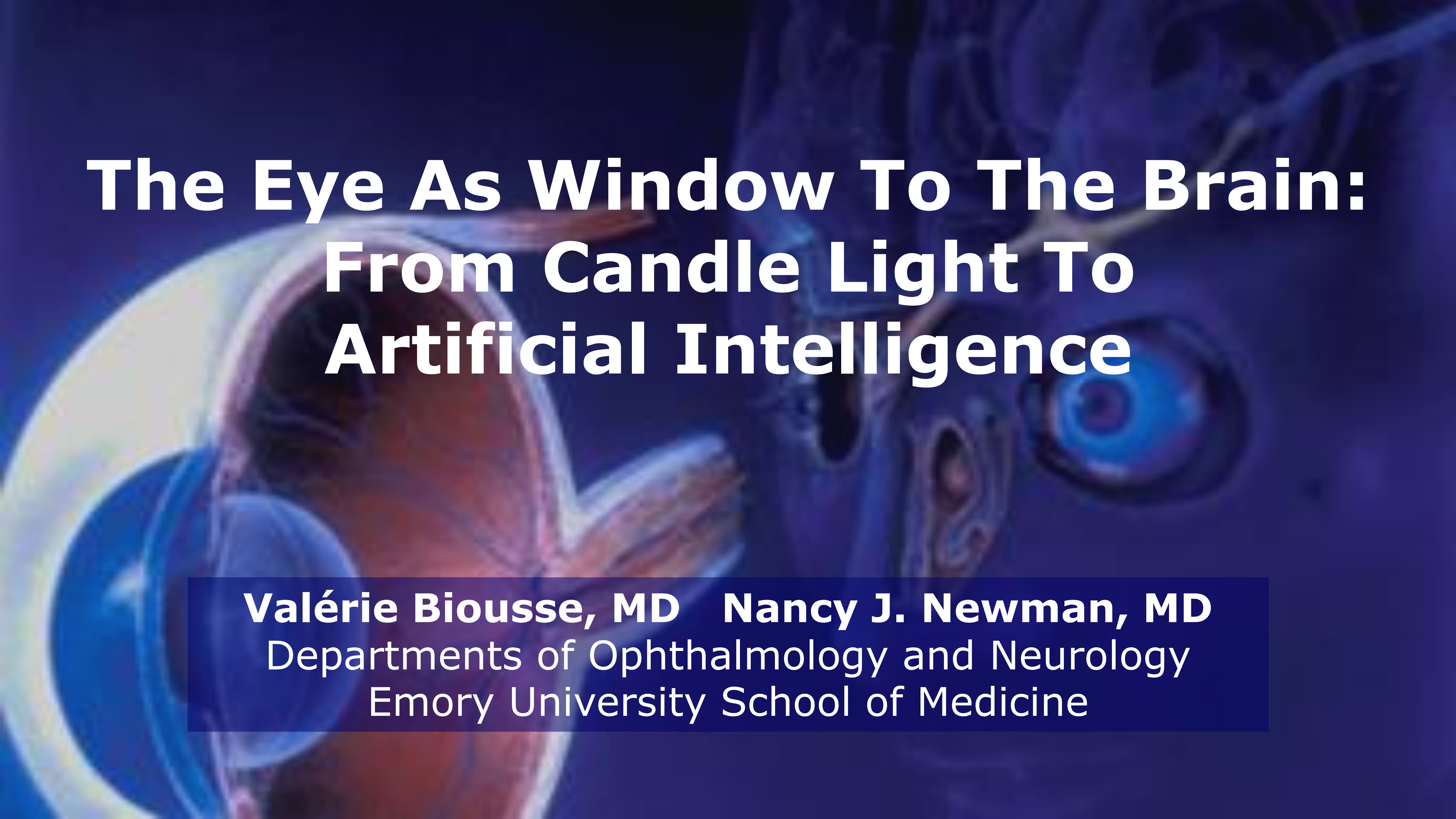


The Eye As Window To The Brain: From Candle Light To Artificial Intelligence

Valérie Biousse, MD   Nancy J. Newman, MD
Departments of Ophthalmology and Neurology
Emory University School of Medicine

Disclosures and Funding Sources

- **No relevant disclosures:**
  - VB: Consultant for Gensight and Neurophoenix
  - NJN: Consultant for Gensight, Neurophoenix, Santhera/Chiesi, Stealth
- **Funding:**

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

KNIGHTS TEMPLAR EYE FOUNDATION, Inc.

RPB Research to Prevent Blindness

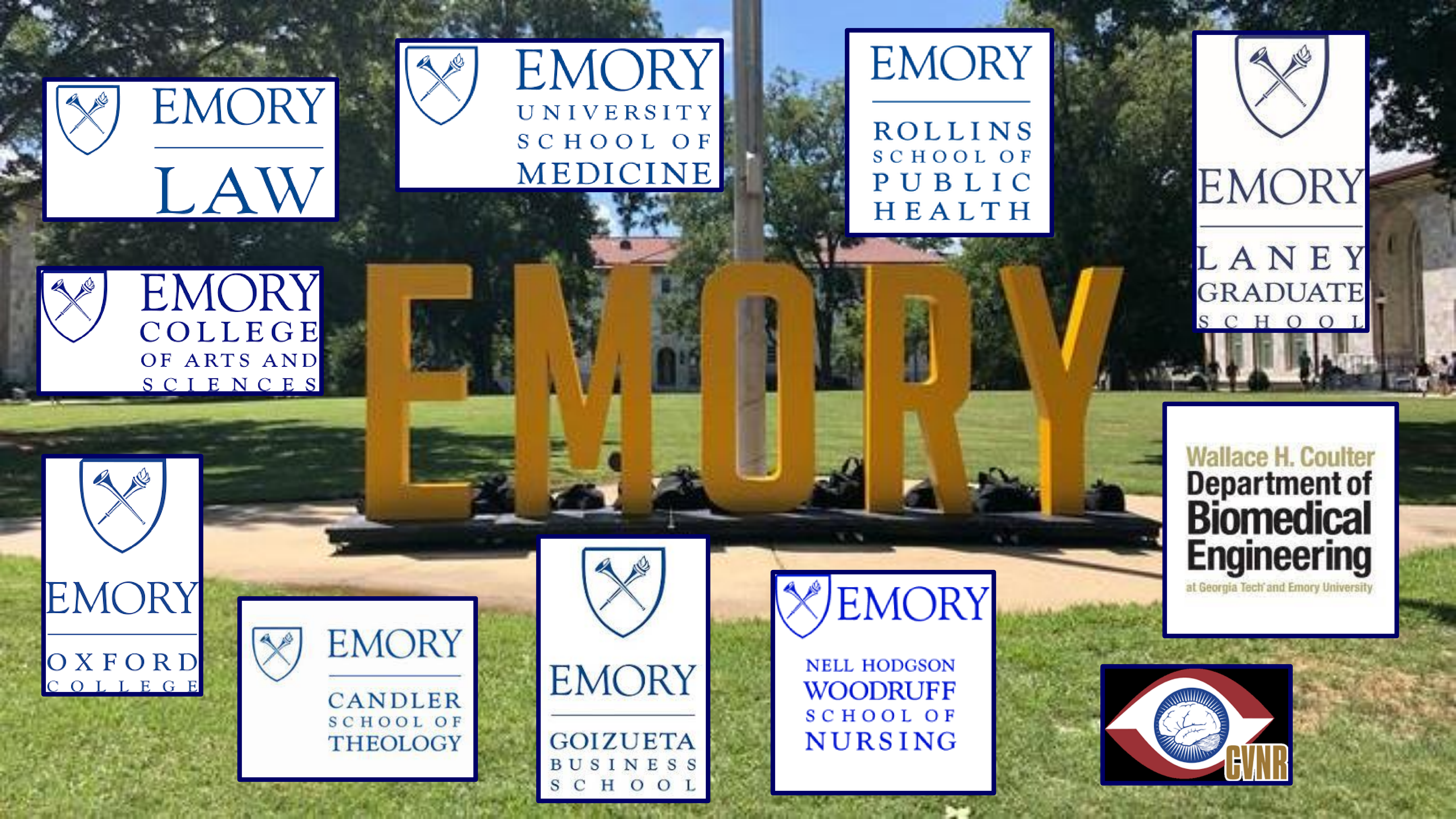
AMERICAN ACADEMY OF NEUROLOGY

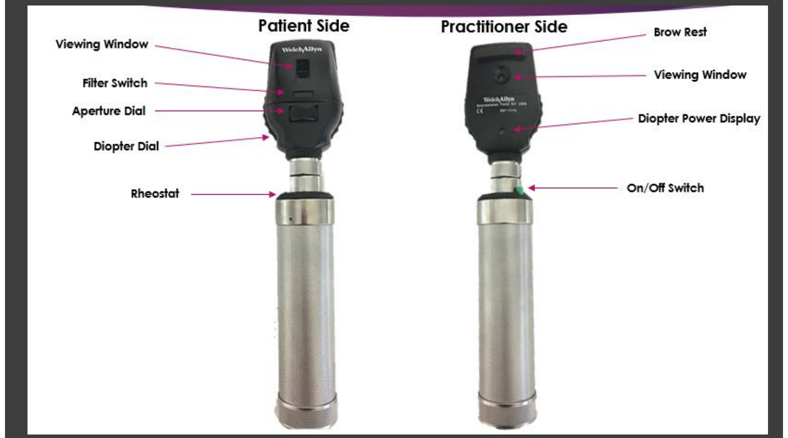
Atlanta Clinical & Translational Science Institute
Community · Discovery · Training

SINGAPORE EYE RESEARCH INSTITUTE
MINISTRY OF HEALTH SINGAPORE
Singapore National Eye Centre
SingHealth
DUKE NUS GRADUATE MEDICAL SCHOOL SINGAPORE

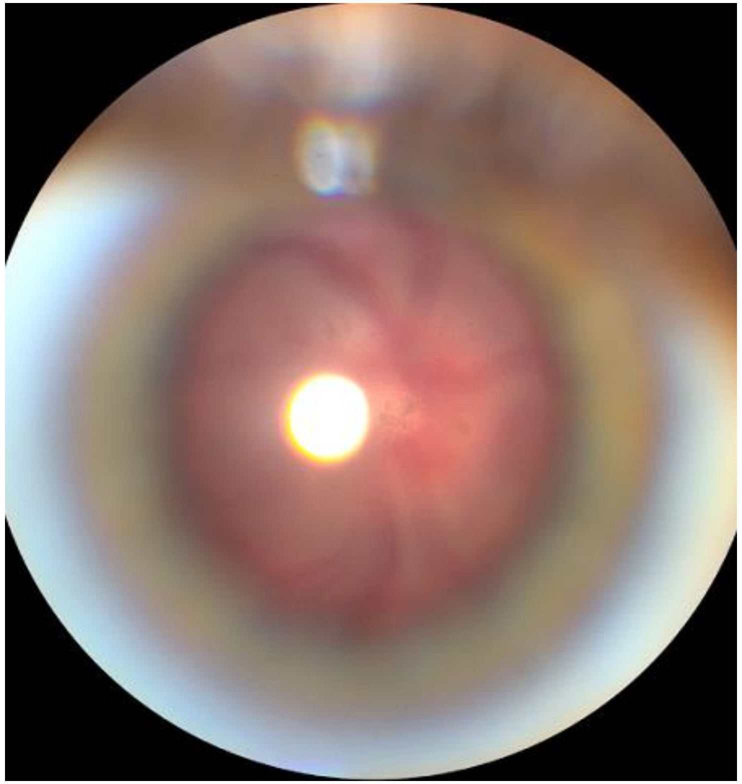
Agency for Science, Technology and Research
SINGAPORE

EMORY UNIVERSITY SCHOOL OF MEDICINE

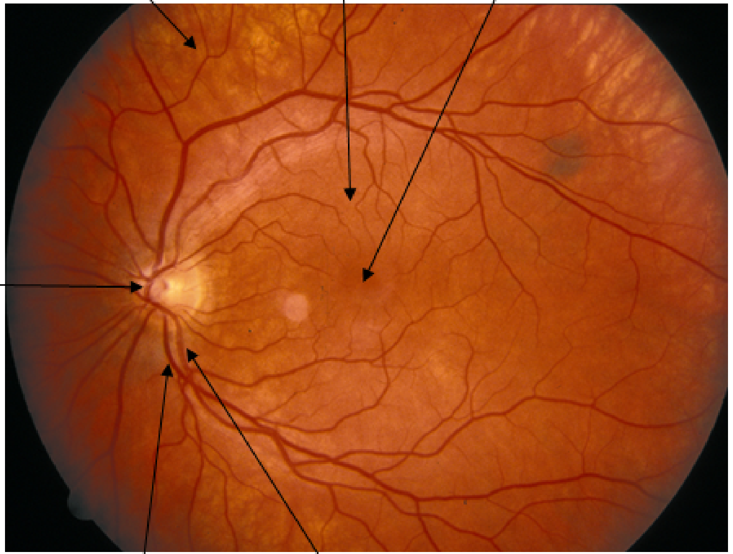

EMORY LAW
EMORY UNIVERSITY SCHOOL OF MEDICINE
EMORY ROLLINS SCHOOL OF PUBLIC HEALTH
EMORY LANEY GRADUATE SCHOOL
EMORY COLLEGE OF ARTS AND SCIENCES
EMORY
Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University
EMORY OXFORD COLLEGE
EMORY CANDLER SCHOOL OF THEOLOGY
EMORY GOIZUETA BUSINESS SCHOOL
EMORY NELL HODGSON WOODRUFF SCHOOL OF NURSING
CVNR



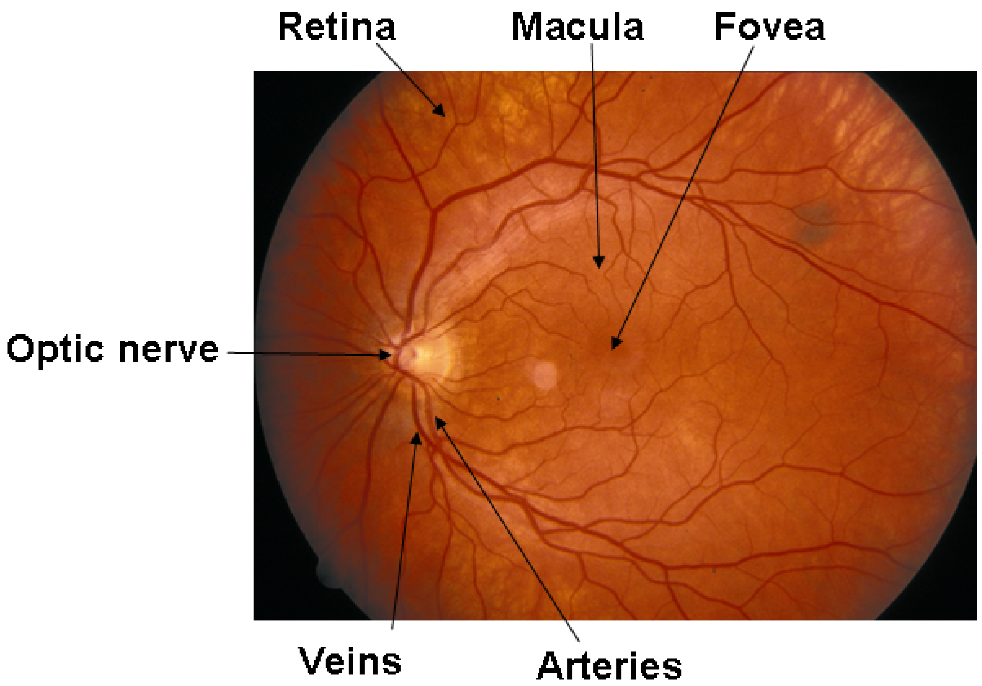
DIRECT OPHTHALMOSCOPE

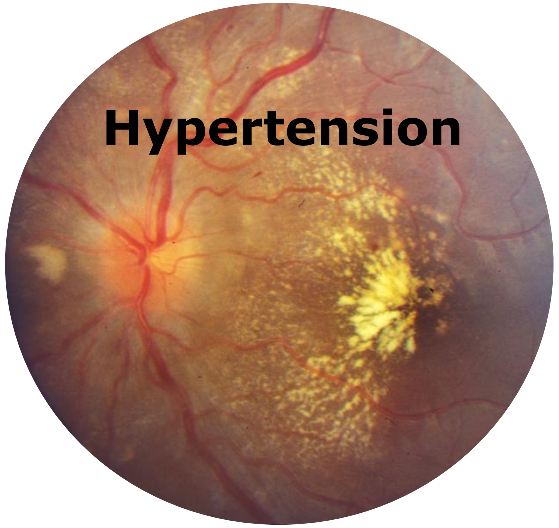


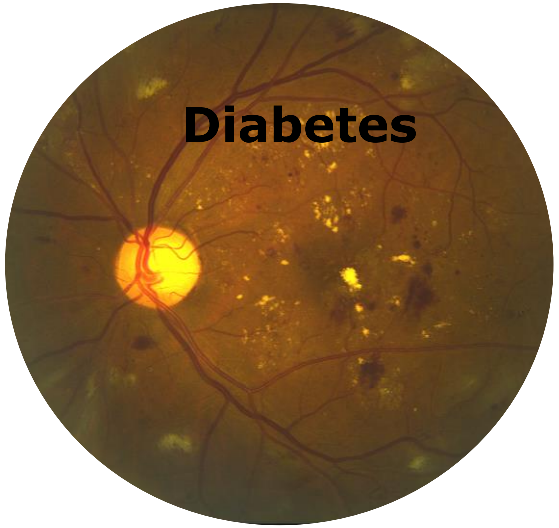
Examination of the ocular fundus

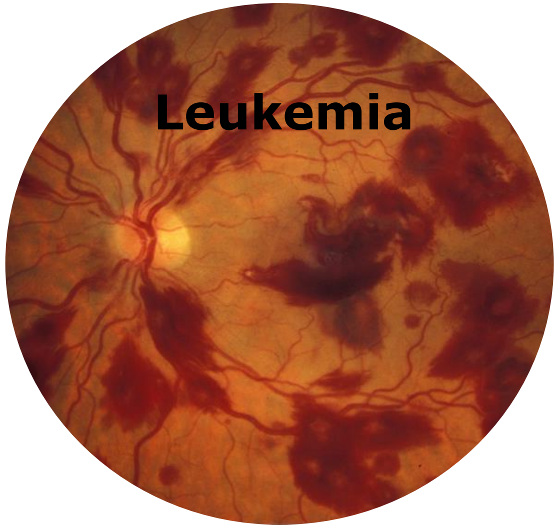


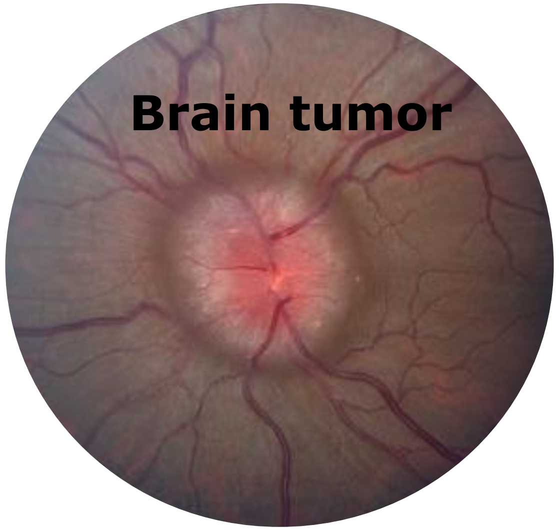
Examination of the ocular fundus





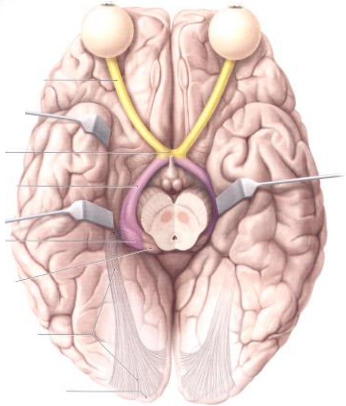


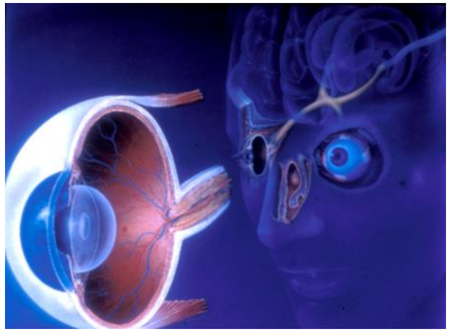




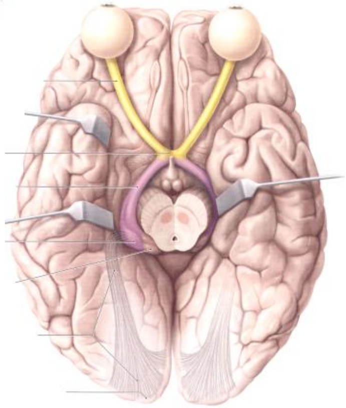
Biousse V, Newman NJ. Neuro-Ophthalmology Illustrated. Thieme New York, NY. 3rd Ed, 2019

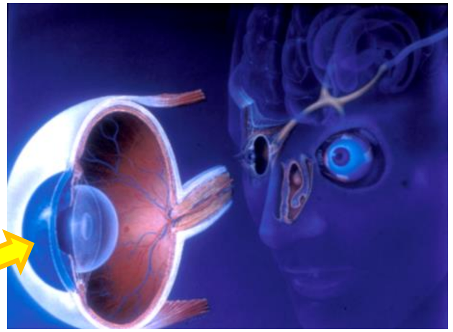
Swollen Optic Nerve





Swollen Optic Nerve



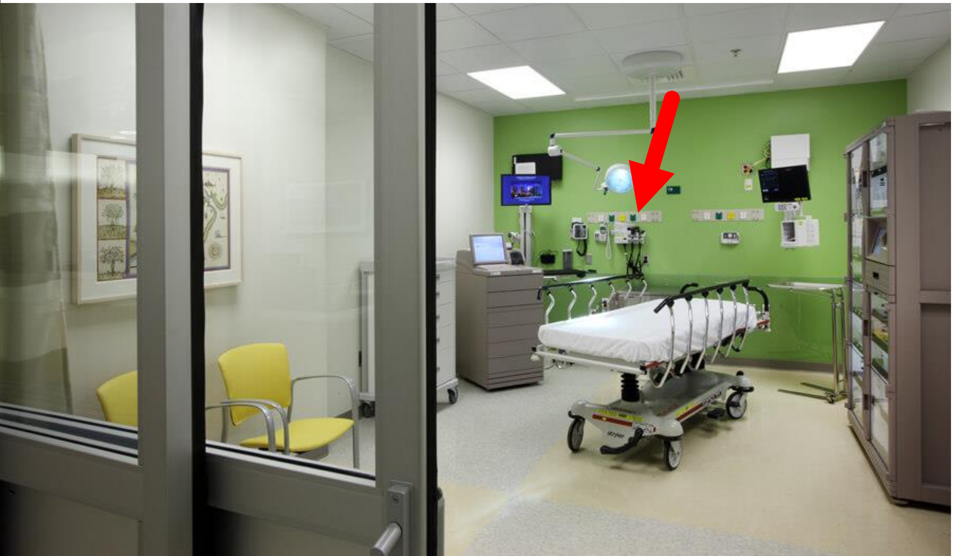


- **Optic nerve disease**
  - Blindness
- **Brain disease**
  - Disability, death
- **Elevated intracranial pressure**
  - Brain tumor, bleed, clot
  - Blindness from chronic optic nerve swelling (papilledema)

The eye is a window to the brain

Direct Ophthalmoscopes are Everywhere!

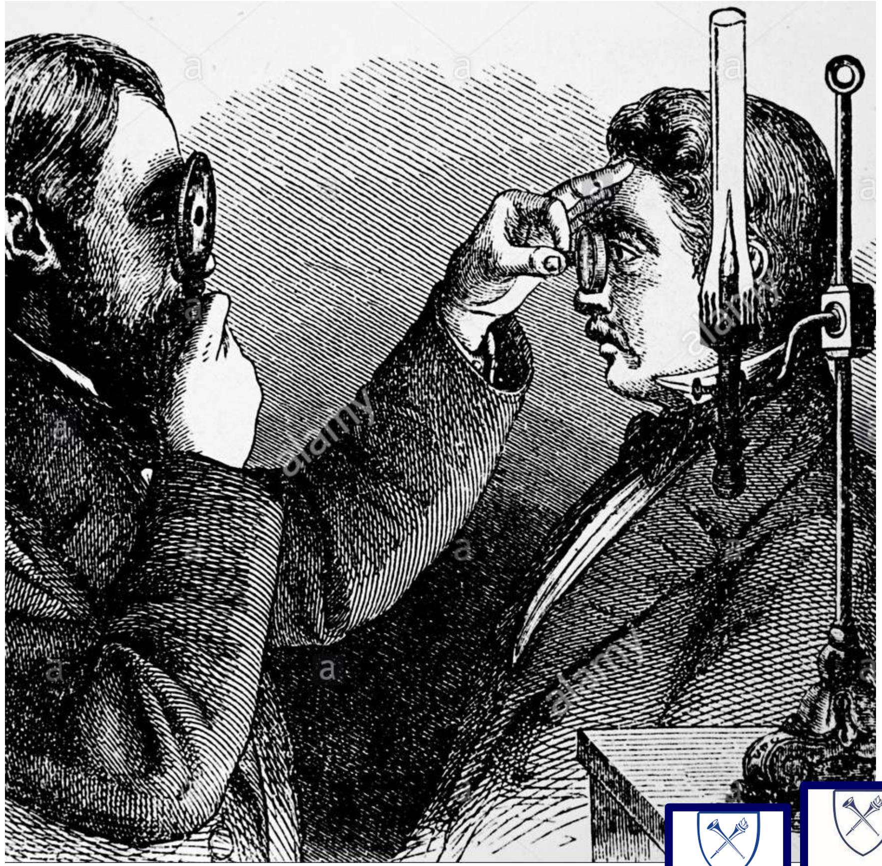
Ophthalmoscopy = Standard of care

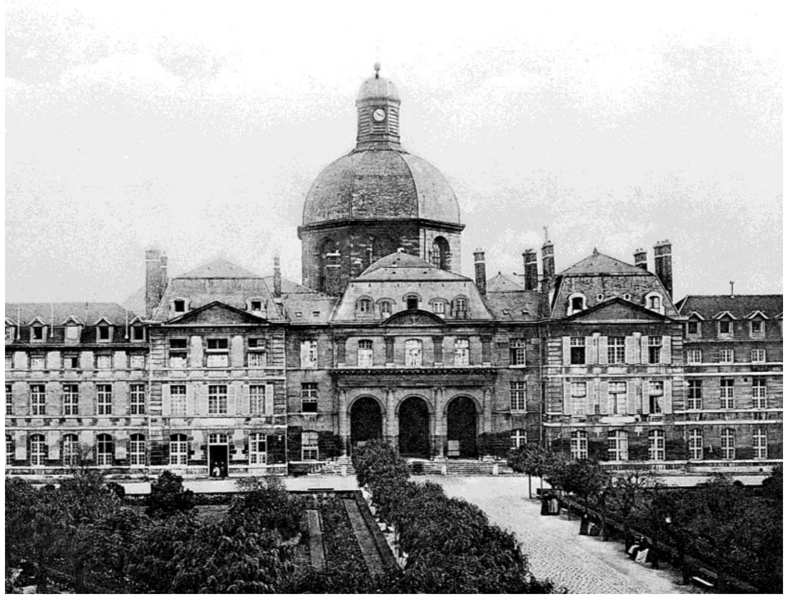


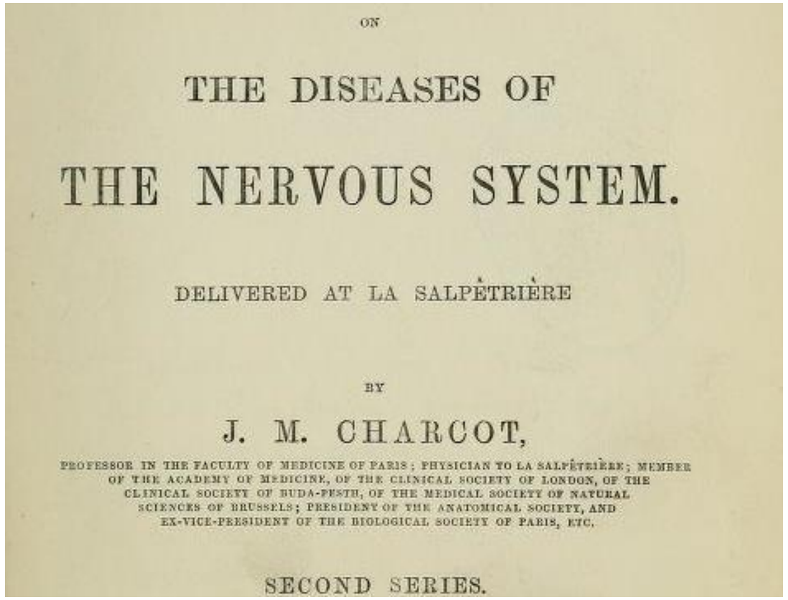
- **Ophthalmoscopes mandatory in most clinical settings!**
- Learning how to use an ophthalmoscope is part of the basic curriculum in most medical schools

Direct ophthalmoscope = an old tool…

- **1850:** German physician Hermann von Helmholtz, who devoted much of his career to studying the eye and the physics of vision and perception, demonstrates his ophthalmoscope to the Berlin Physical Society. This invention revolutionizes ophthalmology.







ON

THE DISEASES OF

THE NERVOUS SYSTEM.

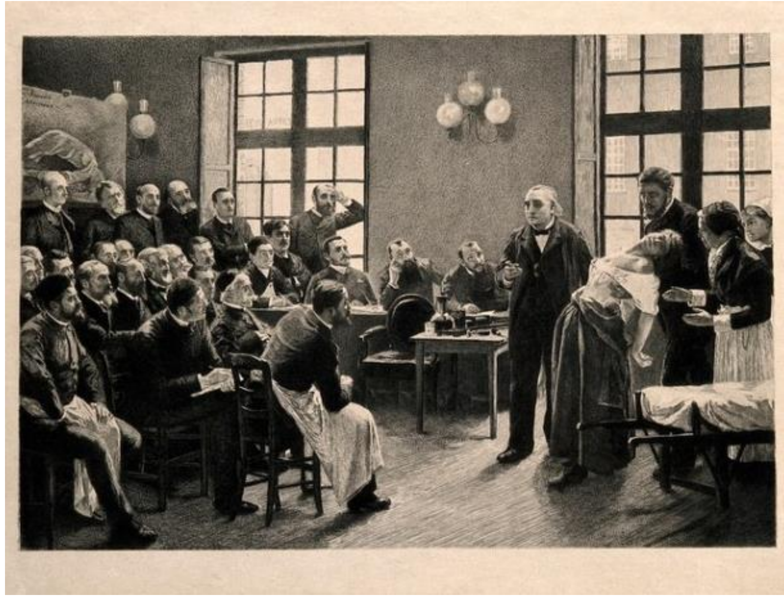
DELIVERED AT LA SALPÊTRIÈRE

BY

J. M. CHARCOT,

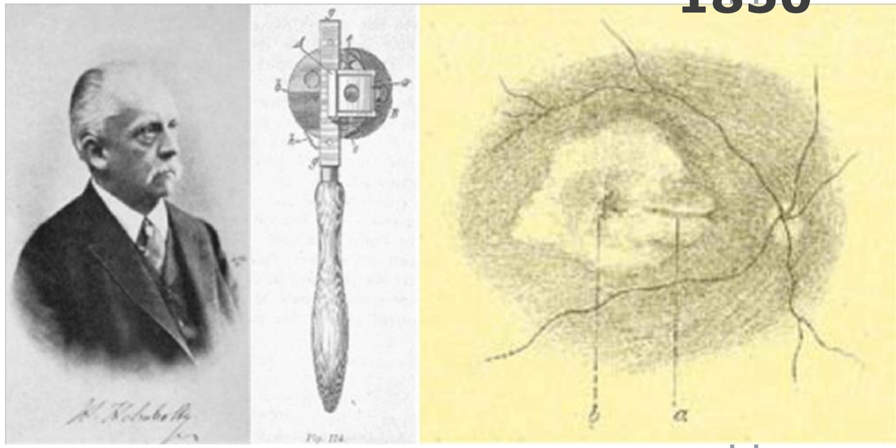
PROFESSOR IN THE FACULTY OF MEDICINE OF PARIS; PHYSICIAN TO LA SALPÊTRIÈRE; MEMBER OF THE ACADEMY OF MEDICINE, OF THE CLINICAL SOCIETY OF LONDON, OF THE CLINICAL SOCIETY OF BUDA-PESTH, OF THE MEDICAL SOCIETY OF NATURAL SCIENCES OF BRUSSELS; PRESIDENT OF THE ANATOMICAL SOCIETY, AND EX-VICE-PRESIDENT OF THE BIOLOGICAL SOCIETY OF PARIS, ETC.

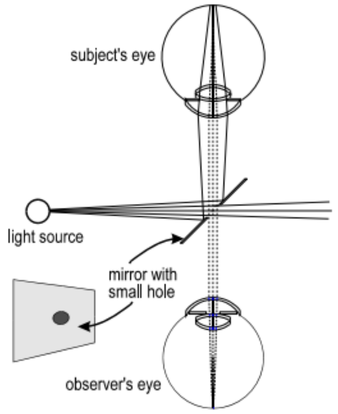
SECOND SERIES.



- **1881:** French neurologist Jean-Martin Charcot adopts the ophthalmoscope to diagnose neurologic disorders: *"Now in this difficulty, the ophthalmoscopic art came to give us its decisive aid"*.
- The eye officially becomes a "window to the brain".

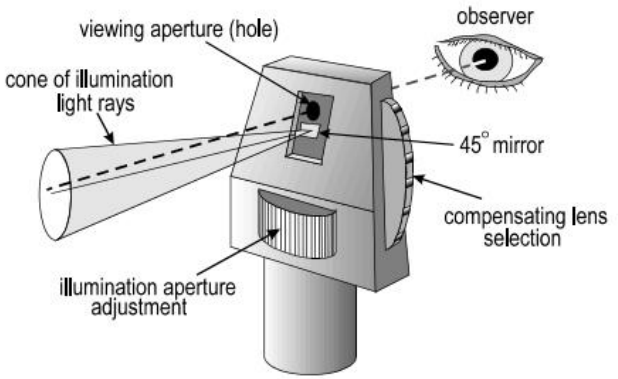
1850



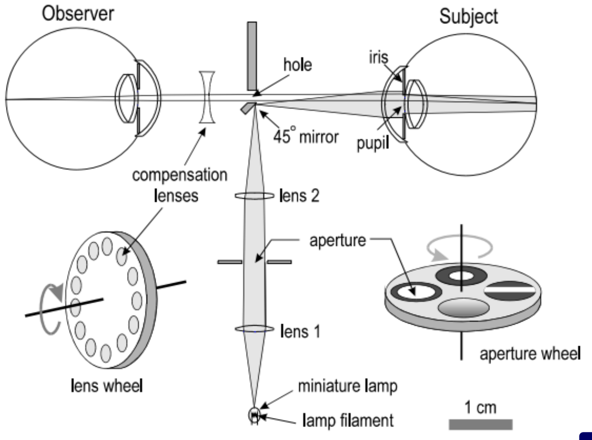


Fundamental design of the direct ophthalmoscope realized by Babbage and Helmholtz. Illumination rays from light source indicated by dark lines; rays reflected from subject's retina indicted by dashed lines.

2021



Drawing of a modern, direct opthalmoscope showing key features.



Detailed structure of the direct ophthalmoscope showing the illumination and viewing optical systems.

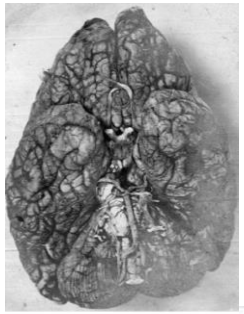
1850 ⟶ 2021

- Modern direct ophthalmoscope not much better than the old one…
- Modern non-ophthalmology trained doctors not comfortable with the direct ophthalmoscope
- Modern doctors prefer more modern ways of looking at the brain

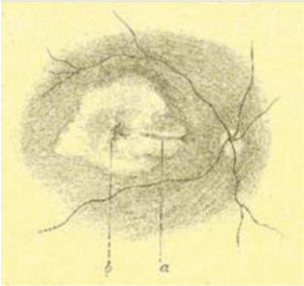
Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University

From Post-mortem Autopsy To Modern Neuroimaging

Autopsy

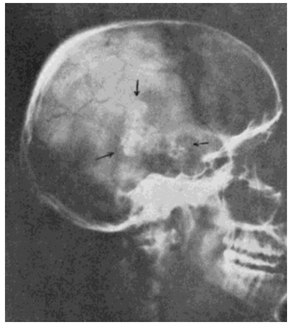


Ophthalmoscopy
1850

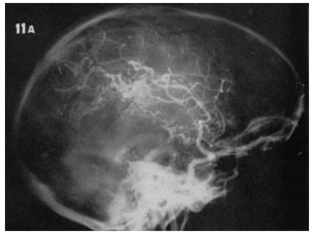


X-Ray
1885

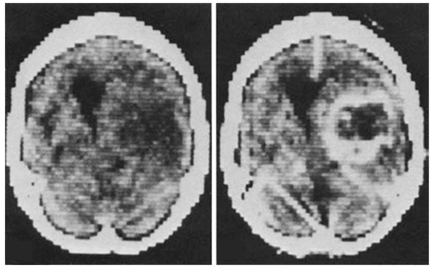
1918
Pneumo encephalography

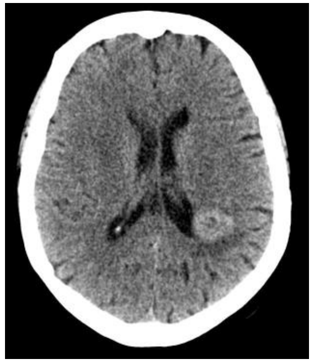


1949
Cerebral angiography

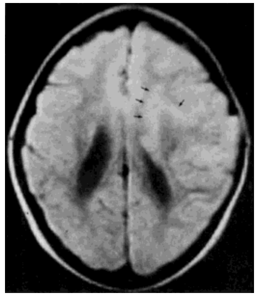


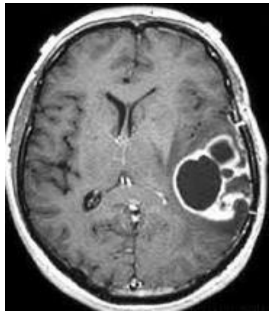
Computed tomography
1971



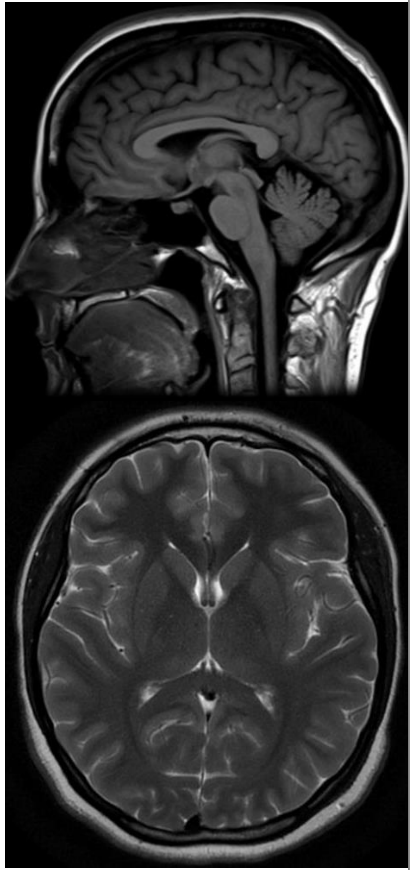


Magnetic resonance imaging
1977-1984





Normal brain imaging does not rule out brain disease, especially elevated intracranial pressure



- Cerebral venous thrombosis
- Meningitis
- Idiopathic intracranial hypertension

Section Editors: Valerie Biousse, MD
Koto Ishida, MD

Cerebral Venous Sinus Thrombosis in the COVID-19 Pandemic

Chaitanya B. Medicherla, MD, Rachel A. Pauley, MD, Adam de Havenon, MD, Shadi Yaghi, MD, Koto Ishida, MD, Jose L. Torres, MD

Background: Recent studies ha
increased thromboembolic events i
virus Disease 2019 (COVID-19).
thrombosis (CVST) is a form of thr
been observed as a neuro-ophthal
COVID-19.
Methods: Review of the scientific li
Results: In this article, we repor
epidemiology, clinical presentation
pathophysiology, and management
19.
Conclusion: CVST is an uncommon
with variable phenotypes and multip
complications can be severe, incl
deficits and death. Current observ
risk of CVST may be profoundly
COVID-19 pandemic, thus promptin
disease presentation, pathogenesis

Journal of Neuro-Ophthalmology 2020;40:457–462
doi: 10.1097/WNO.0000000000001122

EXPERT REVIEW OF VACCINES
https://doi.org/10.1080/14760584.2021.1949294

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

COVID-19 vaccines and thrombosis with thrombocytopenia syndrome

Chih-Cheng Lai[a], Wen-Chien Ko[b], Chih-Jung Chen[c], Po-Yen Chen[d], Yhu-Chering Huang[c], Ping-Ing Lee[e] and Po-Ren Hsueh[f,g]

[a]Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan, Taiwan; [b]Department of Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [c]Division of Pediatric Infectious Diseases, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan; [d]Department of Pediatrics, Section of Infection, Taichung Veterans General Hospital, Taichung, Taiwan; [e]Department of Pediatrics, National Taiwan University Children's Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [f]Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [g]Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan

A tale too often told

- 28 year old obese woman goes to an Emergency Department with severe headaches, nausea and vomiting
  - Normal examination
- Sent home with a diagnosis of “migraine”

- **2 weeks later:** decreased vision in both eyes - Goes back to same Emergency Department
  - Head CT normal
  - Sent home with an outpatient Neurology appointment
- **3 weeks from onset:** vision and headaches worse
  - Neurologist: "Normal examination"
  - Sent to Ophthalmologist…

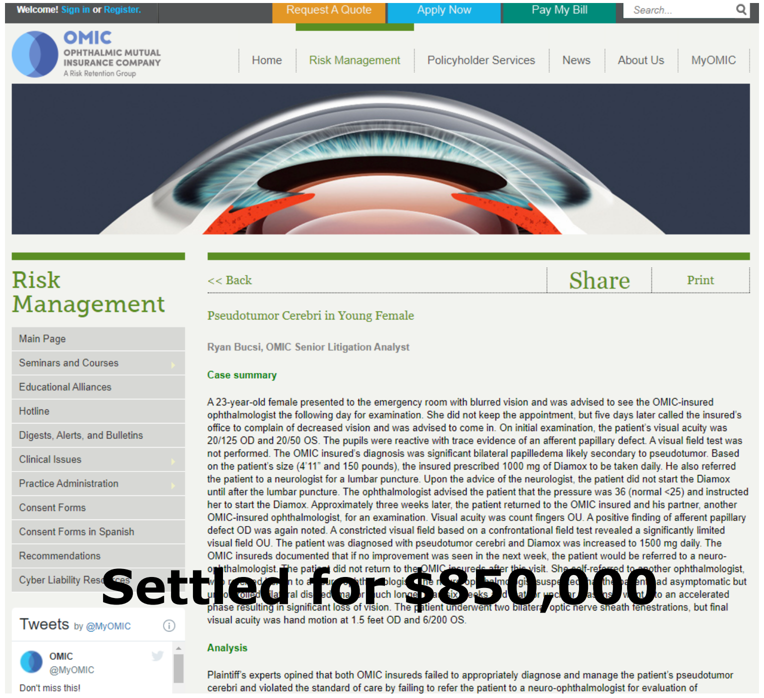
Bilateral optic nerve edema with headaches = Elevated intracranial pressure (papilledema)

No Light Perception

Light Perception

FUNDUSCOPIC EXAMINATION SHOULD HAVE BEEN DONE ON DAY 1!

Missed papilledema



<< Back | Share | Print

Pseudotumor Cerebri in Young Female

Ryan Bucsi, OMIC Senior Litigation Analyst

Case summary

A 23-year-old female presented to the emergency room with blurred vision and was advised to see the OMIC-insured ophthalmologist the following day for examination. She did not keep the appointment, but five days later called the insured's office to complain of decreased vision and was advised to come in. On initial examination, the patient's visual acuity was 20/125 OD and 20/50 OS. The pupils were reactive with trace evidence of an afferent papillary defect. A visual field test was not performed. The OMIC insured's diagnosis was significant bilateral papilledema likely secondary to pseudotumor. Based on the patient's size (4'11" and 150 pounds), the insured prescribed 1000 mg of Diamox to be taken daily. He also referred the patient to a neurologist for a lumbar puncture. Upon the advice of the neurologist, the patient did not start the Diamox until after the lumbar puncture. The ophthalmologist advised the patient that the pressure was 36 (normal <25) and instructed her to start the Diamox. Approximately three weeks later, the patient returned to the OMIC insured and his partner, another OMIC-insured ophthalmologist, for an examination. Visual acuity was count fingers OU. A positive finding of afferent papillary defect OD was again noted. A constricted visual field based on a confrontational field test revealed a significantly limited visual field OU. The patient was diagnosed with pseudotumor cerebri and Diamox was increased to 1500 mg daily. The OMIC insureds documented that if no improvement was seen in the next week, the patient would be referred to a neuro-ophthalmologist. The patient did not return to the OMIC insureds after this visit. She self-referred to another ophthalmologist, [illegible] ad asymptomatic but [illegible] to an accelerated phase resulting in significant loss of vision. The patient underwent two bilateral optic nerve sheath fenestrations, but final visual acuity was hand motion at 1.5 feet OD and 6/200 OS.

Analysis

Plaintiff's experts opined that both OMIC insureds failed to appropriately diagnose and manage the patient's pseudotumor cerebri and violated the standard of care by failing to refer the patient to a neuro-ophthalmologist for evaluation of

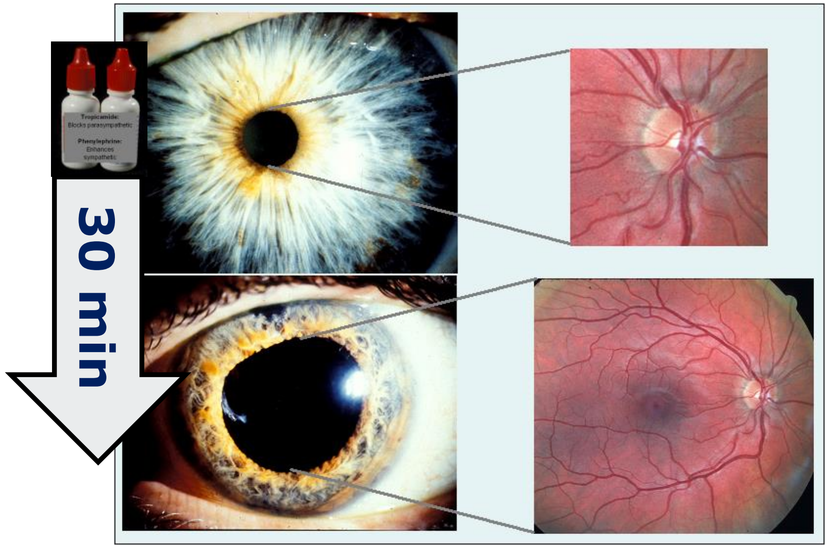
Settled for $850,000

- Devastating outcome (blindness)
- Enormous cost to society
- Law suit (medical malpractice)

Stewarts acted for a client, RM, who received a settlement of £4.3m following an online video mediation. The claim arose from a delay in treating a cerebral venous sinus thrombosis (CVST), which caused raised intracranial pressure.

Stunkel L, Sharma RA, Mackay DD, Wilson B, Van Stavern GP, Newman NJ, Biousse V. Patient Harm Due to Diagnostic Error of Neuro Ophthalmologic Conditions. Ophthalmology. 2021 Mar 11:S0161-6420(21)00193-7

Why is ophthalmoscopy rarely performed in the ED and Neurology Clinics ?



- Limited training
- Difficult without pupillary dilation
- Direct ophthalmoscope difficult to use and limited view
- Inability to recognize the findings

Non-mydriatic fundus photography

Direct ophthalmoscopy is diffi

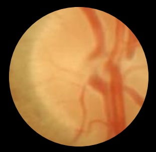


FOTO ED

Fundus photography
vs.
Ophthalmoscopy
Trial Outcomes
in the Emergency Department

National Eye Institute
NATIONAL INSTITUTES OF HEALTH

KNIGHTS TEMPLAR EYE FOUNDATION, Inc.

RPB
Research to Prevent Blindness

AMERICAN ACADEMY OF NEUROLOGY

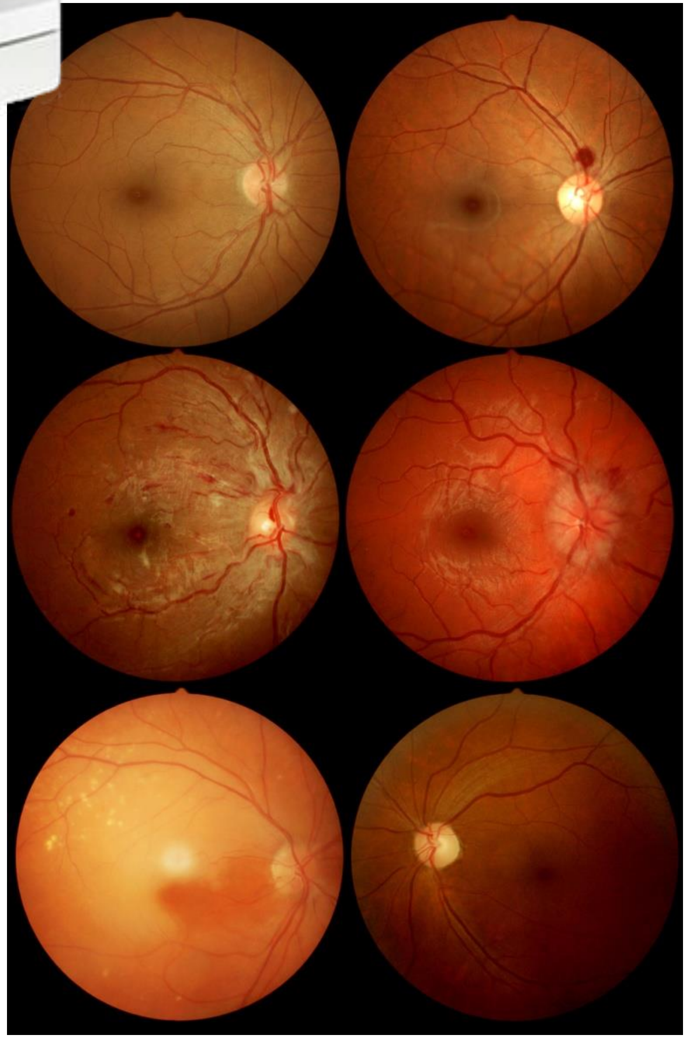
Atlanta Clinical & Translational Science Institute
Community · Discovery · Training

FOTO-ED

Emory University
Emergency Medicine

EMORY EYE CENTER
Neuro-ophthalmology

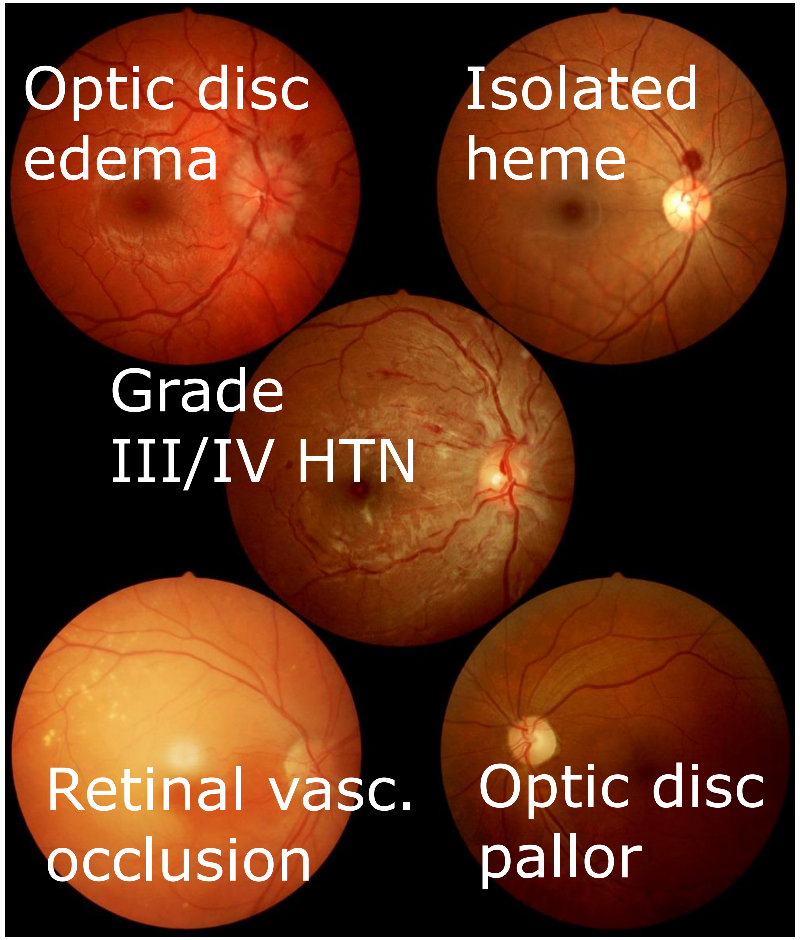
- **Non-mydriatic fundus cameras**
  - Easy for non-ophthalmic trained individuals to use
  - No pupillary dilation
  - Able to take quality photographs of the posterior pole
  - Reveals unrecognized findings in ED



Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. N Engl J Med 2011; 364: 387–9

"Relevant" Findings

- Patients with:
  - Headaches
  - Severe hypertension
  - Focal neurologic symptoms
  - Visual loss
- Compare ED providers' detection rate for relevant findings
- **Should change patients' care in the ED**



"Relevant" Findings

- Patients with:
  - Headaches
  - Severe hypertension
  - Focal neurologic symptoms
  - Visual loss
- Compare ED providers' detection rate for relevant findings
- **Should change patients' care in the ED**

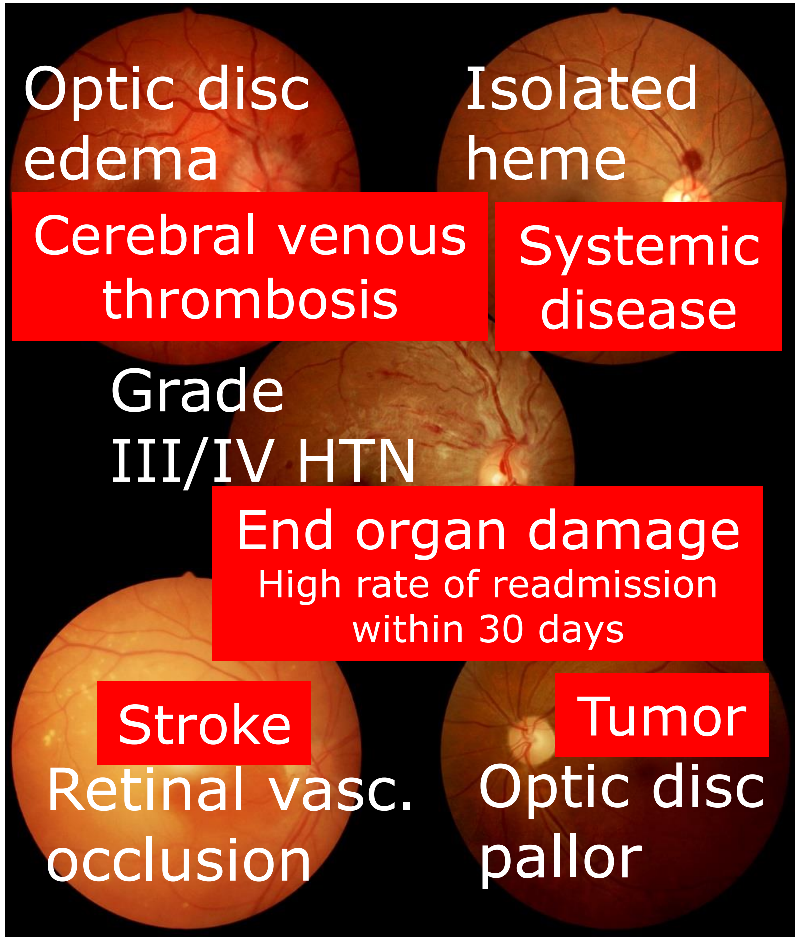


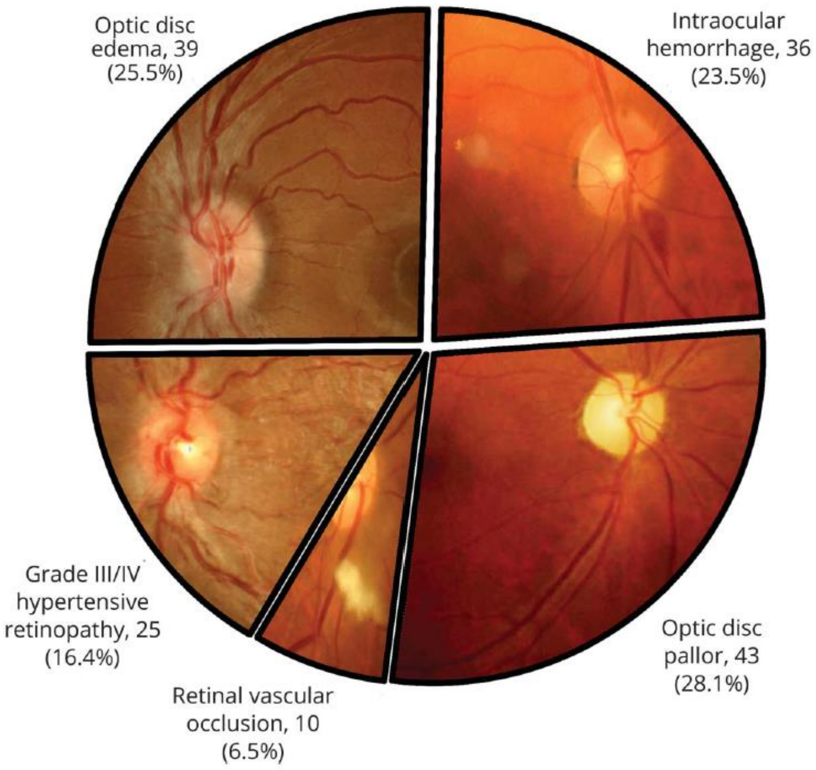
FOTO ED

General Methods

	Phase 1	Phase 2	Phase 3
ED	Ophthalmoscopy alone 1734 photos 350 patients	Photograhs 1503 photos 354 patients	Photographs + Education 2347 photos 587 patients
Neuro-Ophthalmologist	Fundus Photography Readings within 24 Hours		

FOTO-ED Relevant Findings in 11.8%

Figure 4 Pie chart shows the distribution of the 153 (11.8%) relevant findings observed among 1,291 patients enrolled in the 3 phases of the Fundus Photography vs Ophthalmoscopy Trial Outcomes in the Emergency Department (FOTO-ED) study



1/9 patients in ED with headache, severe hypertension, focal neurology deficit, or visual loss has ocular fundus findings that should change acute management/disposition

Biousse V, Bruce BB, Newman NJ. Ophthalmoscopy in the 21st century: The 2017 H. Houston Merritt Lecture. Neurology 2018; 90: 167–75

Non-Mydriatic Fundus Camera in ED

	Phase I	Phase II
ED Examination Method	**Direct ophthalmoscopy**	**Non-mydriatic photography**
# of patients' fundi viewed by ED-MD		
# of abnormalities detected by ED-MD		

Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. N Engl J Med 2011; 364: 387–9

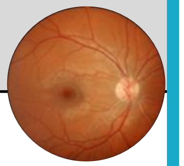
Non-Mydriatic Fundus Camera in ED

	Phase I	Phase II
ED Examination Method	**Direct ophthalmoscopy**	**Non-mydriatic photography**
# of patients’ fundi viewed by ED-MD	**48/350 (14%)**	
# of abnormalities detected by ED-MD		

Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. N Engl J Med 2011; 364: 387–9

FOTO-ED Non-Mydriatic Fundus Camera in ED

	Phase I	Phase II
ED Examination Method	**Direct ophthalmoscopy**	**Non-mydriatic photography**
# of patients' fundi viewed by ED-MD	**48/350 (14%)**	
# of abnormalities detected by ED-MD	**0/44 (0%)**	



Bruce BB, Lamirel C, Wright DW, Ward A, Heilpern KL, Biousse V, Newman NJ Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in the emergency department. N Engl J Med 2011; 364: 387–9

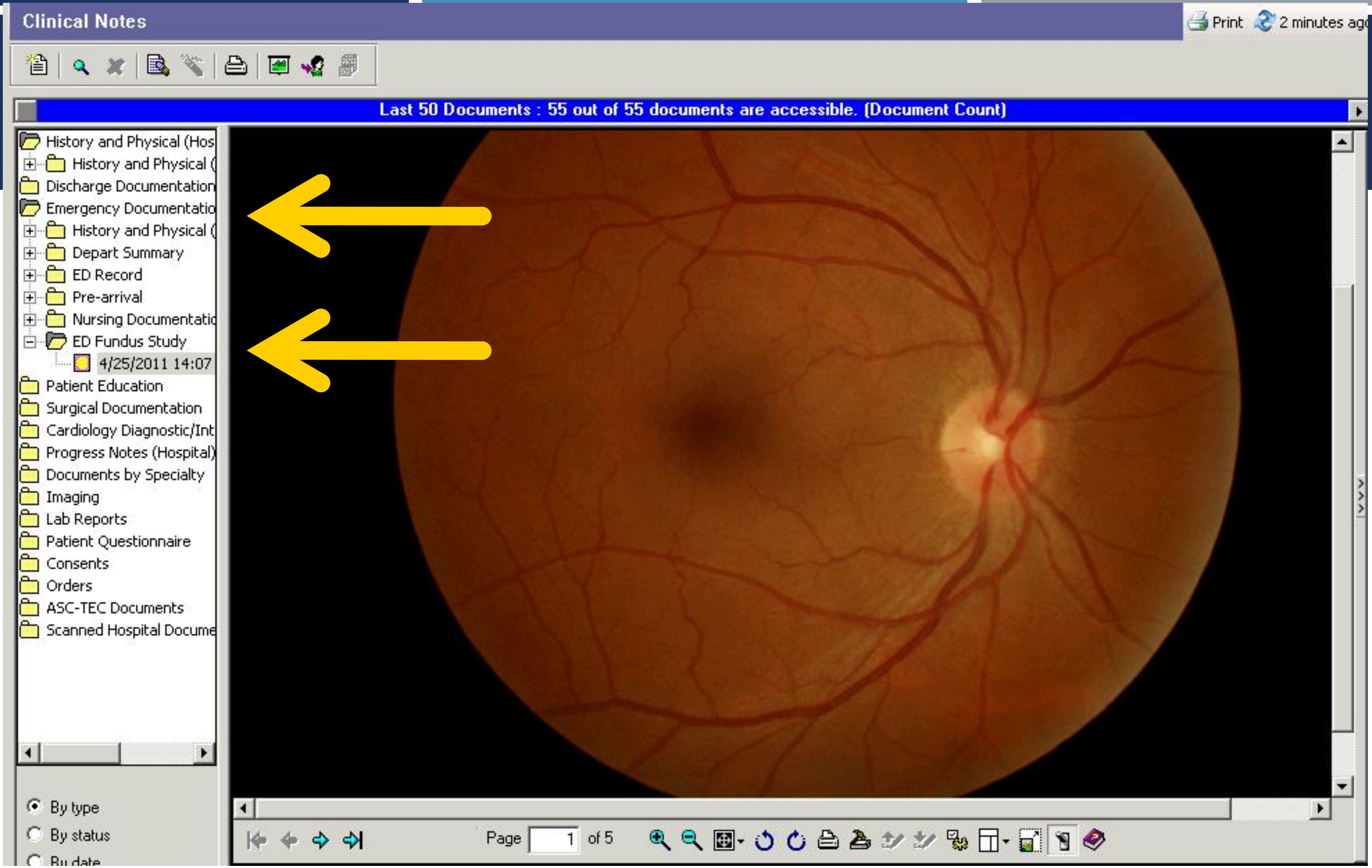
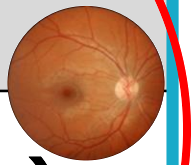

Clinical Notes
Print
2 minutes ago
Last 50 Documents : 55 out of 55 documents are accessible. (Document Count)
History and Physical (Hos
History and Physical (
Discharge Documentation
Emergency Documentatio
History and Physical (
Depart Summary
ED Record
Pre-arrival
Nursing Documentatio
ED Fundus Study
4/25/2011 14:07
Patient Education
Surgical Documentation
Cardiology Diagnostic/Int
Progress Notes (Hospital)
Documents by Specialty
Imaging
Lab Reports
Patient Questionnaire
Consents
Orders
ASC-TEC Documents
Scanned Hospital Docume
By type
By status
By date
Page 1 of 5

FOTO-ED Non-Mydriatic Fundus Camera in ED

	Phase I	Phase II
ED Examination Method	 **Direct ophthalmoscopy**	**Non-mydriatic photography** 
# of patients' fundi viewed by ED-MD	**48/350 (14%)**	**239/355 (68%)**
# of abnormalities detected by ED-MD	**0/44 (0%)**	**16/35 (46%)**

*ED providers correctly identified **86% of normal** fundi as normal on fundus photos*

Bruce BB, Thulasi P, Fraser CL, Keadey MT, Ward A, Heilpern KL, Wright DW, Newman NJ, Biousse V. Diagnostic accuracy and use of nonmydriatic ocular fundus photography by emergency physicians: phase II of the FOTO-ED study. Ann Emerg Med 2013; 62: 28–33

EMORY UNIVERSITY SCHOOL OF MEDICINE

STOP TEACHING OPHTHALMOSCOPY TO MEDICAL STUDENTS?

Mackay DD, Garza PS, Bruce BB, Newman NJ, Biousse V. The demise of direct ophthalmoscopy: A modern clinical challenge. Neurol Clin Pract 2015; 5: 150–7

STOP TEACHING OPHTHALMOSCOPY TO MEDICAL STUDENTS?

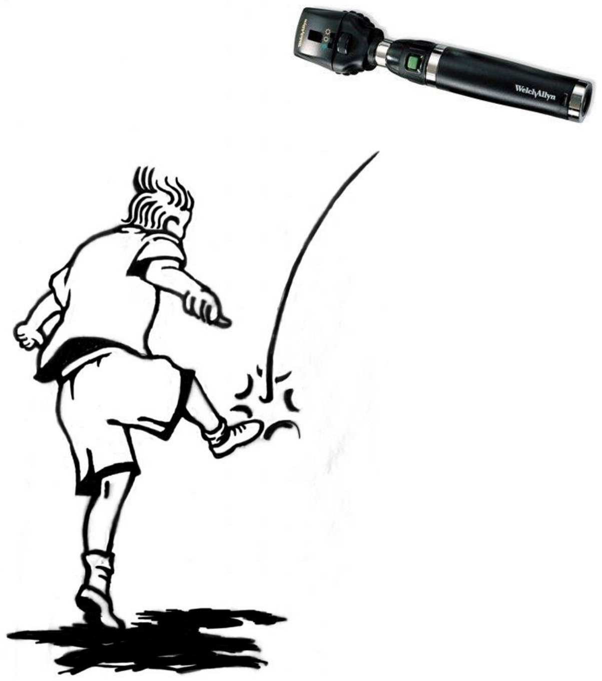
OPHTHALMOSCOPY

SHOULD HAVE BEEN DONE ON DAY 1!

No Light Perception

Light Perception

STOP TEACHING OPHTHALMOSCOPY TO MEDICAL STUDENTS?



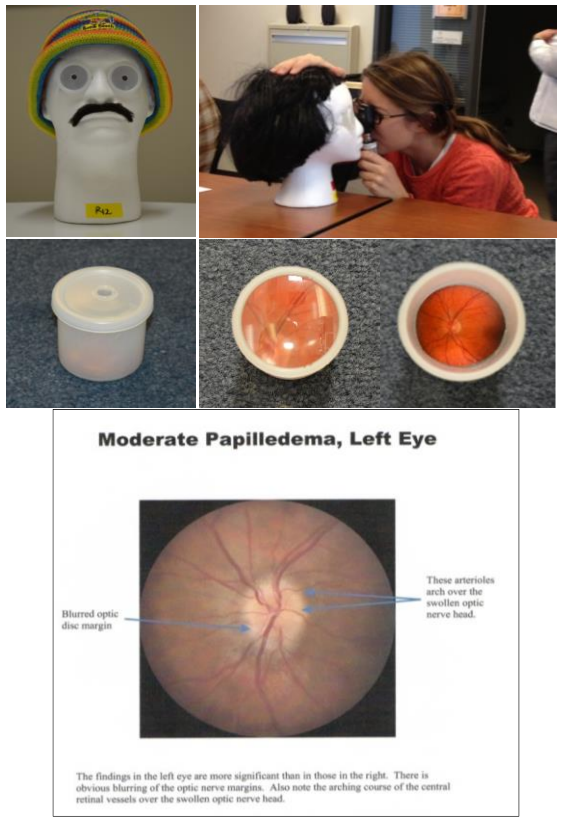
OCULAR FUNDUSCOPIC EXAMINATION

SHOULD HAVE BEEN DONE ON DAY 1!

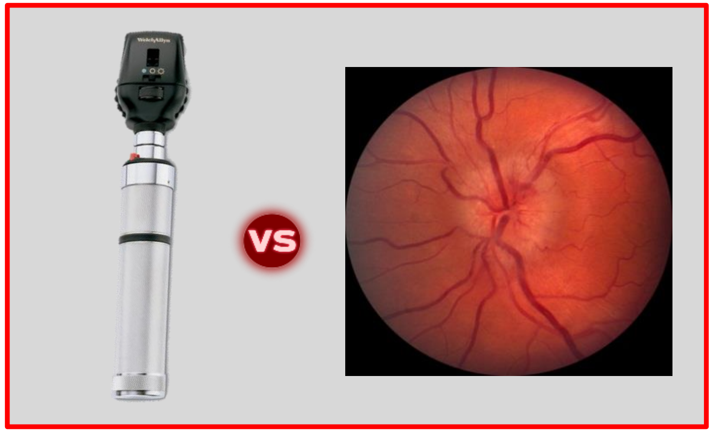
No Light Perception

Light Perception

Teaching Ophthalmoscopy to Medical Students: TOTEMS



- Medical students: Year 1 (n=138)
- Direct ophthalmoscope vs photograph interpretation
  - On humans and simulators



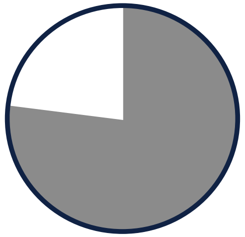
Kelly LP, Garza PS, Bruce BB, Graubart EB, Newman NJ, Biousse V. Teaching ophthalmoscopy to medical students (the TOTeMS study). Am J Ophthalmol 2013; 156: 1056–61

Teaching Ophthalmoscopy to Medical Students: TOTEMS – *Am J. Ophthalmol 2013*

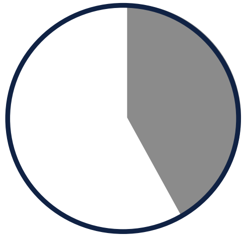
- M1s performed significantly better identifying fundus features with photographs ($p<0.001$) than on simulator
  - 85% correct answers on photographs
- Fundus photographs: easiest and least frustrating
- 70% preferred photographs to simulators for ocular fundus assessment
- 49% said they would attempt direct ophthalmoscopy during clinical rotations over the next year

1 Year Retention Study (Medical Students Year 2): **TOTEMS II**

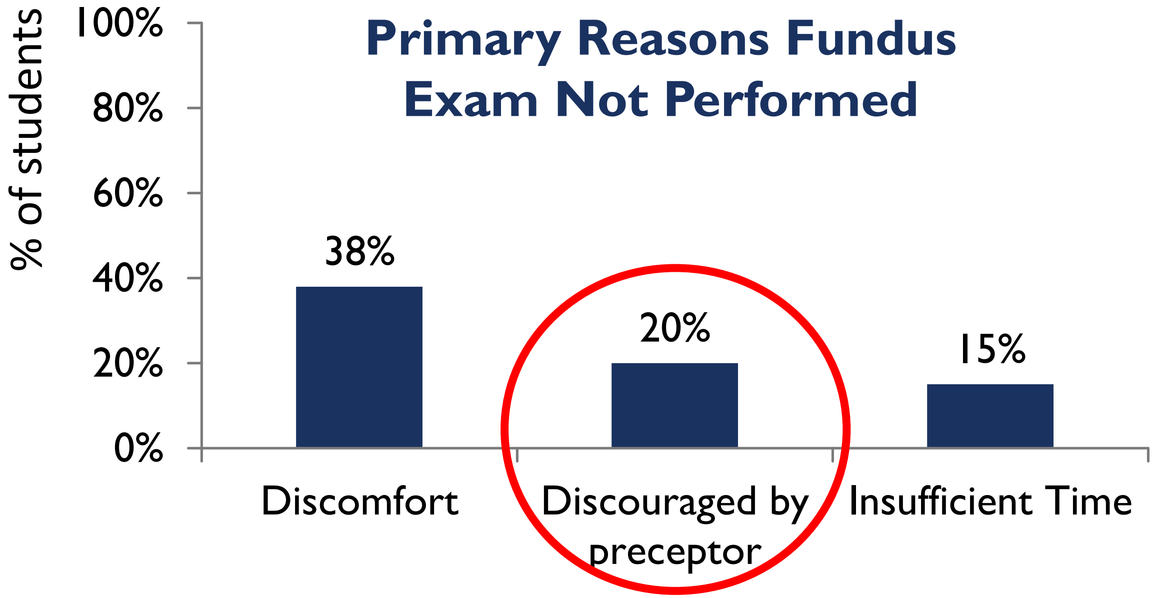
- M2s again more accurate interpreting ocular fundus photographs than simulators ($p<0.001$)
- Self-reported median frequency of ophthalmoscopy over previous year: < 10%



77% uncomfortable with ophthalmoscopy



42% would not perform ophthalmoscopy during general exam



Mackay DD, Garza PS, Bruce BB, Bidot S, Graubart EB, Newman NJ, Biousse V. Teaching ophthalmoscopy to medical students (TOTeMS) II: A one-year retention study. Am J Ophthalmol. 2014; 157: 747-8

Fundus Examination Is More Important Than The Method Used

-45 minutes online tutorial with pre- and post self assessment

-Traditional ophthalmoscopy workshop coupled with fundus photographs interpretation

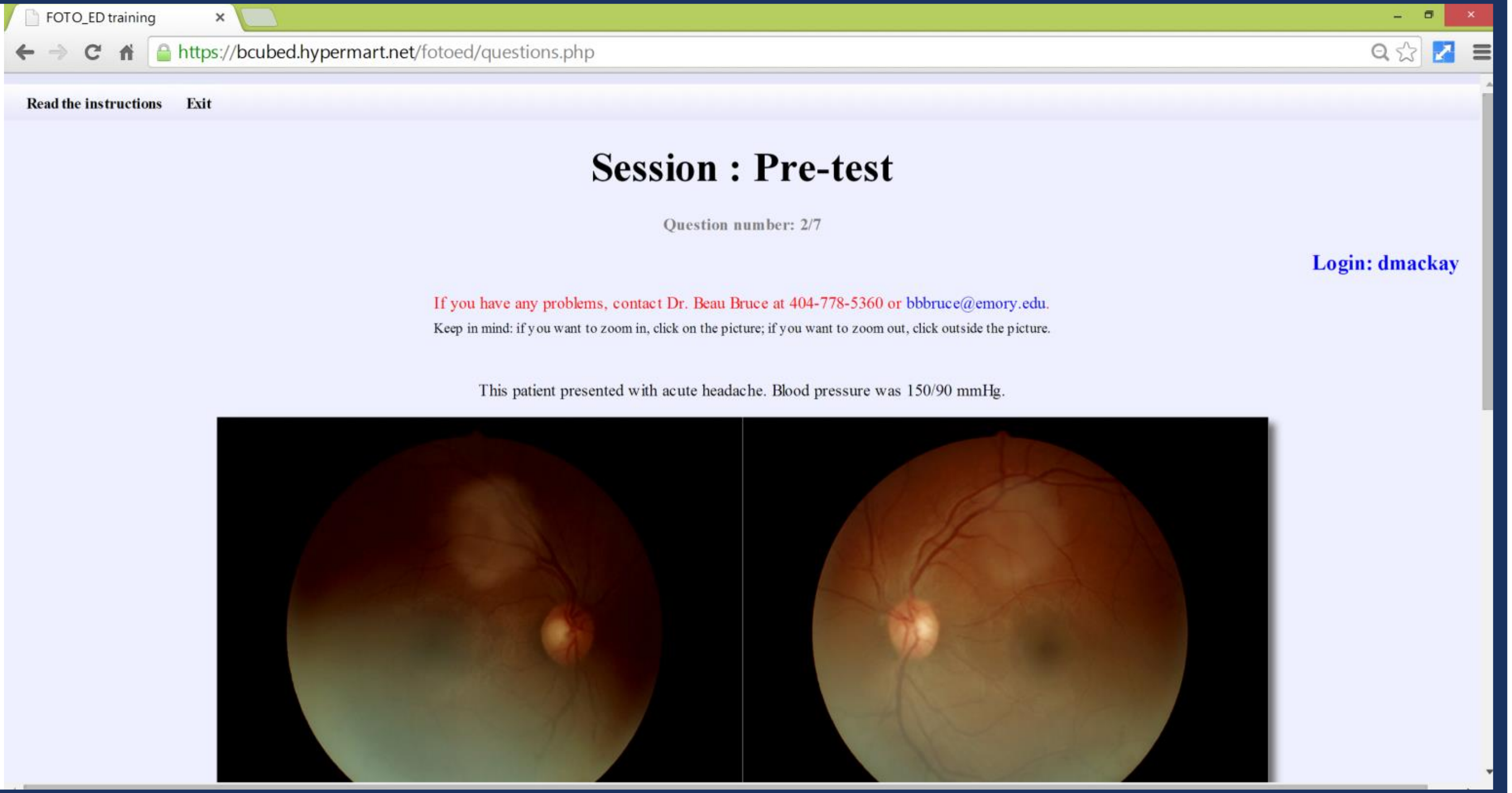
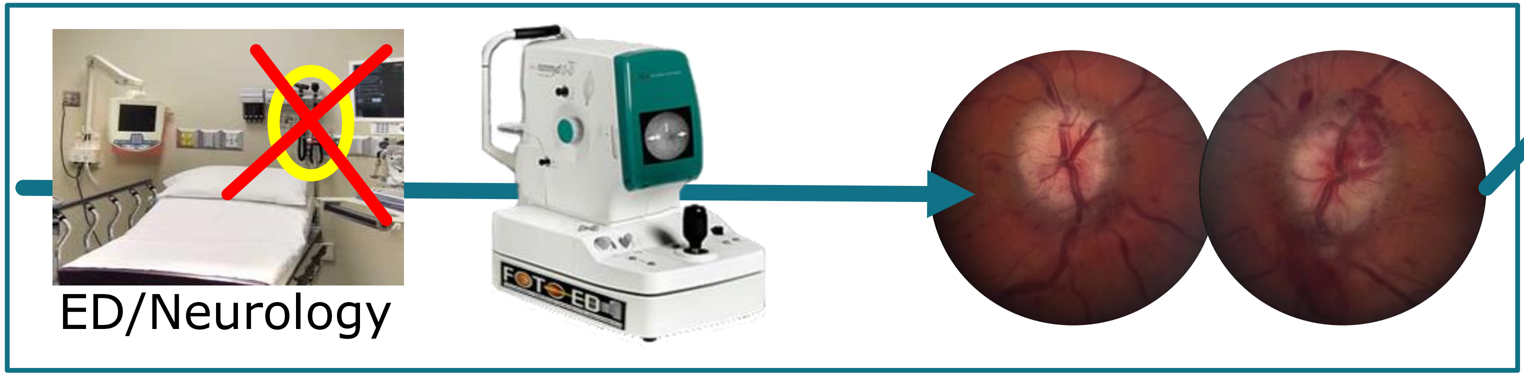


FOTO-ED Non-Mydriatic Fundus Camera in ED

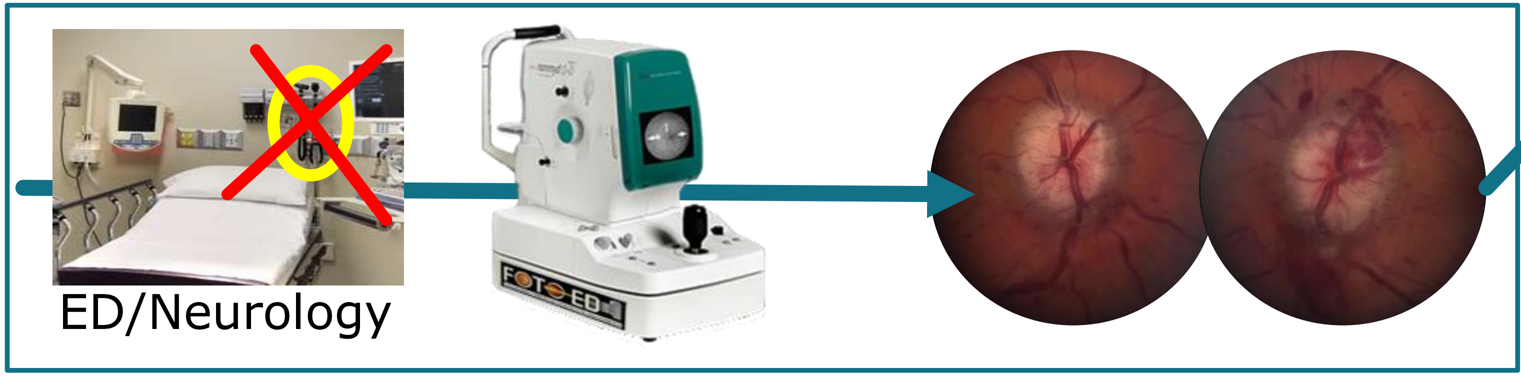


Onsite interpretation by ED provider (Phase II)

Onsite interpretation by ED provider after training (Phase III)

Bruce BB, Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in neurologic emergencies. JAMA Neurol 2015; 72: 455–9

FOTO-ED Non-Mydriatic Fundus Camera in ED



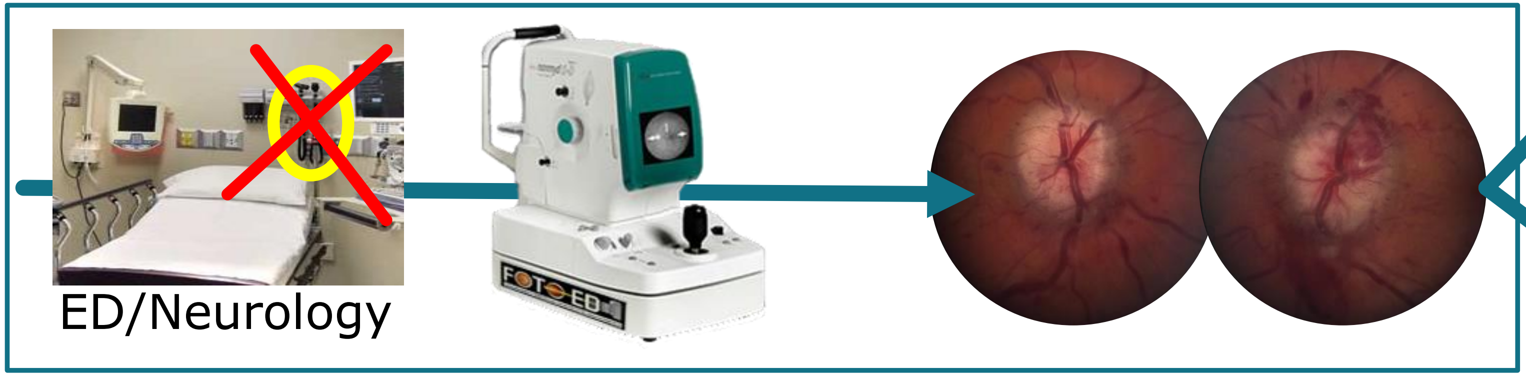
Onsite interpretation by ED provider (Phase II)

Onsite interpretation by ED provider after training (Phase III)

Phase III FOTO-ED: No improvement of ED providers' performance after training

Bruce BB, Biousse V, Newman NJ. Nonmydriatic ocular fundus photography in neurologic emergencies. JAMA Neurol 2015; 72: 455–9

Non-Mydriatic Fundus Camera in ED

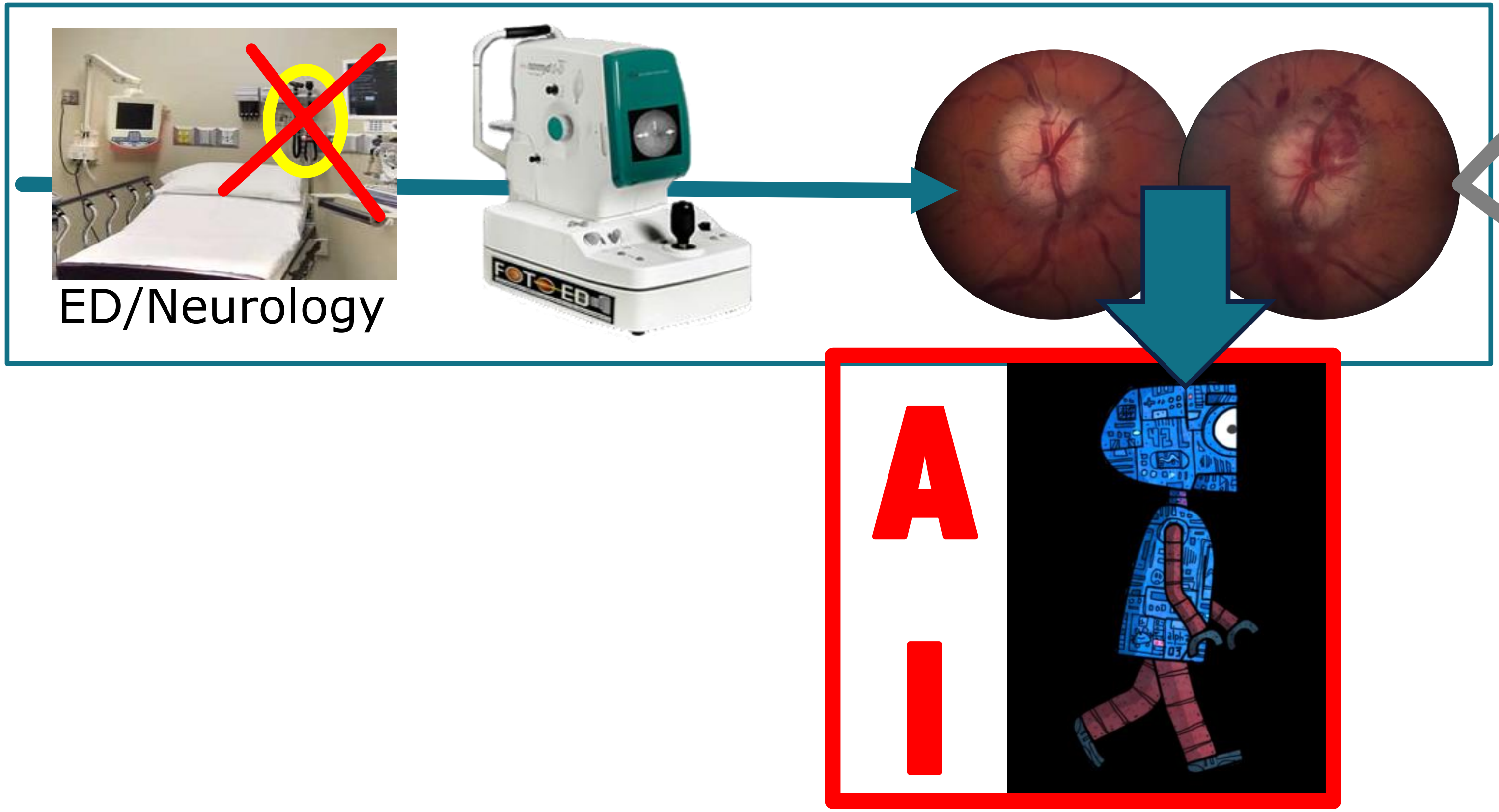


Onsite interpretation by ED provider / neurologist with ophthalmology consultation if abnormal or unsure

Remote interpretation by ophthalmologist (tele-ophthalmology/ teleconsultation)

- **Liability:**
  - **ED and neurologists do not know how to interpret photos**
  - **Ophthalmologists need clinical information**
- **Billing**

Non-Mydriatic Fundus Camera in ED

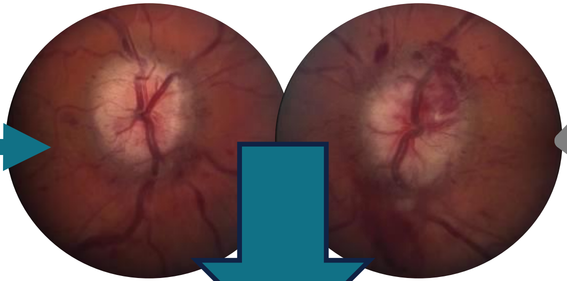


Onsite interpretation by ED provider / neurologist with ophthalmology consultation if abnormal or unsure

Remote interpretation by ophthalmologist (tele-ophthalmology/ teleconsultation)

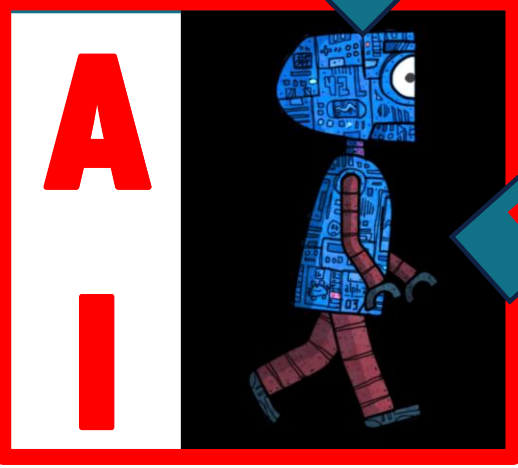
Non-Mydriatic Fundus Camera in ED

ED/Neurology



Onsite interpretation by ED provider / neurologist with ophthalmology consultation if abnormal or unsure

ote terpretation by ophthalmologist (tele-ophthalmology/ teleconsultation)



DIAGNOSTIC AID

Artificial Intelligence and Digital Technology in Ophthalmology

[VERY] *Basic Overview*

Artificial intelligence and deep learning in ophthalmology

Daniel Shu Wei Ting,[1] Louis R Pasquale,[2] Lily Peng,[3] John Peter Campbell,[4] Aaron Y Lee,[5] Rajiv Raman,[6] Gavin Siew Wei Tan,[1] Leopold Schmetterer,[1,7,8,9] Pearse A Keane,[10] Tien Yin Wong[1]

Br J Ophthalmol 2018

For numbered affiliations see end of article.

Correspondence to
Dr Daniel Shu Wei Ting, Assistant Professor in Ophthalmology, Duke-NUS Medical SchoolSingapore National Eye Center, Singapore 168751, Singapore; daniel.ting.s.w@singhealth.com.sg

Received 4 September 2018
Revised 17 September 2018
Accepted 23 September 2018

ABSTRACT

Artificial intelligence (AI) based on deep learning (DL) has sparked tremendous global interest in recent years. DL has been widely adopted in image recognition, speech recognition and natural language processing, but is only beginning to impact on healthcare. In

results, medicolegal issues, and physician and patient acceptance of the AI 'black-box' algorithms. DL could potentially revolutionise how ophthalmology is practised in the future. This review provides a summary of the state-of-the-art DL systems described for ophthalmic applications, potential challenges in clinical deployment and the path forward.

ocular imaging, principally fundus photographs and optical coherence tomography (OCT). Major ophthalmic diseases which DL techniques have been used for include diabetic retinopathy (DR),[11–15] glaucoma,[11 16] age-related macular degeneration (AMD)[11 17 18] and retinopathy of prematurity

middle-income countries. The use of DL, coupled with telemedicine, may be a long-term solution to screen and monitor patients within primary eye care settings. This review summarises new DL systems for ophthalmology applications, potential challenges in clinical deployment and potential paths forward.

Deep Learning is already changing everything in ophthalmology!

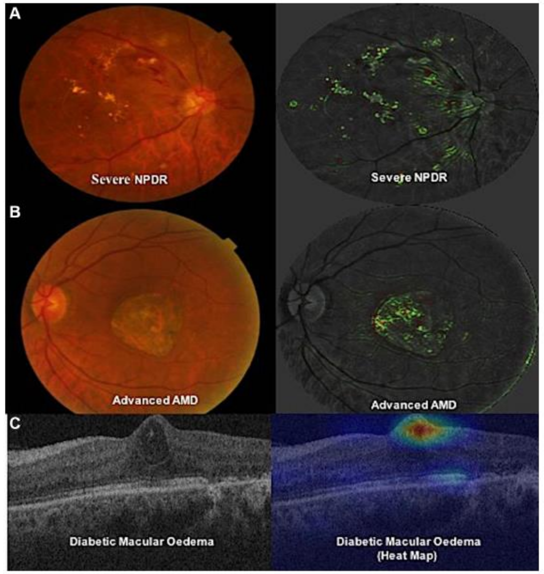


Figure 2 Some examples of heat maps showing the abnormal areas in the retina. (A) Severe non-proliferative diabetic retinopathy (NPDR); (B) geographic atrophy in advanced age-related macular degeneration (AMD) on fundus photographs[11]; and (C) diabetic macular oedema on optical coherence tomography.

U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary

News & Events

Home › News & Events › Newsroom › Press Announcements

FDA News Release

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release: April 11, 2018

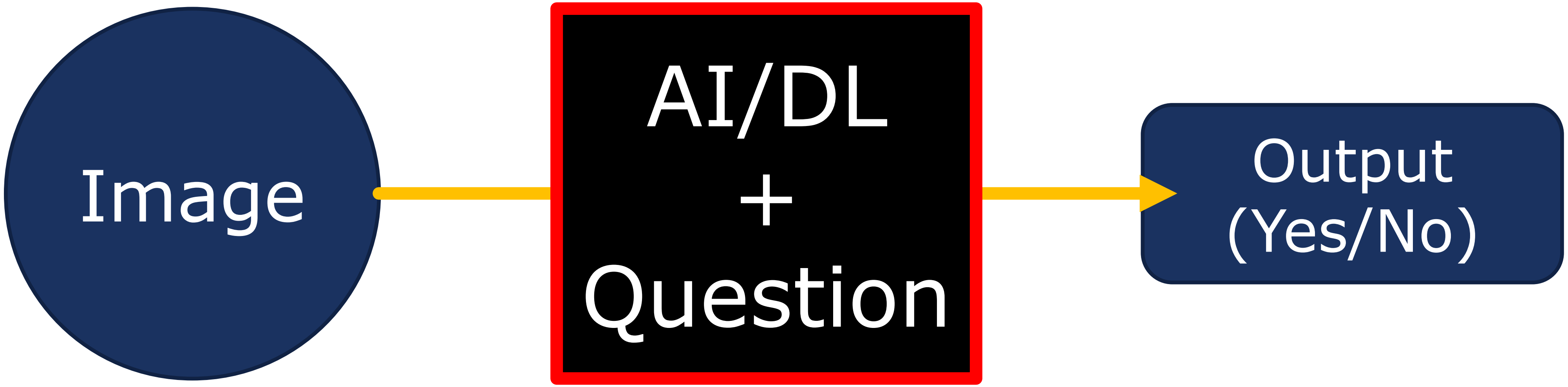
Release

Español

The U.S. Food and Drug Administration today permitted marketing of the first medical device to use artificial intelligence to detect greater than a mild level of the eye disease diabetic retinopathy in adults who have diabetes.

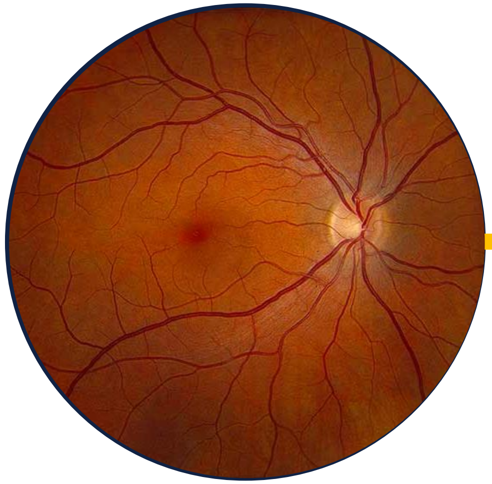
Diabetic retinopathy occurs when high levels of blood sugar lead to damage in the blood vessels of the retina, the light-sensitive tissue in the back of the eye. Diabetic retinopathy is the most common cause of vision loss among the more than 30 million Americans living with diabetes and the leading cause of vision impairment and

Artificial Intelligence And Deep Learning



Wallace H. Coulter
Department of
Biomedical
Engineering
at Georgia Tech and Emory University

Artificial Intelligence And Deep Learning: Many applications in ophthalmology



AI/DL
Diabetic retinopathy ?

No

AI/DL
Diabetic retinopathy ?

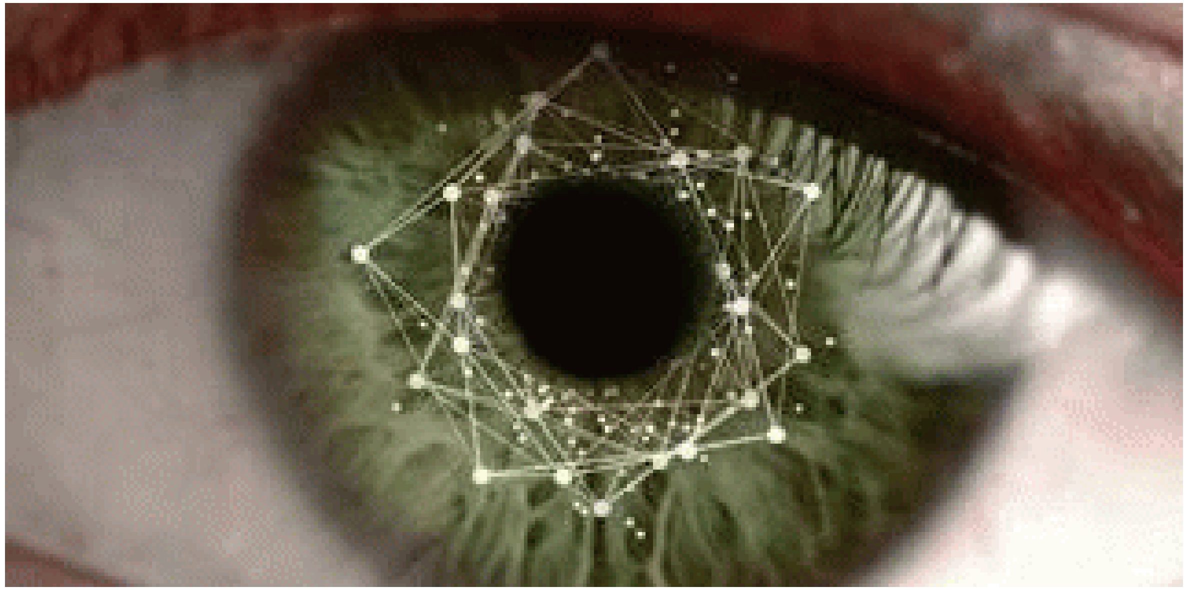
Yes

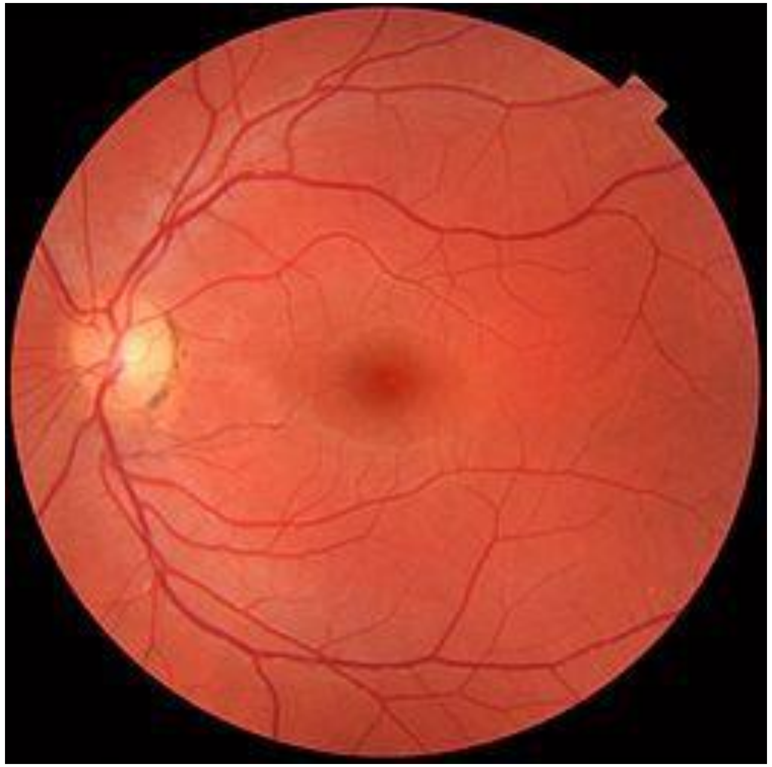
Female or Male Gender?

Google's AI can see through your eyes what doctors can't

Susan Ruyu Qi Follow

Nov 26, 2018 · 2 min read





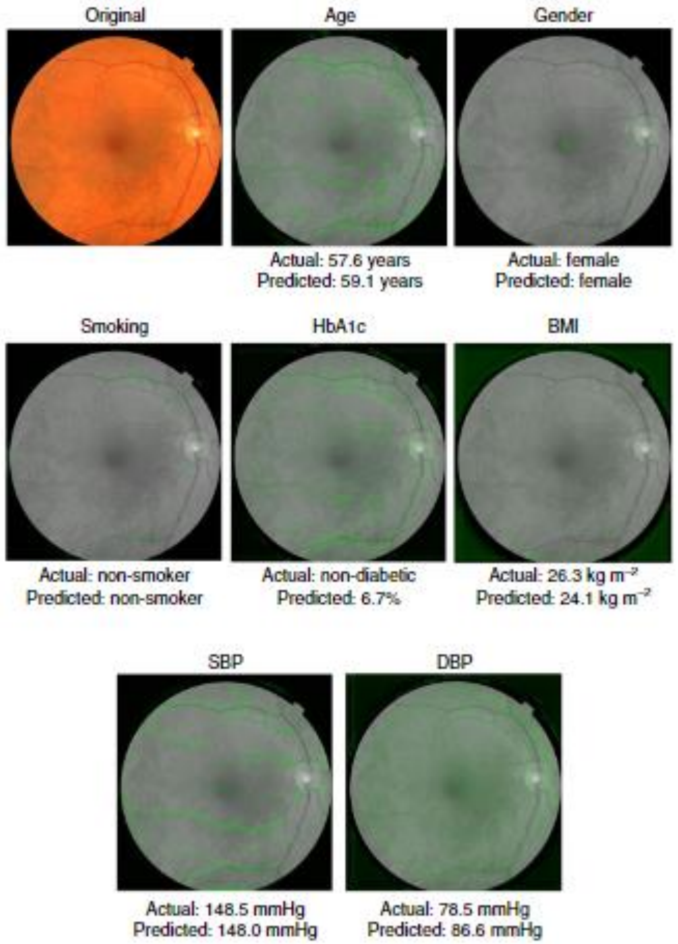
ARTICLES
https://doi.org/10.1038/s41551-018-0195-0

nature biomedical engineering

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]

Traditionally, medical discoveries are made by observing associations, making hypotheses from them and then designing and running experiments to test the hypotheses. However, with medical images, observing and quantifying associations can often be difficult because of the wide variety of features, patterns, colours, values and shapes that are present in real data. Here, we show that deep learning can extract new knowledge from retinal fundus images. Using deep-learning models trained on data from 284,335 patients and validated on two independent datasets of 12,026 and 999 patients, we predicted cardiovascular risk factors not previously thought to be present or quantifiable in retinal images, such as age (mean absolute error within 3.26 years), gender (area under the receiver operating characteristic curve (AUC) = 0.97), smoking status (AUC = 0.71), systolic blood pressure (mean absolute error within 11.23 mmHg) and major adverse cardiac events (AUC = 0.70). We also show that the trained deep-learning models used anatomical features, such as the optic disc or blood vessels, to generate each prediction.



Five Important Rules in AI *(Daniel Ting, MD PhD)*

- **1-Right question**
- **2-Right data**
- **3-Right partners**
- **4-Right concepts and methods**
- **5-Right enabler**

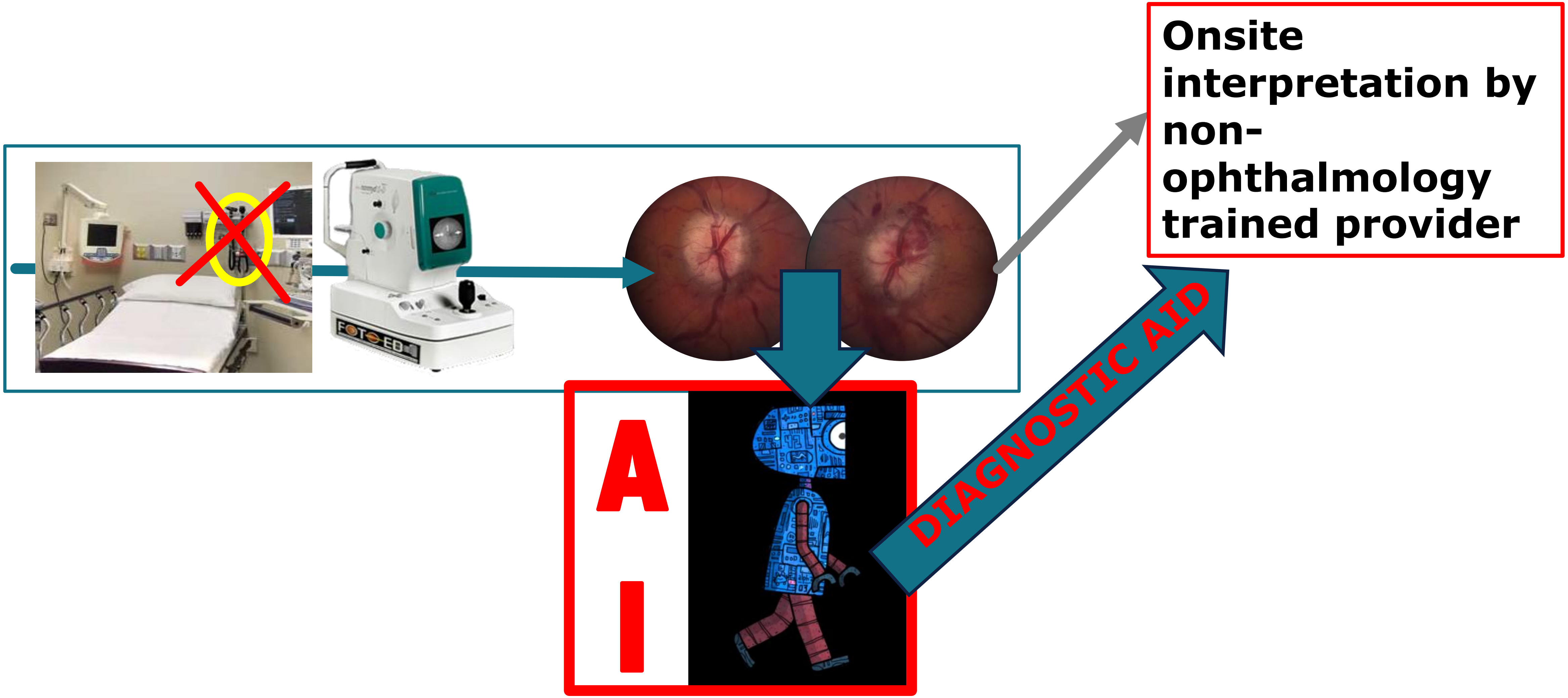
Artificial Intelligence and Deep Learning

- **Large data sets** of images associated with definite diagnosis (made by humans) – *reference standard (ground truth)*
- **Training data set** (tell the machine what is what; then the machine will teach itself): train until machine performant enough – *randomly presented batches*
- **Validation data set** (confirm that the machine can answer the question reliably) – *parameter selection/tuning*
- **External validation** (test the machine on different data sets) – *different centers/cameras/populations (generalization of findings)*

Artificial Intelligence to Replace Ophthalmoscopy

Possible?

Optic nerve photographs and AI



The Brain and Optic Nerve Study with Artificial Intelligence (BONSAI)

Dan Milea MD PhD, Valérie Biousse MD, Nancy J Newman MD, Raymond P Najjar PhD, Caroline Vasseneix MD, Jiang Zhubo MSc, Yong Liu PhD, Daniel Ting MD PhD, Tien Yin Wong MD PhD, *for the BONSAI Group*

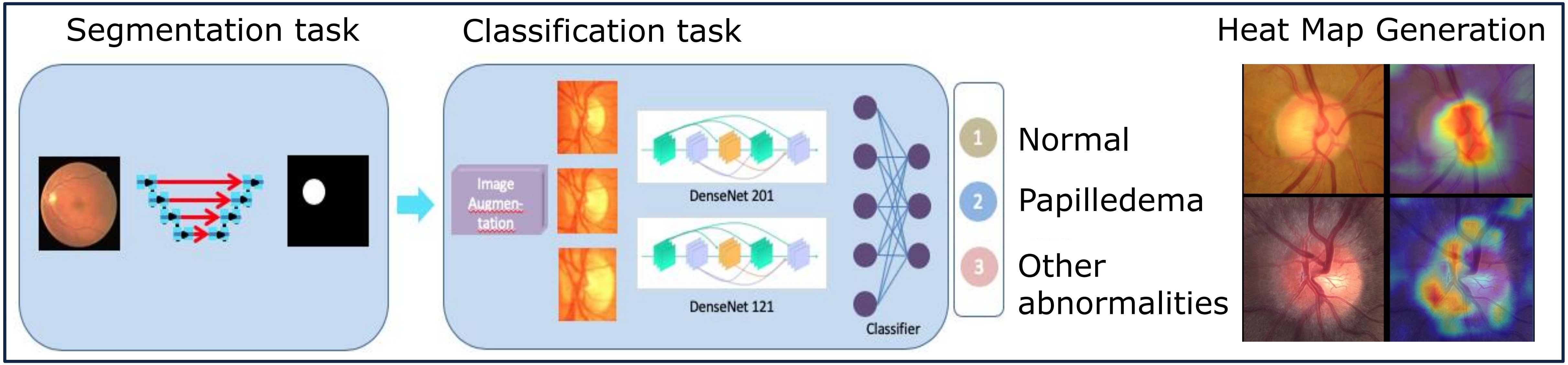
Funding MINISTRY OF HEALTH SINGAPORE
MOH CS-IRG 2015

Five Important Rules in AI *(Daniel Ting, MD PhD)*

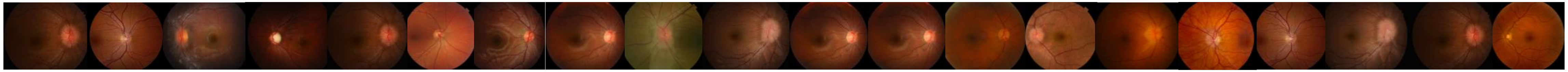
- **1-Right question:** papilledema or not?
- **2-Right data:** fundus photographs from 25 international centers (large number, diverse data)
- **3-Right partners:** expert neuro-ophthalmologists (international group) and AI team (Singapore)
- **4-Right concepts and methods:** excellent clinical and digital operational flow
- **5-Right enabler:** implementation, outcome, commercialization (pending @Singapore)

BONSAI Group:
25 Centers, 70 investigators, 19 Countries

BONSAI Deep Learning System
Automatic classification of optic discs



- 1) Quality check
- 2) Is the disc **normal** vs abnormal?
- 3) Is the abnormal disc **papilledema** (raised ICP) vs other?

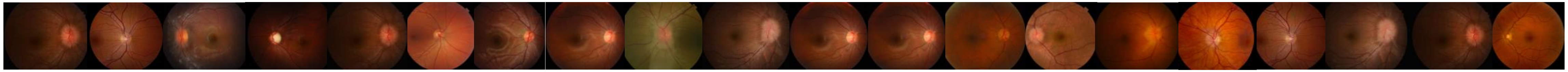


BONSAI Deep Learning System
Automatic classification of optic discs

- 15,846 ocular fundus photographs
  - 9769 normal
  - 2508 papilledema
  - 3569 other disc abnormalities

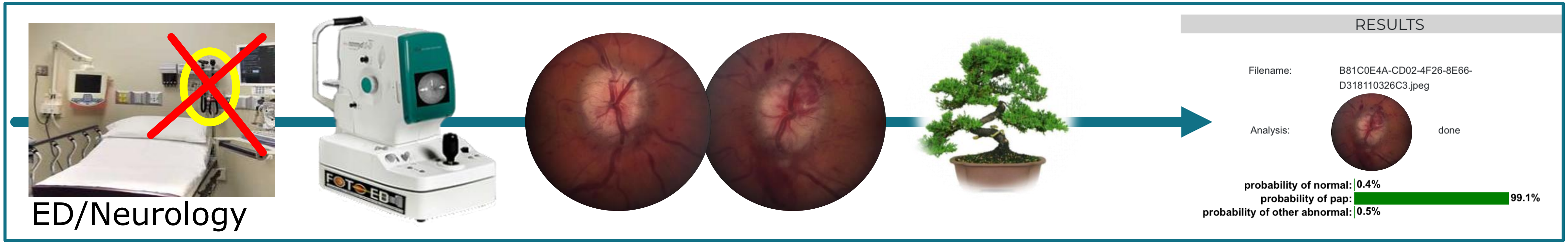
Training and validation:
14,341 photographs
(80/20%)
from 19 centers

External validation:
1505 photographs
from 3 centers



BONSAI Deep Learning System
Automatic classification of optic discs

- **Fundus Photography with AI as diagnostic aid in non-ophthalmic settings** (no clinical information):



BONSAI Deep Learning System

Aut

- Func d in non-

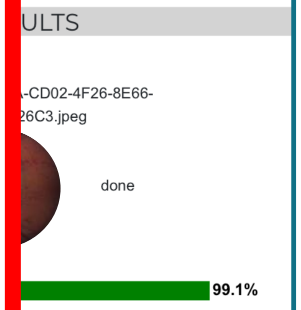
ED/Neurol

RESULTS

Filename: B81C0E4A-CD02-4F26-8E66-D318110326C3.jpeg

Analysis:  done

probability of normal: 0.4%
probability of pap: 99.1%
probability of other abnormal: 0.5%



Discrimination of:
Normal Discs vs. Discs With Papilledema

- Area under curve (AUC) for the detection of papilledema of 0.96 (95% CI, 0.95 to 0.97)
- Sensitivity of 96.4% (95% CI, 93.9 to 98.3)
- Specificity of 84.7% (95% CI, 82.3 to 87.1)

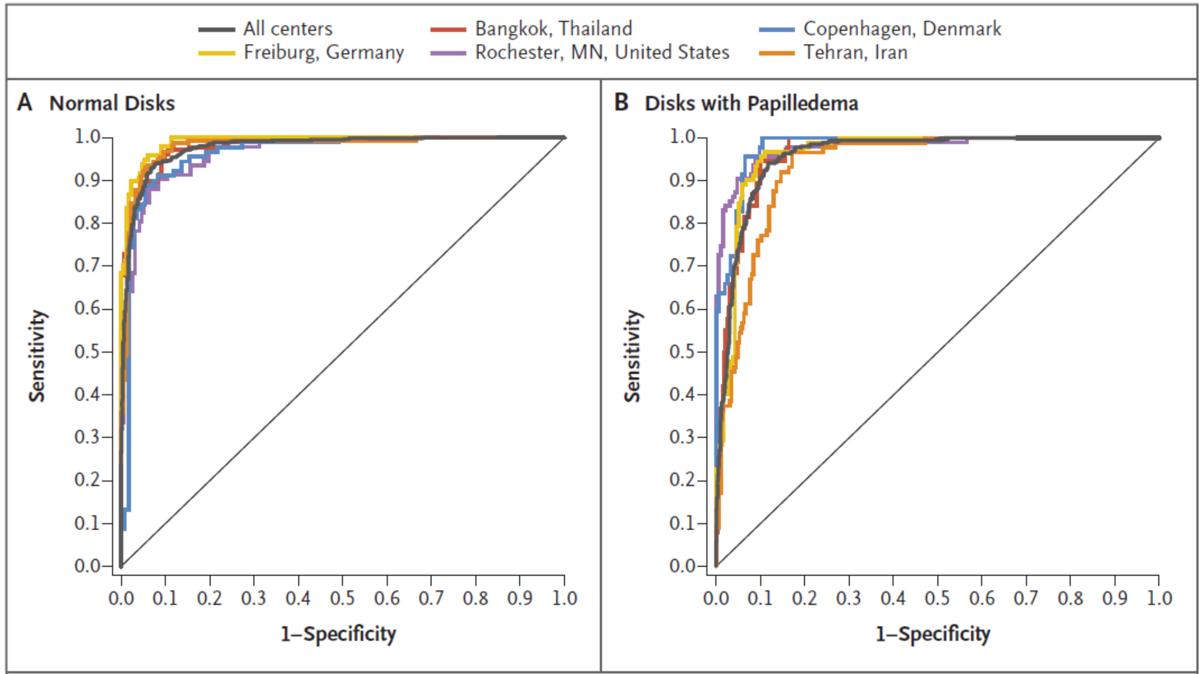


Figure 1. Performance of the Deep-Learning System for the Detection of Normal Disks and Disks with Papilledema in the External-Testing Data Sets.

The external-testing data sets included ocular fundus photographs from five centers with diverse ethnic backgrounds. As shown in Panel A, the deep-learning system discriminated normal optic disks from abnormal ones, with areas of the receiver-operating-characteristic curve (AUCs) that ranged from 0.96 to 0.99 and an overall AUC of 0.98 (95% CI, 0.97 to 0.98). As shown in Panel B, the deep-learning system discriminated disks with papilled
from normal disks and disks with nonpapilledema abnormalities, with AUCs that ranged from 0.93 to 0.98 and
overall AUC of 0.96 (95% CI, 0.95 to 0.97).

Photograph

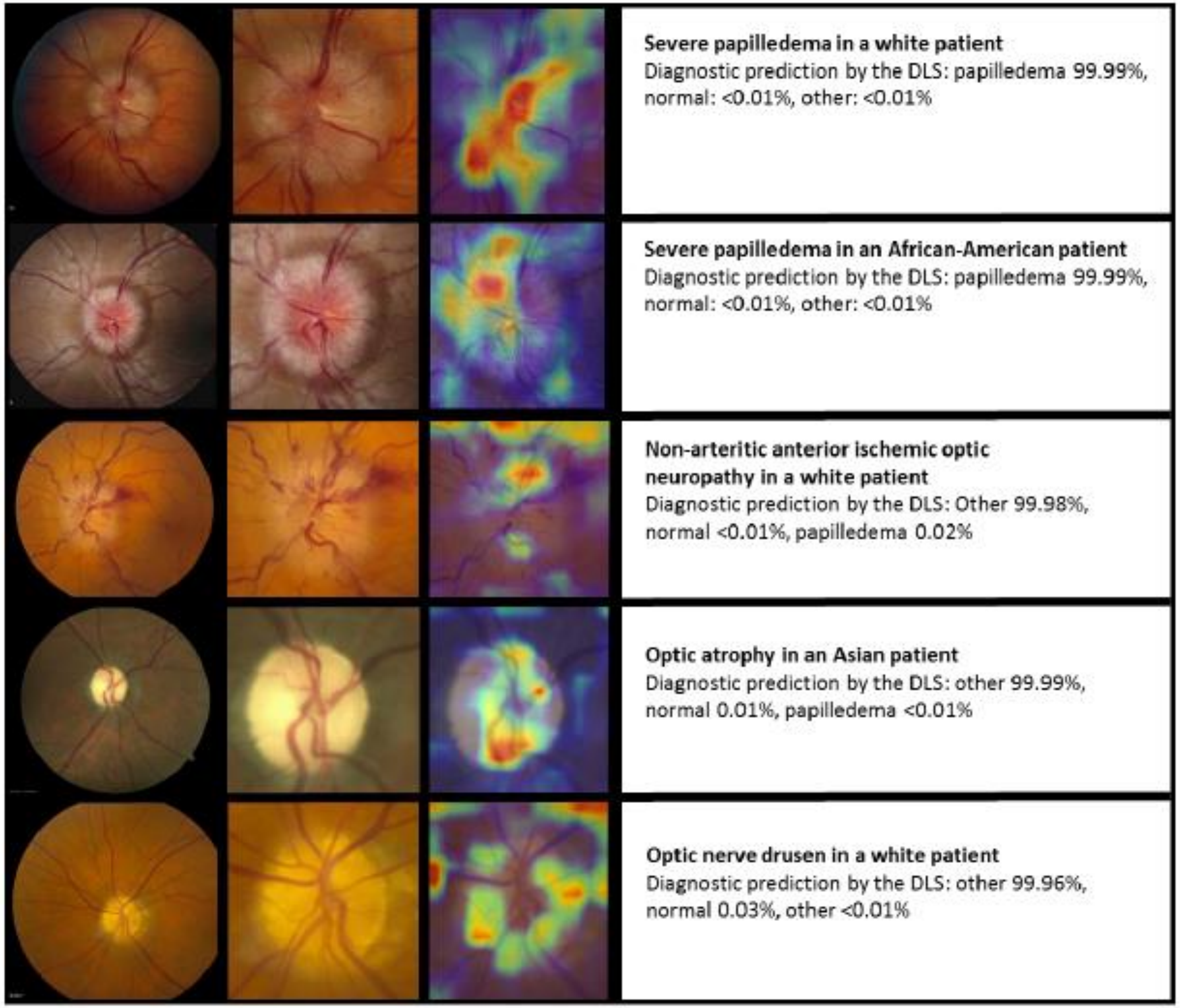
Quality check

Cropping
Disc centered

Heat map generation

Analysis

Probability



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2020 VOL. 382 NO. 18

Artificial Intelligence to Detect Papilledema from Ocular Fundus Photographs

D. Milea, R.P. Najjar, Z. Jiang, D. Ting, C. Vasseneix, X. Xu, M. Aghsaei Fard, P. Fonseca, K. Vanikieti, W.A. Lagrèze, C. La Morgia, C.Y. Cheung, S. Hamann, C. Chiquet, N. Sanda, H. Yang, L.J. Mejico, M.-B. Rougier, R. Kho, Thi H.C. Tran, S. Singhal, P. Gohier, C. Clermont-Vignal, C.-Y. Cheng, J.B. Jonas, P. Yu-Wai-Man, C.L. Fraser, J.J. Chen, S. Ambika, N.R. Miller, Y. Liu, N.J. Newman, T.Y. Wong, and V. Biousse, for the BONSAI Group*

ABSTRACT

BACKGROUND

Nonophthalmologist physicians do not confidently perform direct ophthalmoscopy. The use of artificial intelligence to detect papilledema and other optic-disk abnormalities from fundus photographs has not been well studied.

METHODS

We trained, validated, and externally tested a deep-learning system to classify optic disks as being normal or having papilledema or other abnormalities from 15,846 retrospectively collected ocular fundus photographs that had been obtained with pharmacologic pupillary dilation and various digital cameras in persons from multiple ethnic populations. Of these photographs, 14,341 from 19 sites in 11 countries were used for training and validation, and 1505 photographs from 5 other sites were used for external testing. Performance at classifying the optic-disk appearance was evaluated by calculating the area under the receiver-operating-characteristic curve (AUC), sensitivity, and specificity, as compared with a reference standard of clinical diagnoses by neuro-ophthalmologists.

RESULTS

The training and validation data sets from 6779 patients included 14,341 photographs: 9156 of normal disks, 2148 of disks with papilledema, and 3037 of disks with other abnormalities. The percentage classified as being normal ranged across sites from 9.8 to 100%; the percentage classified as having papilledema ranged across sites from zero to 59.5%. In the validation set, the system discriminated disks with papilledema from normal disks and disks with nonpapilledema abnormalities with an AUC of 0.99 (95% confidence interval [CI], 0.98 to 0.99) and normal from abnormal disks with an AUC of 0.99 (95% CI, 0.99 to 0.99). In the external-testing data set of 1505 photographs, the system had an AUC for the detection of papilledema of 0.96 (95% CI, 0.95 to 0.97), a sensitivity of 96.4% (95% CI, 93.9 to 98.3), and a specificity of 84.7% (95% CI, 82.3 to 87.1).

CONCLUSIONS

A deep-learning system using fundus photographs with pharmacologically dilated pupils differentiated among optic disks with papilledema, normal disks, and disks with nonpapilledema abnormalities. (Funded by the Singapore National Medical Research Council and the SingHealth Duke–NUS Ophthalmology and Visual Sciences Academic Clinical Program.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wong at the Singapore National Eye Center, 11 Third Hospital Ave., Singapore 168751, Singapore, or at wong.tien.yin@singhealth.com.sg.

*A list of the members of the BONSAI Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Milea and Najjar and Mr. Jiang and Drs. Liu, Newman, Wong, and Biousse contributed equally to this article.

This article was published on April 14, 2020, and updated on May 6, 2020, at NEJM.org.

N Engl J Med 2020;382:1687-95.
DOI: 10.1056/NEJMoa1917130

EDITORIALS

AI for the Eye — Automated Assistance for Clinicians Screening for Papilledema

Isaac Kohane, M.D., Ph.D.

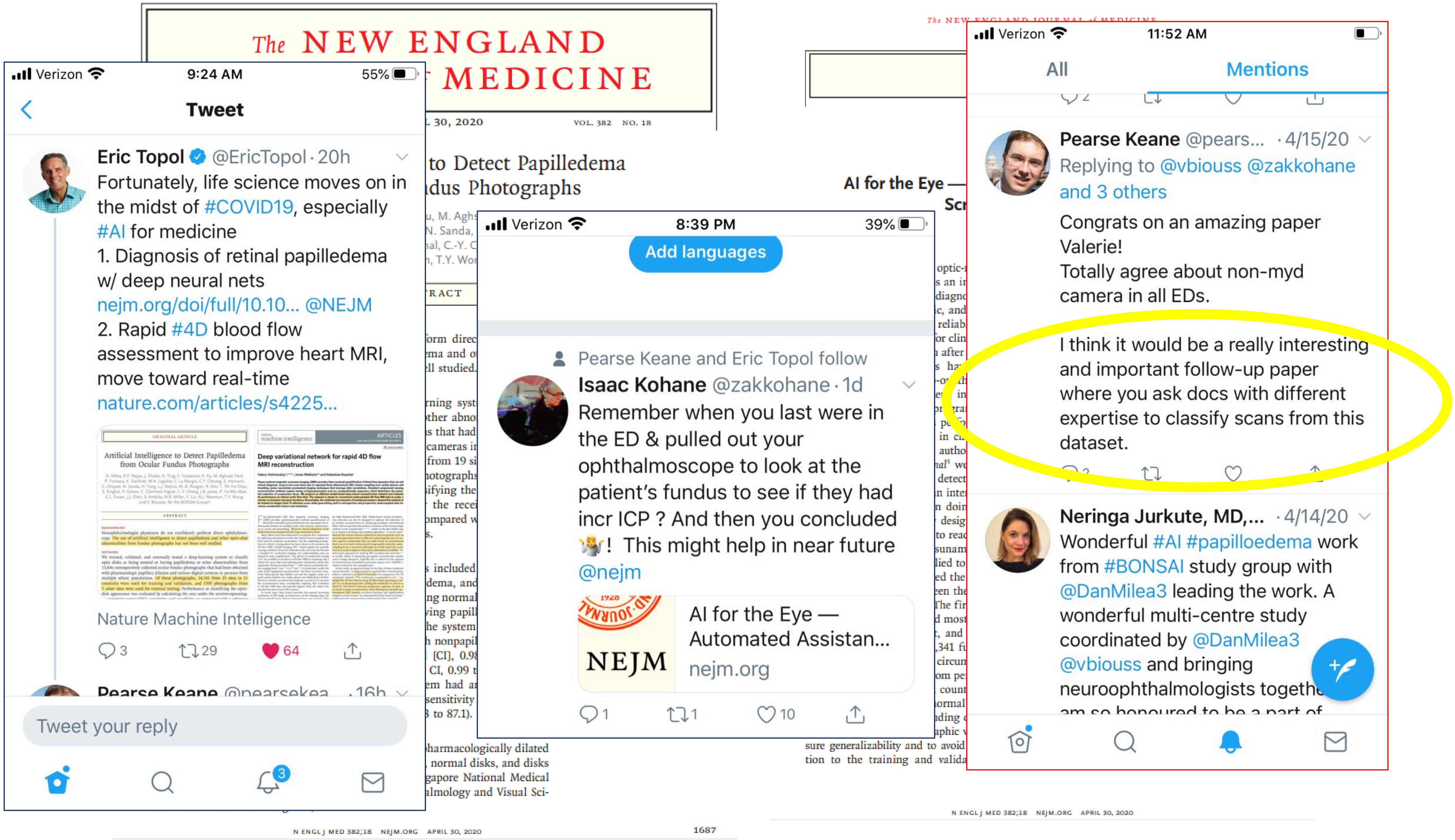
Accurate assessment of the optic-nerve head, the optic disk, by funduscopy is an important, cost-effective, and noninvasive diagnostic tool for a variety of ocular, neurologic, and inflammatory conditions. Unfortunately, reliable funduscopic assessment is challenging for clinicians working with undilated pupils[1]; even after mydriatic dilation, nonophthalmologists have considerably lower accuracy[2] than neuro-ophthalmologists in detecting optic-disk disorders, including papilledema. Could computer programs examining digital funduscopic images perform at the level of neuro-ophthalmologists in classifying disorders of the optic disk? The authors of the study now published in the *Journal*[3] were encouraged by previous studies for the detection of diabetic retinopathy[4] to undertake an international study to answer this question. In doing so, they adopted a retrospective study design that will become increasingly familiar to readers of medical journals because of the tsunami of machine-learning investigations applied to medical data.[5]

The fuel that has powered the recent success of machine learning has been the availability of two aspects of "big" data. The first is large data sets. Usually the largest and most representative data sets perform the best, and in the current report, a training set of 14,341 funduscopic images that included the full circumference of the optic nerve was obtained from persons of different ethnic groups across 11 countries. The study required a large range of normal and abnormal funduscopic findings, including cases of papilledema, with enough geographic variation to ensure generalizability and to avoid bias.[6] In addition to the training and validation sets, the investigators used an external set of 1505 images from 5 countries to test the trained algorithm. (In the absence of institutional-review-board or data-sharing infrastructure, obtaining the images from each site may have been an undertaking of greater magnitude than the machine-learning effort at the heart of this study.)

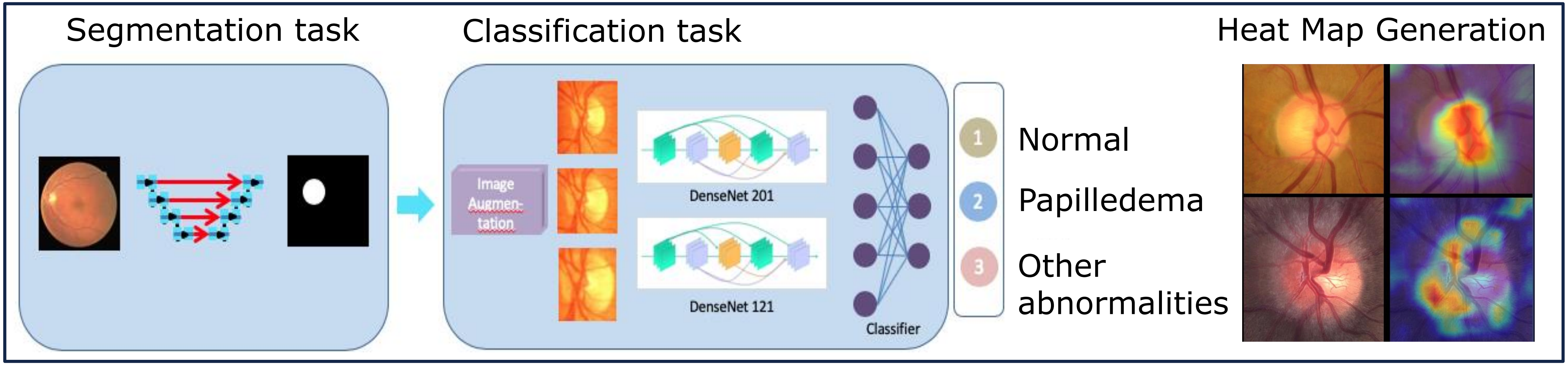
The second aspect driving success in machine learning has been the availability of labels that describe the data so that in a supervised learning approach the algorithm may define those characteristics of the raw data that best correspond to the labels. In this investigation, experts at each clinical site were required to accurately label whether the funduscopic images were abnormal and whether the abnormalities were due to papilledema using both the image and contextual clinical data. Not only does this entail a substantial effort in expert labeling of thousands of images, but it also means that the performance of these machine-learning algorithms is limited to matching the performance of the best expert consensus.

After this very extensive multinational effort, the algorithm that was tested on the external data set performed well in distinguishing disks with papilledema from other disks (normal disks and disks with nonpapilledema abnormalities). The sensitivity was 96% and the specificity 85%. As is usually the case, this performance was inferior to that obtained on the internal-validation data set, which shows the importance of having breadth and representativeness in training data for artificial-intelligence projects.

The shortcomings of this study are also instructive. How well the performance of the

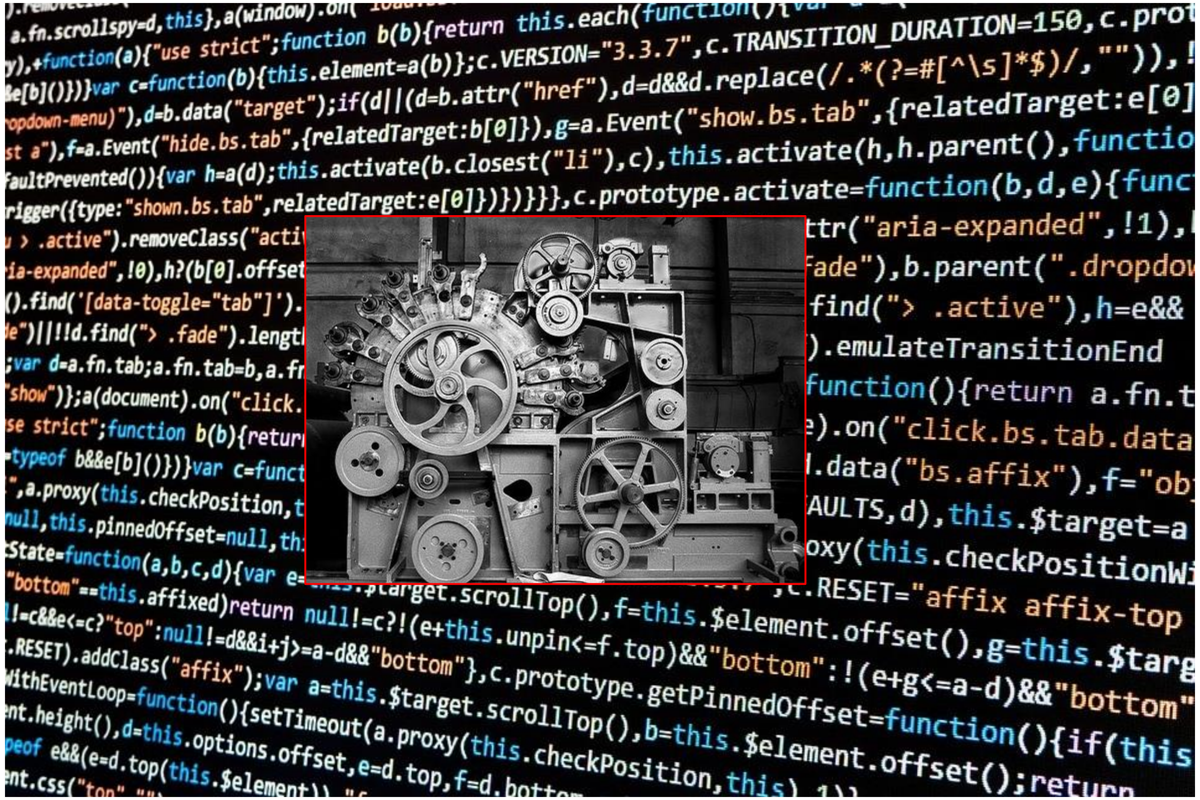

The NEW ENGLAND JOURNAL of MEDICINE
Verizon 9:24 AM 55%
Tweet
Eric Topol @EricTopol · 20h
Fortunately, life science moves on in the midst of #COVID19, especially #AI for medicine
1. Diagnosis of retinal papilledema w/ deep neural nets nejm.org/doi/full/10.10... @NEJM
2. Rapid #4D blood flow assessment to improve heart MRI, move toward real-time nature.com/articles/s4225...
Artificial Intelligence to Detect Papilledema from Ocular Fundus Photographs
Deep variational network for rapid 4D flow MRI reconstruction
Nature Machine Intelligence
3 29 64
Pearse Keane @pearsekea... · 16h
Tweet your reply
Verizon 8:39 PM 39%
Add languages
Pearse Keane and Eric Topol follow
Isaac Kohane @zakkohane · 1d
Remember when you last were in the ED & pulled out your ophthalmoscope to look at the patient's fundus to see if they had incr ICP ? And then you concluded 🤷‍♂️! This might help in near future @nejm
AI for the Eye — Automated Assistan...
nejm.org
NEJM
1 1 10
Verizon 11:52 AM
All
Mentions
Pearse Keane @pears... · 4/15/20
Replying to @vbiouss @zakkohane and 3 others
Congrats on an amazing paper Valerie!
Totally agree about non-myd camera in all EDs.
I think it would be a really interesting and important follow-up paper where you ask docs with different expertise to classify scans from this dataset.
Neringa Jurkute, MD,... · 4/14/20
Wonderful #AI #papilloedema work from #BONSAI study group with @DanMilea3 leading the work. A wonderful multi-centre study coordinated by @DanMilea3 @vbiouss and bringing neuroophthalmologists togethe
AI for the Eye —
N ENGL J MED 382;18 NEJM.ORG APRIL 30, 2020 1687

BONSAI Deep Learning System

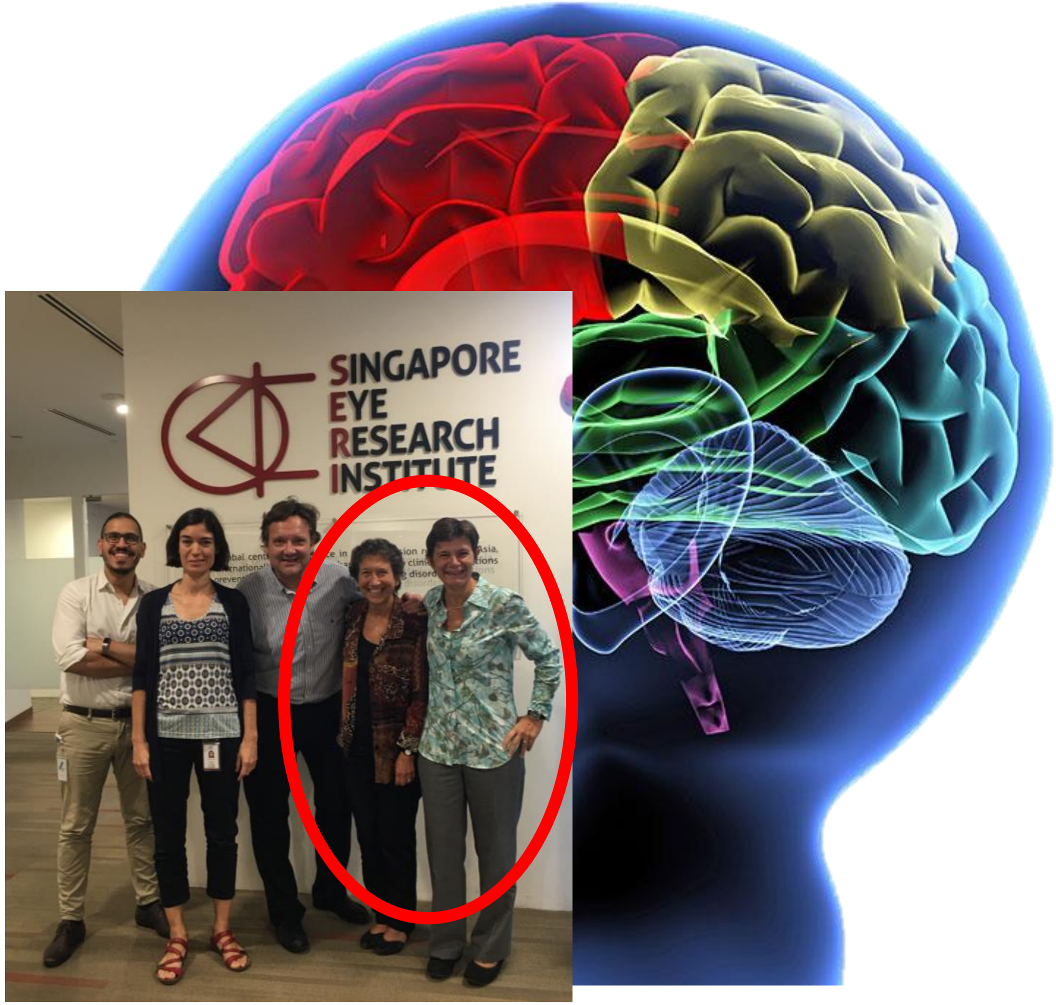


Can the BONSAI deep learning system perform as well [or better] than expert neuro-ophthalmologists?

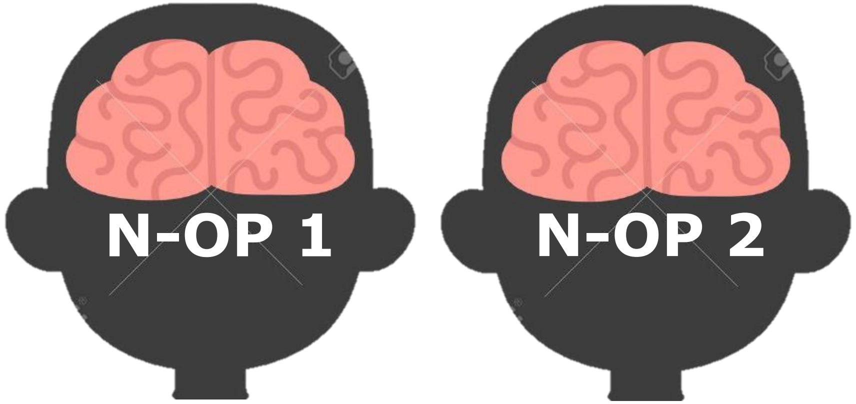
Human vs Machine



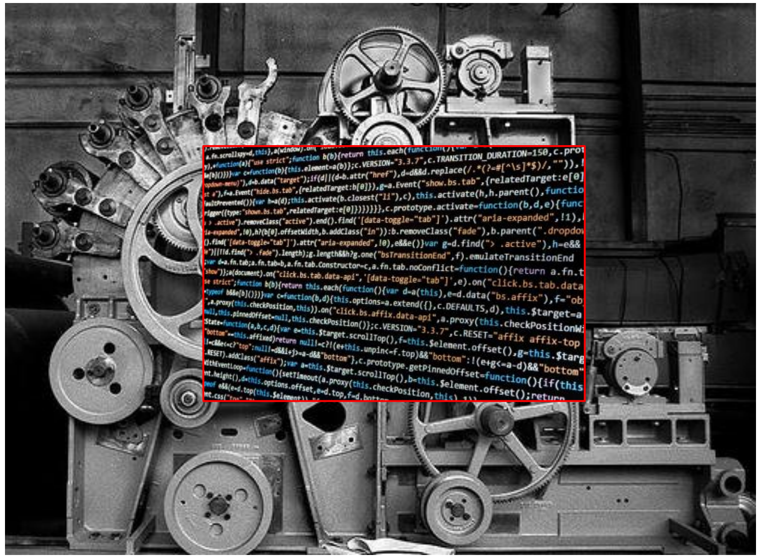
Human vs Machine



Human vs Machine



vs



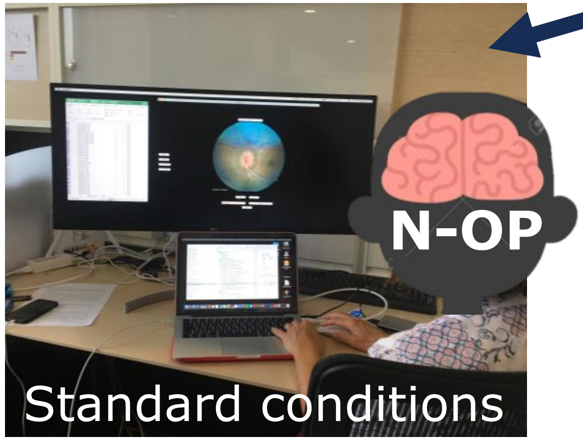
- New dataset of 800 standard digital fundus photographs
- Randomly selected from 3 neuro-ophthalmology centers (Copenhagen, Mayo Clinic Rochester, Seoul)

Human vs Machine

- 800 fundus photographs
  - 400 normal
  - 201 papilledema
  - 199 other disc abnormalities

Randomly presented

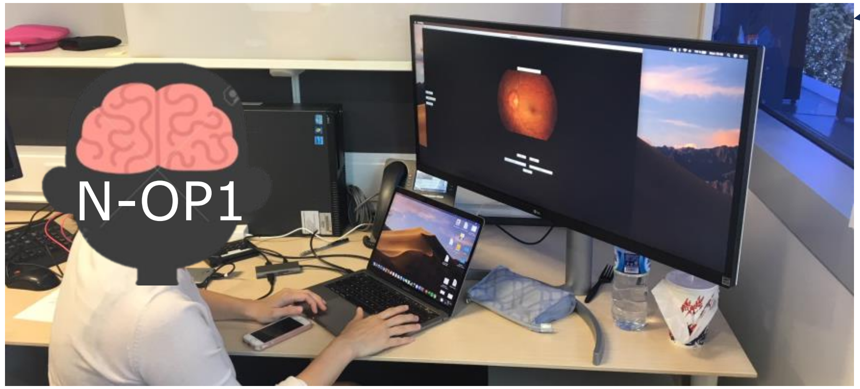
- **One eye only**
- **No demographic or clinical information**
- Independent review

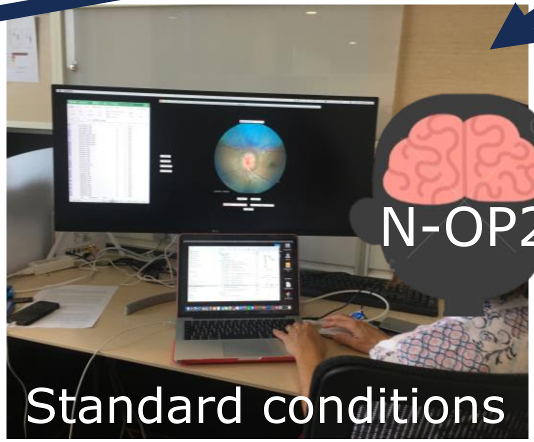


Human vs Machine

- 800 fundus photographs
  - 400 normal
  - 201 papilledema
  - 199 other disc abnormalities

- **One eye only**
- **No demographic or clinical information**
- Independent review

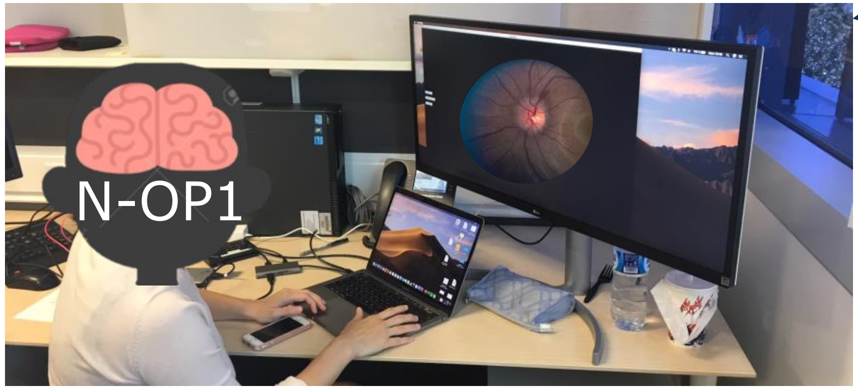


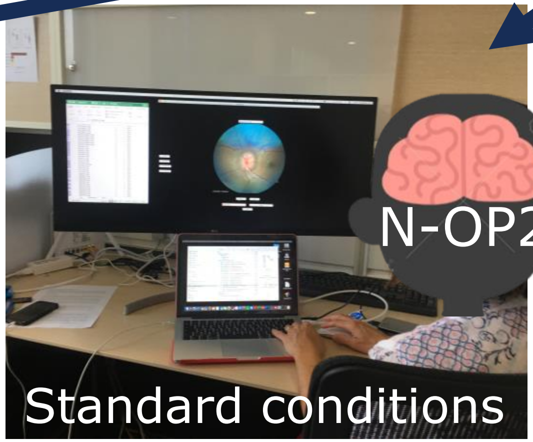


Human vs Machine

- 800 fundus photographs
  - 400 normal
  - 201 papilledema
  - 199 other disc abnormalities

- **One eye only**
- **No demographic or clinical information**
- Independent review

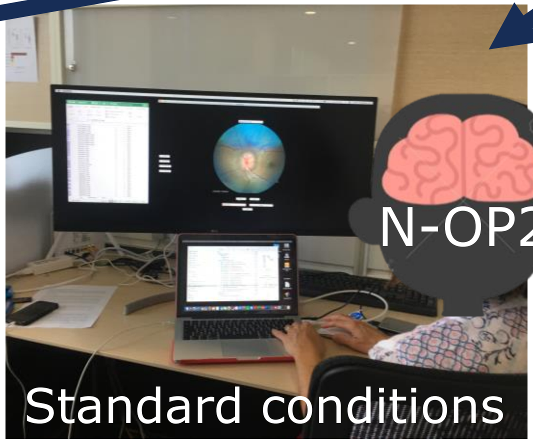




Human vs Machine

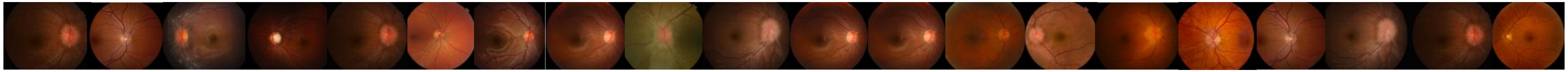
- 800 fundus photographs
  - 400 normal
  - 201 papilledema
  - 199 other disc abnormalities

- **One eye only**
- **No demographic or clinical information**
- Independent review



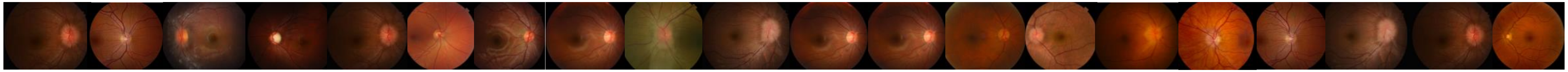
Time to classify 800 photographs– Human vs Machine

Grader	Time
N-Op1	61 minutes
N-Op2	74 minutes

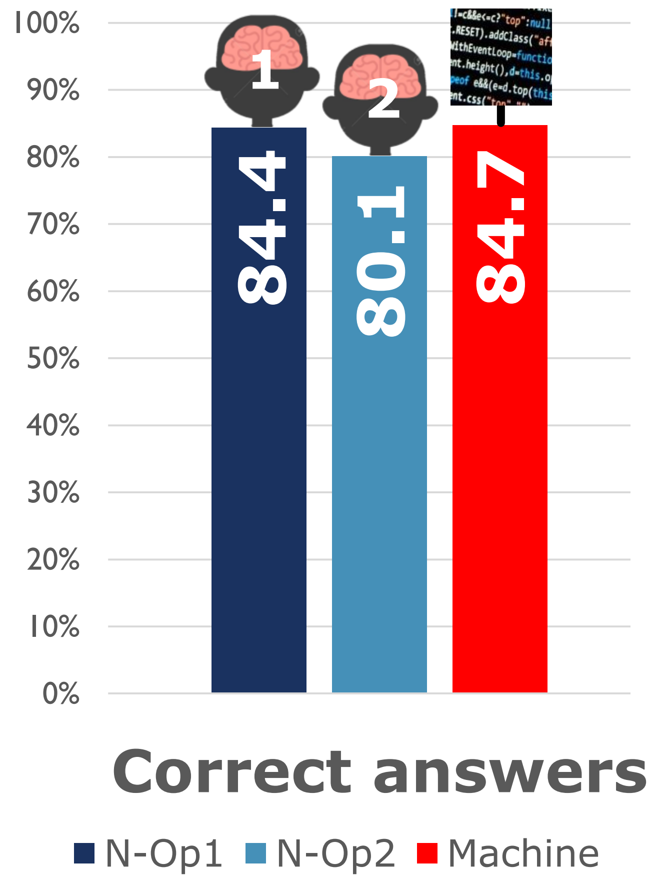


Time to classify 800 photographs– Human vs Machine

Grader	Time
N-Op1	61 minutes
N-Op2	74 minutes
Machine	25 seconds

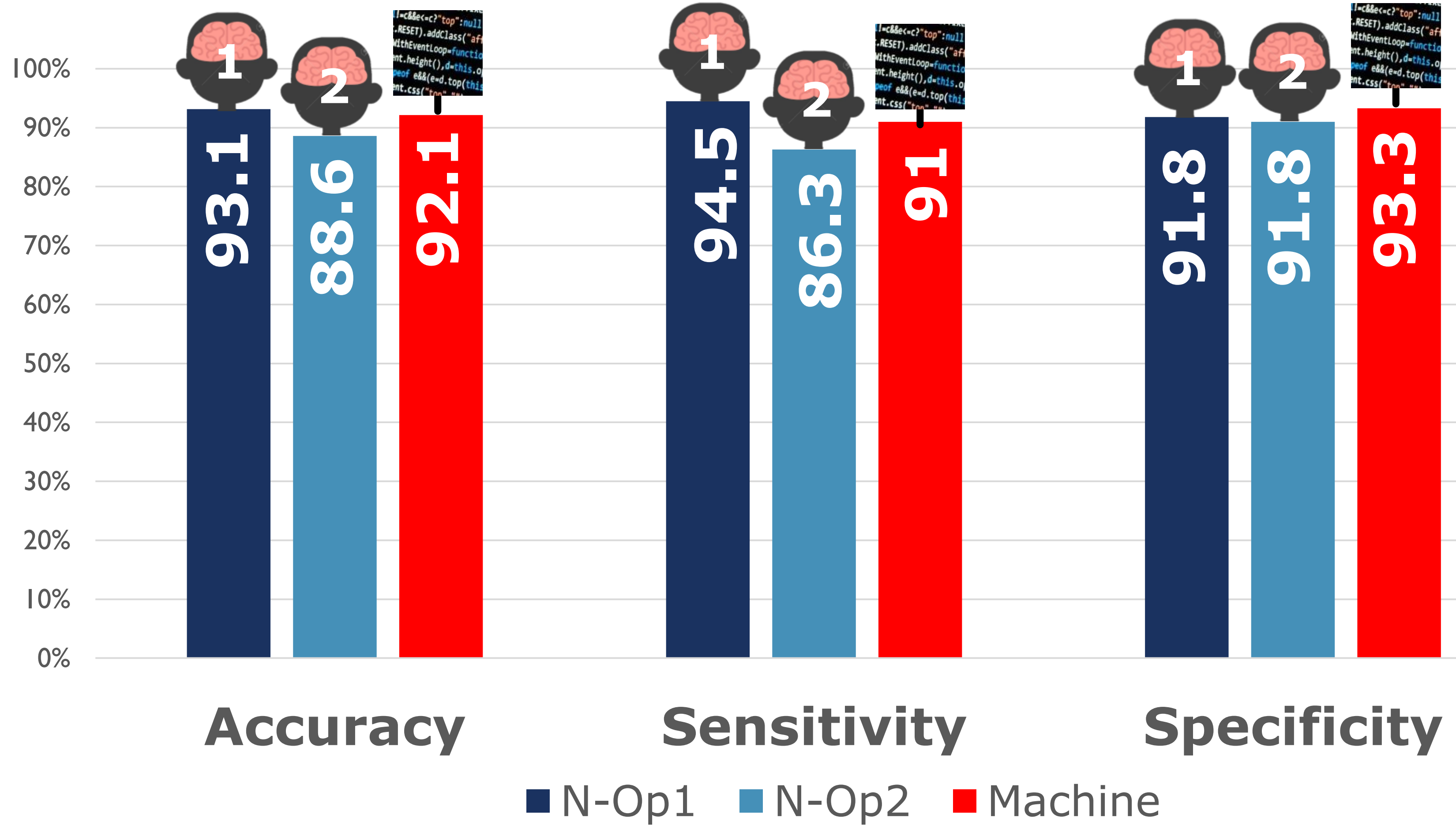


Correct Answers – Human vs Machine

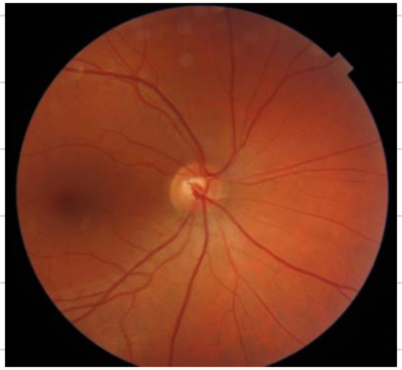


- **Identification of:**
  - Normal
  - Papilledema
  - Other optic disc abnormality
- **Eye level**
- **No clinical information**

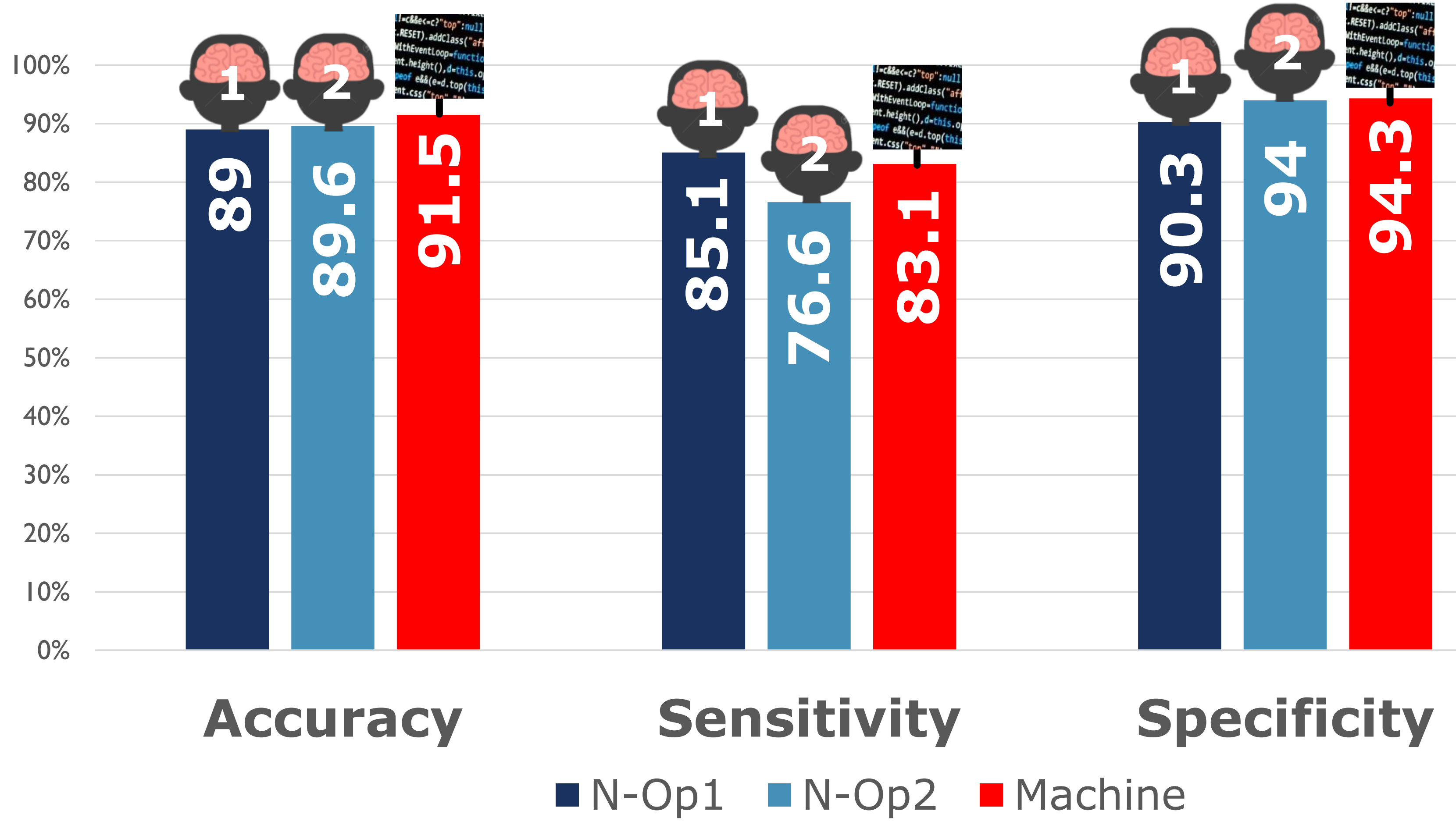
Recognition of Normal Optic Discs– Human vs Machine



Eye level



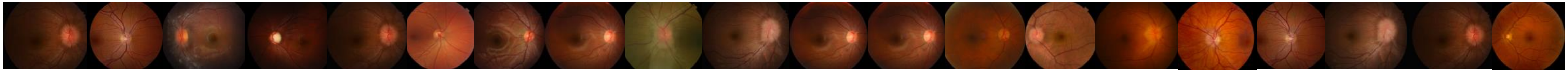
Identification of Papilledema– Human vs Machine



Eye level

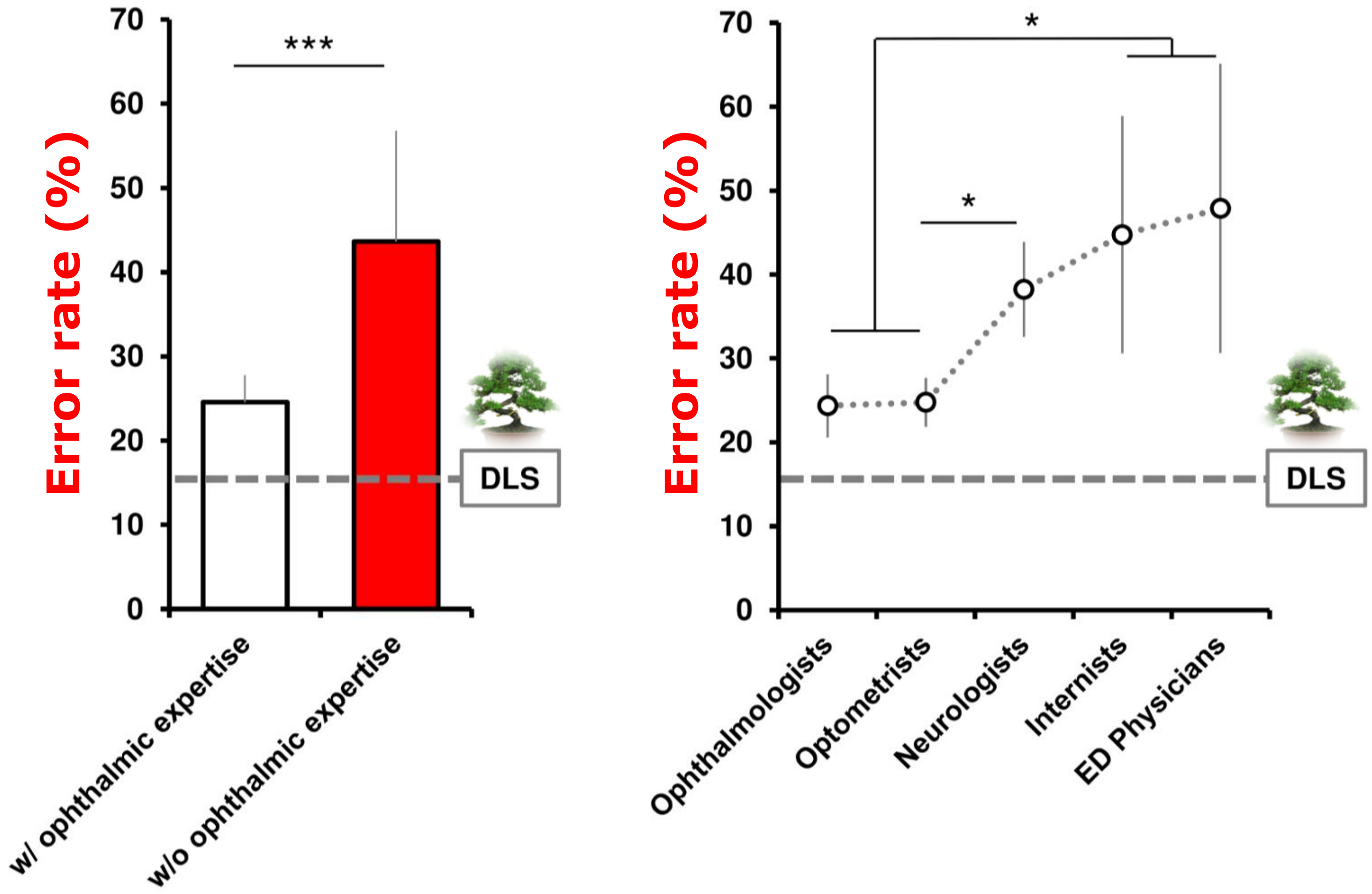
Conclusions – BONSAI - Human vs Machine

- **Classification of optic nerve appearance (normal vs papilledema vs other optic disc abnormalities) by the BONSAI Deep Learning System:**
  - Very fast (25 seconds vs >1 hour by humans)
  - At least as good as two expert neuro-ophthalmologists (>25 y experience) without clinical information and at the eye level (therefore, still helpful even if only one eye photograph of good quality)



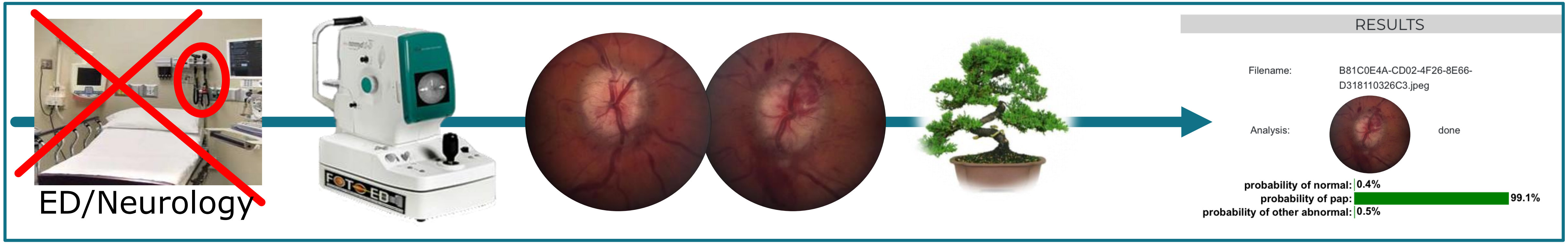
Biousse V, Newman NJ, Najjar RP, Vasseneix C, Xu X, Ting DS, Milea LB, Hwang JM, Kim DH, Yang HK, Hamann S, Chen JJ, Liu Y, Wong TY, Milea D; BONSAI (Brain and Optic Nerve Study with Artificial Intelligence) Study Group. Optic Disc Classification by Deep Learning versus Expert Neuro-Ophthalmologists. Ann Neurol. 2020; 88: 785-95

BONSAI DLS vs non neuro-ophthalmologists



BONSAI DLS for Optic Nerve Interpretation

- **Trained deep learning system with direct application as diagnostic aid:**
  - => likely better than ophthalmoscopy or self-interpretation of fundus photographs in ED settings and Neurology clinics
  - Next step: test in real-life settings [non-ophthalmologists]



Five Important Rules in AI (Daniel Ting, MD PhD)

- **1-Right question:** papilledema or not?
- **2-Right data:** fundus photographs from 25 international centers (large number, diverse data)
- **3-Right partners:** expert neuro-ophthalmologists (international group) and AI team (Singapore)
- **4-Right concepts and methods:** excellent clinical and digital operational flow
- **5-Right enabler:** implementation, outcome, commercialization (pending @Singapore)

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

FDA NEWS RELEASE

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

Share Tweet Linkedin

ents

For Immediate Release: April 11, 2018

The U.S. Food and Drug Administration today perm
device to use artificial intelligence to detect greater t
diabetic retinopathy in adults who have diabetes.

Diabetic retinopathy occurs when high levels of bloo
vessels of the retina, the light-sensitive tissue in the
the most common cause of vision loss among the m
with diabetes and the leading cause of vision impair
age adults.

"Early detection of retinopathy is an important part
people with diabetes, yet many patients with diabet
diabetic retinopathy since about 50 percent of them
basis," said Malvina Eydelman, M.D., director of the
Nose and Throat Devices at the FDA's Center for De
"Today's decision permits the marketing of a novel a
can be used in a primary care doctor's office. The FI
availability of safe and effective digital health device
needed health care."

DIGITAL DIAGNOSTICS

About Careers Products International Newsroom Resources Contact

The IDx-DR system uses the Topcon NW400 robotic retinal camera (Topcon Medical Systems, Oakland, New Jersey)

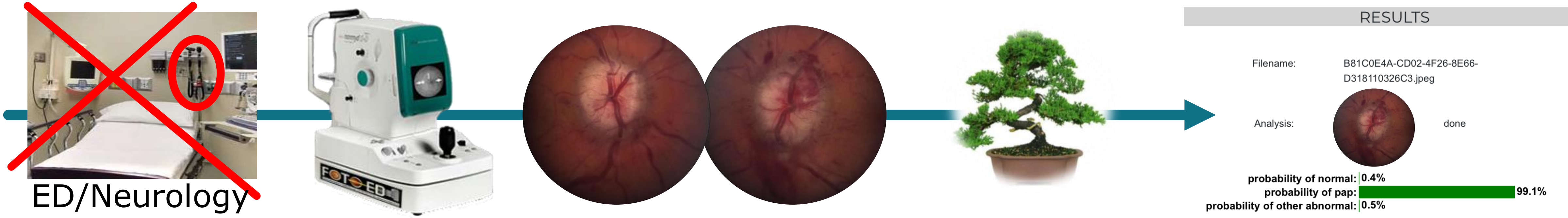
IDx-DR

IDx-DR is an AI diagnostic system that autonomously diagnoses patients for diabetic retinopathy and macular edema

With IDx-DR you get:

- Immediate diagnostic results at the point of care
- No need for specialist overread or telemedicine call backs
- Simple user interface
- Seamlessly integrates into your workflow

BONSAI DLS for Optic Nerve Interpretation



ANY nonmydriatic camera

BONSAI DLS as webtool or software installed on any camera for onsite immediate results

Probability optic nerve:
-normal
-papilledema
-other

Thank You!