Research IT to Facilitate Advanced Imaging for Glaucoma Management

Linda Zangwill, PhD

Director of Clinical Research Hamilton Glaucoma Center

Director Imaging Data Evaluation and Analysis (IDEA) Reading Center

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University of California, San Diego

VITERBI FAMILY SHILEY EYE INSTITUTE

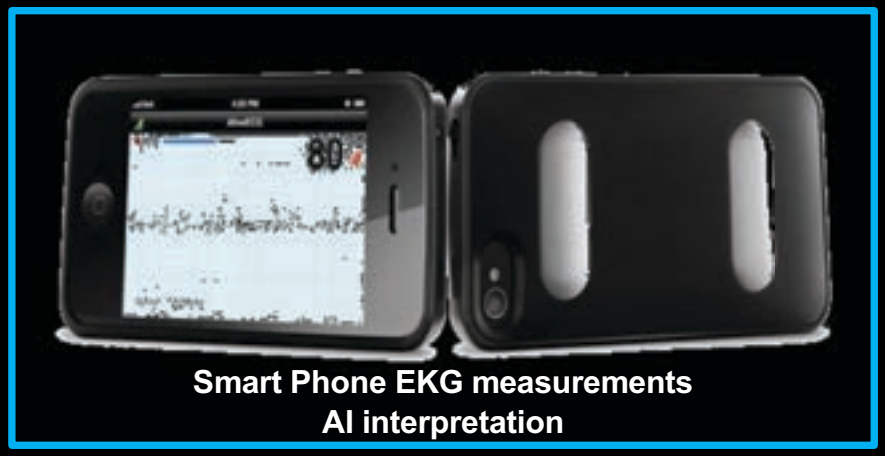
UCSD Hamilton Glaucoma Center

Artificial intelligence is changing our lives

Recommendation Engines

Autonomous Driving

Object Detection



Personal Sensors and Medical Tests

AI will transform health care

VIEWPOINT

Deep Learning—A Technology With the Potential to Transform Health Care

Geoffrey Hinton, PhD
Google Brain Team and Department of Computer Science, University of Toronto, Ontario, Canada

Viewpoint and Editorial

Widespread application of artificial intelligence in health care has been anticipated for half a century. For most of that time, the dominant approach to artificial intelligence was inspired by logic: researchers assumed that the essence of intelligence was manipulating symbolic expressions, using rules of inference. This approach produced expert systems and graphical models that attempted to automate the reasoning processes of experts. In the last decade, however, a radically different approach to artificial intelligence, called deep learning, has produced major breakthroughs and is now used on billions of digital devices for complex tasks such as speech recognition, image interpretation, and language translation. The purpose of this Viewpoint is to give health care professionals an intuitive understanding of the technology underlying deep learning. In an accompanying Viewpoint, Naylor[1] outlines some of the factors propelling adoption of this technology in medicine and health care.

retrain a convolutional neural network that had previously been trained to recognize everyday objects in cluttered images. The skin lesion images used for retraining varied widely in quality, and no further information was provided to the convolutional neural network other than the image pixels and the lesion label. The network and groups of 21 to 25 board-certified dermatologists then reviewed subsets of the unlabeled test images and decided whether the correct clinical course was a biopsy for possible malignancy or reassurance of the patient. Sensitivity for the majority of the dermatologists was lower than that of the convolutional neural network when matched for specificity, and their specificity was lower than that of the convolutional neural network when matched for sensitivity for identifying images with melanoma, as well as for images of basal and squamous cell carcinoma.

A Brief History of Artificial Neural Networks

JAMA. 2018;320(11):1101-1102

AI will transform health care

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A Brief History of Artificial Neural Networks

First FDA approval

Ophthalmology Times
CUTTING-EDGE ADVANCEMENTS

Applying AI in fundus images

FDA decision changes scope of healthcare delivery; increases patient access to early detection of DR

JAMA. 2018;320(11):1101-1102

AI of Retinal Images is Making Headlines

NewStatesman

HEALTHCARE 25 JANUARY 2017

AI on the NHS: how machine intelligence could save the eyesight of thousands

Google Deepmind's artificial intelligence can spot the early signs of serious eye diseases

Google hopes AI can predict heart disease by looking at retinas

USA Today Feb 2018

Edward C. Baig, USA TODAY

GOOGLE'S AI EYE DOCTOR GETS READY TO GO TO WORK IN INDIA

Google Brain AI research group

The New York Times

March 19, 2019

India Fights Diabetic Blindness With Help From A.I.

FDA grants breakthrough device designation to artificial intelligence diagnostic system

Feb. 5, 2018

February 5, 2018

The FDA is expediting the review of an artificial intelligence-based diagnostic system for the autonomous detection of diabetic retinopathy, according to a press release

Google hopes AI can predict heart disease by looking at retinas

Edward C. Baig, USA TODAY

USA TODAY February 19, 2018

nature biomedical engineering

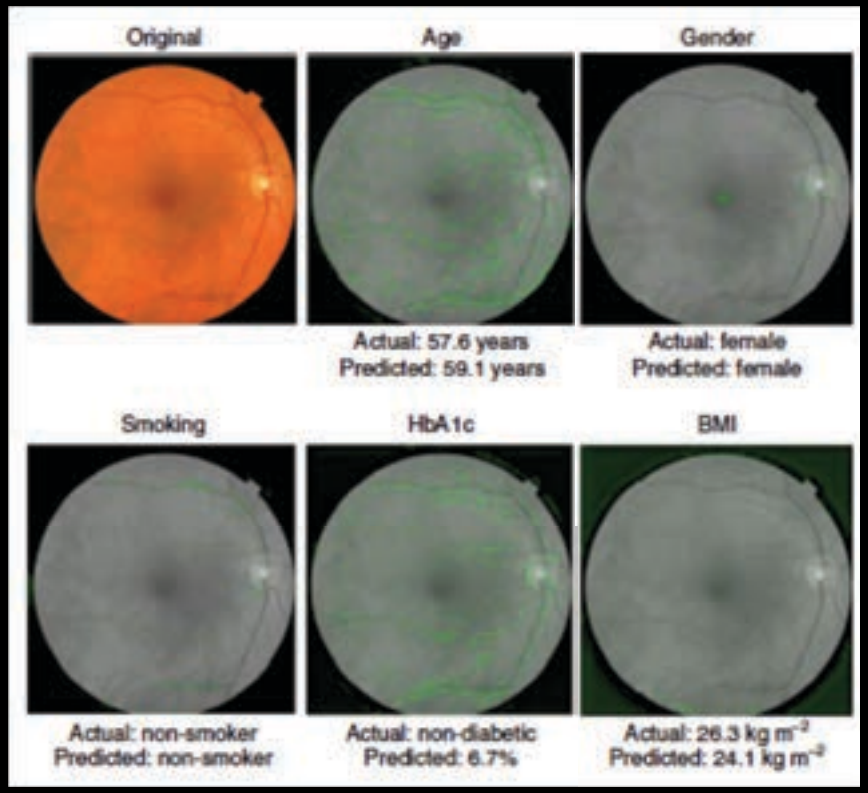
ARTICLES

https://doi.org/10.1038/s41551-018-0195-0

Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning

Ryan Poplin[1,4], Avinash V. Varadarajan[1,4], Katy Blumer[1], Yun Liu[1], Michael V. McConnell[2,3], Greg S. Corrado[1], Lily Peng[1,4]* and Dale R. Webster[1,4]

2018



Prediction Accuracy

Age: ± 3.3 yrs

Gender: 97%

Systolic BP: ±11.2mmHg

Deep Learning Analysis of Fundus Photographs Accurately Detects Glaucoma

SCIENTIFIC REPORTS

OPEN

Received: 28 August 2018
Accepted: 29 October 2018
Published online: 12 November 2018

Performance of Deep Learning Architectures and Transfer Learning for Detecting Glaucomatous Optic Neuropathy in Fundus Photographs

Mark Christopher[1], Akram Belghith[1], Christopher Bowd[1], James A. Proudfoot[1], Michael H. Goldbaum[1], Robert N. Weinreb[1], Christopher A. Girkin[2], Jeffrey M. Liebmann[3] & Linda M. Zangwill[1]

The ability of deep learning architectures to identify glaucomatous optic neuropathy (GON) in fundus photographs was evaluated. A large database of fundus photographs (n = 14,822) from a racially and ethnically diverse group of individuals (over 33% of African descent) was evaluated by expert reviewers and classified as GON or healthy. Several deep learning architectures and the impact of transfer learning were evaluated. The best performing model achieved an overall area under receiver operating characteristic (AUC) of 0.91 in distinguishing GON eyes from healthy eyes. It also achieved an AUC of 0.97 for identifying GON eyes with moderate-to-severe functional loss and 0.89 for GON eyes with mild functional loss. A sensitivity of 88% at a set 95% specificity was achieved in detecting moderate-to-severe GON. In all cases, transfer improved performance and reduced training time. Model visualizations indicate that these deep learning models relied on, in part, anatomical features in the inferior and superior regions of the optic disc, areas commonly used by clinicians to diagnose GON. The results suggest that deep learning-based assessment of fundus images could be useful in clinical decision support systems and in the automation of large-scale glaucoma detection and screening programs.

Overarching Research Goals

- Improve our understanding of the complex relationship between structural and functional change over time in the aging and glaucoma eye
- Develop computational, machine learning and statistical techniques to improve glaucomatous change detection

Glaucoma Background

Normal Vision

Glaucoma

Images courtesy of the National Eye Institute

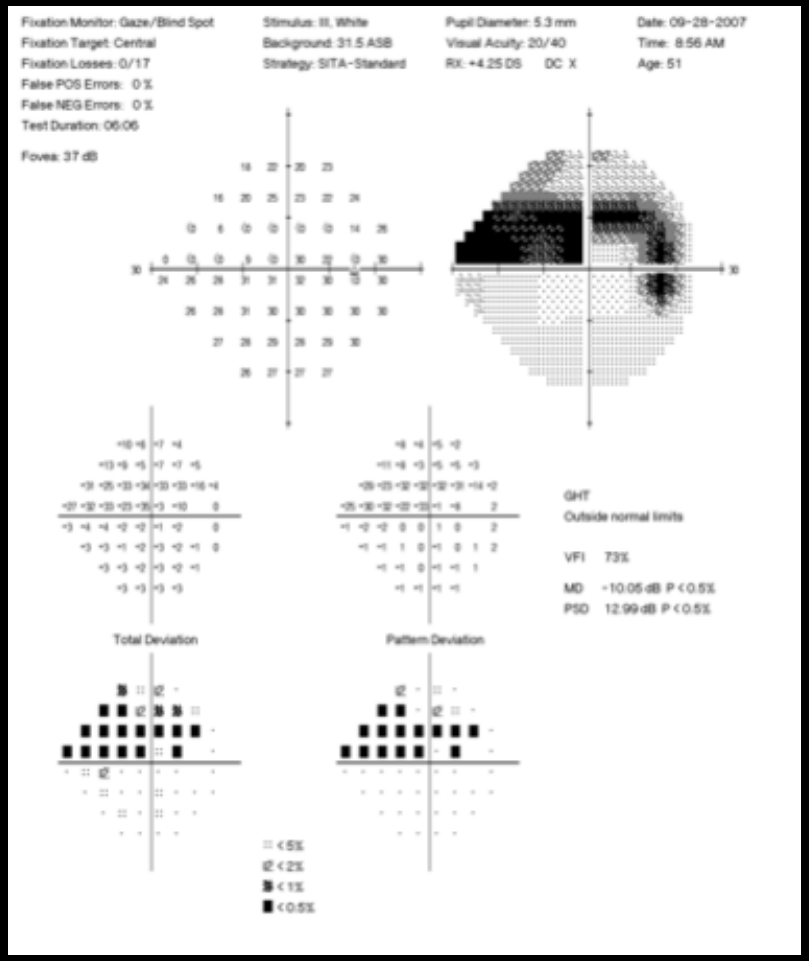
Visual Field Test of Peripheral Vision

- Small white flash on white background.
- How bright must it be for you to see it?

Humphrey Visual Field Analyzer

Visual Field Test of Peripheral Vision

Visual Field Test
Showing Peripheral Vision Loss
in Black

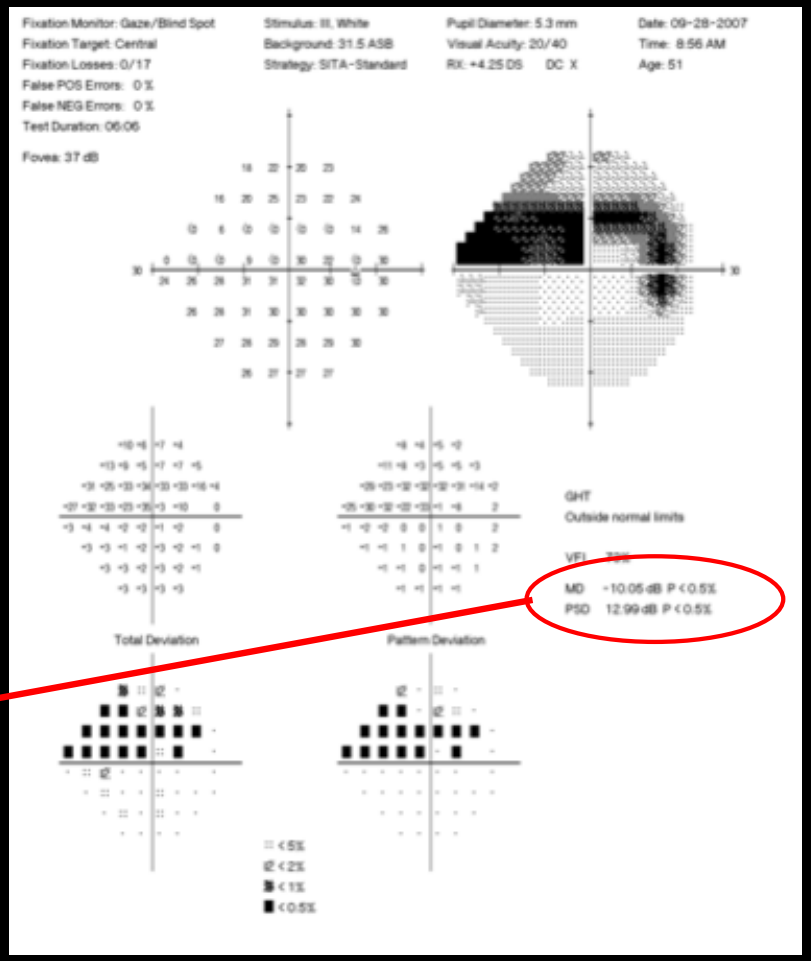


Humphrey Visual Field Analyzer

Background: Glaucoma is a disease associated with progressive retinal ganglion cell loss with characteristic optic disc and visual field damage

Photograph of the back of the eye

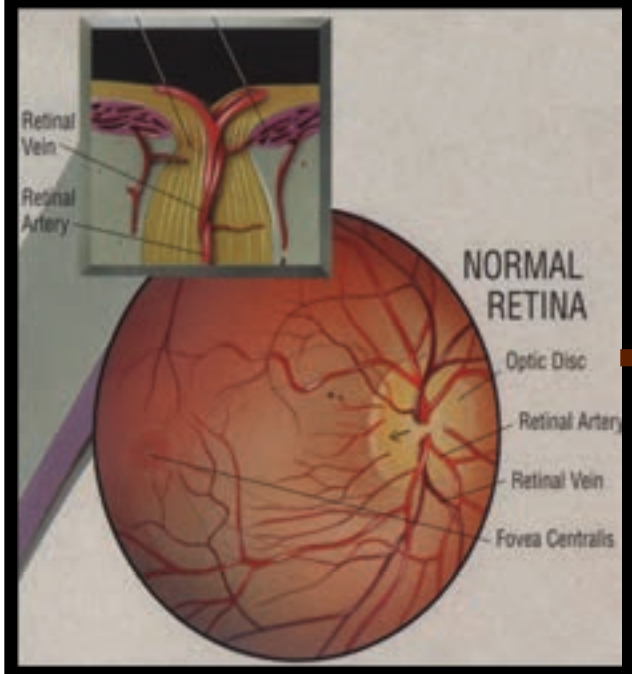
Visual Field Test
Showing Peripheral Vision Loss in Black

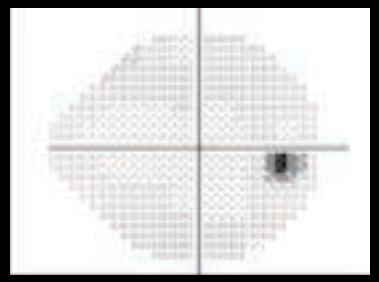


Mean Deviation (MD)
-10.8 dB
reflects severe glaucoma

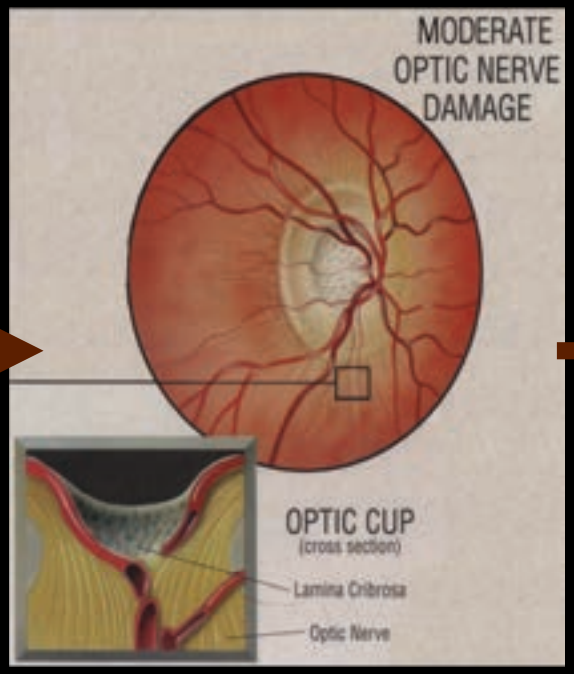
Background: Glaucoma causes characteristic structural and functional changes

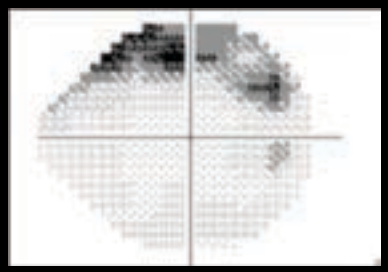
Normal



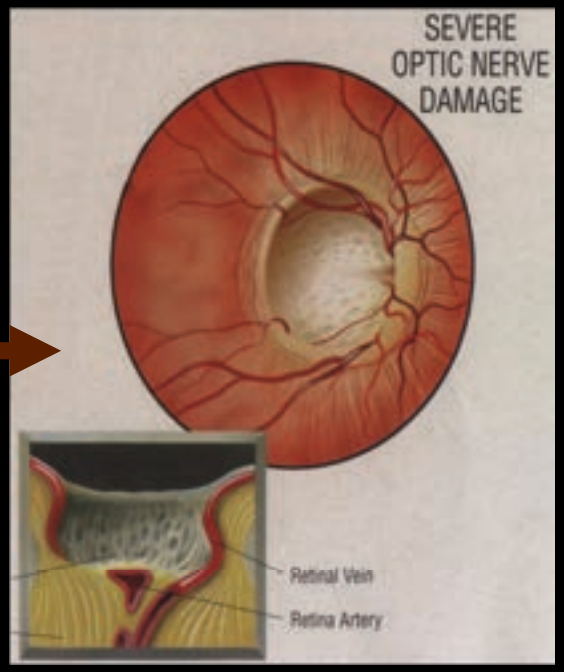


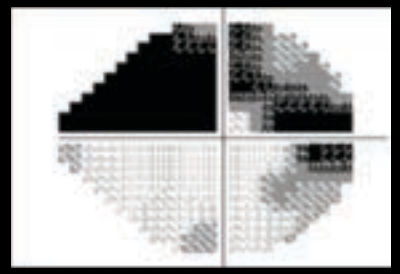
Moderate





Severe



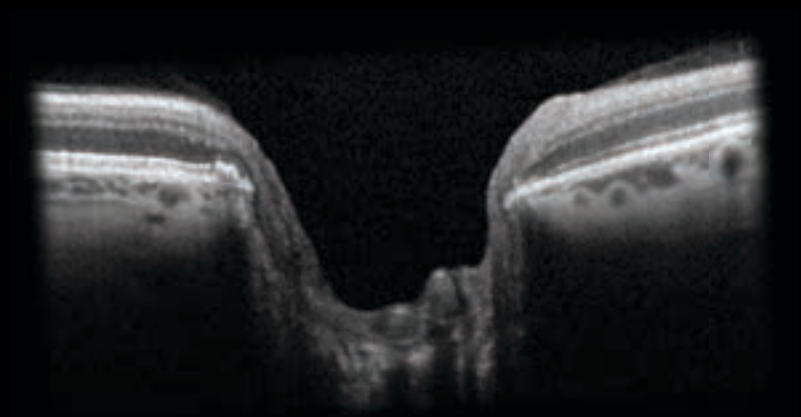


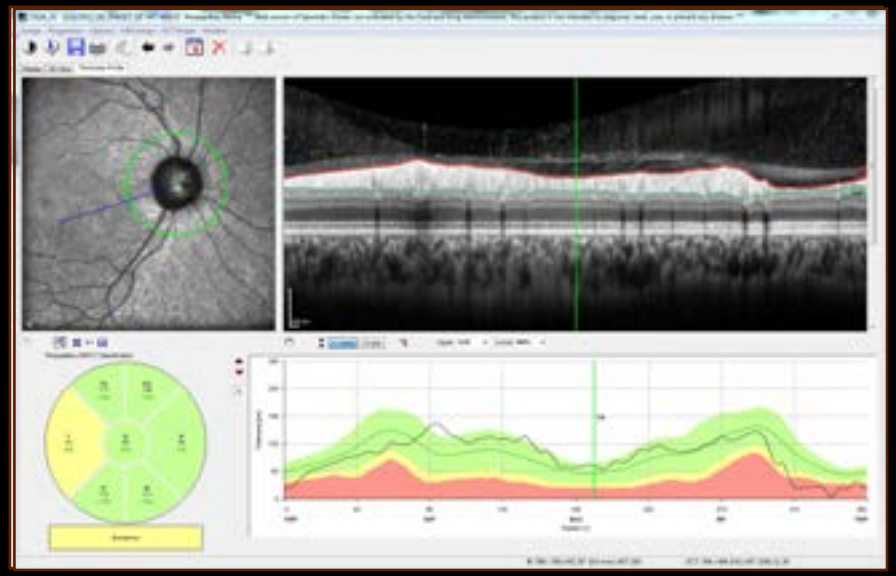
Historically, optic disc evaluation has been subjective with descriptions of change primarily qualitative

1995

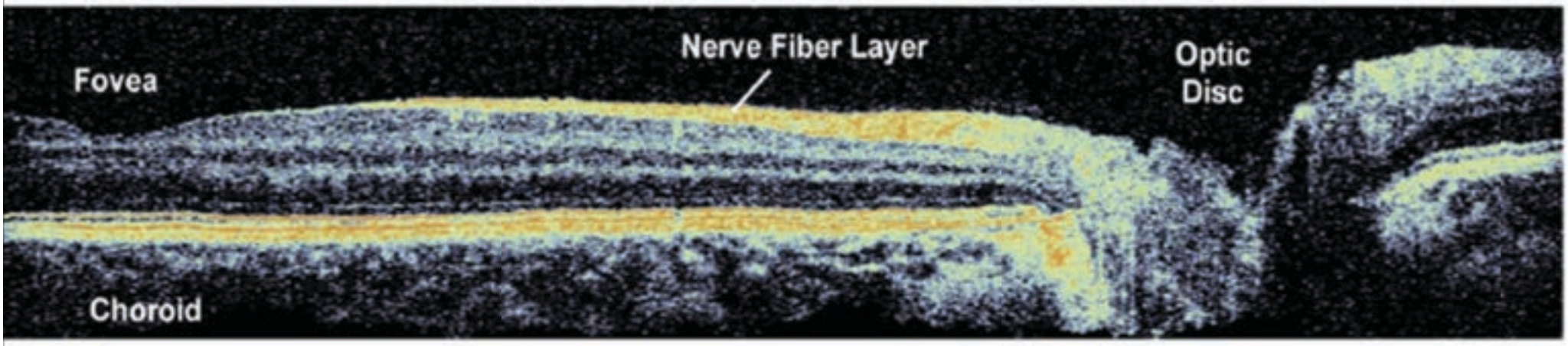
1996

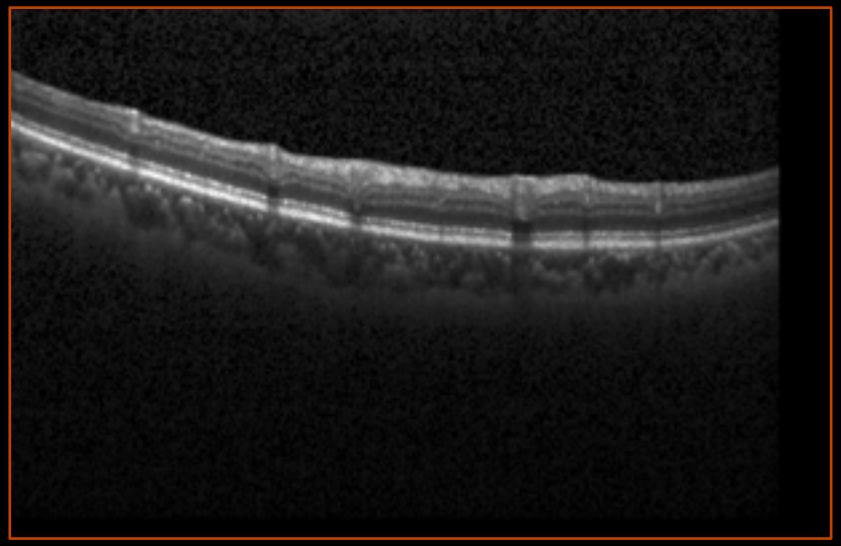
Tremendous Advances in Imaging Optical Coherence Tomography (OCT) Instruments

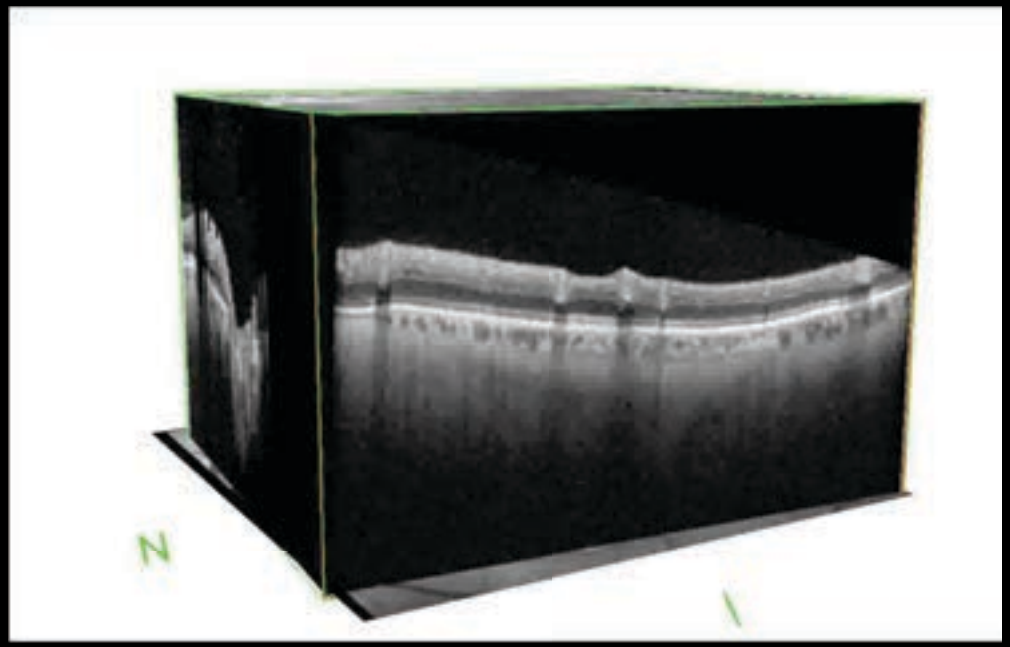




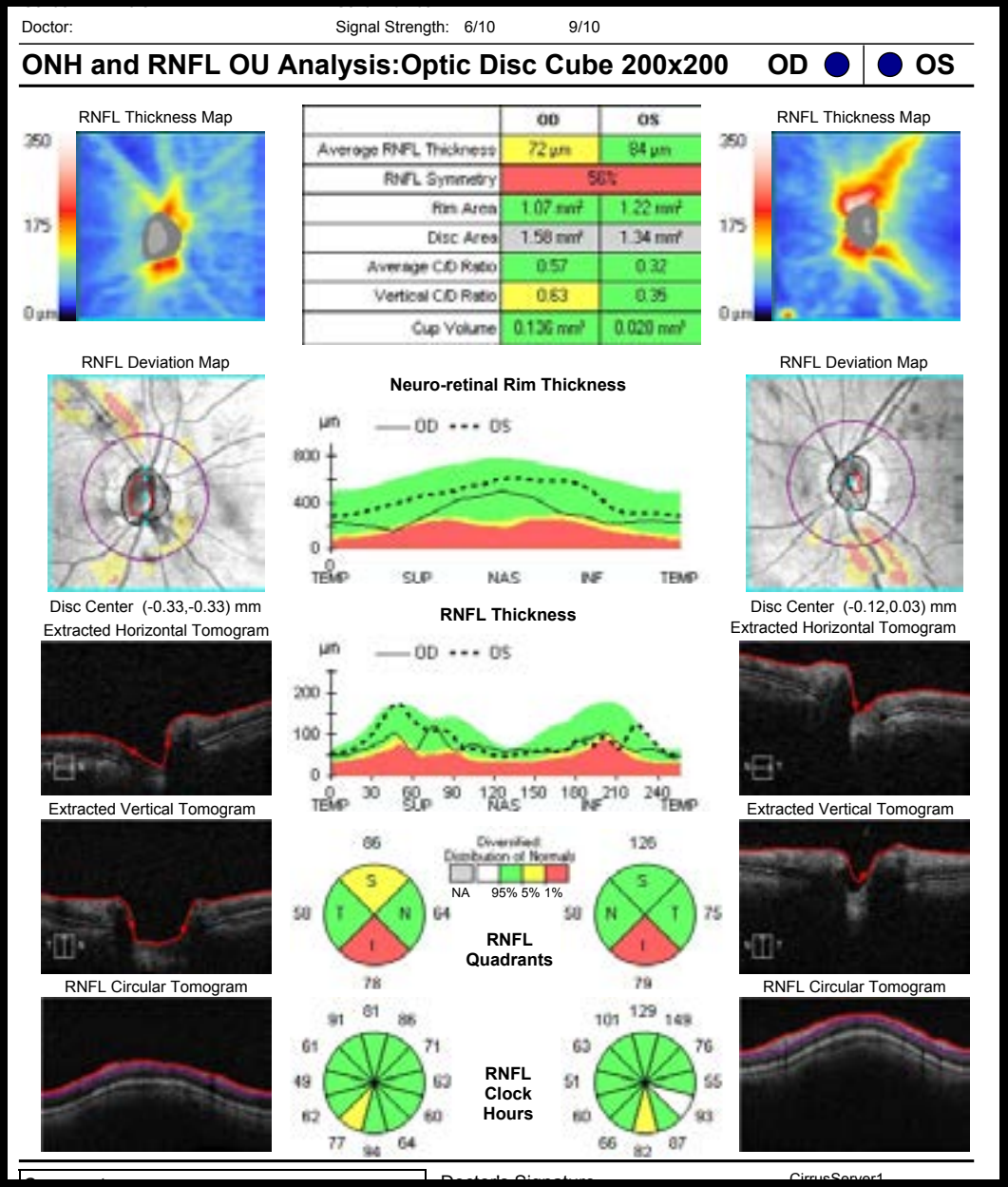
Virtual Histology
3D Window into the Retina







SDOCT Optic Nerve Head Scan



	OD	OS
Average RNFL Thickness	72 µm	84 µm
RNFL Symmetry	56%	
Rim Area	1.07 mm²	1.22 mm²
Disc Area	1.58 mm²	1.34 mm²
Average C/D Ratio	0.57	0.32
Vertical C/D Ratio	0.63	0.35
Cup Volume	0.136 mm³	0.020 mm³

Rim Information

Cup Information

Disc Information

RNFL Information

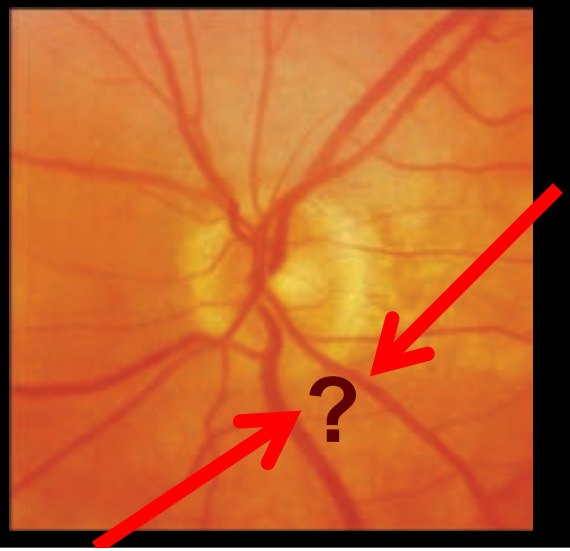
Imaging instruments show change that is difficult to detect in photographs

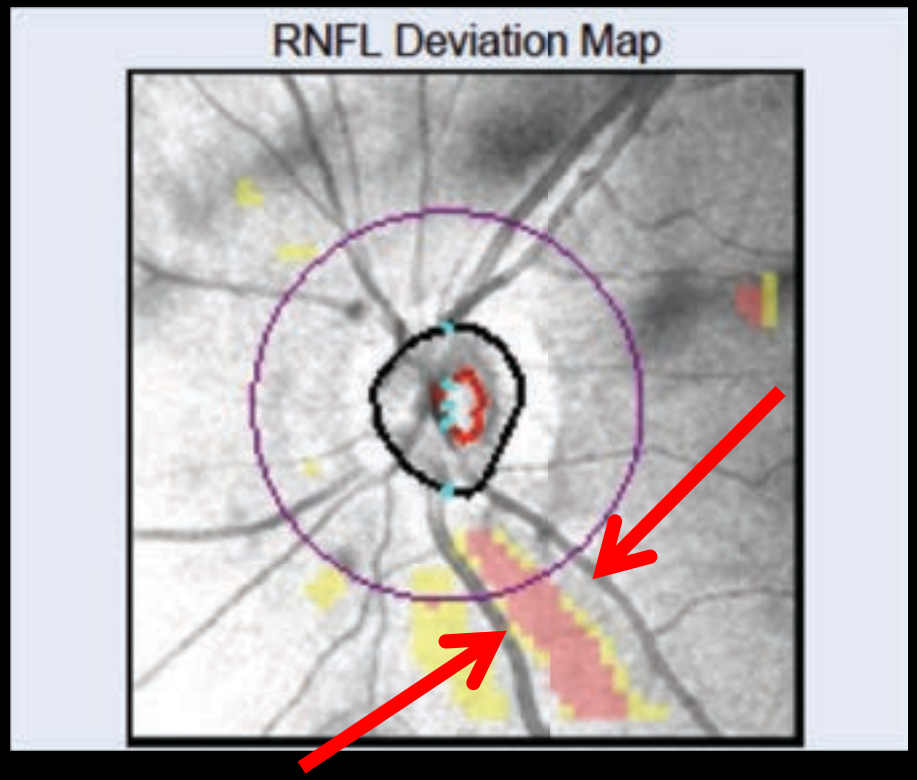
Photograph

Image

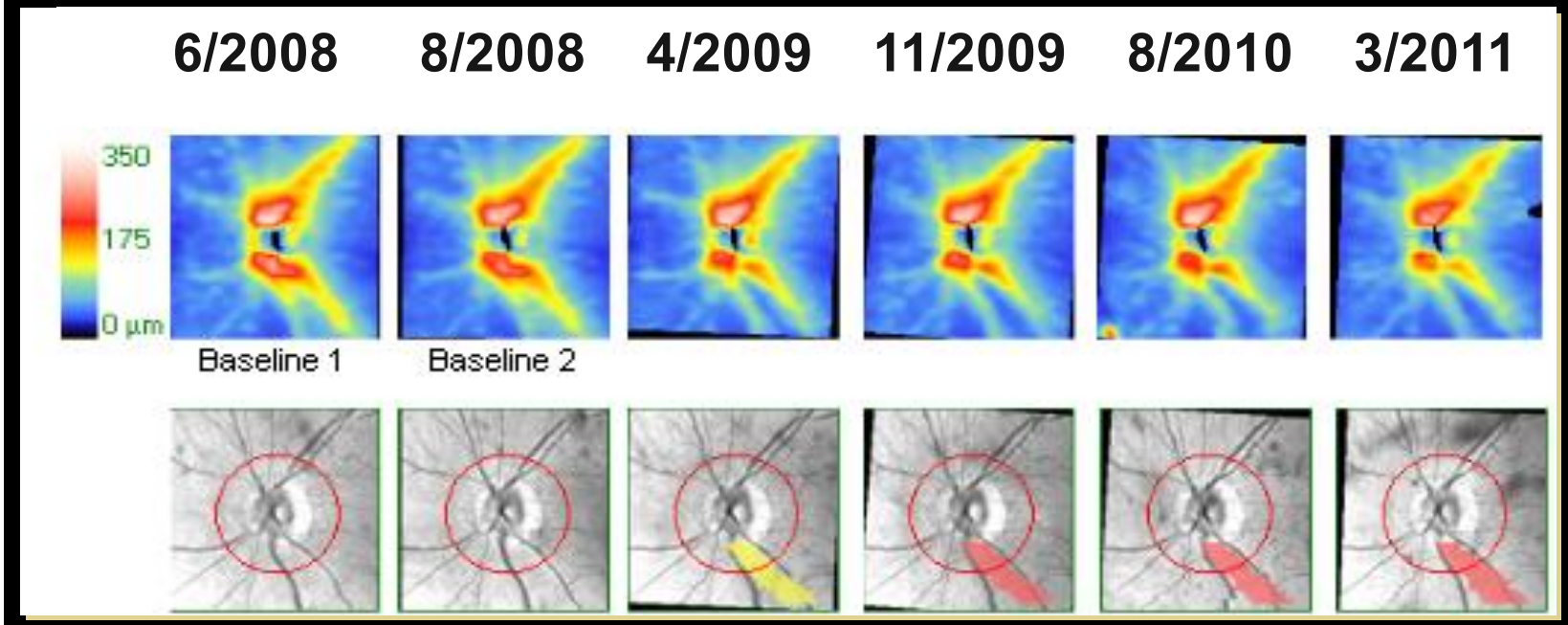
2008

2010

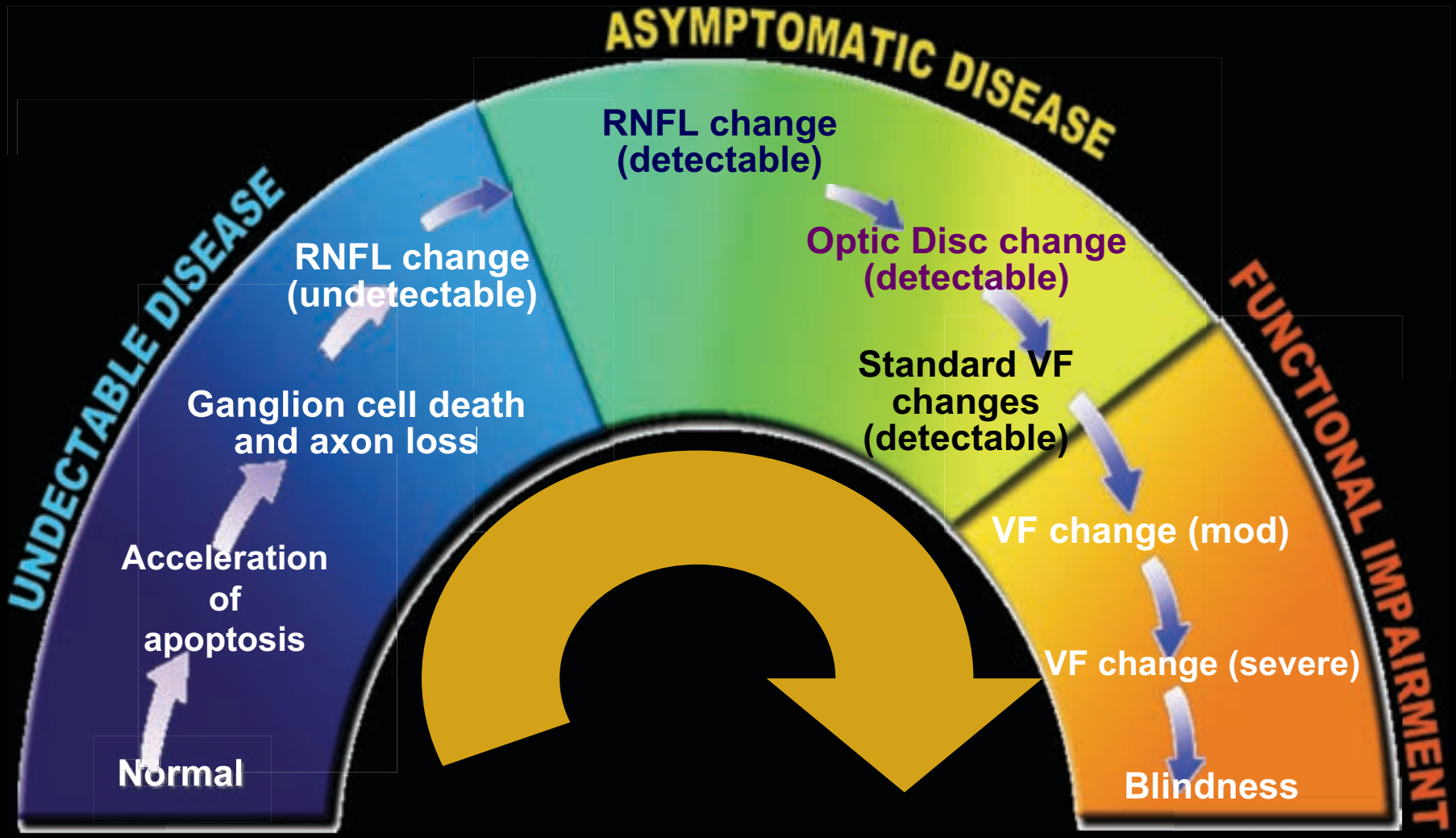




Progression Detection Example: Spectral Domain Optical Coherence Tomograph

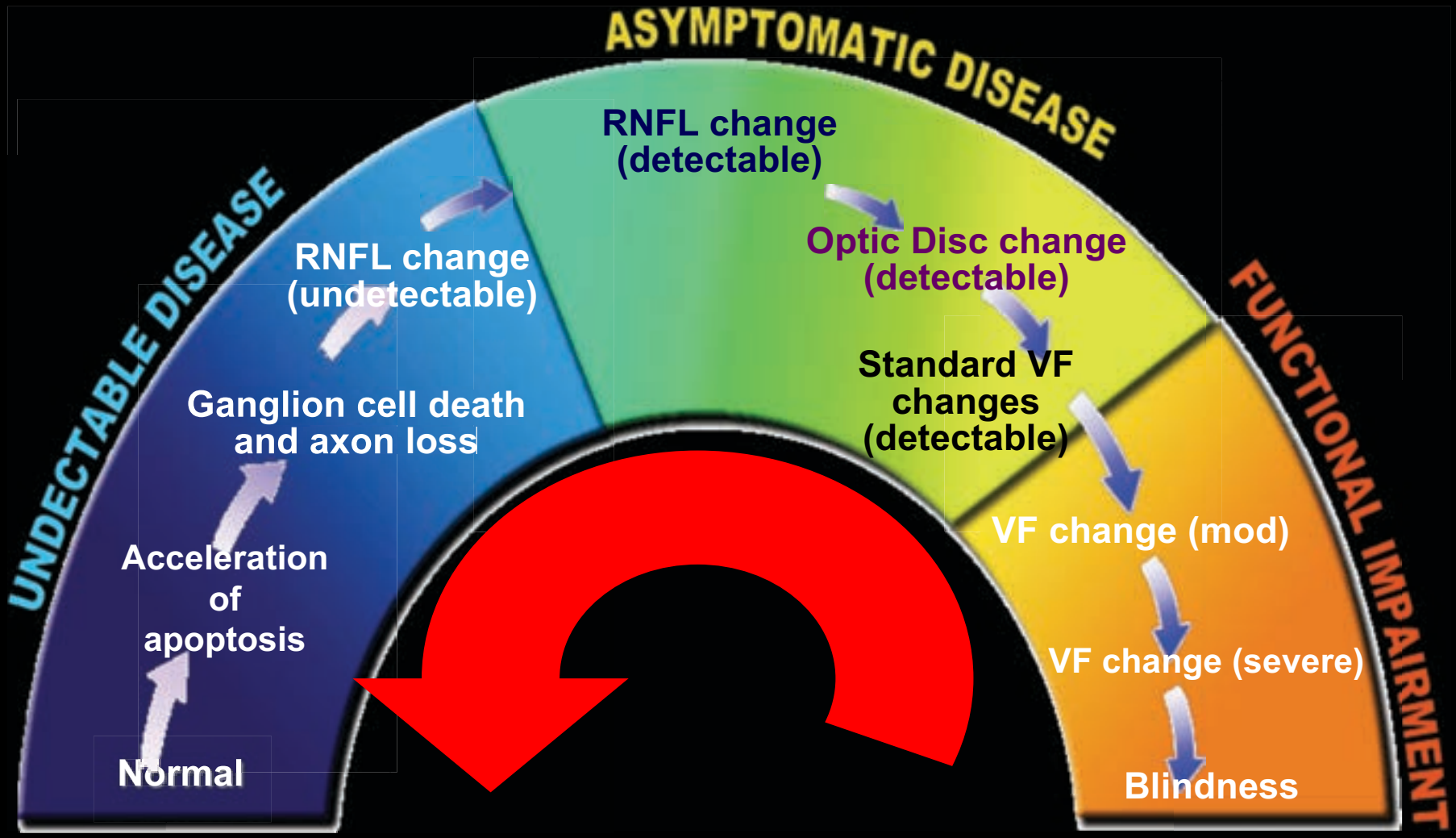


The Glaucoma Continuum (circa 2004)



Adapted From: Weinreb RN et. al. *Am J Ophthalmol* 138: 458-467, 2004.

What is Detectable is Changing



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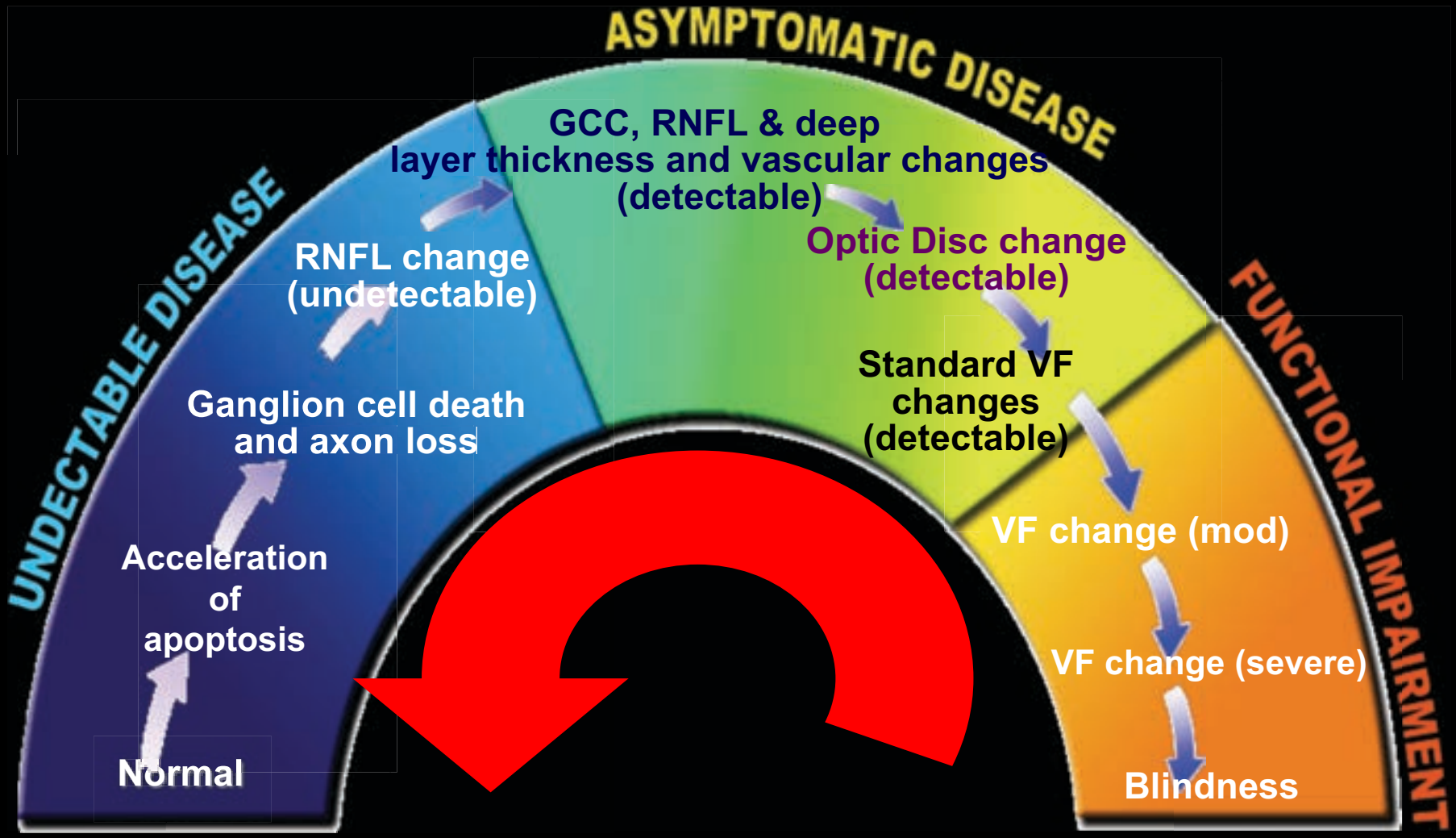
What is Detectable is Changing



Adapted From: Weinreb RN et. al. *Am J Ophthalmol* 138: 458-467, 2004.

Outline: Use of Research IT

1. **Clinical Research IT Infrastructure (4 NIH/Fdn/Industry studies)**
   - EPIC for scheduling patients
   - ACTRI supported RedCAP for data entry/management
   - Servers for document sharing
2. **Reading Center IT Infrastructure (7 NIH/Fdn/Industry studies)**
   - Supports numerous multicenter NIH, industry and foundation studies.
   - FileMakerPro databases
   - Image review stations and servers for image QC and data distribution
   - ACTRI supported RedCAP and Vellos for data entry and management;
   - Servers for curated data sharing among staff, investigators and trainees
   - Software
3. **Computational Ophthalmology Core**
   - Custom segmentation software
   - Artificial intelligence/ Deep learning strategies to detect glaucoma
   - Triton Shared Computing Cluster (TSCC) GPU and CPU

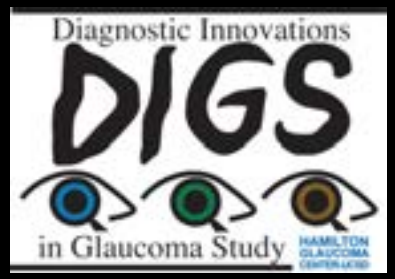
Hamilton Glaucoma Center Clinical Research Team

Clinical Research Coordinators:

Eunice Williams-Steppe MS
(supervisor)

Tess Acera
Veronica Rubio
Walter Siqueiros Garcia

UCSD Funded Clinical Cohort Studies and Co-investigators



1995 – present (NIH)
Myopia and Glaucoma Focus 2017-present

LM Zangwill (PI)

FA Medeiros, RN Weinreb

C Bowd, A Belghith, PA Sample

2002- present (NIH)
Lamina Focus 2017-present

M Fazio, CA Girkin, LM Zangwill (co-PIs)

JM Liebmann, PA Sample, RN Weinreb

Ocular Hypertension Treatment Study
20-year follow-up (NIH)
2015-present added OCT
LM Zangwill (PI)

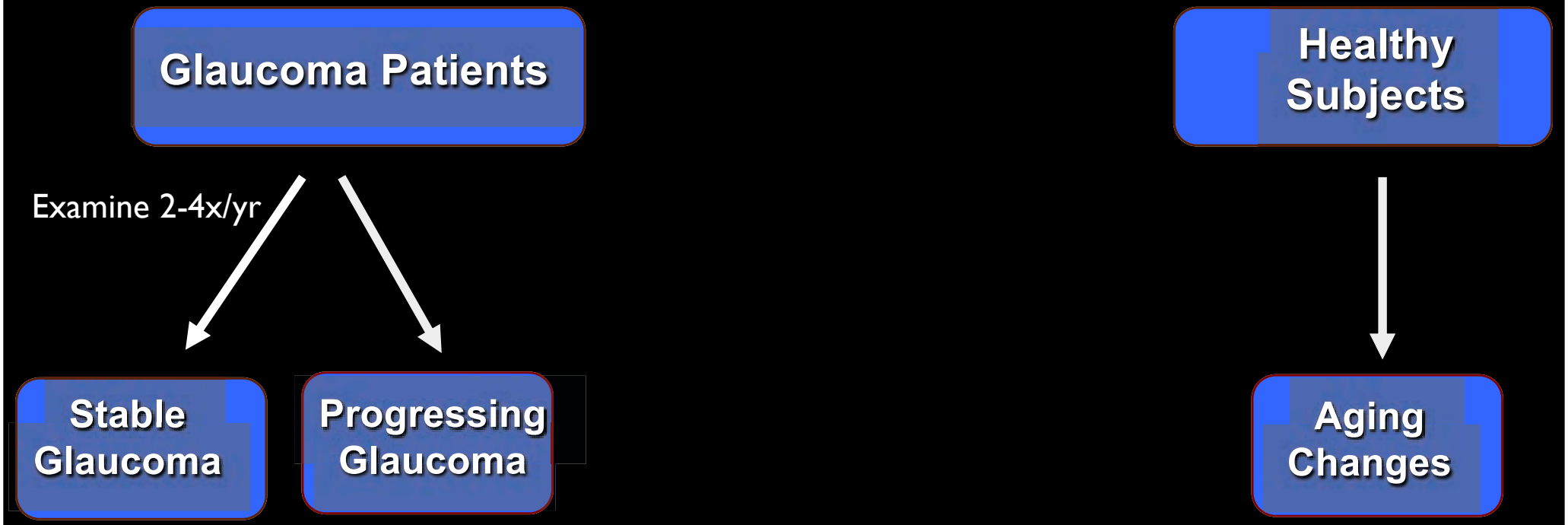
CSLO Ancillary Study (1995-2010)

2017-2019

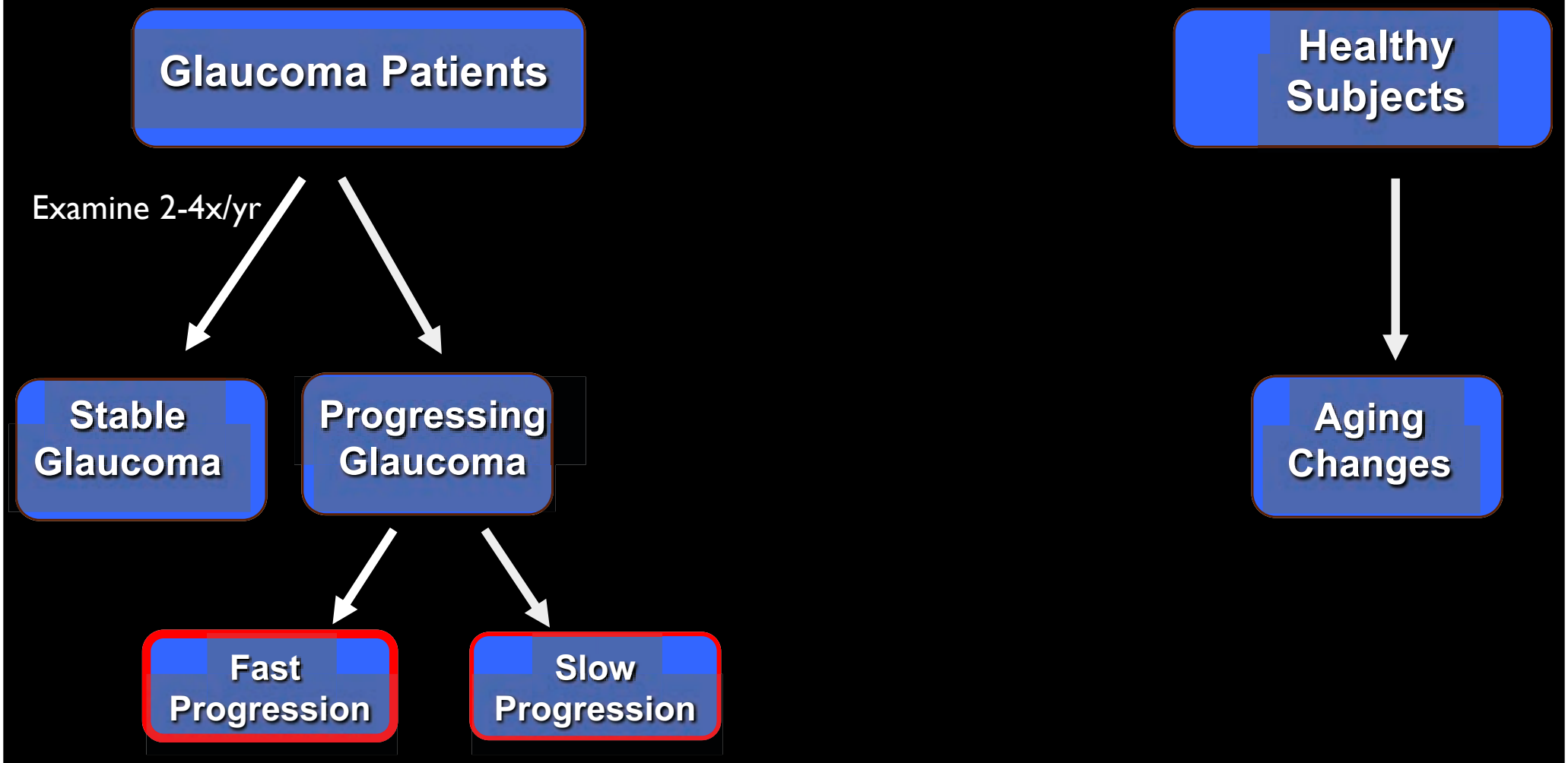
Lamina and OCTA Focus
LM Zangwill (PI)

Diagnostic Innovations in Glaucoma Study

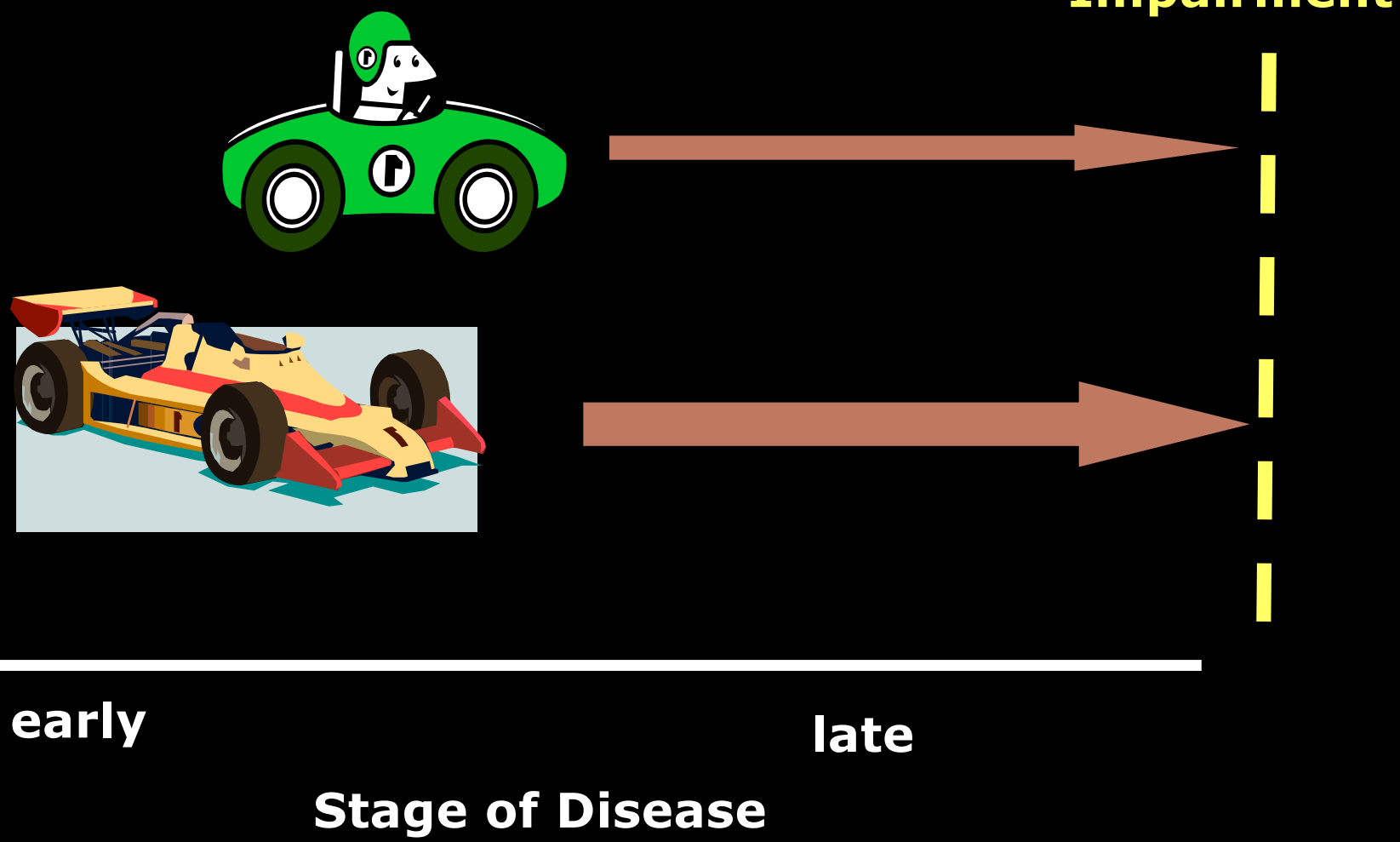
African Descent and Glaucoma Evaluation Study



Identify fast progressing eyes early



Why is knowing the rate of glaucomatous change important?



Adapted from Garway-Heath

OCT to measure rate of RNFL loss

Rates of Retinal Nerve Fiber Layer Thinning in Glaucoma Suspect Eyes

Atsuya Miki, MD, PhD,[1,2] Felipe A. Medeiros, MD, PhD,[1] Robert N. Weinreb, MD,[1] Sonia Jain, PhD,[3] Feng He, MS,[3] Lucie Sharpsten, PhD,[1] Naira Khachatryan, MD, PhD,[1] Na'ama Hammel, MD,[1] Jeffrey M. Liebmann, MD,[4,5] Christopher A. Girkin, MD,[6] Pamela A. Sample, PhD,[1] Linda M. Zangwill, PhD[1]

Ophthalmol 2014: 121:1350-1358

Miki et al Ophthalmol 2014

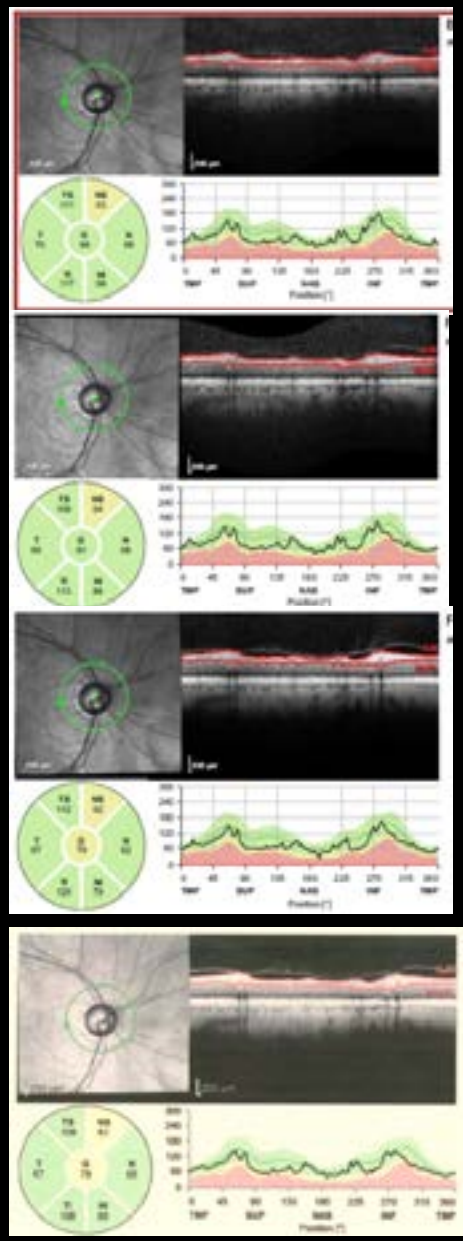
ADAGES/DIGS Glaucoma Suspects

Spectralis OCT

Glaucoma Suspects
No Repeatable
Visual Field Damage
(n=469 eyes)

Median follow-up: 2.5 yrs.

Median no. OCT exams: 4.7



Miki et al Ophthalmol 2014

ADAGES/DIGS Glaucoma Suspects

Glaucoma Suspects
No Repeatable
Visual Field Damage
(n=469 eyes)

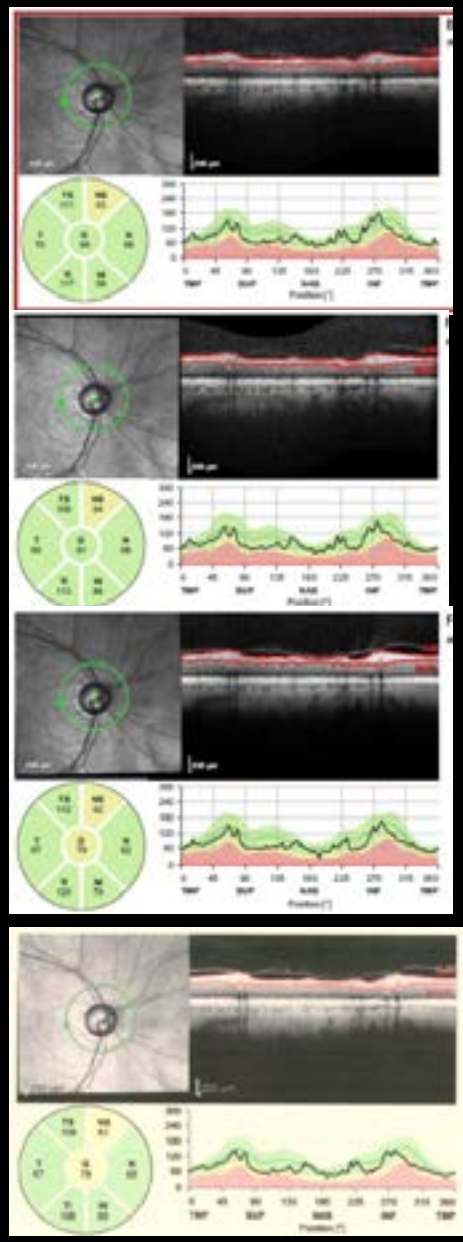
Median follow-up: 2.5 yrs.

Median no. OCT exams: 4.7

No Visual Field
Damage
(n=420)

Visual Field
Damage
(n=49)

Spectralis



Miki et al Ophthalmol 2014

Rate of average SDOCT RNFL Loss is 2x faster in eyes that developed VF Damage

Glaucoma Suspects No Repeatable Visual Field Damage (n=469 eyes)

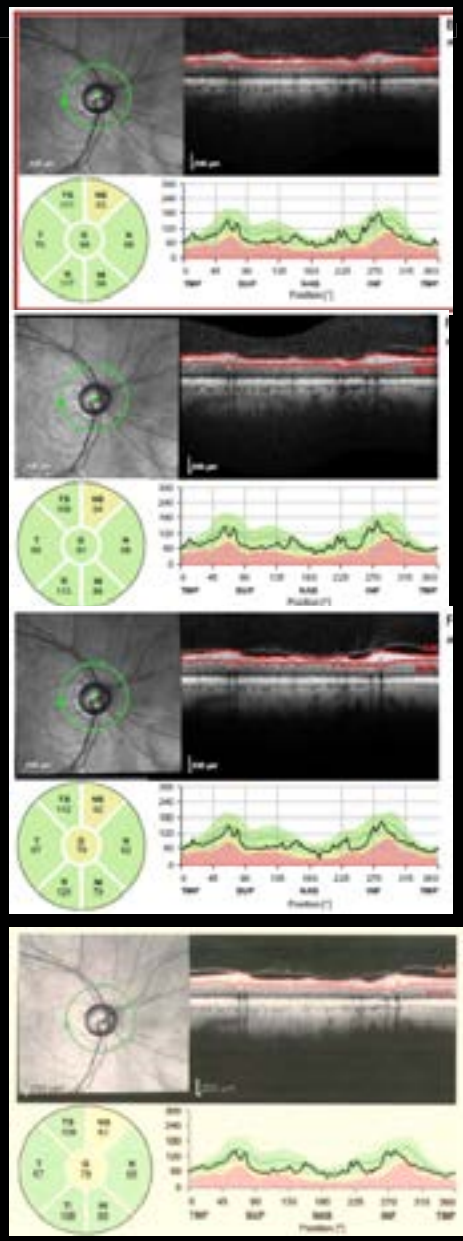
Median follow-up: 2.5 yrs.

Median no. OCT exams: 4.7

No Visual Field Damage (n=420) → **-0.63 µm/year**

Visual Field Damage (n=49) → **-1.36 µm/year**

2x faster (p=0.0003)



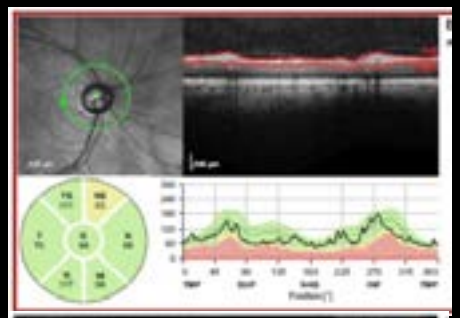
Miki et al Ophthalmol 2014

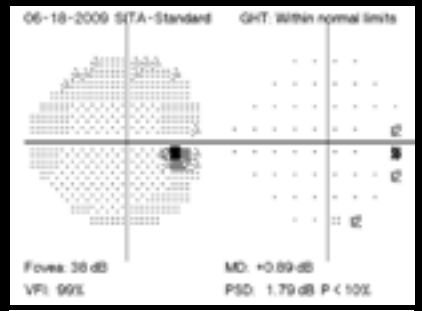
Case. Developed VF damage

SDOCT

Visual Field

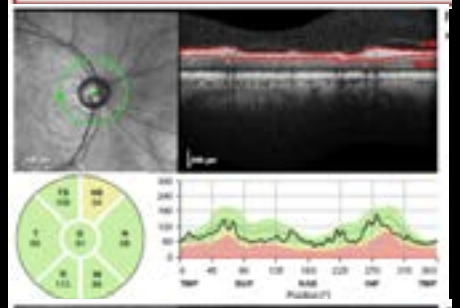
2009

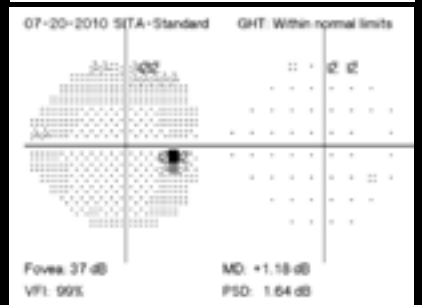




MD
0.98 dB

2010

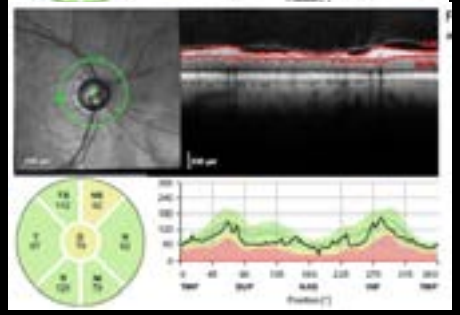


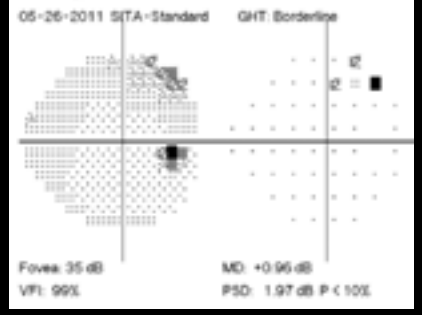


1.18 dB

2011

?

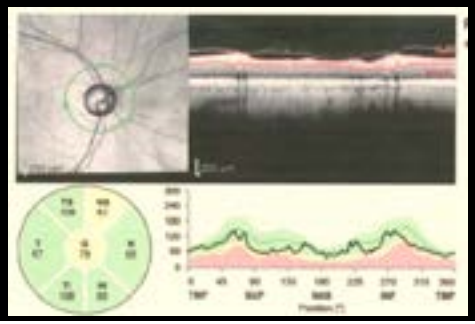


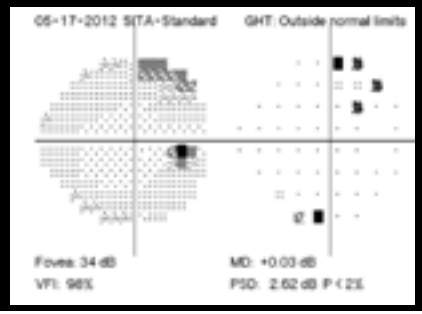


0.96 dB

2012

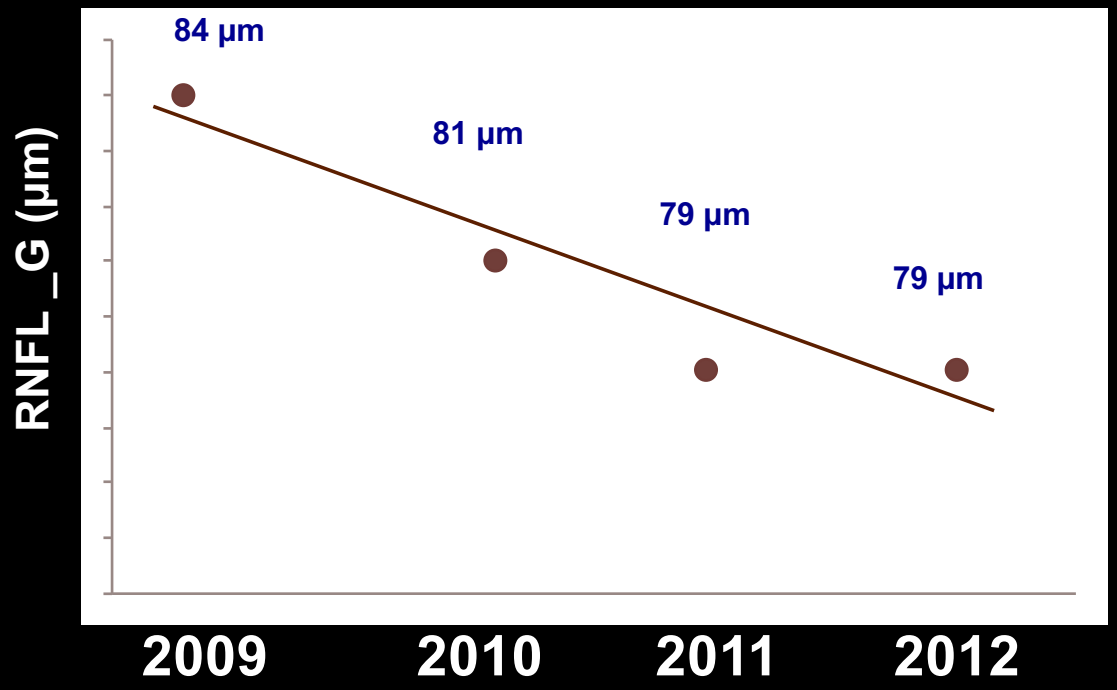
?

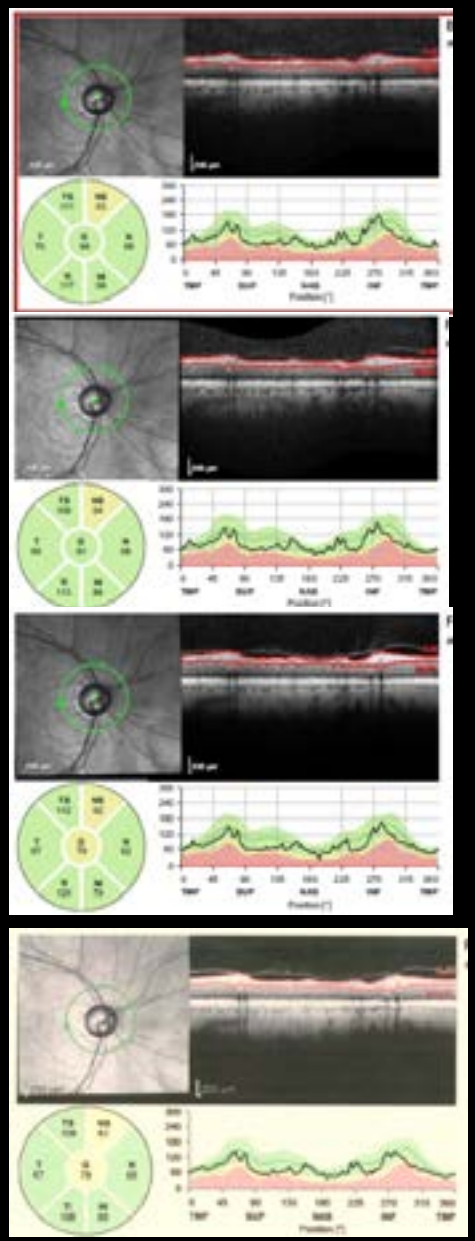




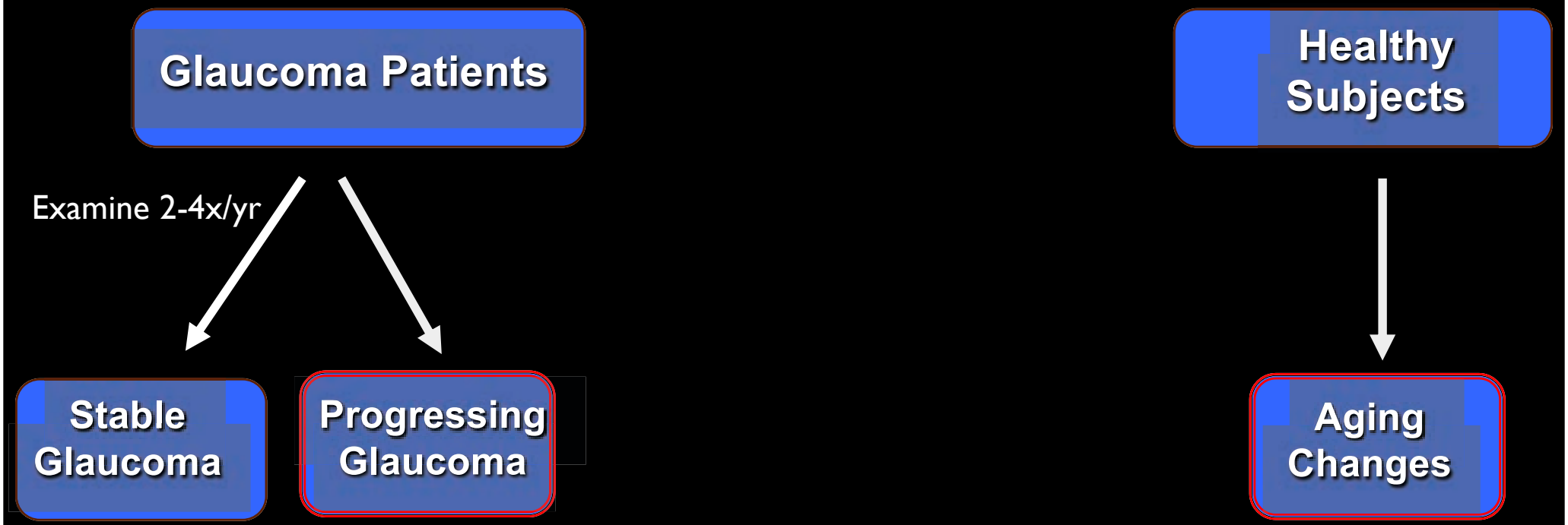
0.03 dB

Case 1. RNFL slope -1.70µm/year
Developed VF damage





Challenge: Glaucomatous change or aging change? Instruments can't differentiate on their own



1. **Clinical Research IT Infrastructure (4 NIH/Fdn/Industry studies)**
   - EPIC for scheduling patients
   - ACTRI supported RedCAP for data entry/management
   - Servers for document sharing (IRB, Forms,)

Outline: Use of Research IT

1. **Clinical Research IT Infrastructure (4 NIH/Fdn/Industry studies)**
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   - Custom segmentation software
   - Artificial intelligence/ Deep learning strategies to detect glaucoma
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   -

Hamilton Glaucoma Center Imaging Data Evaluation and Analysis (IDEA) Reading Center Team

Coordinators:

Keri Dirkes MPH
(supervisor)

Maria Hunsicker
Suzanne Vega MPH

IDEA CENTER
Imaging Data Evaluation & Analysis Center
Hamilton Glaucoma Center, University California San Diego

IDEA Center Role: Imaging Instruments

- Perform centralized data processing and analysis for study sponsors
- Certify image acquisition operators
- Monitor quality
- Provide feedback to study center personnel
- Determine diagnostic classification (if required by study protocol)
- Identify progression

IDEA CENTER
Imaging Data Evaluation & Analysis Center
Hamilton Glaucoma Center, University California San Diego

Reading Centers for NIH and Industry Studies (2019)

National Eye Institute Funding:

Diagnostic Innovations in Glaucoma Study (DIGS): Myopia

African Descent in Glaucoma Evaluation Study (ADAGES IV): Lamina

Ocular Hypertension Treatment Study (OHTS) 20 yr follow-up

Diagnosis and Monitoring of Glaucoma with OCTA

Machine Learning methods for Detecting Disease-Related Functional and Structural Change in Glaucoma

Brightfocus Foundation Funding

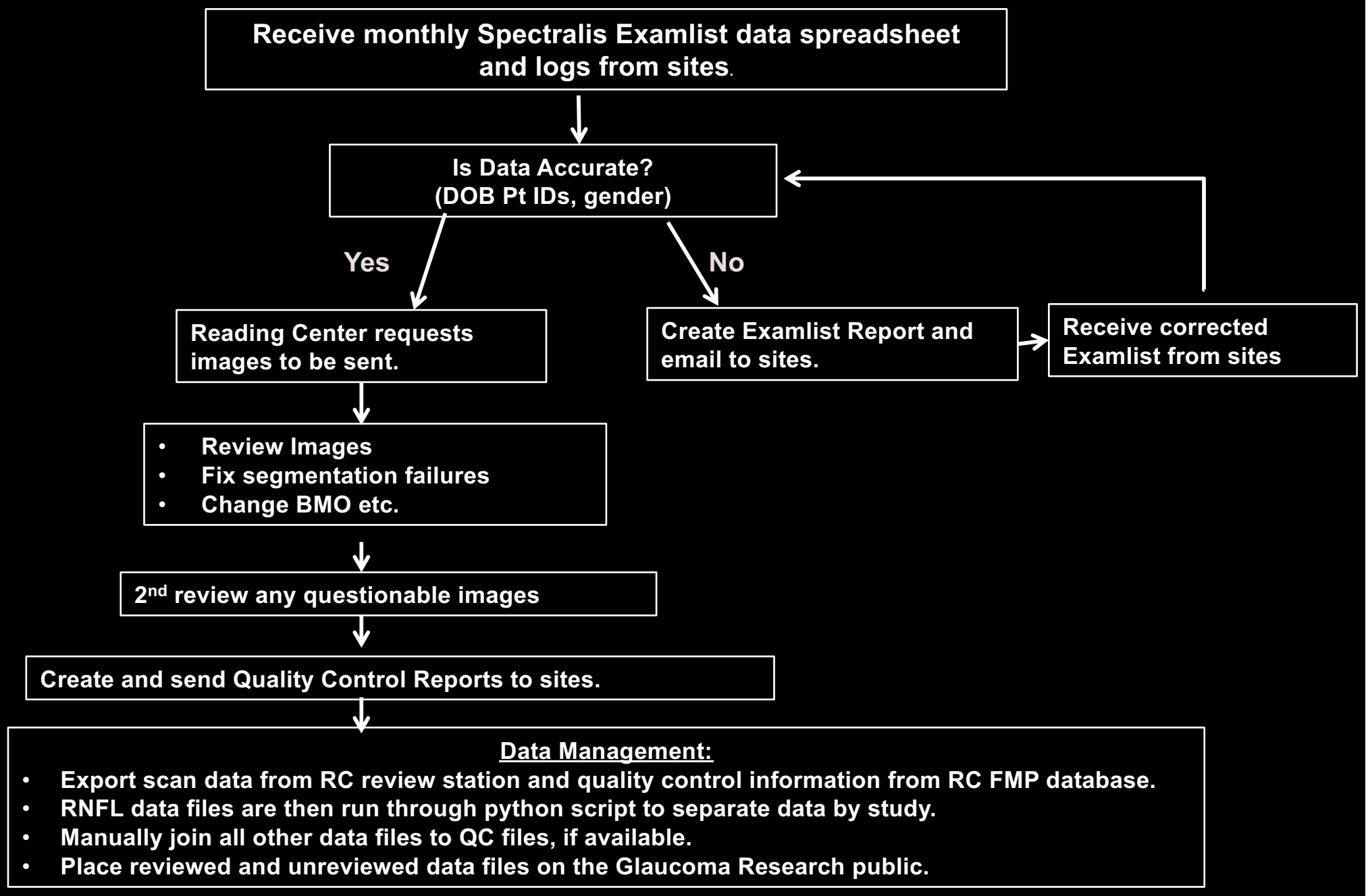
"Role of Microvasculature in the Pathophysiology of Glaucoma"

Industry Funding

-Heidelberg Engineering: ANTERION Imaging Agreement Study

-Pfizer

Reading Center Pipeline



Over 200,000 OCT Images reviewed!

Over 100,000 visual fields reviewed!

Curated data sharing on secure servers for analysis

Outline: Use of Research IT

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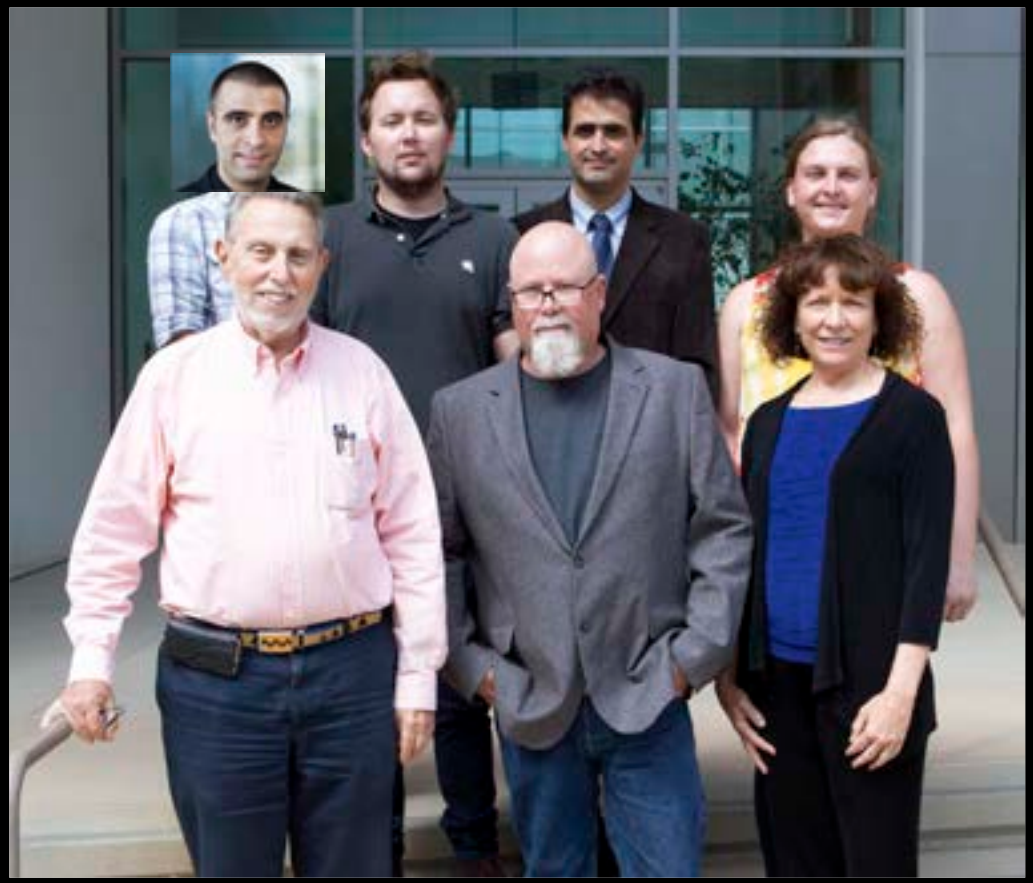
Hamilton Glaucoma Center Computational Ophthalmology Team

Akram Belghith, PhD
Christopher Bowd, PhD
Mark Christopher, PhD
Jade Dohelman
Michael Goldbaum, MD
Sasan Moghimi, MD
Linda M. Zangwill, PhD



Deep Learning Analysis of Fundus Photographs Accurately Detects Glaucoma

SCIENTIFIC REPORTS

OPEN

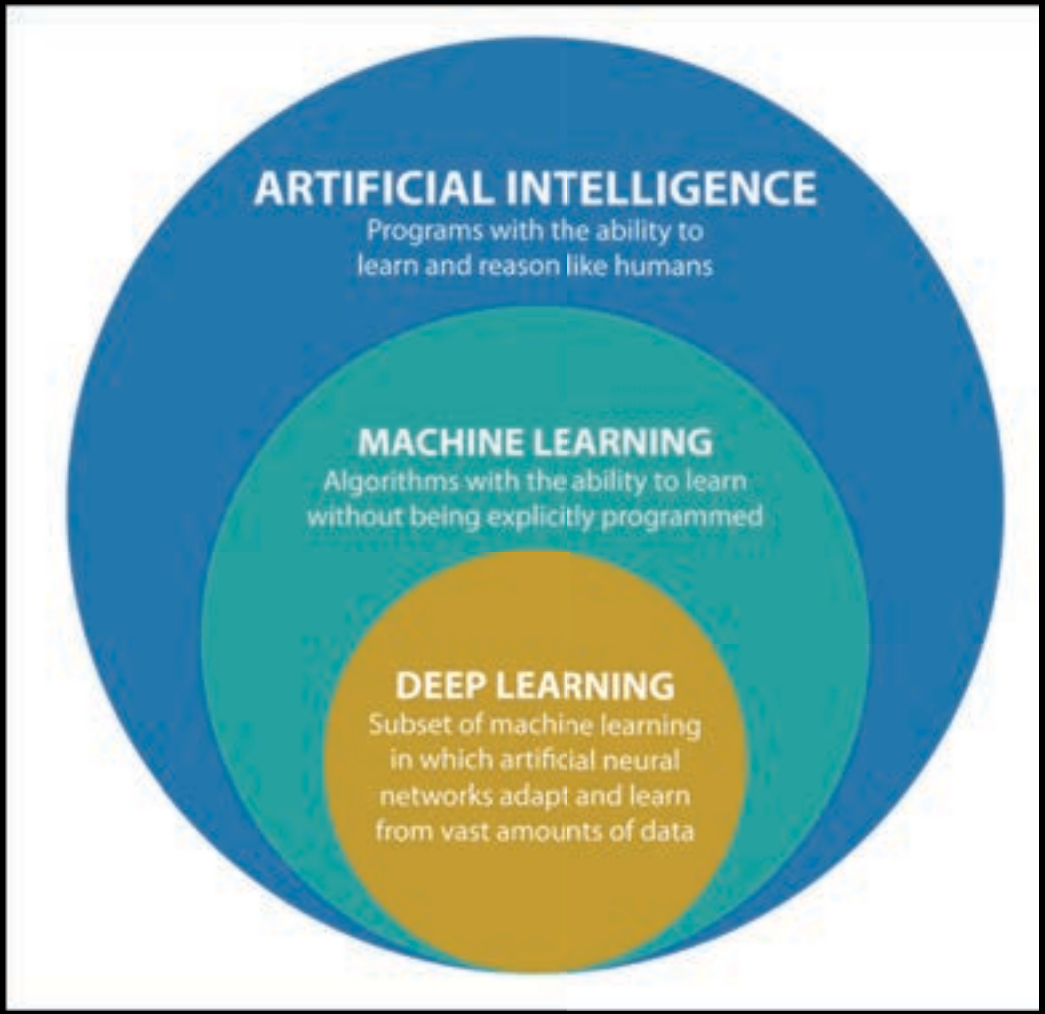
Received: 28 August 2018
Accepted: 29 October 2018
Published online: 12 November 2018

Performance of Deep Learning Architectures and Transfer Learning for Detecting Glaucomatous Optic Neuropathy in Fundus Photographs

Mark Christopher[1], Akram Belghith[1], Christopher Bowd[1], James A. Proudfoot[1], Michael H. Goldbaum[1], Robert N. Weinreb[1], Christopher A. Girkin[2], Jeffrey M. Liebmann[3] & Linda M. Zangwill[1]

The ability of deep learning architectures to identify glaucomatous optic neuropathy (GON) in fundus photographs was evaluated. A large database of fundus photographs (n = 14,822) from a racially and ethnically diverse group of individuals (over 33% of African descent) was evaluated by expert reviewers and classified as GON or healthy. Several deep learning architectures and the impact of transfer learning were evaluated. The best performing model achieved an overall area under receiver operating characteristic (AUC) of 0.91 in distinguishing GON eyes from healthy eyes. It also achieved an AUC of 0.97 for identifying GON eyes with moderate-to-severe functional loss and 0.89 for GON eyes with mild functional loss. A sensitivity of 88% at a set 95% specificity was achieved in detecting moderate-to-severe GON. In all cases, transfer improved performance and reduced training time. Model visualizations indicate that these deep learning models relied on, in part, anatomical features in the inferior and superior regions of the optic disc, areas commonly used by clinicians to diagnose GON. The results suggest that deep learning-based assessment of fundus images could be useful in clinical decision support systems and in the automation of large-scale glaucoma detection and screening programs.

What is artificial intelligence (AI) and deep learning?

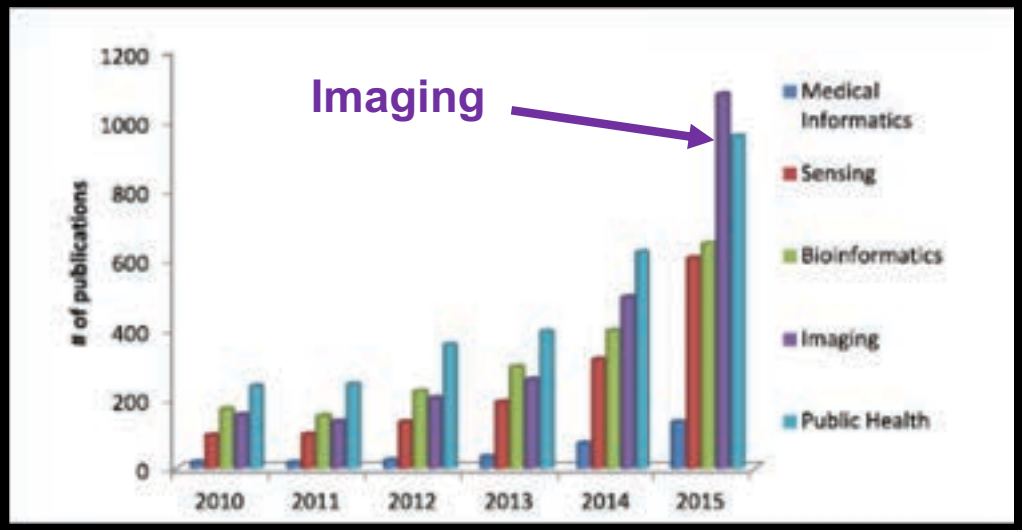


https://www.argility.com/argility-ecosystem-solutions/iot/machine-learning-deep-learning/

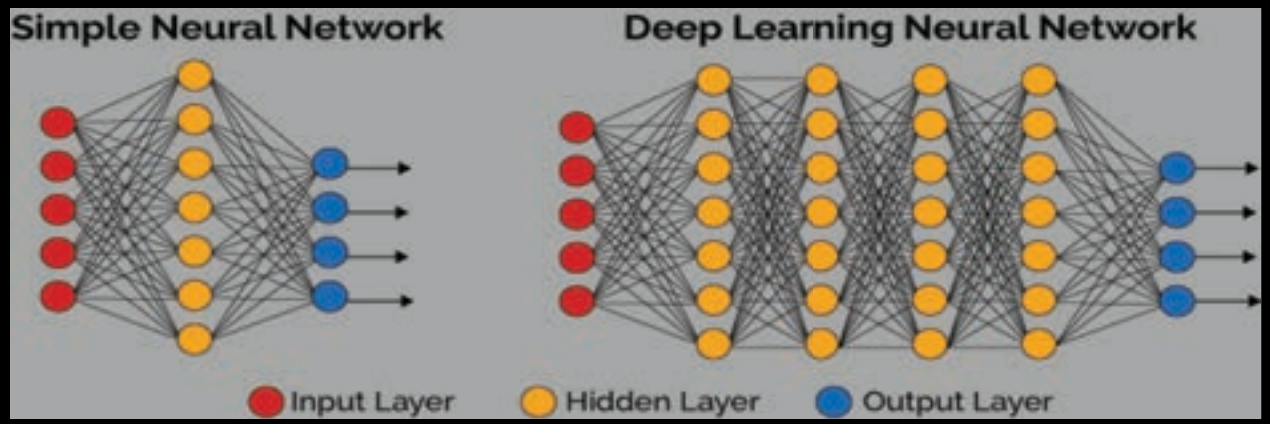
Deep Learning: Tremendous Progress in Last 5 Years

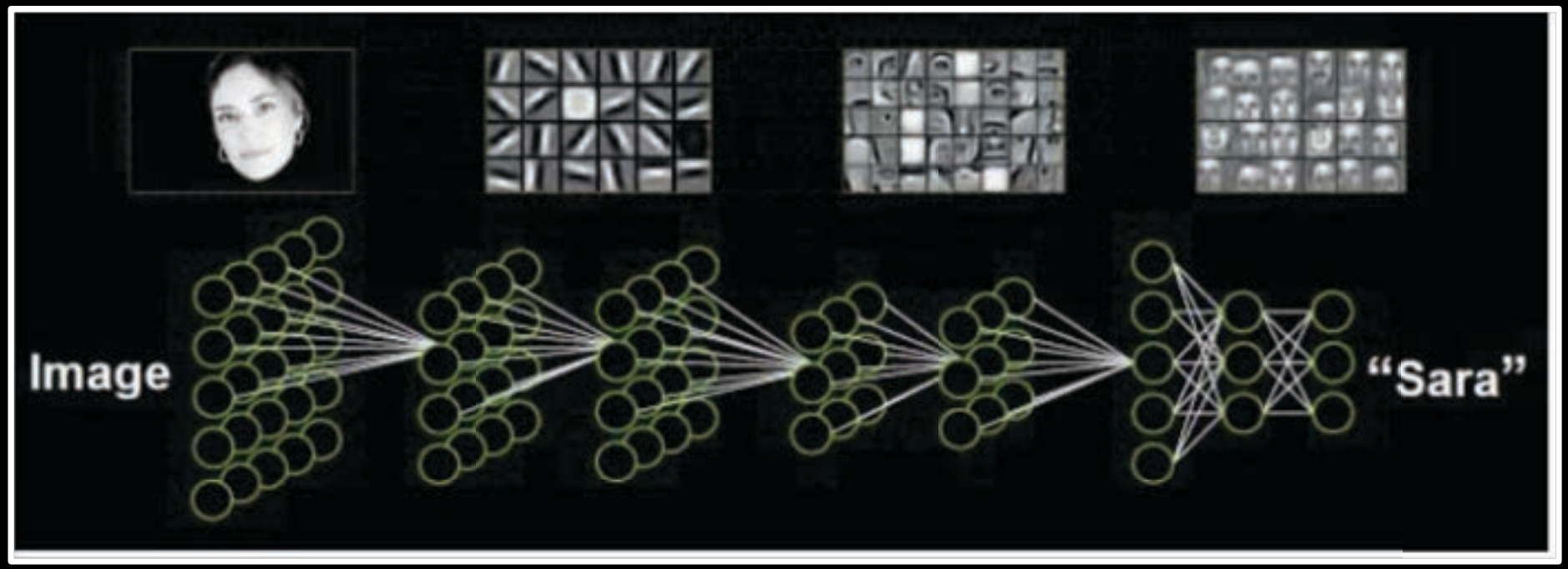
- Computational power (GPUs etc.)
- Software (Caffe, TensorFlow, Theono etc)
- Large datasets
- Transfer Learning

Published papers using deep learning in health informatics



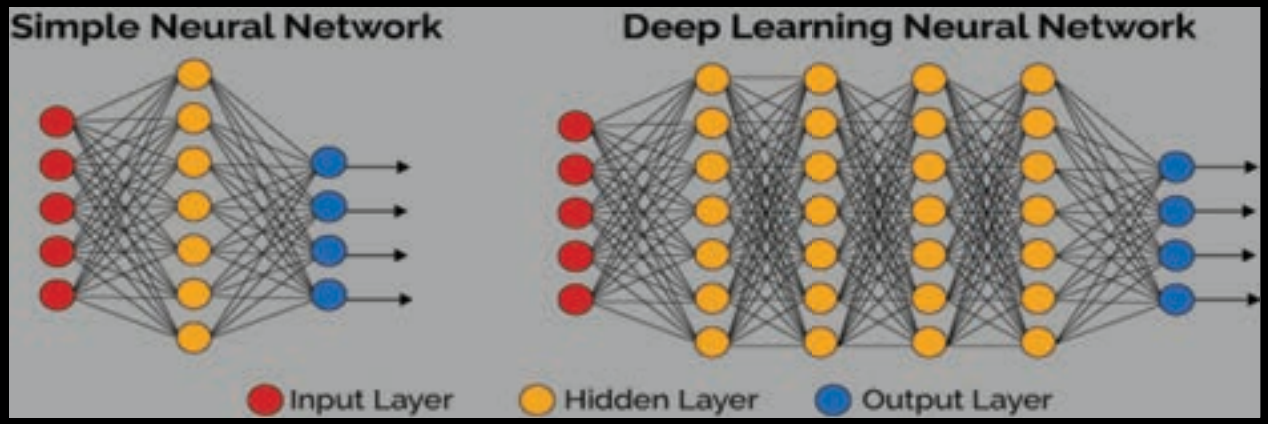
Deep Learning with Convolutional Neural Networks (CNNs) models complex patterns within images

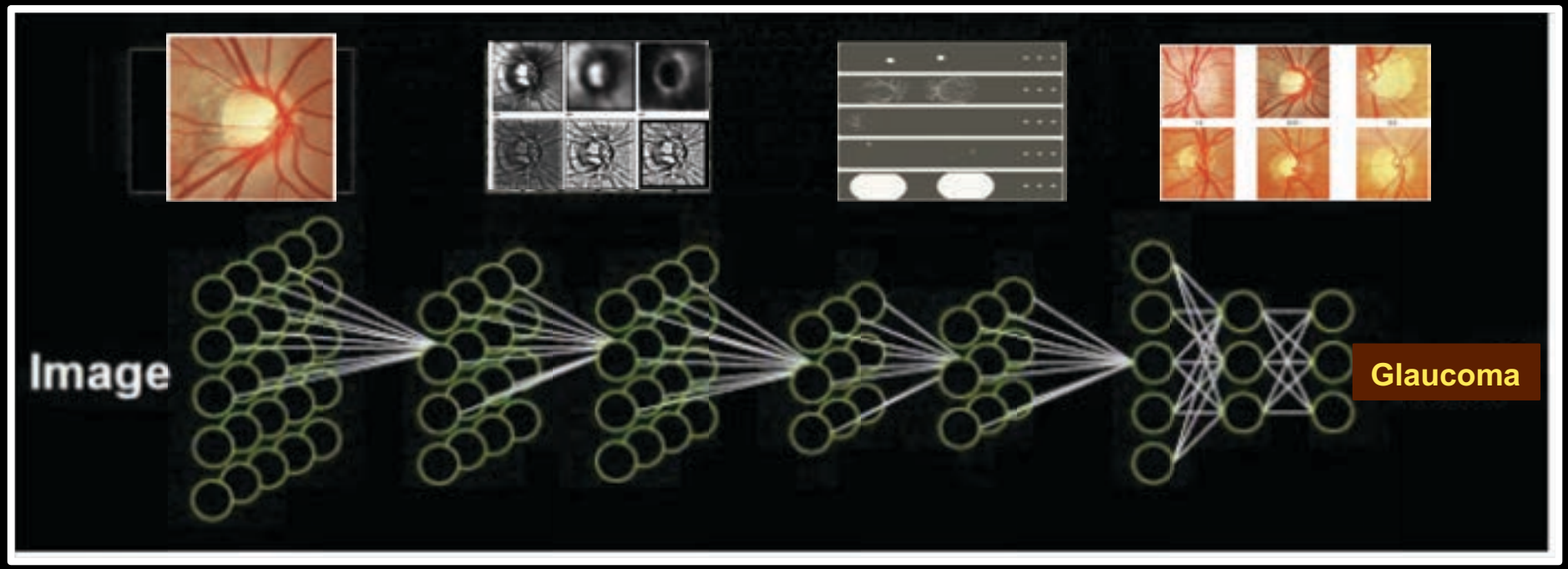




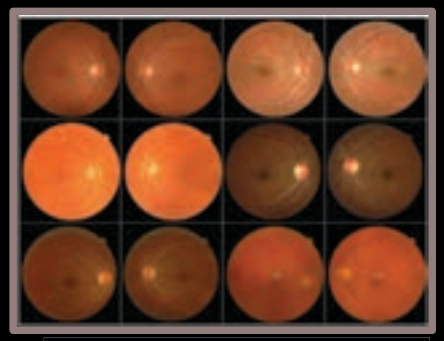
Courtesy of Michael Abramoff, MD, PhD

Deep Learning with Convolutional Neural Networks (CNNs) models complex patterns within images

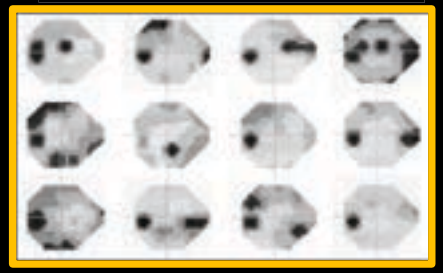




Deep Learning Workflow (supervised)



Lots of labeled data



Training set

Learn deep neural net

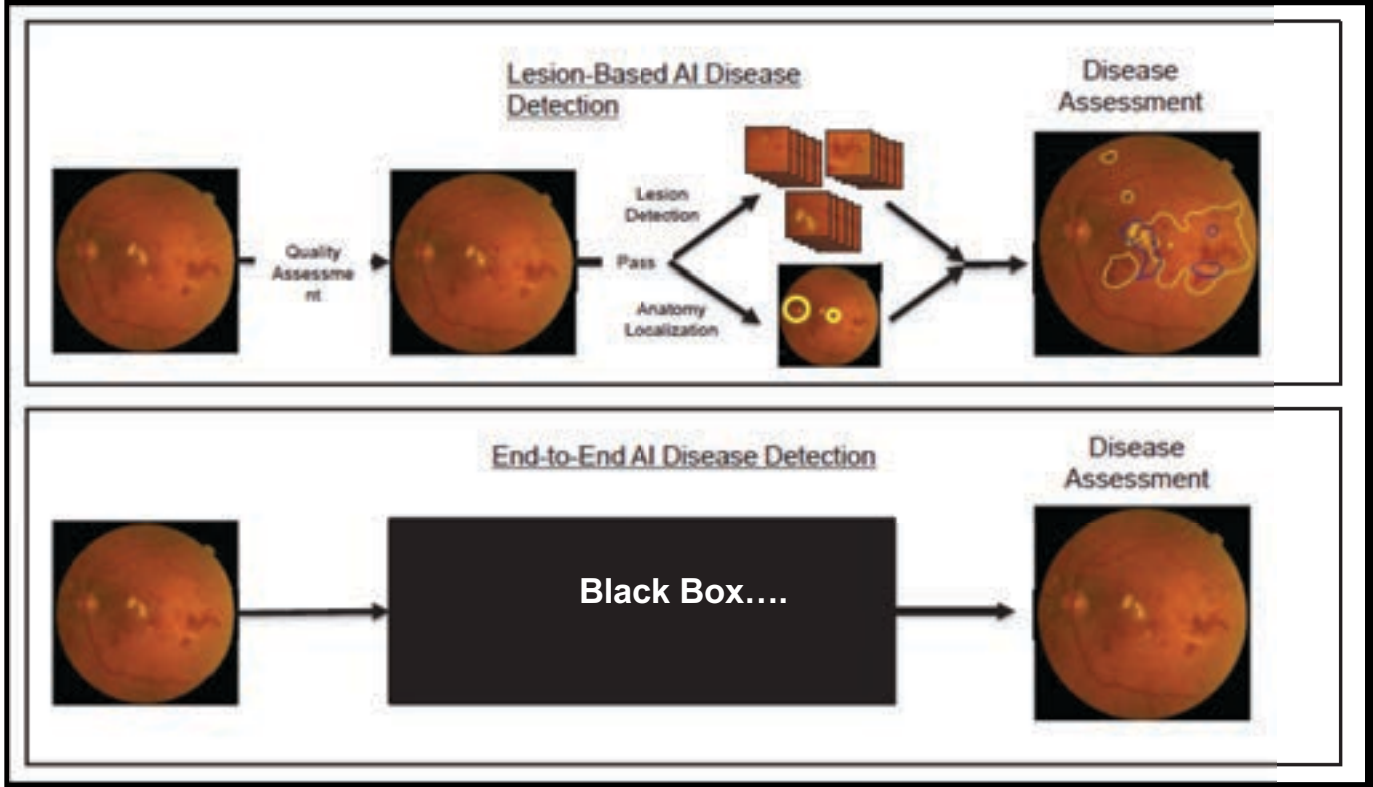
Adjusts
- parameters
- network
- architecture

Black box

Validate

Independent validation set

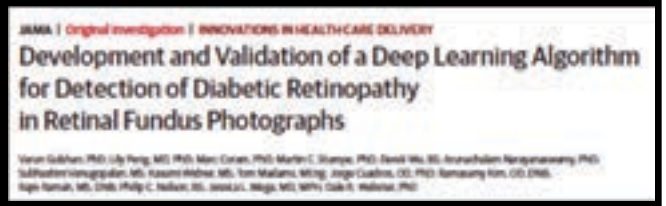
Deep Learning Algorithm Design (Lesion based vs black box)




Retina

Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning

Michael David Abràmoff,[1-3] Yiyue Lou,[4] Ali Erginay,[5] Warren Clarida,[3] Ryan Amelon,[3] James C. Folk,[1,3] and Meindert Niemeijer[3]


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

Courtesy of Michael Abramoff, MD, PhD

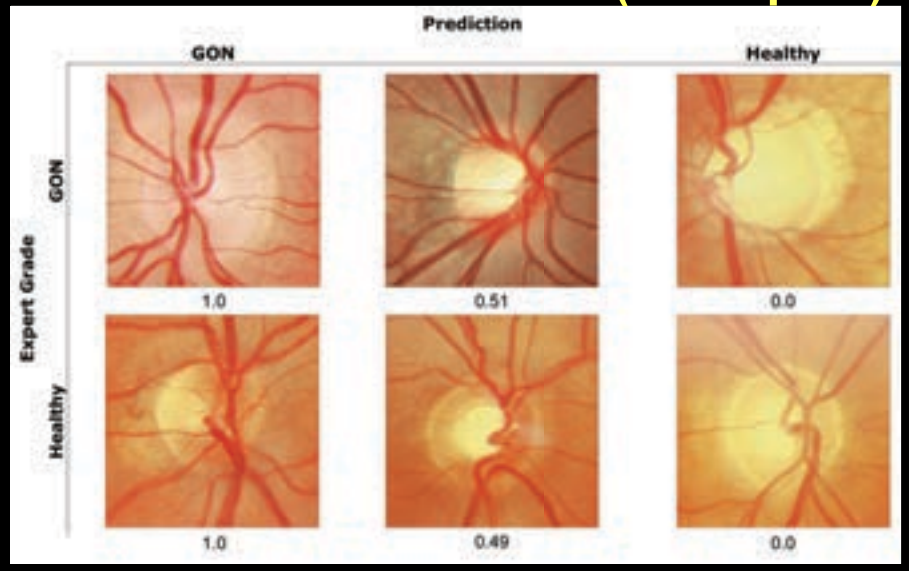
Good Diagnostic Accuracy: Deep Learning to Identify Glaucoma From Photos

Area Under Receiver Operating Characteristic Curves		
	AUC (95% CI)	Visual Field MD (dB)
Any Glaucoma	0.91 (0.89 - 0.93)	-4.1 ± 6.0
Moderate to serve glaucoma	0.98 (0.96 – 0.99)	Worse than -6

Methods

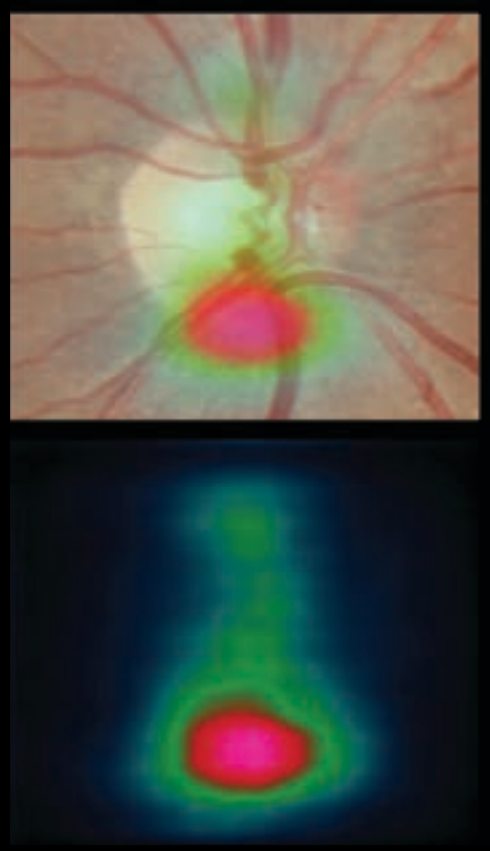
- Deep CNN architecture
- Classification: normal / glaucomatous
- Optic Disc Photograph Dataset:
  - 14,822 images (4,363 eyes)
  - 148,220 w/ translations + OD/OS flip
- Transfer learning using ImageNet

Prediction Probabilities (Examples)

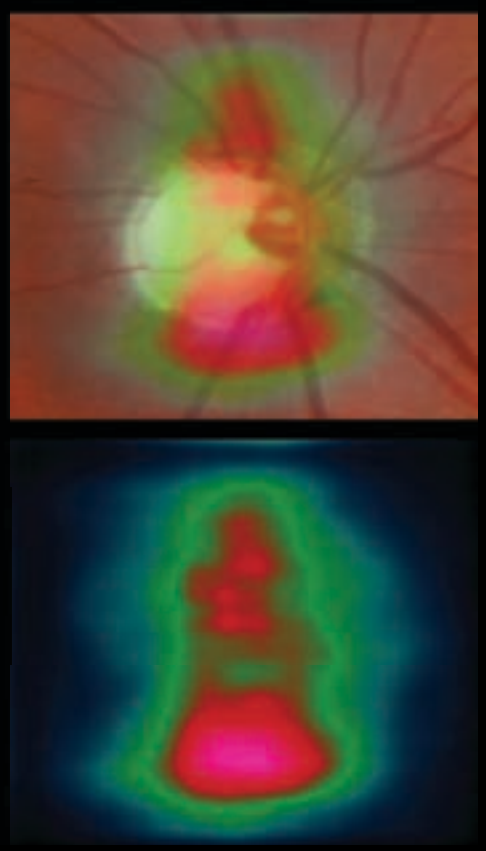


Opening the Black Box:
Mean Occlusion Maps Showing Most Significant Regions Used

Healthy Eye

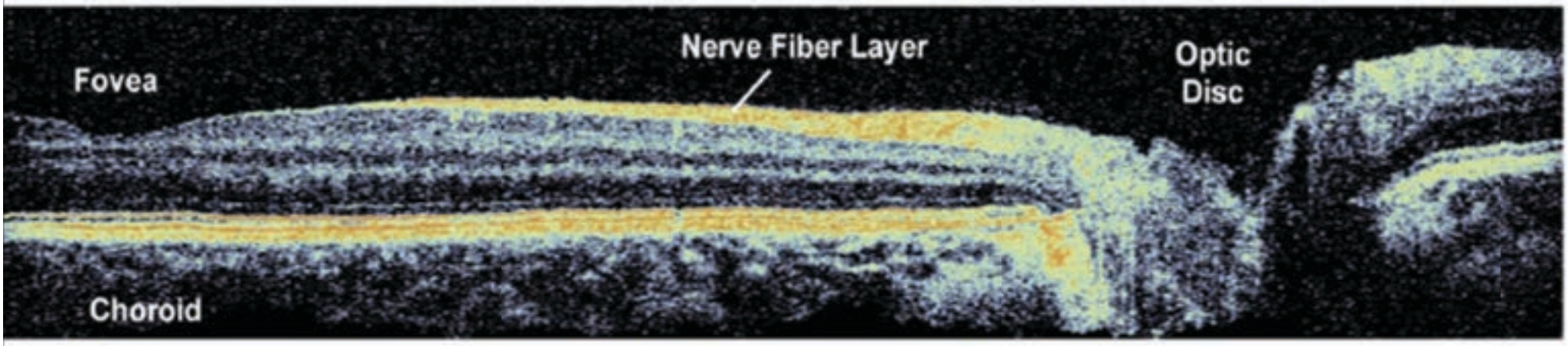


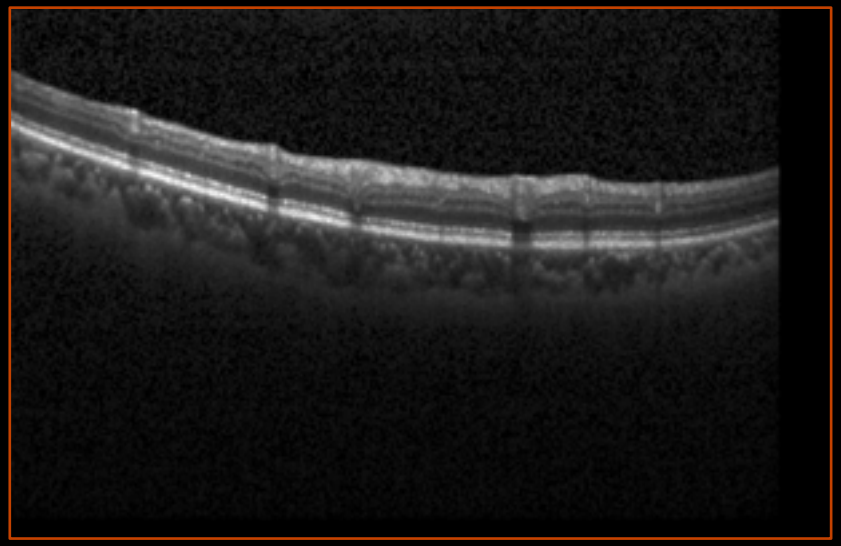
Glaucoma Eye

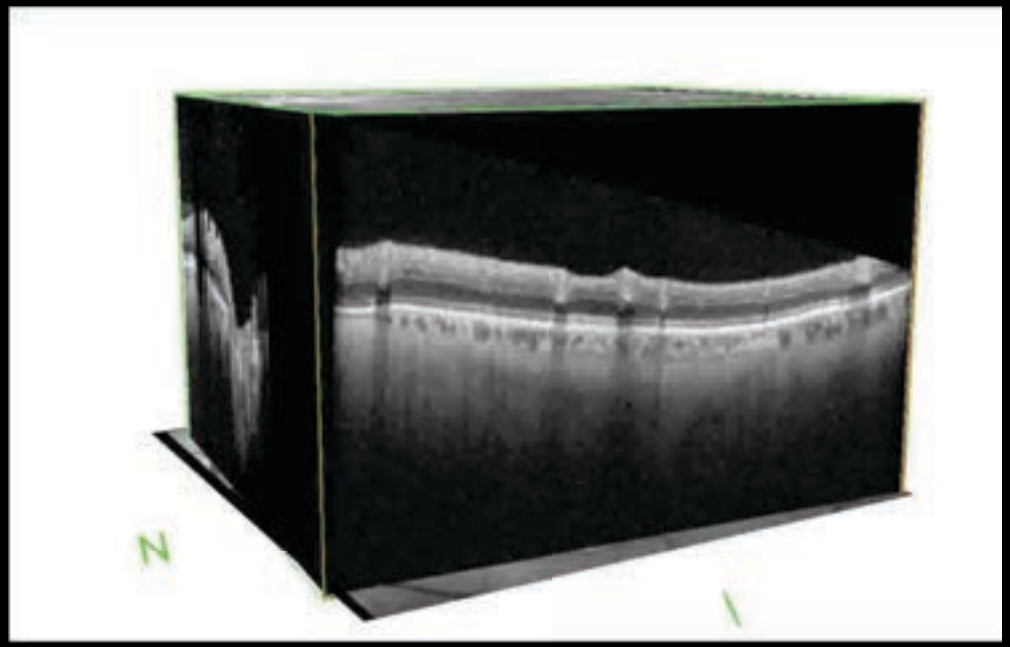


bright pink regions:
large impact on model predictions

OCT: Virtual Histology
3D Window into the Retina







Novel Computational Algorithms
San Diego Automated Layer Segmentation Analysis (SALSA)

- Image Processing Pipeline

SALSA Documentation

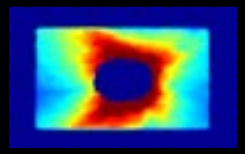
Release 0.1

Deep Learning of RNFL Enface OCT Scans Improves Prediction of VF Damage Compared to RFNL Thickness

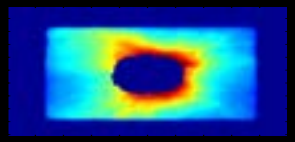
(Christopher M et al…. Zangwill LM: ARVO 2018)

Input: Spectralis optic disc scans

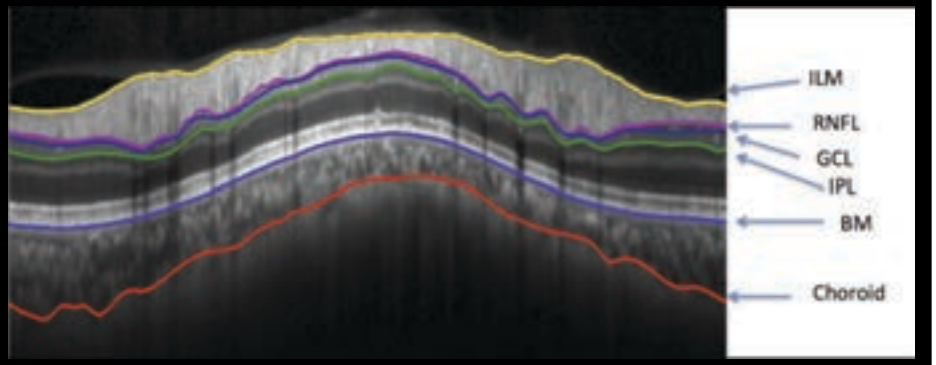
Segmented w/ San Diego Automated Segmentation Algorithm (SALSA)



Healthy RNFL thickness maps



Glaucoma RNFL thickness maps



Train/ Validation set:	3879 scans (968 eyes)	4923 scans (741 eyes)
Test Set:	965 scans (117 eyes)	741 scans (89 eyes)

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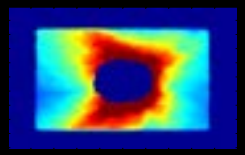

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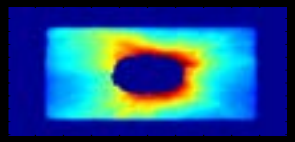

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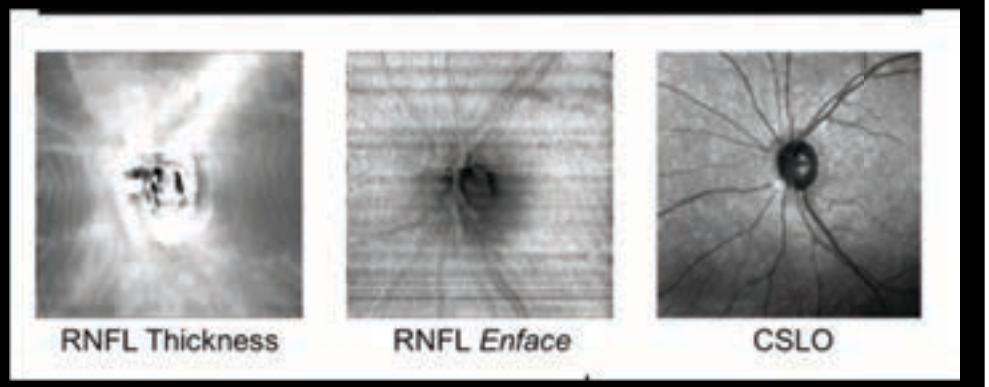


- Transfer Learning (ImageNet)
- Mean RNFL thickness used as comparison

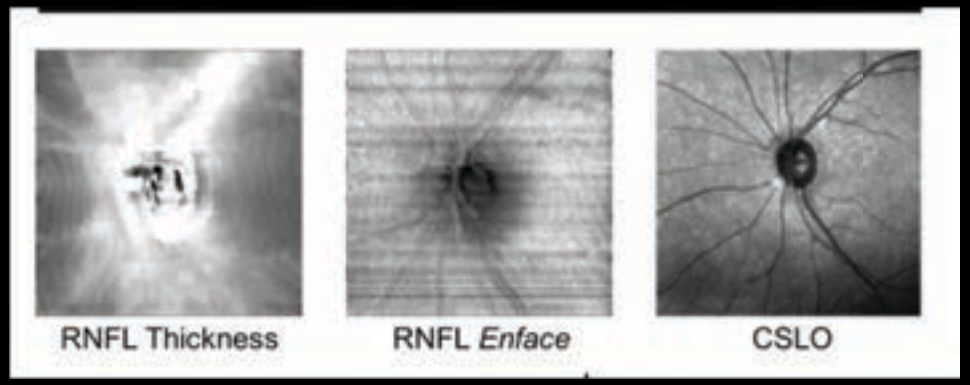
Deep Learning of RNFL Enface OCT Scans Improves Prediction of VF Damage Compared to RFNL Thickness

(Christopher M et al…. Zangwill LM: ARVO 2018)

Output: Prediction of Visual Field Damage

1. Glaucomatous VF damage: Yes/No
2. Quantitative Parameters: MD, PSD

3 Convolutional Neural Networks:



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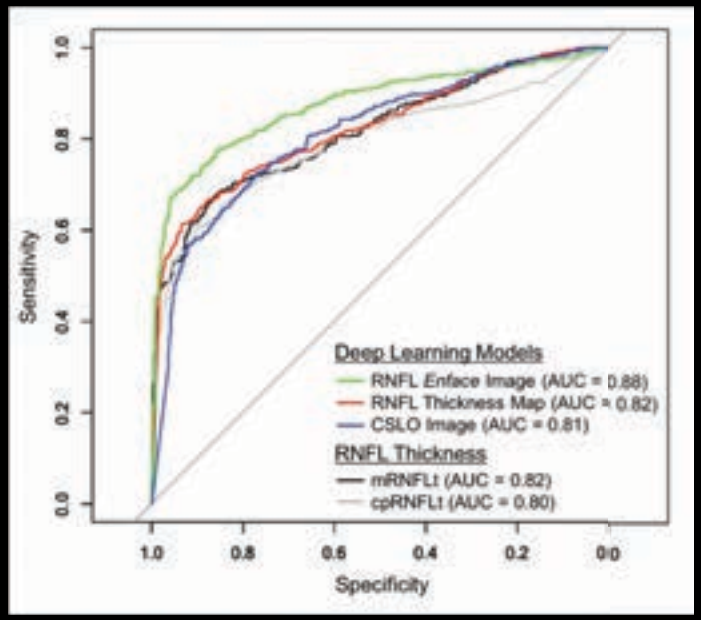

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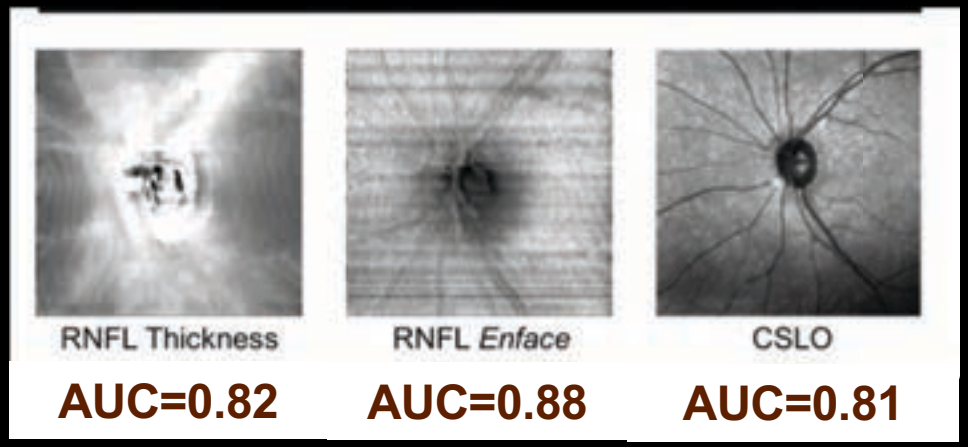

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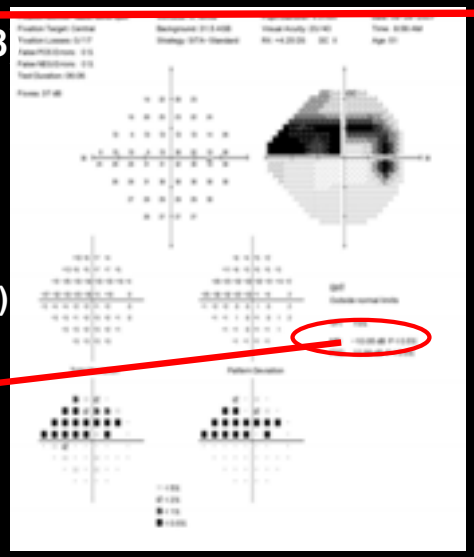
(Christopher M et al…. Zangwill LM: ARVO 2018

Output: Prediction of Visual Field Damage

1. Glaucomatous VF damage: Yes/No
2. Quantitative Parameters: MD

Mean Deviation (MD) -10.8 dB reflects severe glaucoma



Model	MD R^2 (95% CI)	MD Mean Absolute Error (dB)
Deep Learning Models		
RNFL Thickness Map	0.63 (0.57 – 0.68)	2.8 (2.6 – 3.0)
RNFL *Enface* Image	**0.70 (0.64 – 0.74)**	**2.5 (2.3 – 2.7)**
CSLO Image	0.48 (0.41 – 0.54)	3.1 (2.9 – 3.4)
Thickness		
Mean RNFL thickness	0.40 (0.35 – 0.44)	3.8 (3.6 – 4.1)
Circumpapillary RNFL thickness	0.45 (0.40 – 0.50)	3.7 (3.4 – 3.9)

Research IT used

TSCC Triton Shared Computing Cluster (TSCC)
CPU and GPU Clusters

Amazon Web Services

20+ TB servers

Software licenses etc.

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Hamilton Glaucoma Center Investigators welcome new students, postdocs, and collaborators

Akram Belghith, PhD
Christopher Bowd, PhD
Andrew Camp, MD
Mark Christopher, PhD
Huiyuan Hou, MD
Elham Ghahari, MD
Michael Goldbaum, MD
Haksu Kyung, MD
John Liu, PhD
Patricia Manalastas, MD
Sasan Moghimi, MD
Rafaela Penteado, MD
Robert N. Weinreb, MD
Derek Welsbie, MD PhD
Diya Yang, MD
Adeleh Yarmohammadi, MD
Linda M. Zangwill, PhD

Thank you!

UC San Diego Hamilton Glaucoma Center
Shiley Eye Institute
Viterbi Family Department of Ophthlamology

Outline: Use of Research IT (Servers +)

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   - Triton Shared Computing Cluster (TSCC) GPU and CPU

111,884 Spectralis Scans Acquired (AL, NY and SD received through Dec 2018)

GMPE From August 2014	ONH-RC			Posterior Pole			OCTA					
	All			All			Macula	ONH				
# scans	3202			3283			648	703				
# Participants (# eyes)	701 (1354)			688 (1211)			~314					
Years of follow-up, median (IQR)	0.5 (2.9)	25% 3+ years f-up		0.5 (2.9)	25% 3+ years f-up							
# of visits, median (IQR)	4.0 (4.0)			4.0 (5.0)								

Pre-GMPE	RNFL Circle			ONH Cube			Macula Cube			ONH EDI		
	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma
# scans	29309	7032	22150	8230	1870	6360	9864	1985	7637	5475	1259	4216
# Participants (# eyes)	**771 (1499)**	282 (558)	473 (910)	**732 (1418)**	272 (537)	460 (881)	**726 (1402)**	255 (501)	455 (870)	**651 (1250)**	226 (444)	425 (806)
Years of follow-up, median (IQR)	**3.2 (6.1)**	0.0 (3.9)	4.8 (4.3)	**2.8 (4.7)**	0.1 (3.4)	3.9 (3.1)	**2.9 (5.3)**	0.0 (2.5)	4.2 (3.7)	**2.1 (3.4)**	0.0 (2.2)	2.8 (2.4)
# of visits, median (IQR)	**5.0 (9.0)**	2.0 (4.0)	8.0 (8.0)	**5.0 (8.0)**	2.0 (4.0)	6.0 (7.0)	**5.0 (8.0)**	1.0 (4.0)	7.0 (7.0)	**4.0 (6.0)**	1.0 (4.0)	5.0 (5.0)

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GET PICTURES OF SCANS HERE

Pre-GMPE	RNFL Circle			ONH Cube			Macula Cube			ONH EDI		
	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma	All	Healthy/ Suspect	Glaucoma
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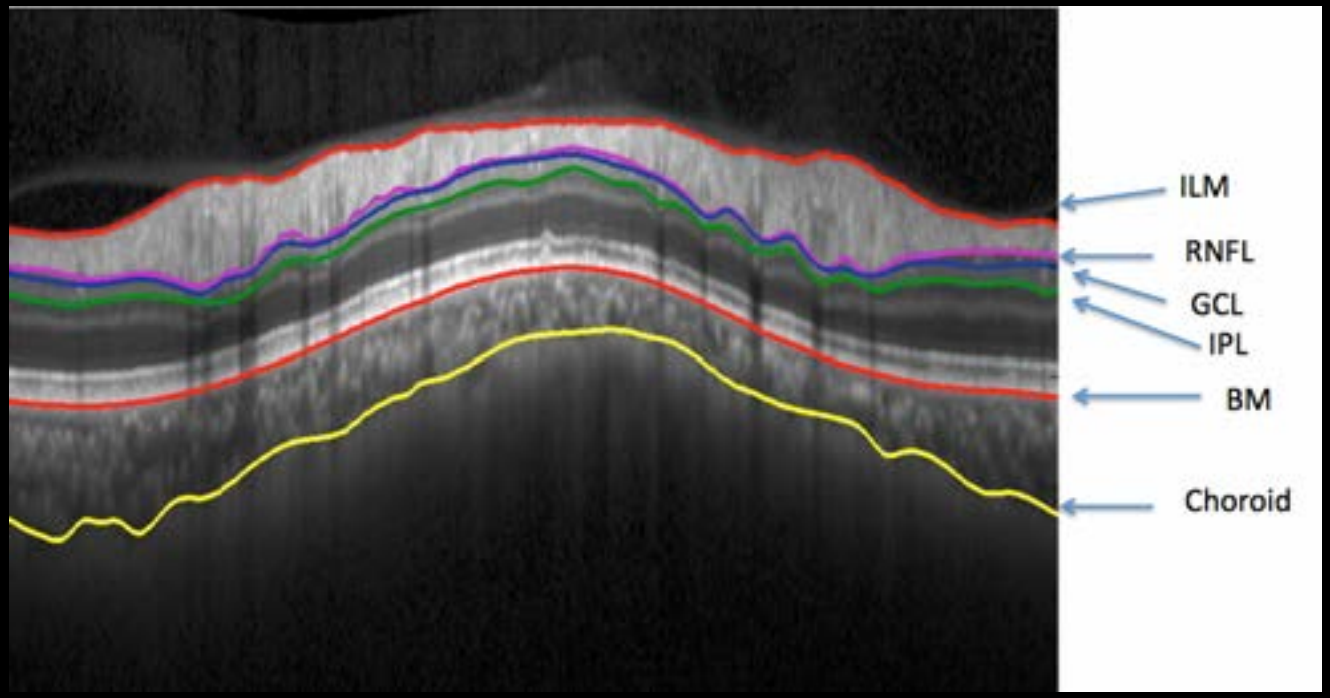
# of visits, median (IQR)	**5.0 (9.0)**	2.0 (4.0)	8.0 (8.0)	**5.0 (8.0)**	2.0 (4.0)	6.0 (7.0)	**5.0 (8.0)**	1.0 (4.0)	7.0 (7.0)	**4.0 (6.0)**	1.0 (4.0)	5.0 (5.0)

Virtual Histology of the Retina

SD-OCT Spectralis circular scan centered on the ONH



SD-OCT Spectralis volume scan centered on the fovea