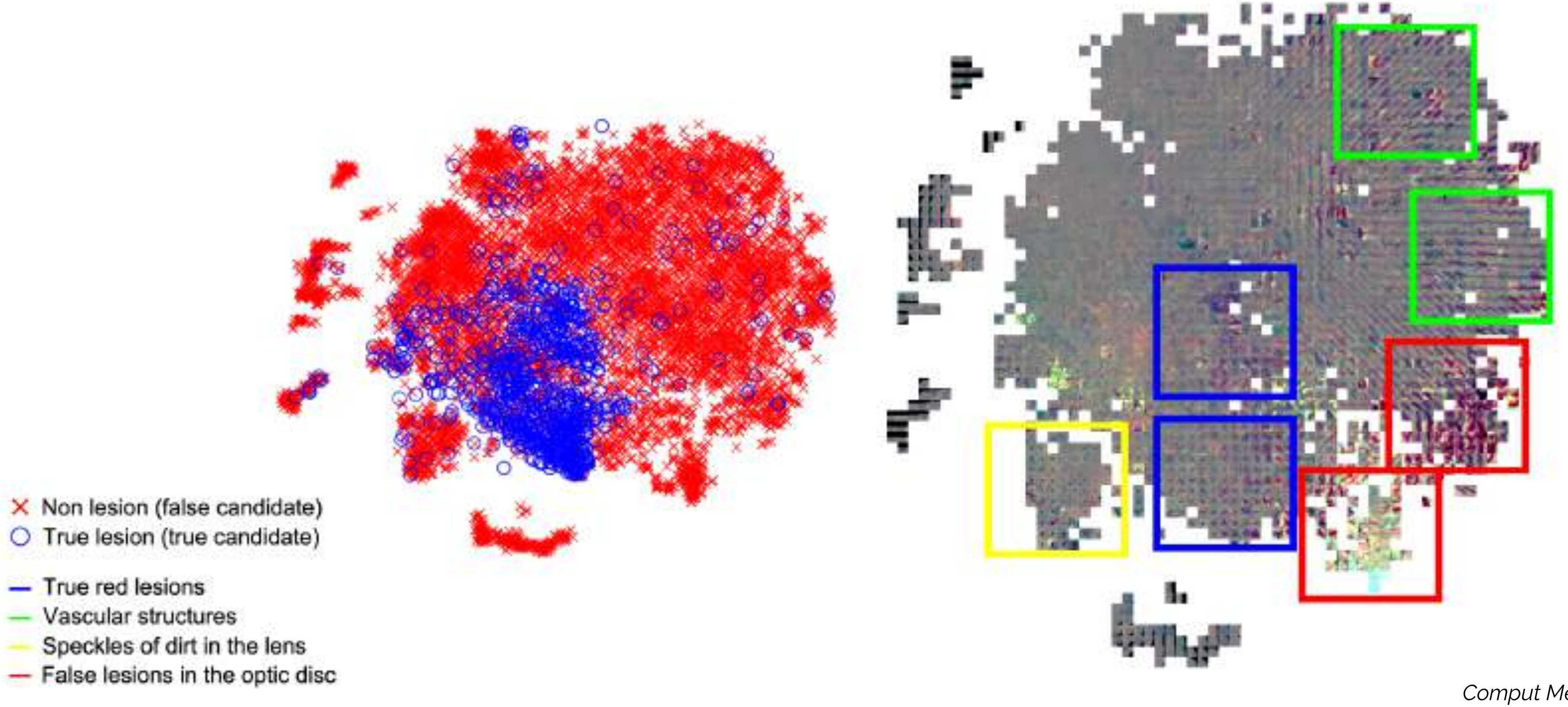

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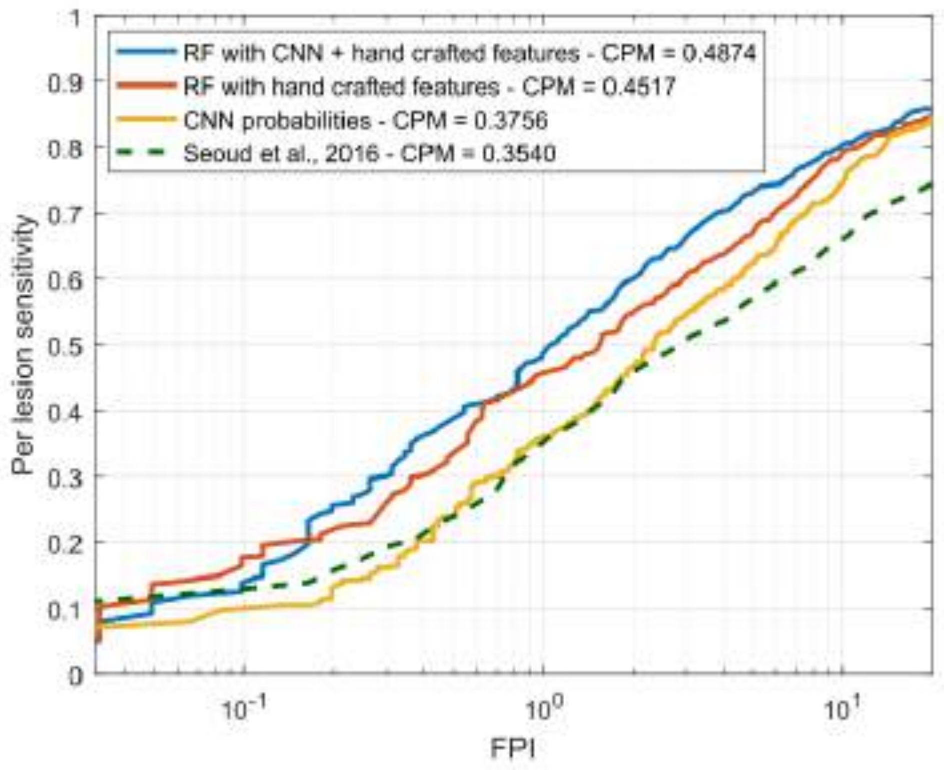
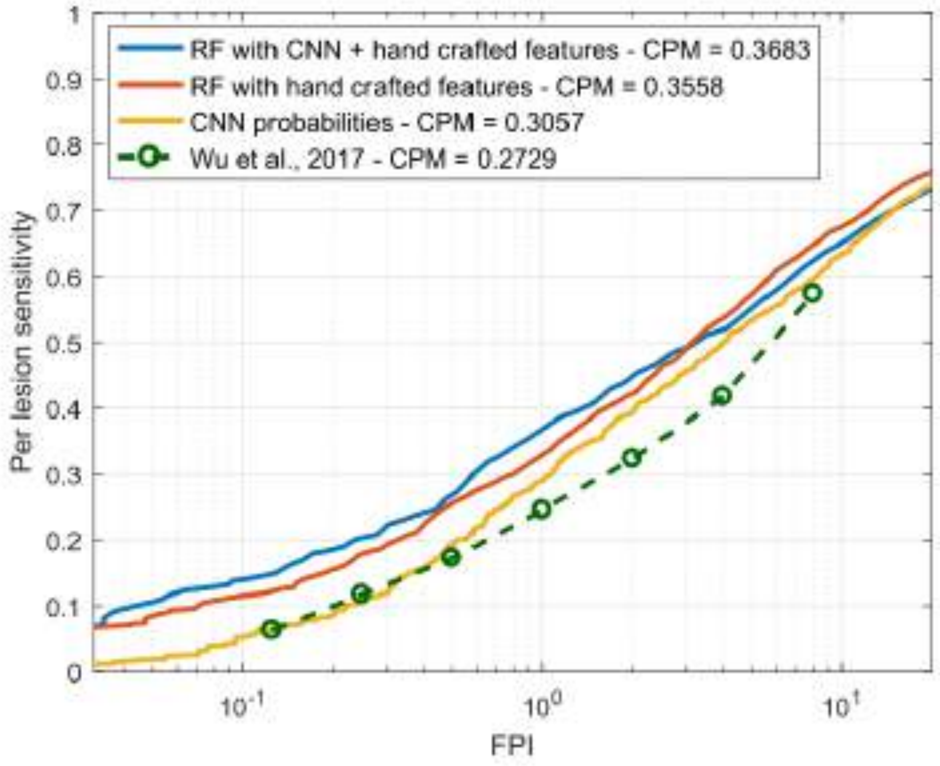
Use cases of machine/deep learning in DR

DR screening based on red lesion detection

DIARETDB1
(61 fundus images)



e-ophtha
(381 fundus images)

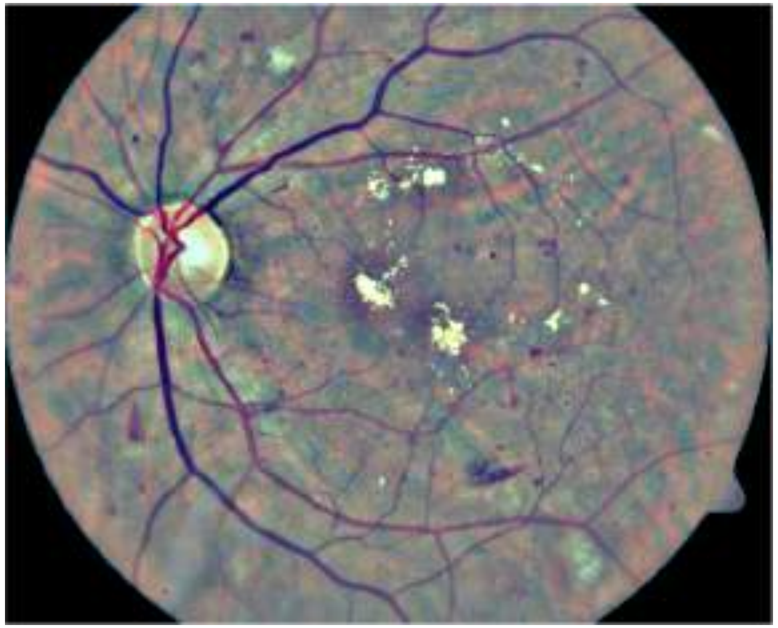


Orlando J.I. et al. (2017).
Comput Methods Programs Biomed

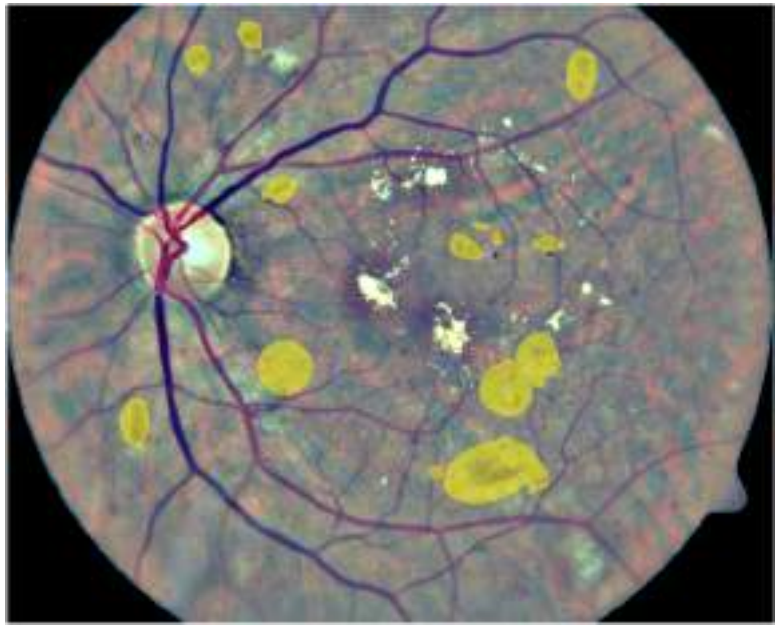
Use cases of machine/deep learning in DR

DR screening based on red lesion detection

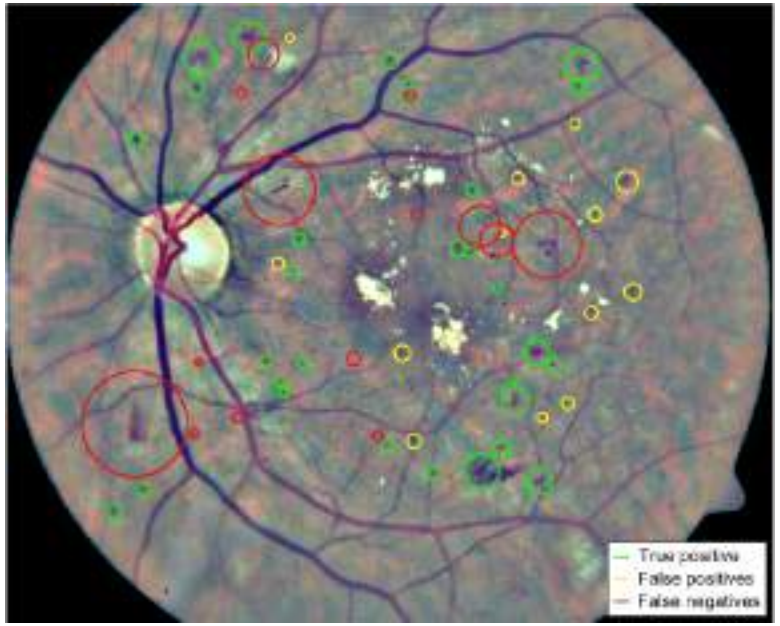
Input image



Ground truth



Prediction

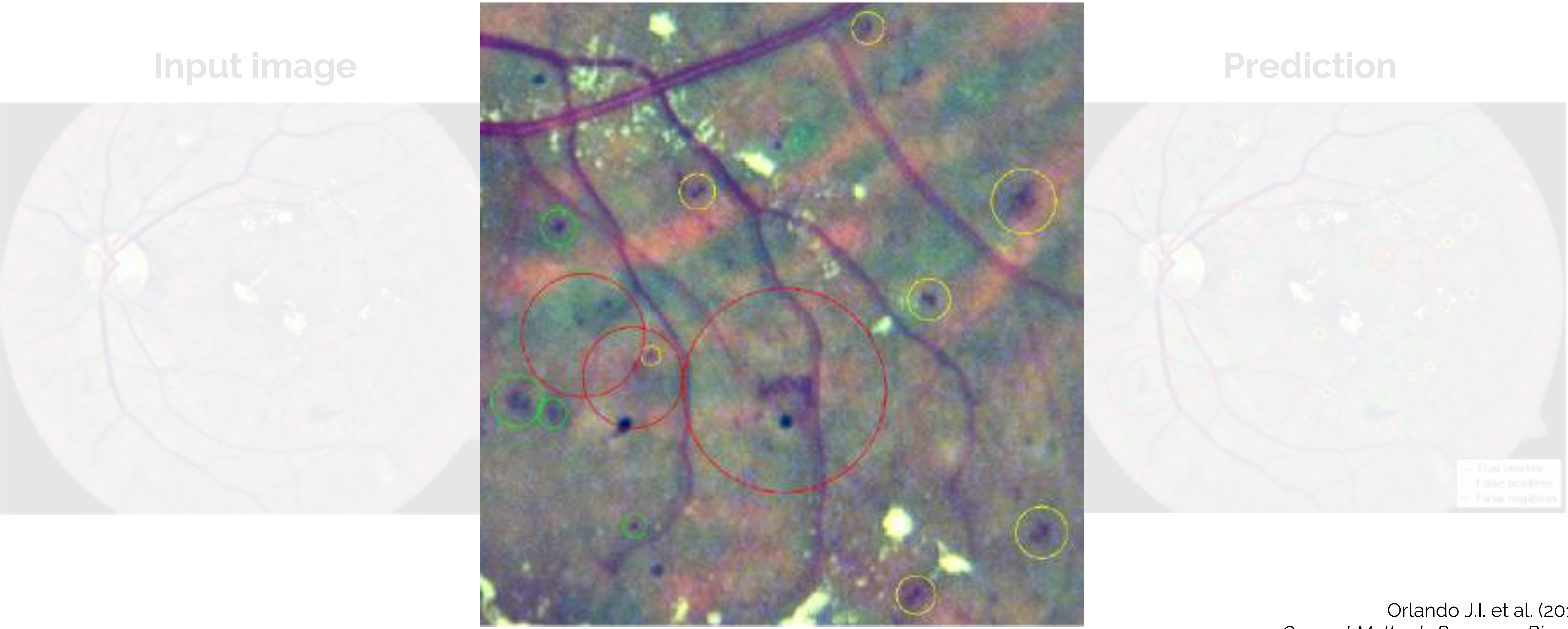


Orlando J.I. et al. (2017).
Comput Methods Programs Biomed

DR screening based on red lesion detection

Input image

Prediction



Orlando J.I. et al. (2017).
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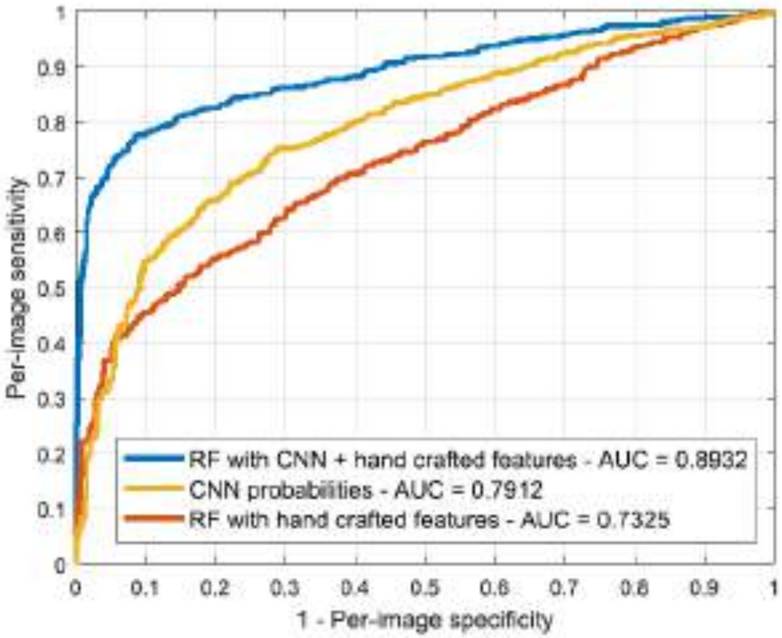
Use cases of machine/deep learning in DR

DR screening based on red lesion detection

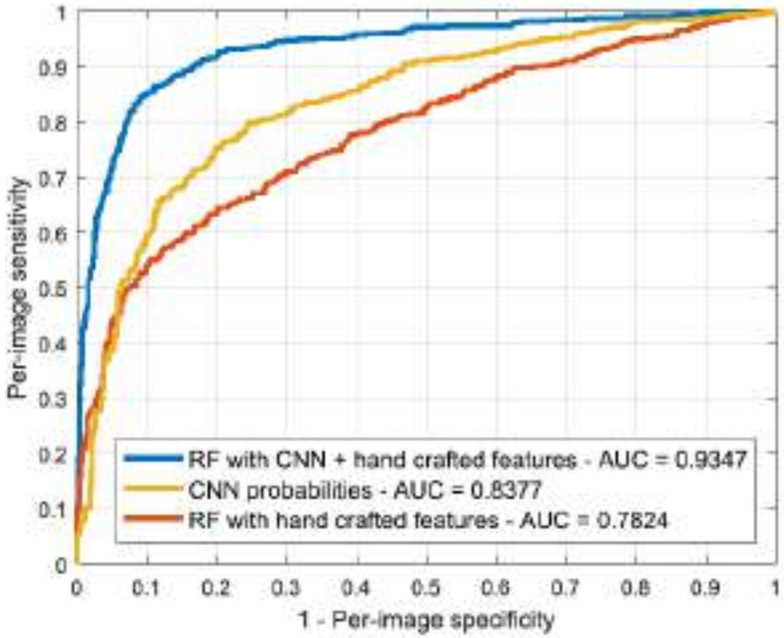
MESSIDOR

(1200 fundus images)

DR screening (R0 vs. R1, R2, R3)



Need to referral detection (R0, R1 vs. R2, R3)



Orlando J.I. et al. (2017).
Comput Methods Programs Biomed

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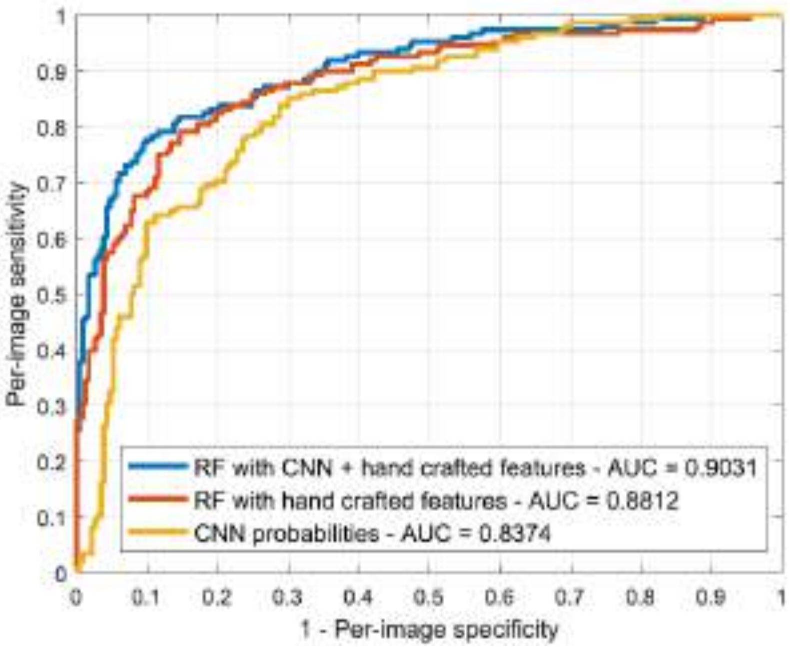
DR screening based on red lesion detection

e-ophtha
(381 fundus images)

DR screening (R0 vs. R1, R2, R3)



Orlando J.I. et al. (2017).
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Use cases of machine/deep learning in DR

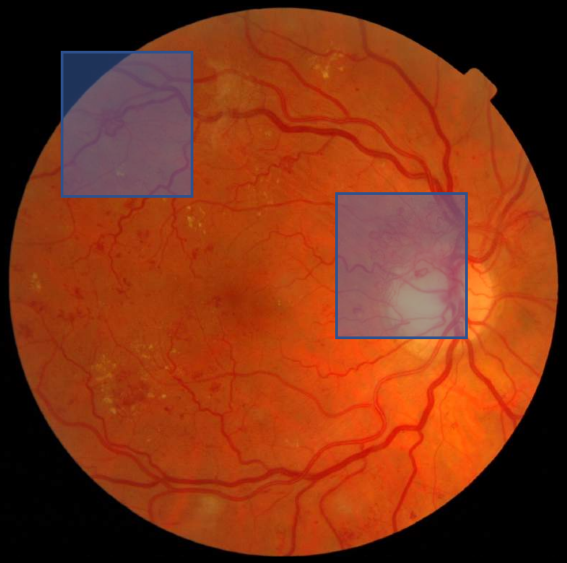
DR screening based on red lesion detection

Method	Screening AUC	Screening Se	Need for referral AUC	Need for referral Se
Expert A [176]	0.9220	0.9450	0.9400	0.9820
Expert B [176]	0.8650	0.9120	0.9200	0.9760
Antal and Hajdu, 2012 [16]	0.8750	-	-	-
Costa *et al.*, 2016 [43]	0.8700	-	-	-
Giancardo *et al.*, 2013 [70]	0.8540	-	-	-
Nandy *et al.*, 2016 [134]	-	-	0.9210	-
Pires *et al.*, 2015 [161]	-	-	0.8630	-
Sánchez *et al.*, 2011 [176]	0.8760	**0.9220**	0.9100	0.9440
Seoud *et al.*, 2016 [180] (DIARETDB1)	0.844	-	-	-
Vo and Verma, 2016 [205] (I)	0.8620	-	0.8910	-
Vo and Verma, 2016 [205] (II)	0.8700	-	0.8870	-
HCF	0.7325	0.7645	0.7824	0.8283
CNN	0.7912	0.8471	0.8377	0.9102
HCF + CNN	**0.8932**	0.9109	**0.9347**	**0.9721**

Orlando J.I. et al. (2017).
Comput Methods Programs Biomed

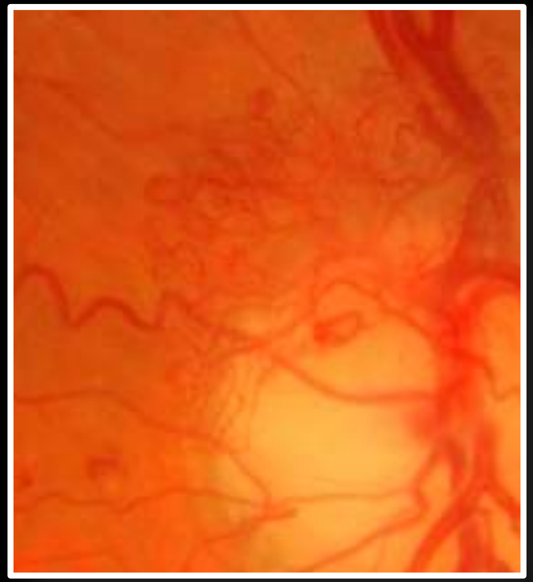
Use cases of machine/deep learning in DR

Proliferative DR detection

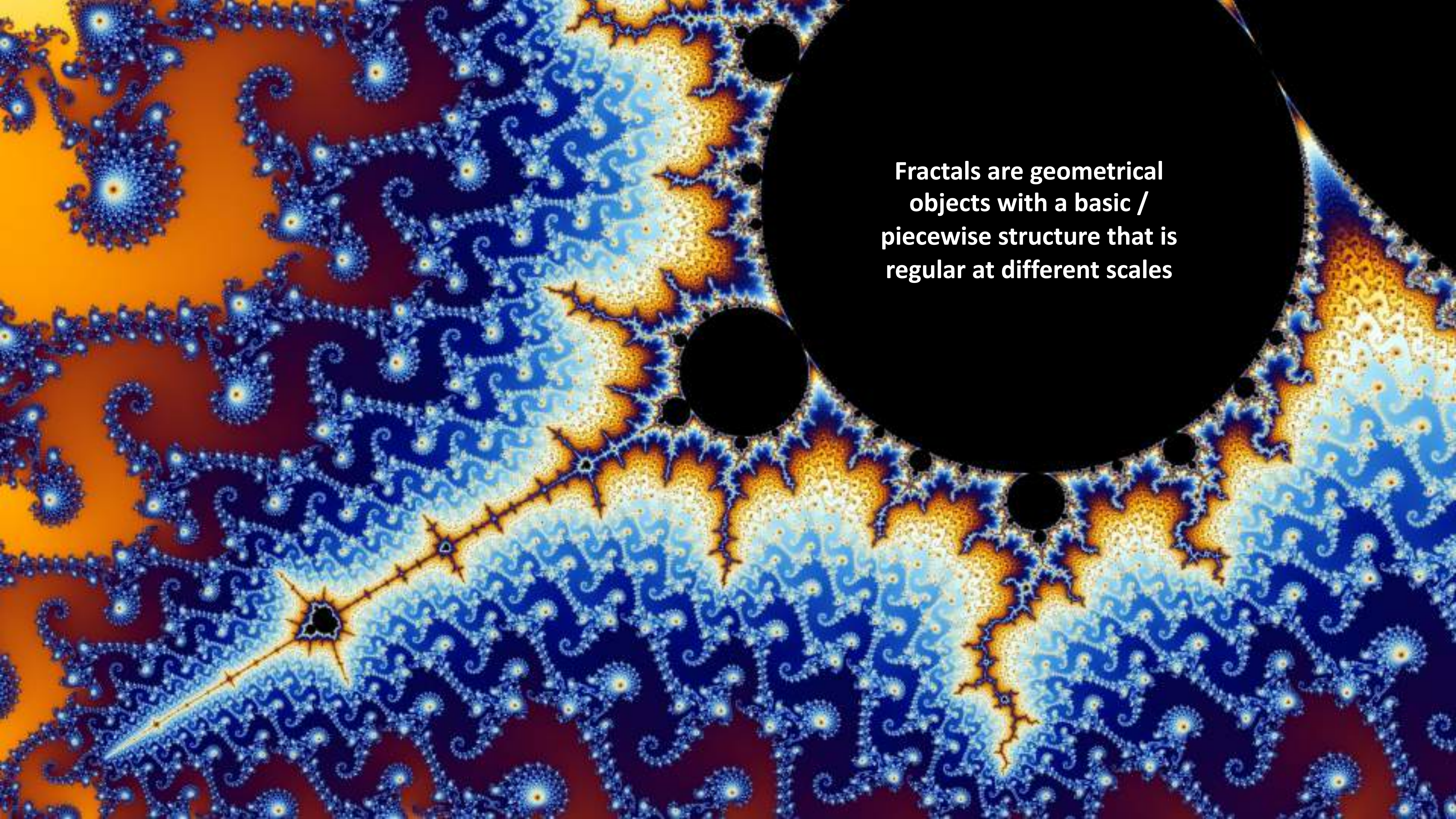


Proliferative DR

Peripheral neovascularization



Optic disc neovascularization



Fractals are geometrical objects with a basic / piecewise structure that is regular at different scales

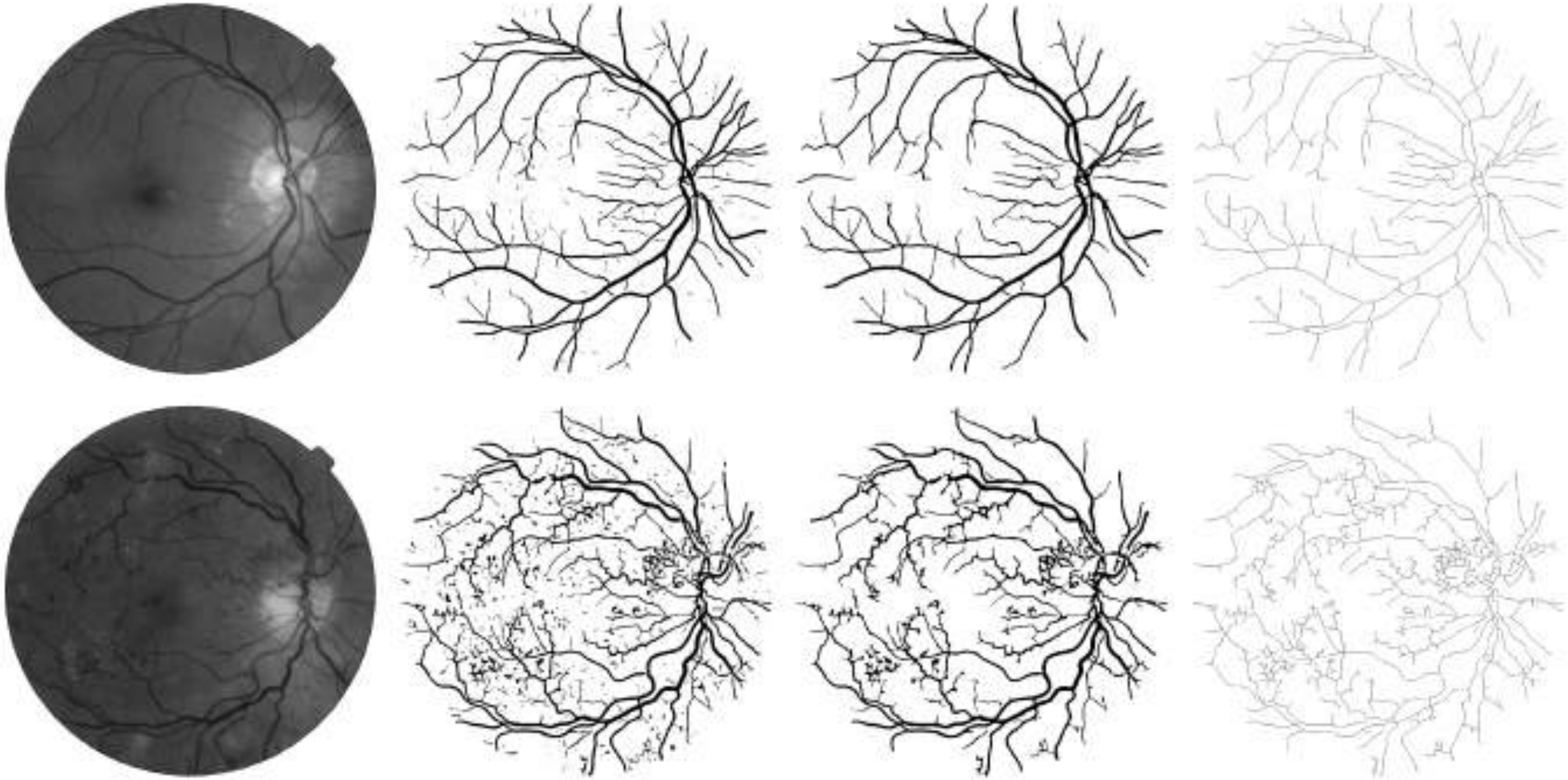

Fractals are also present in
human body structures!

Use cases of machine/deep learning in DR

Proliferative DR detection

Healthy subject

PDR

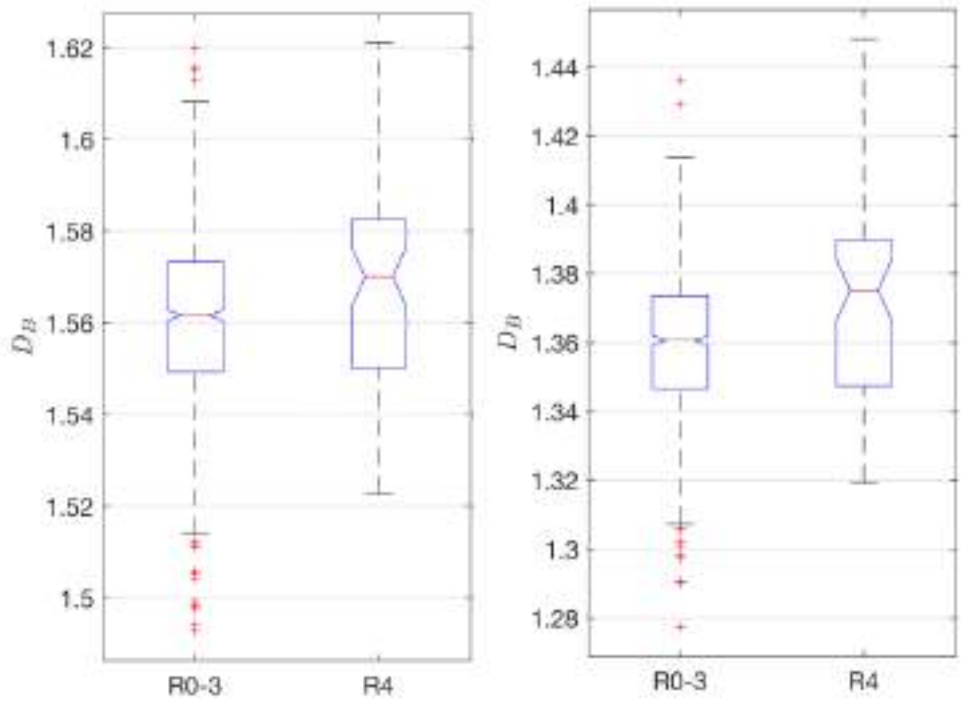


Orlando J.I. et al. (2017). *Med Phys*

Use cases of machine/deep learning in DR

Proliferative DR detection

PDR cases exhibit larger fractal dimension



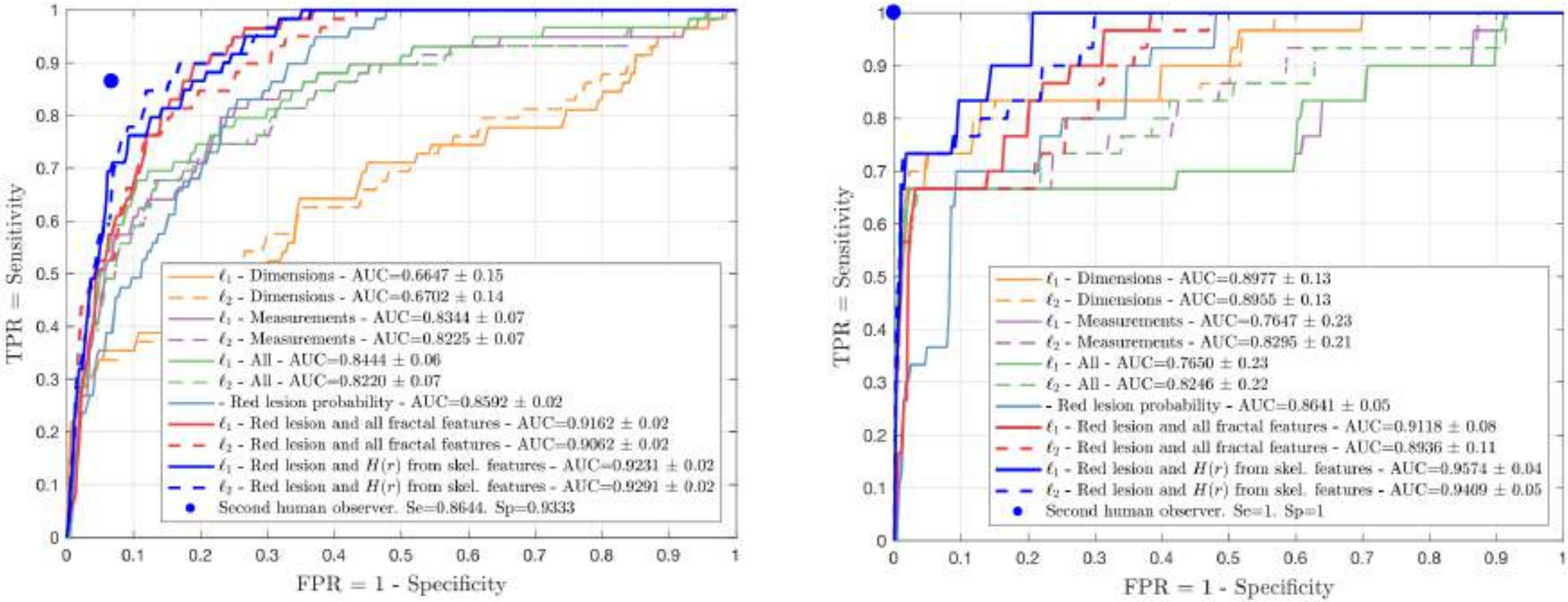
(a) Vessel segmentations. (b) Vessel skeletonizations.

What about using these features for detecting PDR?

Orlando J.I. et al. (2017). *Med Phys*

Use cases of machine/deep learning in DR

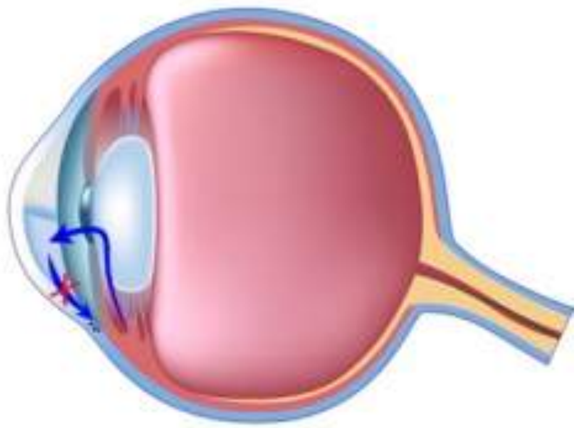
Proliferative DR detection

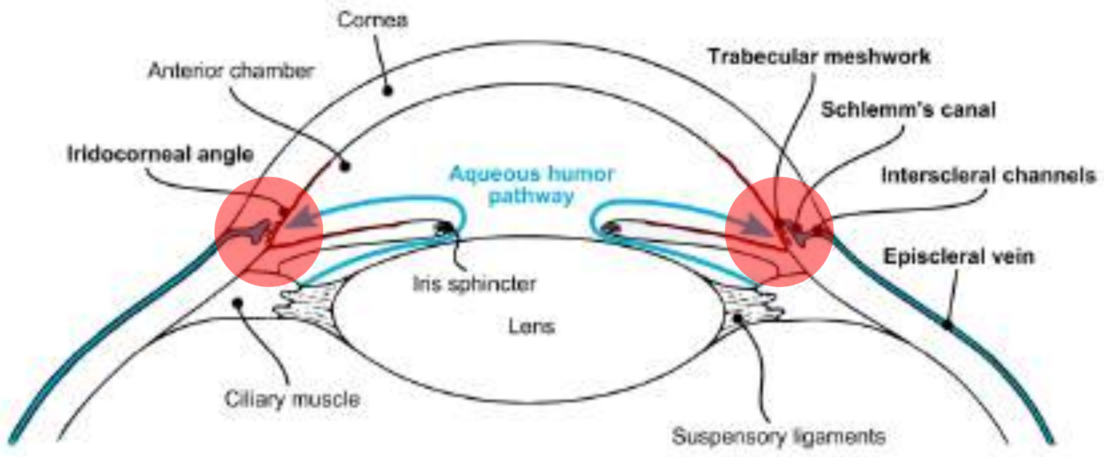


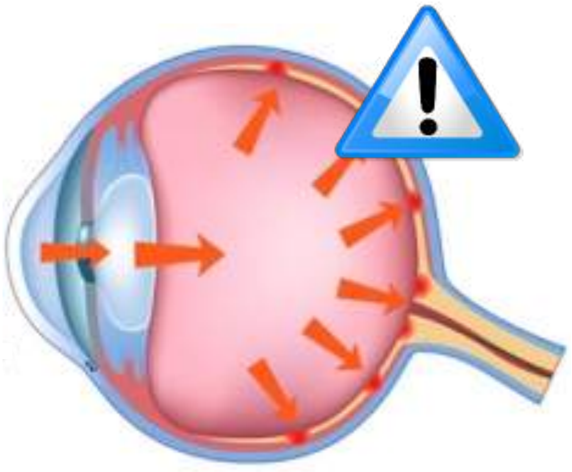
Glaucoma

Known for centuries, still no cure, treatments to hamper its progression

Silent thief of sight, asymptomatic, vision loss is irreversible



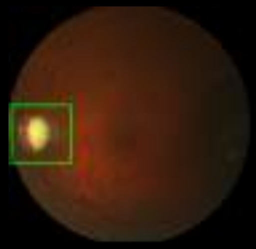




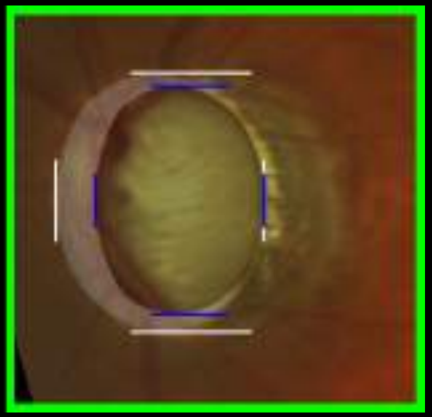
The only observable manifestations of the disease is the irreversible damage in the optic nerve head and the retinal nerve fiber layers

Glaucoma

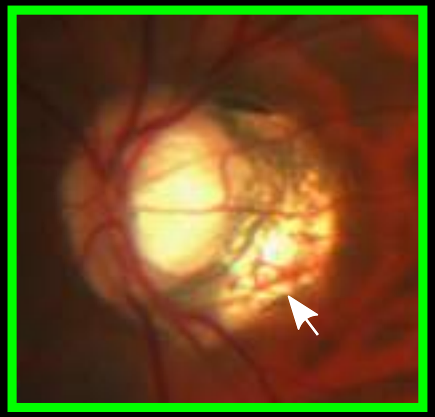
Known for centuries, still no cure, treatments to hamper its progression
Silent thief of sight, asymptomatic, vision loss is irreversible

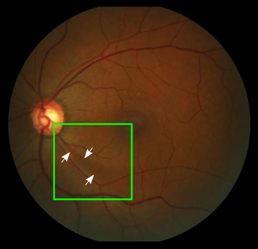


Neuroretinal rim thinning



Parapapillary atrophies (PPA)





Retinal nerve fiber layer defects

The only observable manifestations of the disease is the irreversible damage in the optic nerve head and the retinal nerve fiber layers

Glaucoma

Use cases of machine/deep learning

Early screening

Feature learning
Identify biomarkers

Image classification
Healthy / Glaucomatous

Qualitative feedback

Segmentation
Optic disc/cup, RNFL defects, PPA

Image classification
Healthy / Glaucomatous

Use cases of machine/deep learning in glaucoma

Glaucoma detection using transfer learning

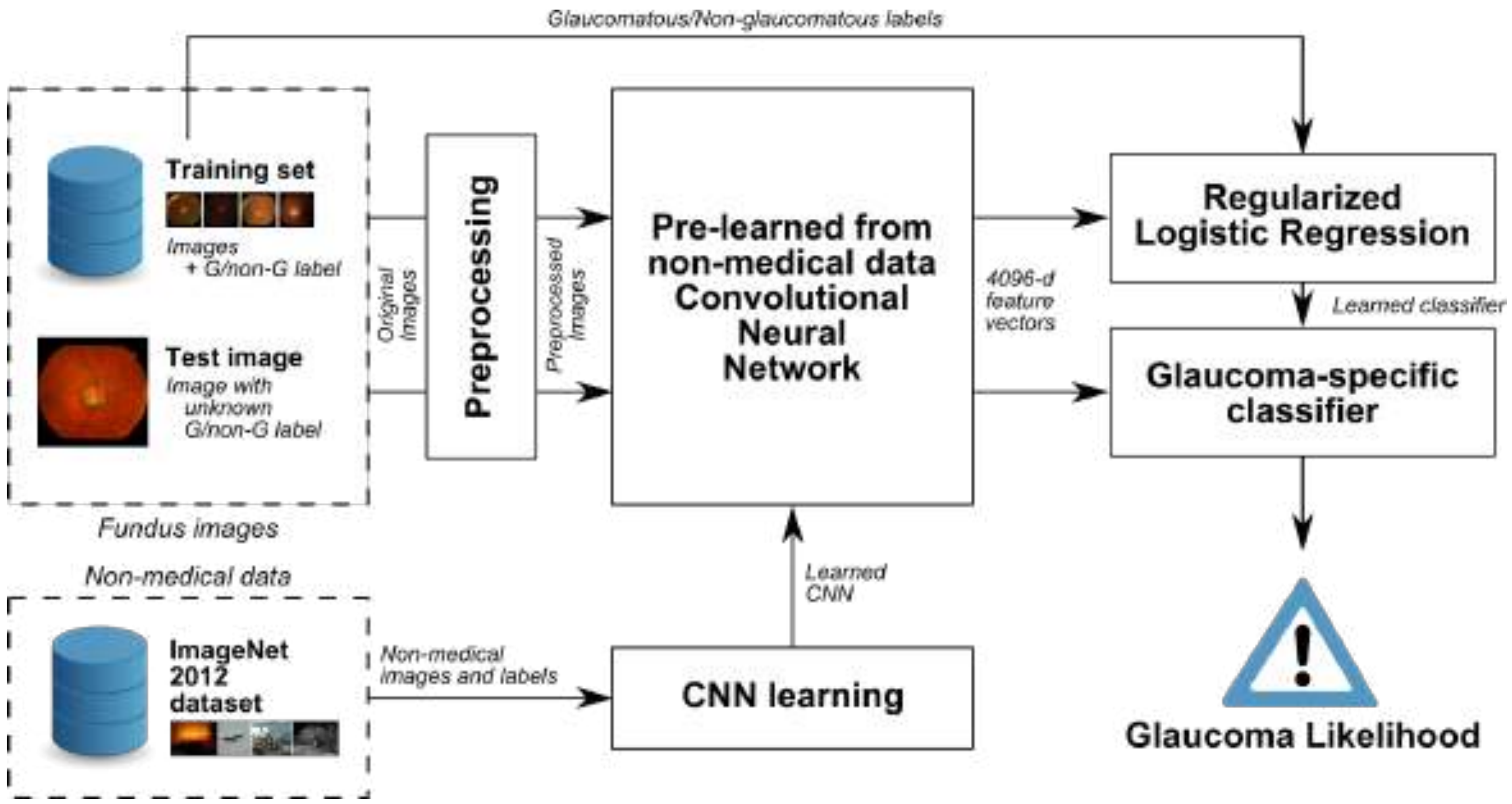
Diagnosis glaucoma from fundus pictures is extremely difficult!

Public available data sets are small and have unreliable labels

Orlando J.I. et al. (2017). *SIPAIM*

Use cases of machine/deep learning in glaucoma

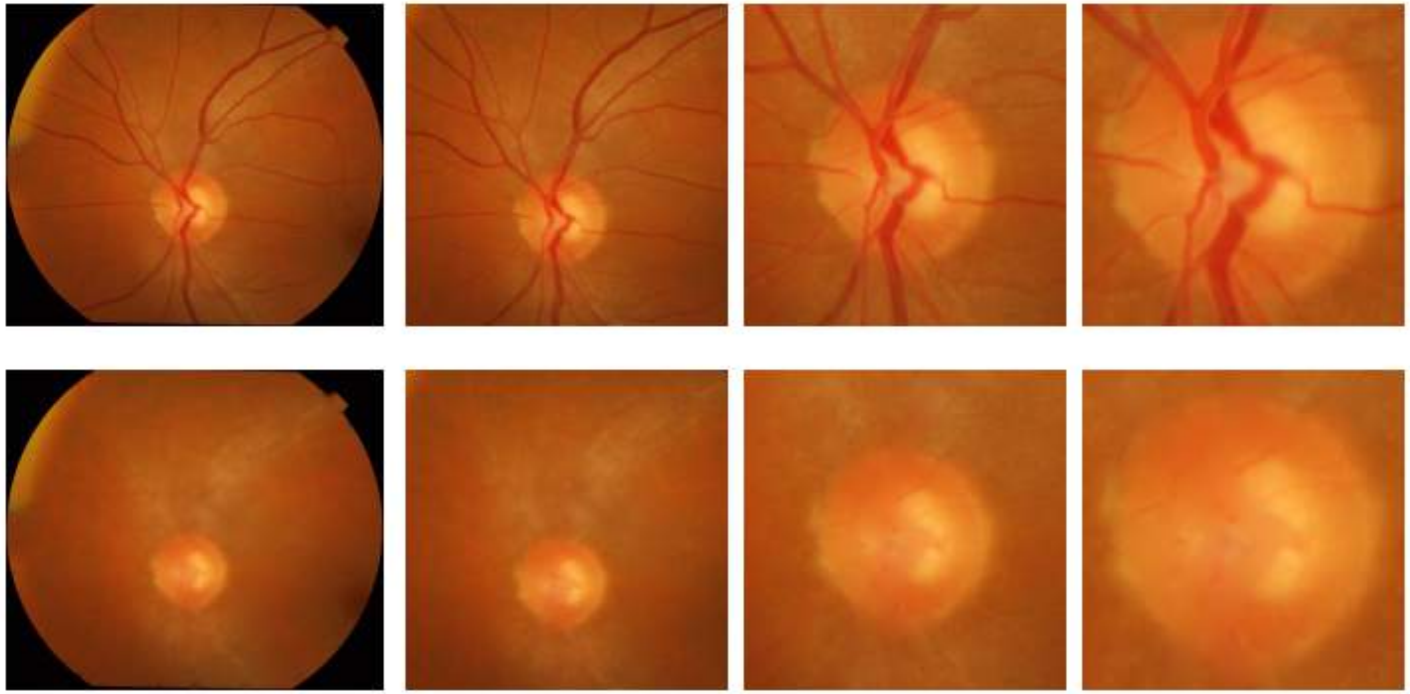
Glaucoma detection using transfer learning



Orlando J.I. et al. (2017). *SIPAIM*

Use cases of machine/deep learning in glaucoma

Glaucoma detection using transfer learning



Orlando J.I. et al. (2017). *SIPAIM*

Use cases of machine/deep learning in glaucoma

Glaucoma detection using transfer learning

Best preprocessing methods	Overfeat	VGG-S
Cropped FOV, without CLAHE, without **vessel inpainting**, 90º augmentation	**0.7626**	0.7212
PPA, without CLAHE, **with vessels inpainted**, without data augmentation	**0.7180**	0.6655

Chakrabarty A. and Sivaswamy J. (2016). *ISBI*. **AUC = 0.78**

Orlando J.I. et al. (2017). *SIPAIM*

REFUGE

Retinal Fundus Glaucoma Challenge

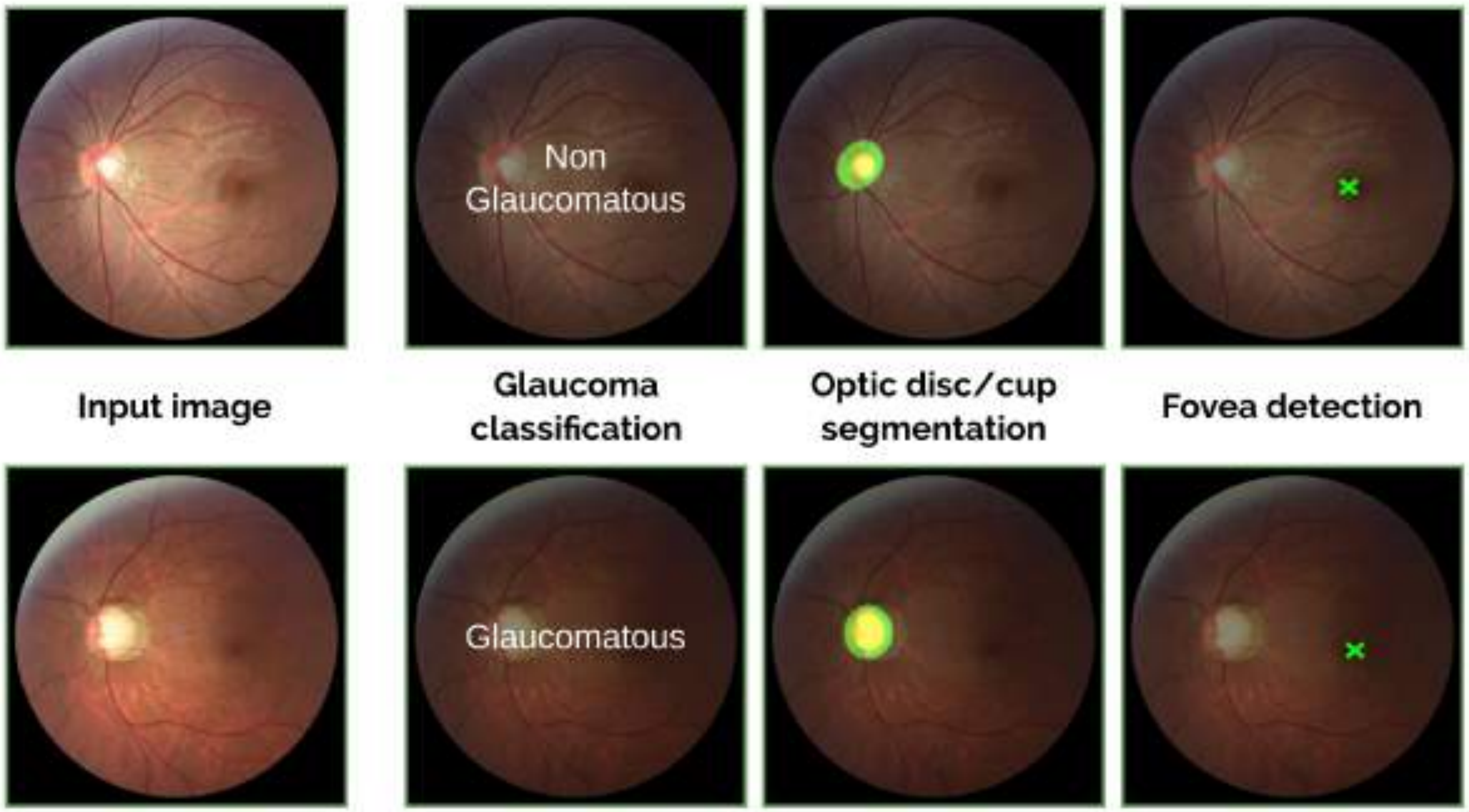
1200 fundus pictures with (reliable) glaucoma annotations

Glaucomatous/Non-glaucomatous, optic disc/cup segmentations, fovea position

Orlando et al. 2019. Unpublished results.

Use cases of machine/deep learning in glaucoma

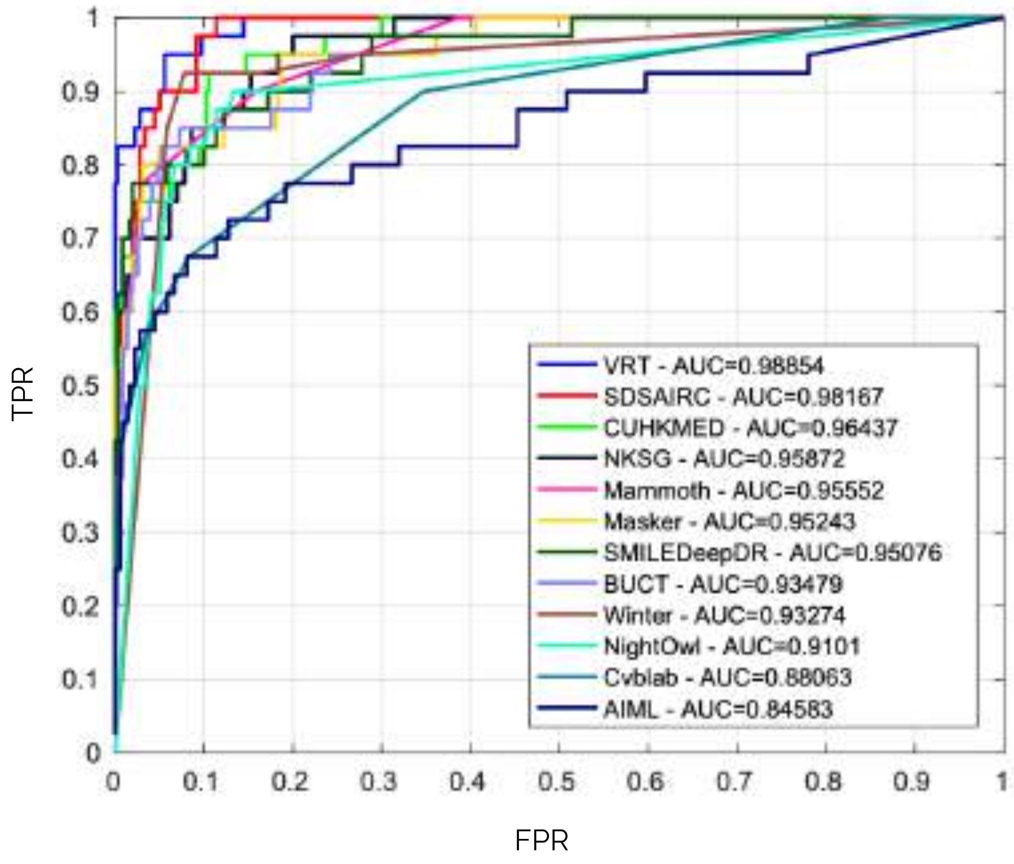
REFUGE challenge



Orlando et al. 2019. Unpublished results.

Use cases of machine/deep learning in glaucoma

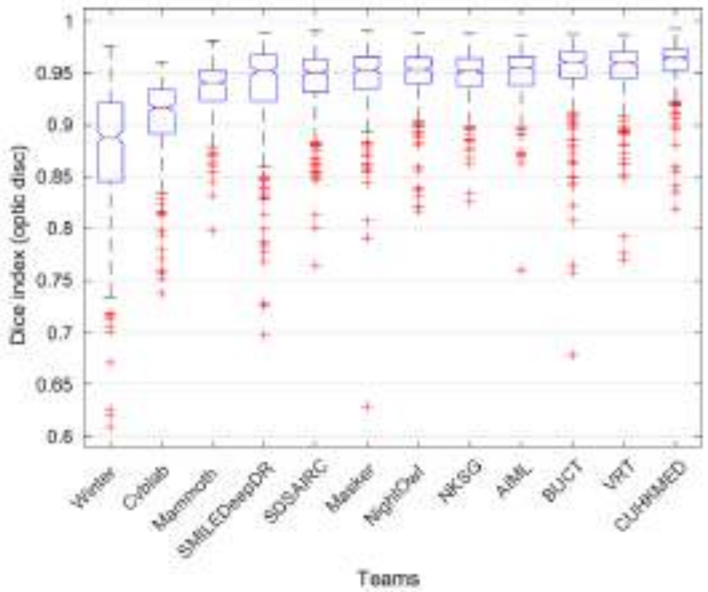
REFUGE challenge



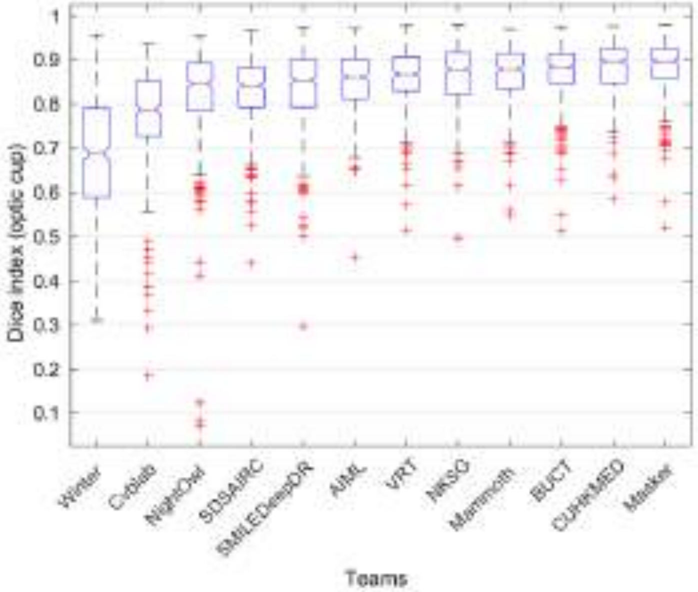
Orlando et al. 2019. Unpublished results.

Use cases of machine/deep learning in glaucoma

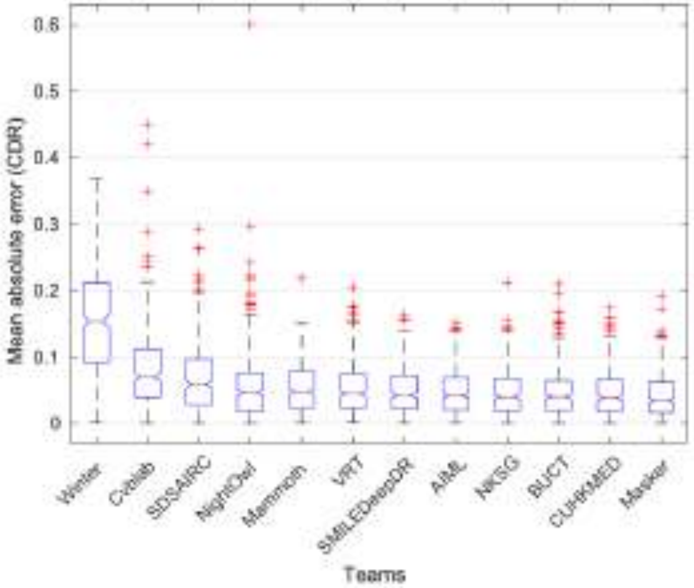
REFUGE challenge



(a) Optic disc segmentation



(b) Optic cup segmentation



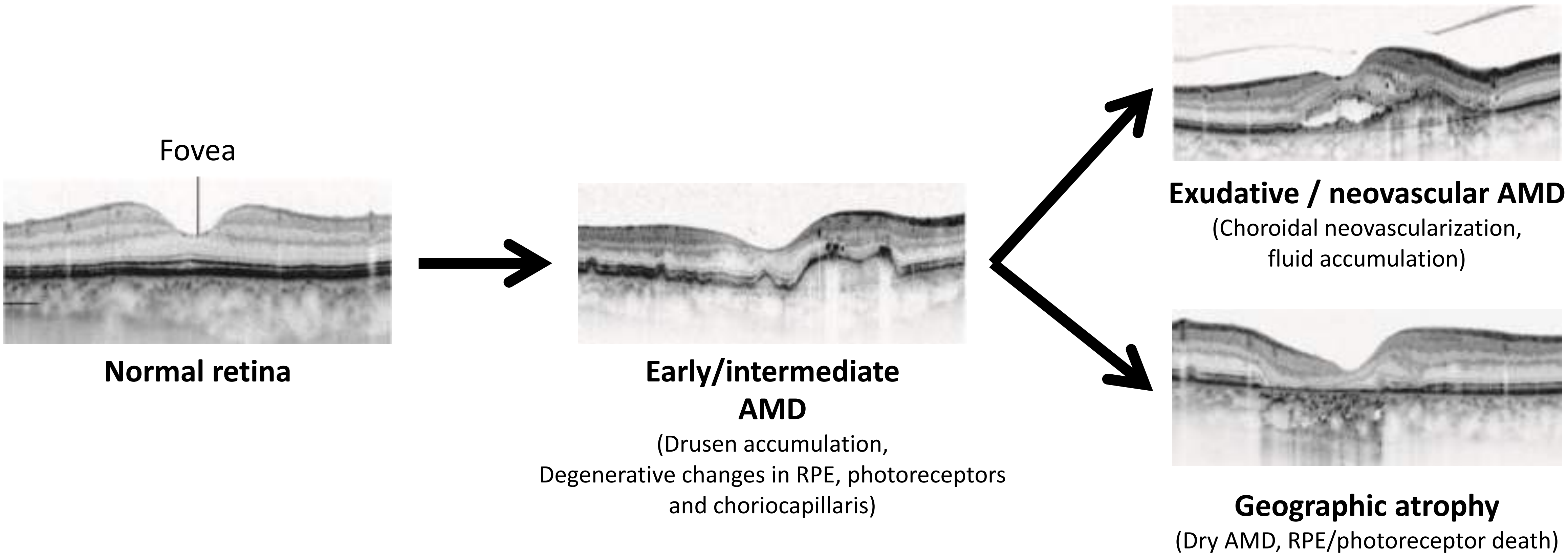
(c) MAE for vCDR

Orlando et al. 2019. Unpublished results.

Age-related Macular Degeneration (AMD)

Most common cause of blindness in people over 65 years in developed countries

Degeneration of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris



Age-related macular degeneration (AMD)

Use cases of machine/deep learning

Early screening

Qualitative feedback

$$\underbrace{\hspace{20em}}$$

Segmentation

Drusen, exudates, photoreceptors, GA

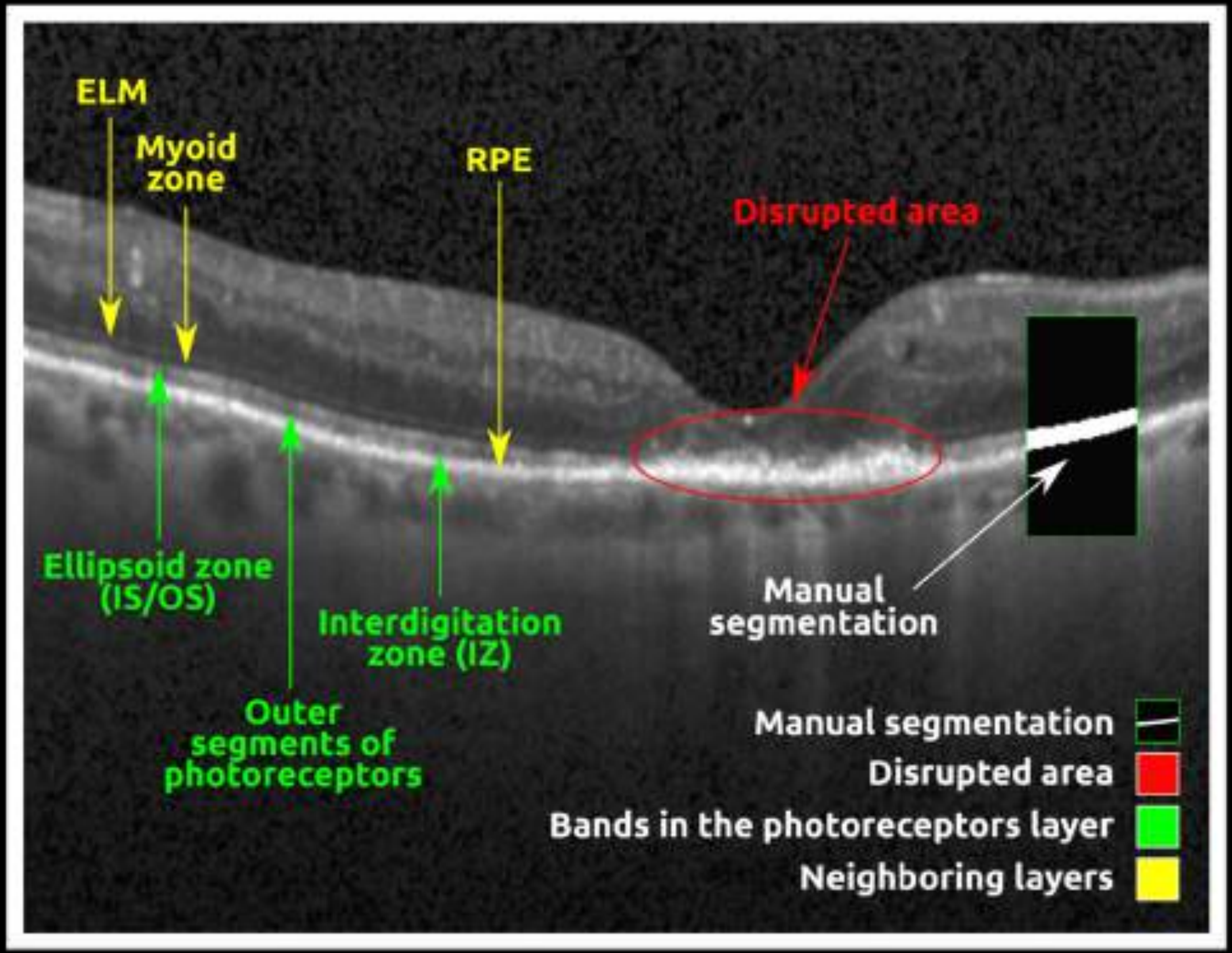
Image classification

AMD grading

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans

Challenging task with high inter- and intra-observer variability



How to solve region ambiguities and/or help readers?

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans

Epistemic Uncertainty estimation

Bayesian SegNet: Model Uncertainty in Deep Convolutional Encoder-Decoder Architectures for Scene Understanding

Alex Kendall, Vijay Badrinarayanan, Roberto Cipolla

(Submitted on 9 Nov 2015 (v1), last revised 10 Oct 2016 (this version, v2))

What Uncertainties Do We Need in Bayesian Deep Learning for Computer Vision?

Alex Kendall, Yarin Gal

(Submitted on 15 Mar 2017 (v1), last revised 5 Oct 2017 (this version, v2))

Monte Carlo sampling with dropout on during test time allows to capture

BETTER RESULTS + MODEL UNCERTAINTY

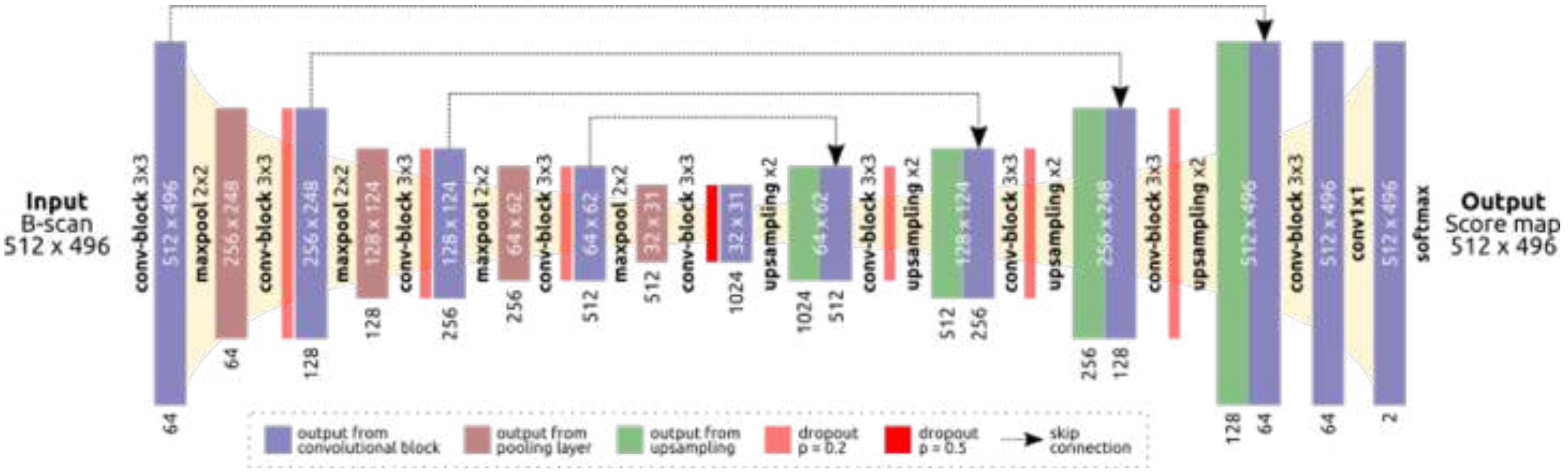
Orlando et al. 2019. Submitted to ISBI

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans: U2-Net

Uncertainty U-Net, Monte Carlo sampling with dropout on during test time

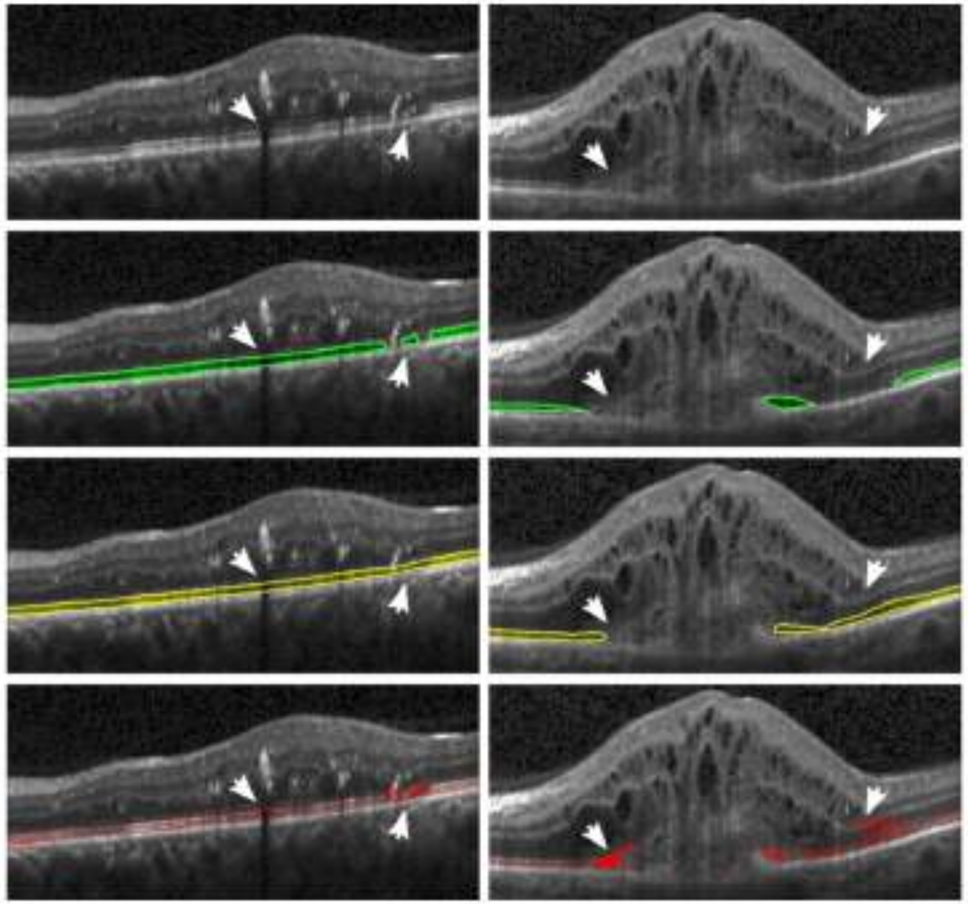
Leaky ReLUs + Batch Norm + Dropout



Orlando et al. 2019. Submitted to ISBI

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans: U2-Net

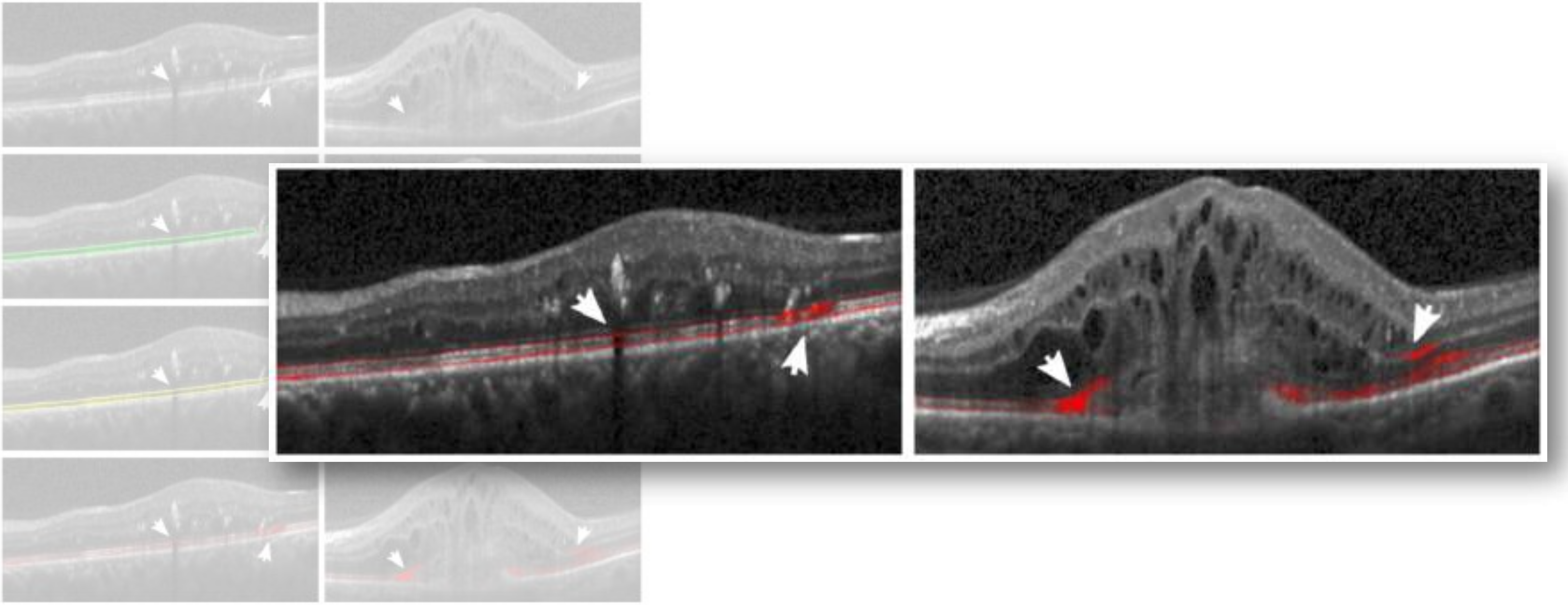


(a) Dice= 0.9196, $\overline{u} = 6.7 \times 10^{-4}$ (b) Dice= 0.5888, $\overline{u} = 13 \times 10^{-4}$

Orlando et al. 2019. Submitted to ISBI

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans: U2-Net



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Use cases of machine/deep learning in AMD

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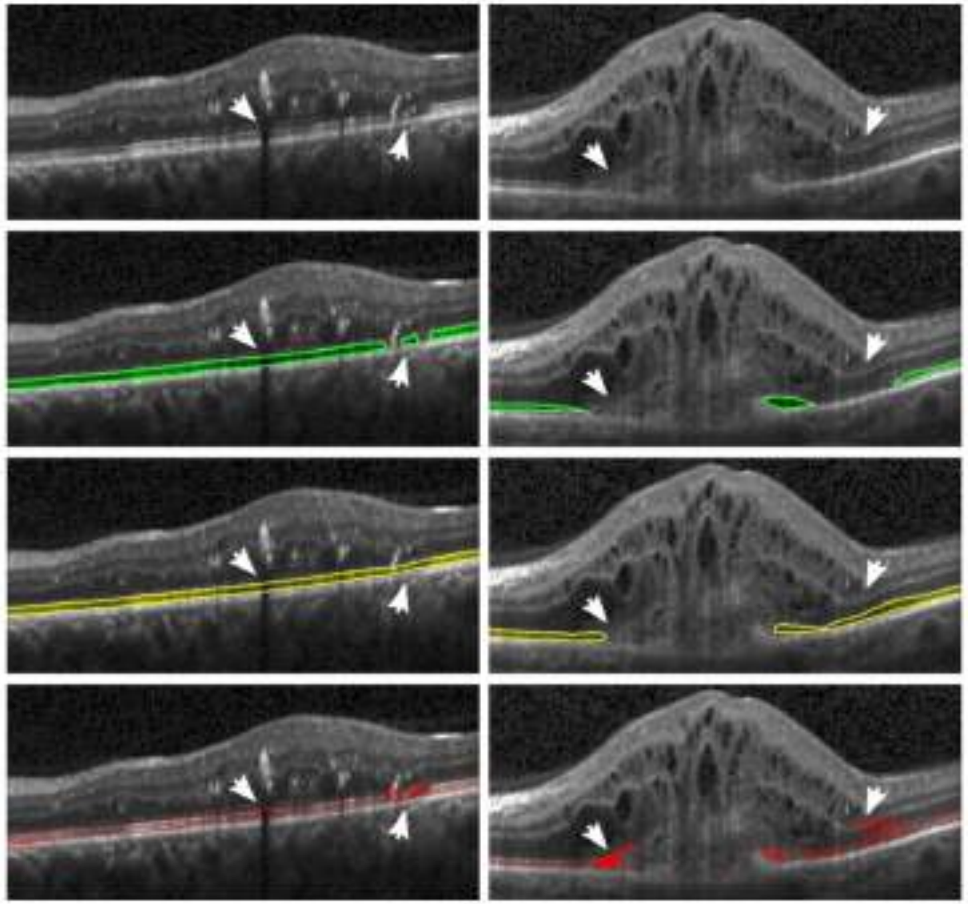

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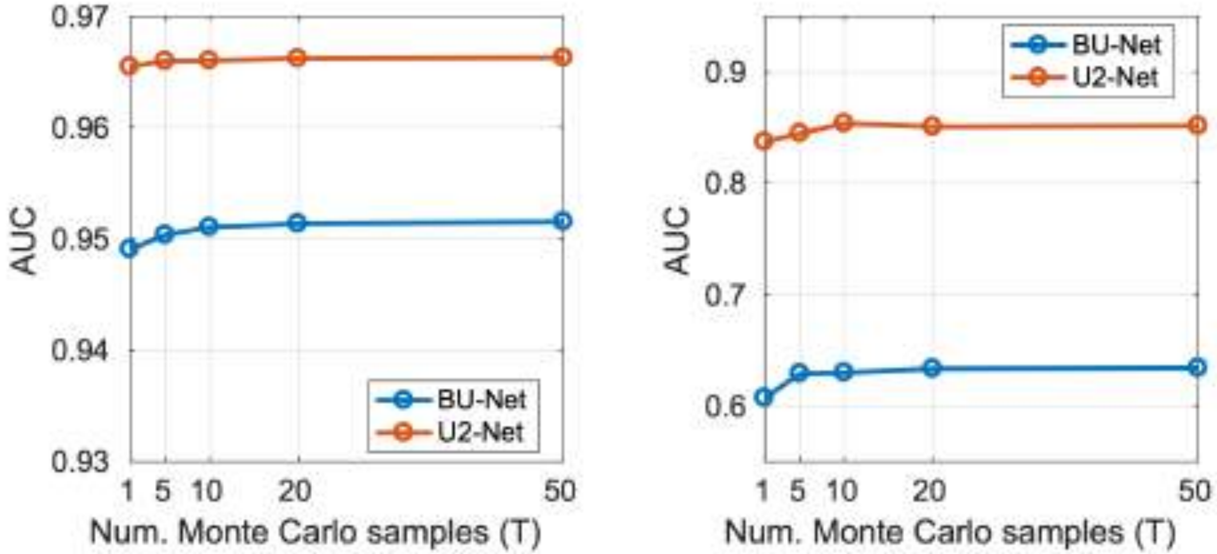
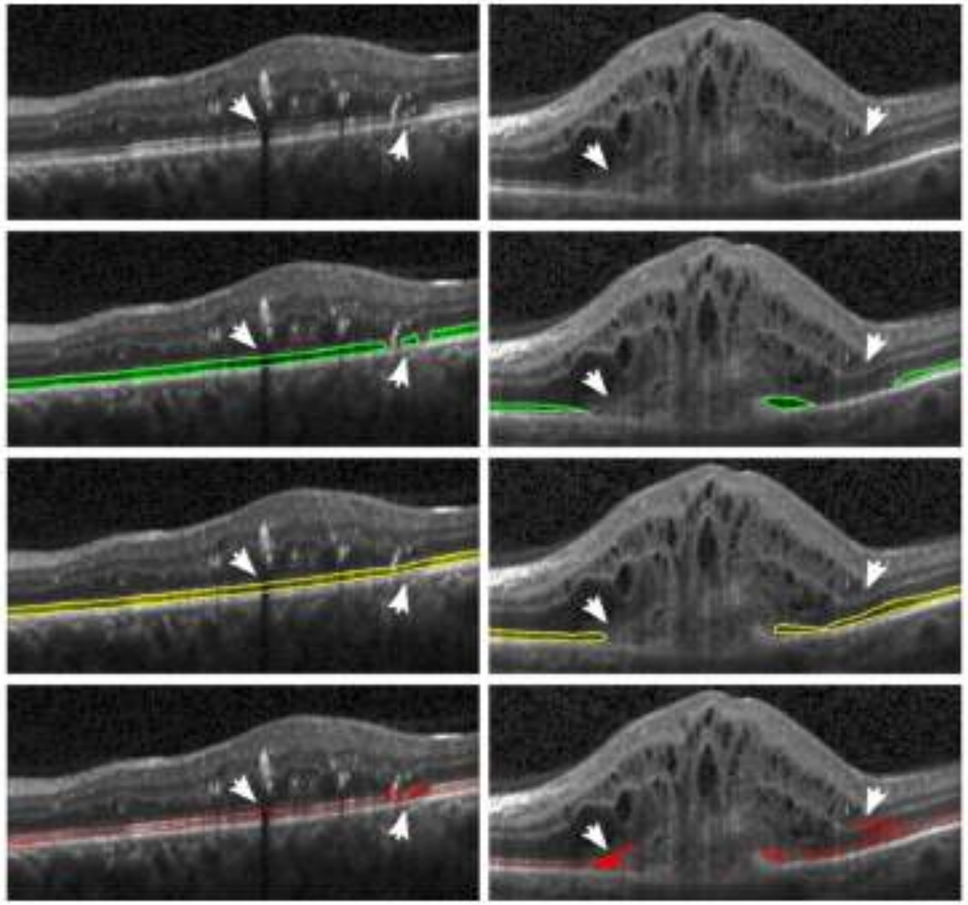


(a) Photoreceptors (b) Disruptions

Orlando et al. 2019. Submitted to ISBI

Use cases of machine/deep learning in AMD

Photoreceptor segmentation in OCT scans: U2-Net



(a) Dice= 0.9196, $\overline{u} = 6.7 \times 10^{-4}$ (b) Dice= 0.5888, $\overline{u} = 13 \times 10^{-4}$

Model	Test set A AMD (early, CNV), DME, RVO			Test set B Late AMD (GA)		
	Photoreceptors		Disruptions	Photoreceptors		Disruptions
	AUC	Dice	AUC	AUC	Dice	AUC
U-Net [10]	0.9566	0.8815 ±0.06	0.5077	0.9390	0.8375 ±0.07	0.8795
BRU-Net [16]	0.9593	0.8767 ±0.08	0.2621	0.9295	0.7890 ±0.13	0.8333
BU-Net $T = 1$	0.9466	0.8647 ±0.08	0.2222	0.8969	0.7311 ±0.14	0.8065
BU-Net $T = 10$	0.9505	0.8678 ±0.08	0.2405	0.8998	0.7428 ±0.14	0.8129
U2-Net $T = 1$	0.9653	0.8932 ±0.04	**0.6712**	**0.9500**	**0.8546 ±0.06**	0.9085
U2-Net $T = 10$	**0.9669**	**0.8943 ±0.04**	0.6417	0.9472	0.8457 ±0.08	**0.9101**

Orlando et al. 2019. Submitted to ISBI

What are we going to talk about today?

~~The eye (and the retina)~~

~~Imaging modalities in ophthalmology~~

~~Retinal diseases: AMD, DR, glaucoma~~

~~Use cases of machine/deep learning~~

Concluding remarks

Telemedicine in ophthalmology

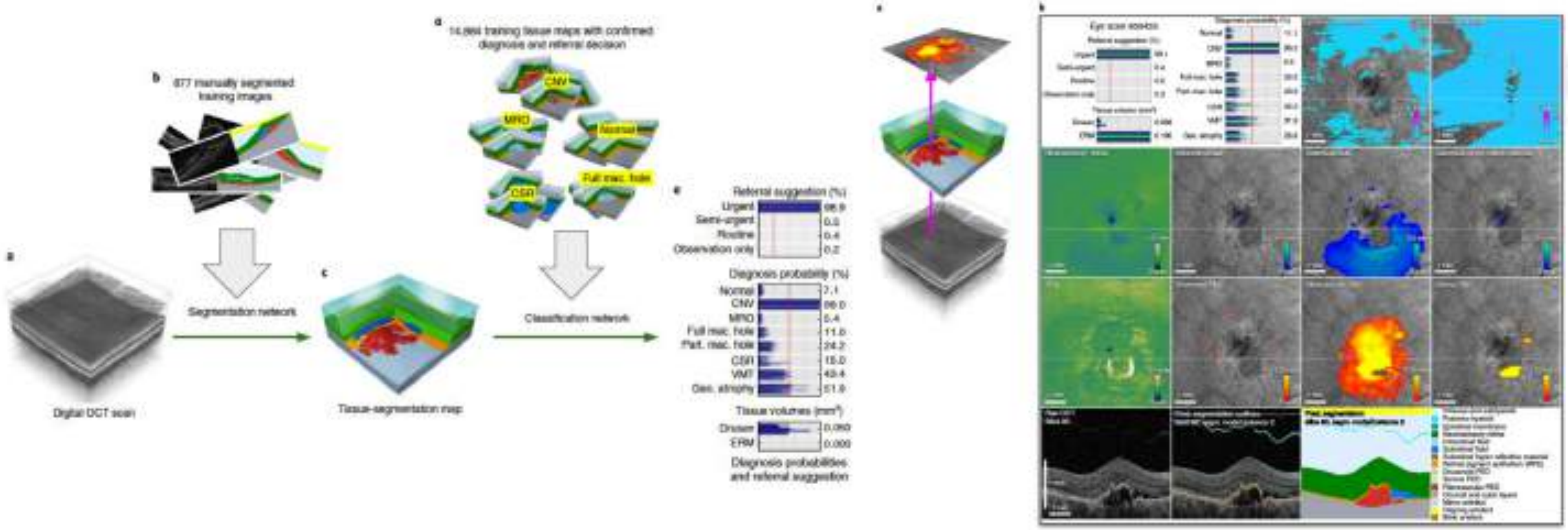
Screening / grading / qualitative feedback

Current & future applications

De Fau et al. 2018. *Nature Medicine*

Telemedicine in ophthalmology

Screening / grading / qualitative feedback

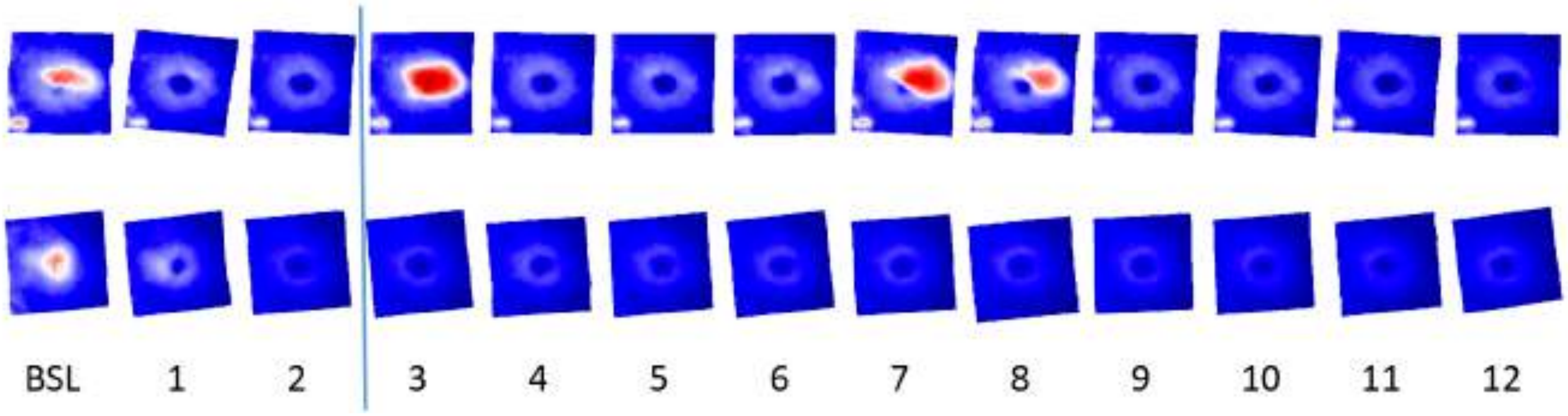


Current & future applications

De Fau et al. 2018. *Nature Medicine*

Personalized medicine

Longitudinal imaging / guidance of therapy



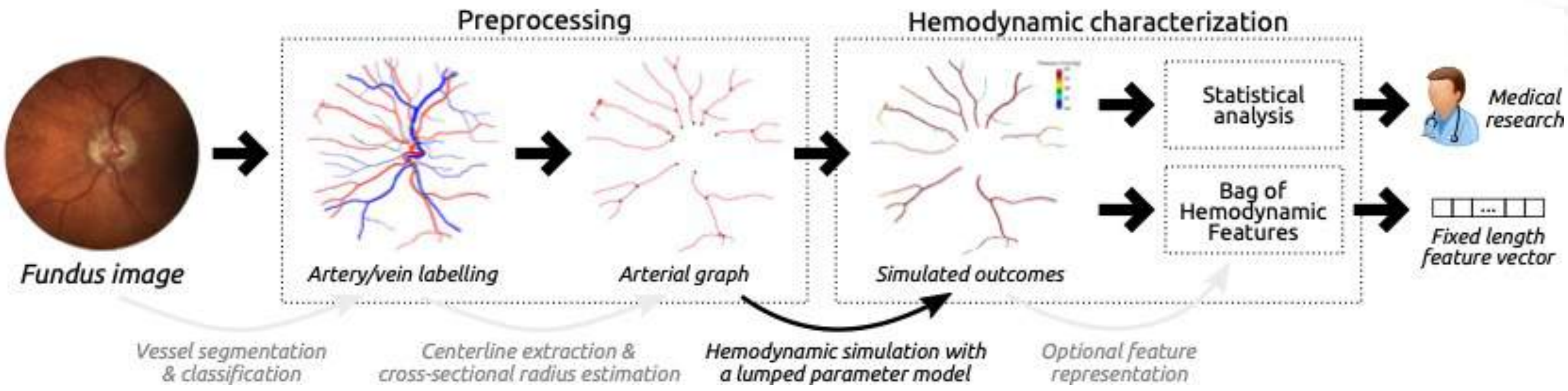
Better planning of anti VEGF therapy

Current & future applications

Vogl et al. 2017. *IEEE TMI*

Data-driven clinical research

Discovery of novel biomarkers for retinal diseases



Current & future applications

Orlando et al. 2018. MICCAI

Medical questions unsolved

Clinical tasks can be benefited by the incorporation of machine learning based tools

Data accumulation + curation + (computer assisted) annotation

Interaction between MD / researchers & computer scientists

Concluding remarks

Thanks for your attention!

Questions?

@ignaciorlando

Machine learning for ophthalmic image analysis

José Ignacio Orlando, PhD

Christian Doppler Laboratory for Ophthalmic Image Analysis (OPTIMA)
Medical University of Vienna

OPTIMA Ophthalmic Image Analysis

MEDICAL UNIVERSITY OF VIENNA

OPTIMA
Ophthalmic Image Analysis

MEDICAL UNIVERSITY OF VIENNA

PhD student in medical image computing and machine/deep learning

FULLY FUNDED POSITION

DIRECT ACCESS TO LARGE-SCALE CLINICAL DATA SETS

VIENNA WAS RECENTLY NAMED THE WORLD'S MOST LIVEABLE CITY (FOR THE 9TH YEAR RUNNING!)

CV and cover letter with interest and research experience to
hrvoje.bogunovic@meduniwien.ac.at