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

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Disclosures and Funding Sources

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

- **Funding:**
DIRECT
OPHTHALMOSCOPE
Examination of the ocular fundus
Examination of the ocular fundus

Hypertension

Diabetes

Leukemia

Brain tumor

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.
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.
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”.
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
From Post-mortem Autopsy To Modern Neuroimaging

- **Autopsy**
  - 1850

- **Ophthalmoscopy**
  - 1850

- **X-Ray**
  - 1885
  - 1918 Pneumoencephalography

- **Computed tomography**
  - 1971

- **Magnetic resonance imaging**
  - 1977-1984

- **1949 Cerebral angiography**
Normal brain imaging does not rule out brain disease, especially elevated intracranial pressure.

- Cerebral venous thrombosis
- Meningitis
- Idiopathic intracranial hypertension
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

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

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
Direct ophthalmoscopy is difficult.
Fundus photography vs. Ophthalmoscopy
Trial Outcomes in the Emergency Department
- **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

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
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
General Methods

**Phase 1**
- Ophthalmoscopy alone
  - 1734 photos
  - 350 patients

**Phase 2**
- Photographs
  - 1503 photos
  - 354 patients

**Phase 3**
- Photographs + Education
  - 2347 photos
  - 587 patients

**Fundus Photography Readings within 24 Hours**
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.

## Non-Mydriatic Fundus Camera in ED

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<thead>
<tr>
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<th>Phase I</th>
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<tr>
<td><strong>ED Examination</strong></td>
<td><strong>Direct ophthalmoscopy</strong></td>
<td><strong>Non-mydriatic photography</strong></td>
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<tr>
<td><strong>Method</strong></td>
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<tr>
<td># of patients’ fundi</td>
<td># of abnormalities detected by</td>
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<td>viewed by ED-MD</td>
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<td># of patients’ fundi viewed by ED-MD</td>
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<td>0/44 (0%)</td>
<td>16/35 (46%)</td>
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**ED providers correctly identified 86% of normal fundi as normal on fundus photos**

STOP TEACHING OPHTHALMOSCOPY TO MEDICAL STUDENTS?

STOP TEACHING OPHTHALMOSCOPY TO MEDICAL STUDENTS?

OPHTHALMOSCOPY SHOULDN'T HAVE BEEN DONE ON DAY 1!

No Light Perception

Light Perception
STOP TEACHING OPTHALMOSCOPY TO MEDICAL STUDENTS?

OCULAR FUNDUSCOPIC EXAMINATION SHOULDN'T 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

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): TOTEEMS II

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

**Primary Reasons Fundus Exam Not Performed**

- Discomfort: 38%
- Discouraged by preceptor: 20%
- Insufficient Time: 15%

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
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

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

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

Remote interpretation by ophthalmologist (tele-ophthalmology/teleconsultation)
Artificial Intelligence and Digital Technology in Ophthalmology

[VERY] *Basic Overview*
Deep Learning is already changing everything in ophthalmology!
Artificial Intelligence And Deep Learning

Image → AI/DL + Question → Output (Yes/No)
Artificial Intelligence And Deep Learning: Many applications in ophthalmology

AI/DL Diabetic retinopathy?  
No

AI/DL Diabetic retinopathy?  
Yes
Google’s AI can see through your eyes what doctors can’t

Female or Male Gender?
Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning

Ryan Poplin1,4, Avinash V. Varadarajan1,4, Katy Blumer3, Yun Liu1, Michael V. McConnell2,3, Greg S. Corrado1, Lily Peng1,4* and Dale R. Webster1,4

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

Onsite interpretation by non-ophthalmology trained provider
The Brain and Optic Nerve Study with Artificial Intelligence (BONSAI)

Dan Milea MD PhD, Valérie Bioussé 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
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
  - 9,769 normal
  - 2,508 papilledema
  - 3,569 other disc abnormalities

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

**External validation:**
1,505 photographs
from 3 centers
Fundus Photography with AI as diagnostic aid in non-ophthalmic settings (no clinical information):
Fundus Photography with AI as diagnostic aid in non-opthalmic settings:

BONSAI Deep Learning System

Automatic classification of optic discs

**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%

ED/Neurology
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)
Photograph
Quality check
Cropping
Disc centered
Heat map generation
Analysis
Probability
Artificial Intelligence to Detect Papilledema from Ocular Fundus Photographs


ABSTRACT

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

METHODS
We trained, validated, and externally tested a deep-learning system to classify optic discs as being normal or having papilledema or other abnormalities from 15,846 retrospectively collected ocular fundus photographs that had been obtained with ophthalmologic 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 1,505 photographs from 5 external sites were used for external testing. Performance at classifying the optic-disc 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 6,799 patients included 14,341 photographs: 8,156 of normal discs, 2,148 of discs with papilledema, and 307 of discs with other abnormalities. The percentage classified as being normal ranged across sites from 98% to 100%; the percentage classified as having papilledema ranged across sites from zero to 59.5%. In the validation set, the system discriminated discs with papilledema from normal discs and discs with nonpapilledema abnormalities with an AUC of 0.99 (99% confidence interval [CI], 0.98 to 0.99) and normal from abnormal discs with an AUC of 0.99 (99% CI, 0.99 to 0.99). In the external-testing data set of 1,505 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 discs with papilledema, normal discs, and discs 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 (all names, academic degrees, and affiliations) are listed in the Appendix. Address reprint requests to Dr. Wong at the Singapore National Eye Centre, 1 Third Hospital Ave, Singapore 168751, Singapore, or at wong-hoyped@ singhealth.com.sg.

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

Dr. Miele and Mr. Najjar and the authors contributed equally to this article.

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

Isaac Kohane, M.D., Ph.D.
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/10.1056/NEJ... @NEJM
2. Rapid #4D blood flow assessment to improve heart MRI, move toward real-time nature.com/articles/s4225...

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

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.

Wonderful #AI papilloedema work from #BONSAl study group with @DanMilea3 leading the work. A wonderful multi-centre study coordinated by @DanMilea3 @vbiouss and bringing neuroophthalmologists together. I am so honoured to be a part of...
Can the BONSAI deep learning system perform as well [or better] than expert neuro-ophthalmologists?
Human vs Machine
Human vs Machine

Agency for Science, Technology and Research
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

Standard conditions

N-OP

Agency for Technology and Innovation
Human vs Machine

- 800 fundus photographs
  - 400 normal
  - 201 papilledema
  - 199 other disc abnormalities
- One eye only
- No demographic or clinical information
- Independent review

Standard conditions

N-OP1

N-OP2
Human vs Machine

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

- One eye only
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- Independent review
Human vs Machine

- 800 fundus photographs
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- One eye only
- No demographic or clinical information
- Independent review

Standard conditions
# Time to classify 800 photographs—Human vs Machine

<table>
<thead>
<tr>
<th>Grader</th>
<th>Time</th>
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<tbody>
<tr>
<td>N-Op1</td>
<td>61 minutes</td>
</tr>
<tr>
<td>N-Op2</td>
<td>74 minutes</td>
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</table>
## Time to classify 800 photographs—Human vs Machine

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</tr>
<tr>
<td>N-Op2</td>
<td>74 minutes</td>
</tr>
<tr>
<td>Machine</td>
<td>25 seconds</td>
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</tbody>
</table>
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

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<tr>
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<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>N-Op1</td>
<td>93.1</td>
<td>94.5</td>
<td>91.8</td>
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<tr>
<td>N-Op2</td>
<td>88.6</td>
<td>86.3</td>
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Eye level
Identification of **Papilledema** – Human vs Machine

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<td>1</td>
<td>89</td>
<td>85.1</td>
<td>90.3</td>
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<td>2</td>
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<td>94</td>
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Eye level: 1, 2
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)

BONSAI DLS vs non neuro-ophthalmologists

- Error rate (%)

![Error rate graph comparing BONSAI DLS and non neuro-ophthalmologists](image)
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)

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

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

Diabetic retinopathy occurs when high levels of blood vessels of the retina, the light-sensitive tissue in the eye, become abnormal and abnormal blood vessels form, which can lead to vision loss.

“The early detection of retinopathy is an important part of care for people with diabetes, yet many patients with diabetes do not receive early care for diabetic retinopathy since about 50 percent of them are asymptomatic,” said Malvina Eydelman, M.D., director of the Ophthalmic Products and Related Devices at the FDA. “Today’s decision permits the marketing of a novel device that can be used in a primary care doctor’s office. The FDA availability of safe and effective digital health device needed health care.”

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 teledmedicine 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!