Ethiek van autonome kunstmatige intelligentie in de gezondheidszorg

Michael D. Abràmoff, MD, PhD

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Founder and Executive Chairman, Digital Diagnostics
Chair, FDA’s Foundational Principles of Algorithmic Interpretation WG

Support: Digital Diagnostics, National Eye Institute R01 EY019112, EY018853, EY017066, NovaGoAG
Conflicts of Interest: Digital Diagnostics – Founder, Executive Chairman, Director, Patents and Investor.
Artificial Intelligence: Autonomous vs Assistive

**Autonomous**
- Medical decision by AI
- No human oversight
- Instantaneous
- Point of Care
- Liability for creator

**Assistive**
- Clinician needed
- Medical decision by clinician
- Liability for clinician

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**IDx-DR Analysis Report**

**Analysis Details**

- **First Name**: Jane
- **Last Name**: Doe
- **ID**: 0000001001
- **Date of Birth**: 01/01/1980
- **Imaging Date/Time**: 01/01/2020 0:45:15 am
- **Result Date/Time**: 01/01/2020 0:45:35 am

**Analysis result**

*Negative for more than mild diabetic retinopathy: Retest in 12 months*

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**Images**

- Images of retinal scans showing negative results.
Creation of a new industry: Autonomous AI in healthcare

- ‘diagnostic AI algorithm’
- Foundation in Ethics
- Clinical trial design / Regulatory Approval
- Standards of Care
- Reimbursement
- Affect patient outcomes / Address health disparities

- First FDA de novo clearance (2018)
- Second FDA clearance with 510k (2020)
- Standards of Medical Care in Diabetes (2020)
- First ever CPT Code 92229 (2019)
- Coverage $55.66 (2020)

- 300+ papers (2008)
- Ethical Foundations (2020)
- Preventing blindness and visual loss

- American Academy of Ophthalmology
- American Diabetes Association
- CMS (Center for Medicare and Medicaid Services)
- Foundation in Ethics


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2018: First ever Autonomous AI FDA Approval

"IDx-DR is the first device authorized for marketing that provides a screening decision without the need for a clinician to also interpret the image."

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.
2018: First autonomous AI clinical trial
And still, the only peer reviewed publication

**ARTICLE**

**OPEN**

**Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices**

Michael D. Abràmoff1,2,4, Phillip T. Lavin5, Michelle Birch6, Nilaay Shah7 and James C. Folk8,2,22

Artificial intelligence (AI) has long promised to increase healthcare affordability, quality and accessibility but FDA, until recently, had never authorized an autonomous AI diagnostic system. This pivotal trial of an AI system to detect diabetic retinopathy (DR) in people with diabetes enroled 900 subjects, with no history of DR at primary care clinics, by comparing to Wisconsin Fundus Photograph Reading Center (FFPC) widefield stereoscopic photography and macular Optical Coherence Tomography (OCT) by FFPC certified photographers, and FFPC grading of Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRS) and Diabetic Macular Edema (DME). More than mild DR (minmDR) was defined as ETDRS level 35 or higher, and/or DME, in at least one eye. AI system operators underwent a standardized training program before study start. Median age was 59 years (range, 22–84 years), among participants, 47.5% of participants were male; 16.1% were Hispanic, 83.3% not Hispanic; 28.6% African American and 63.4% were not 198 (23.8%) had minmDR. The AI system exceeded all pre-specified superiority endpoints at sensitivity of 87.2% (95% CI 81.8–91.2%) (85%), specificity of 90.7% (95% CI 88.3–92.7%) (98.5%), and imageability rate of 96.1% (95% CI 94.6–97.3%), demonstrating AI’s ability to bring specialty-level diagnostics to primary care settings. Based on these results, FDA authorized the system for use by healthcare providers to detect more than mild DR and diabetic macular edema, making it the first FDA authorized autonomous AI diagnostic system in any field of medicine, with the potential to help prevent vision loss in thousands of people with diabetes annually. ClinicalTrials.gov NCT02963441

**INTRODUCTION**

People with diabetes fear visual loss and blindness more than any other complication. Diabetic retinopathy (DR) is the primary cause of blindness and visual loss among working age men and women in the United States and causes more than 24,000 people to lose vision each year.1,2 Adherence to regular eye examinations is necessary to diagnose DR at an early stage, when it can be treated with better prognosis.3,4,5 and have resulted in substantial reductions in visual loss and blindness.6 Despite this, less than 50% of patients with diabetes adhere to the recommended schedule of eye exams.7,8 and adherence has not increased over the last 15 years despite large-scale efforts to increase it.9 To increase adherence, retinal imaging in or close to primary care offices followed by remote evaluation using telemedicine has also been widely studied.10

Artificial intelligence (AI)-based algorithms to detect DR from retinal images have the potential to measure and compare diagnostic accuracy across age, race and ethnicity.11,12,14,15 Studies comparing an AI system against an independent, high-quality gold standard that includes fundus imaging and Optical Coherence Tomography (OCT) imaging protocols have not previously been conducted. FDA has not previously authorized any such system.

The Wisconsin Fundus Photograph Reading Center (FFPC) has historically been the gold standard for trials that require grading of the severity of DR, including the Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial (EDIC/DDCCT). Diabetic Retinopathy Clinical Research Network (DRCCR) studies, as well as pivotal phase III studies.16,17 The FFPC has adopted the use of a widefield stereoscopic retinal imaging protocol (4W-D), that includes four stereoscopic pairs of digital images per eye, each pair covering 43°x47°, equivalent to the area of the retina covered by the older, modified 7-field stereoscopic imaging protocol.18,19 Traditionally, the presence of Diabetic Macular

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“Autonomous AI Creator/Vendor assumes liability for performance commensurate with indications for use”
Policy

Liability

Our AMA advocates that:

➤ Liability and incentives should be aligned so that the individual(s) or entity(ies) best positioned to know the AI system risks and best positioned to avert or mitigate harm do so through design, development, validation and implementation.

➤ Where a mandated use of AI systems prevents mitigation of risk and harm, the individual or entity issuing the mandate must be assigned all applicable liability

➤ Developers of autonomous AI systems with clinical applications (screening, diagnosis, treatment) are in the best position to manage issues of liability arising directly from system failure or misdiagnosis and must accept this liability with measures such as maintaining appropriate medical liability insurance.

"AI algorithms that can inform clinical care decisions will be critical to the future of AI in health care."

—Bobby Mukkamala, MD, AMA Board of Trustees

➤ Outline new professional roles and capacities required to aid and guide health care AI systems

➤ Develop practice guidelines for clinical applications of AI systems

National and state collaboration and strategic planning

Our AMA advocates that:

➤ There should be federal and state interagency...
2020: First Standard of Care supporting Autonomous AI

11.17 [...] Artificial intelligence systems that detect more than mild diabetic retinopathy and diabetic macular edema authorized for use by the FDA represent an alternative to traditional screening approaches (115). [...] 

2020: First Autonomous AI cost-effectiveness analysis

Cost-effectiveness of Autonomous Point-of-Care Diabetic Retinopathy Screening for Pediatric Patients With Diabetes

Risa M. Wolf, MD, Roomasa Channa, MD, Michael D. Abramoff, MD, PhD; Harold P. Lehmann, MD, PhD

**IMPORTANCE** Screening for diabetic retinopathy is recommended for children with type 1 diabetes (T1D) and type 2 diabetes (T2D), yet screening rates remain low. Point-of-care diabetic retinopathy screening using autonomous artificial intelligence (AI) has become available, providing immediate results in the clinic setting, but the cost-effectiveness of this strategy compared with standard examination is unknown.

**OBJECTIVE** To assess the cost-effectiveness of detecting and treating diabetic retinopathy and its sequelae among children with T1D and T2D using AI diabetic retinopathy screening vs standard screening by an eye care professional (ECP).

**DESIGN, SETTING, AND PARTICIPANTS** In this economic evaluation, parameter estimates were obtained from the literature from 1994 to 2019 and assessed from March 2019 to January 2020. Parameters included out-of-pocket cost for autonomous AI screening, ophthalmology visits, and treating diabetic retinopathy, probability of undergoing standard retinal examination, relative odds of undergoing screening, and sensitivity, specificity, and diagnosability of the ECP screening examination and autonomous AI screening.

**MAIN OUTCOMES AND MEASURES** Costs or savings to the patient based on mean patient payment for diabetic retinopathy screening examination and cost-effectiveness based on...
2020: First Autonomous AI payment

» Cost of electricity?
» Cost of R&D?
» Cost effectiveness?
» Free market?

» Discounted human cost
"[...] IDx-DR technology received a new CPT code effective January 1, 2021, specifically, CPT code 92229 for point-of-care automated analysis that uses innovative artificial intelligence technology to perform the interpretation of the eye exam, without requiring that an ophthalmologist interpret the results.”

**CMS finalized Medicare reimbursement at $55.66**

**MPFS states** “We are considering CPT code 92229 to be a diagnostic service under the PFS.”
Autonomous AI is real & Updated for the Pandemic Era

- Diagnoses diabetic retinopathy & diabetic macular edema
- At point of care
- Diagnosis in minutes
- No human oversight
- Integrated with EHR
- CMS / private reimbursement
- Closes care gap for HEDIS/MIPS

Operated by Existing GP Staff
AI Guided Workflow Image Quality Feedback
Robotic Imaging System
Creator Assumes Liability

Safe for COVID Era
Medicare $55 HEDIS/MIPS gap closure

IDX DIABETIC RETINOPATHY
Status: Editted Result - FINAL (Rev. 10/10/2018)

IDX DIABETIC RETINOPATHY
More than mild diabetic retinopathy detected. Refer to an eye care professional.

Medicare $55
HEDIS/MIPS gap closure

Safe for COVID Era

 IDX DIABETIC RETINOPATHY on 6/1/2018

Testing Performed By
Name: Director
Order Details

Creator Assumes Liability

Medicare $55 HEDIS/MIPS gap closure

Safe for COVID Era
Diabetic Eye Exams in Grocery Store

• Safeway retail has primary care clinics in store
• Full-service primary care clinics with primary care MD
• Autonomous AI for diabetic eye exam in diabetes management workflow
• Coordinated Diabetes Care
OUS Adoption – partnership with Orbis – Flying Eye Hospital

Digital Diagnostics platform expansion into new specialties: skin, ... 

Increasing access to specialty coverage

**IDX-DR:** Diabetic Retinopathy and macular edema

**3DermSpot:** Melanoma and other skin cancers
Digital Diagnostics (Formerly IDx)

- **HQ**: Coralville, Iowa
- **Founded**: 2010
- **Mission**: Transform affordability, accessibility and quality of healthcare through automation of diagnoses
- **Employees**: 90+
- **Executive Team**
  - Michael Abramoff - Founder & Exec Chairman
  - John Bertrand - CEO
  - Seth Rainford - President & COO
- **Raise to date**: $70M

https://www.cbinsights.com/research/artificial-intelligence-startup-us-map/
Healthcare problems to be solved by Autonomous AI

Healthcare Cost - Productivity

US Labor Productivity (Output Per Worker Hour)

Health disparities - Access

Eye care availability

Eye care need

Healthcare demand - workforce gap

2. Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice, J AAPOS 2014
5. U.S. Centers for Disease Control level distribution of diagnosed diabetes among U.S adults aged 20 or older, 2013.
Healthcare problems to be solved by Autonomous AI

Health disparities - Access

Healthcare Cost - Productivity

Healthcare demand - workforce gap

2. Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice, AAPOS 2014
3 Phases of AI in Medicine

1. 1960’s: Rule based
   » MYCIN (Minsky, Shortliffe)
   » Physician typing in patient symptoms

2. 1980’s: Machine learning
   » Perceptron, backpropagation: 5th gen
   » Noisy inputs, no digital data

3. 2016: Digital sensors
   » Objective, digital data - images
   » GPUs, Deep-’er’ learning networks

MYCIN respawn the user’s answer

Several questions are skipped.

Has Pt.538 recently had symptoms of persistent headache or other abnormal neurologic symptoms (dizziness, lethargy, etc.)?
** YES

Has Pt.538 recently had objective evidence of abnormal neurologic signs (mucosal rigidity, coma, seizures, etc.) documented by physician observation or examination?
** YES

Note that MYCIN has concluded and informed the user that there is a likely meningitis infection and pursues this line of inquiry.

The CSF cultures will be considered to be associated with MENINGITIS.

Please give the date on which clinical evidence (symptoms, signs, or laboratory tests) of the meningitis first appeared.
** 29-Jan-77 22:15

For how many days has Pt.538 had abnormal neurologic signs?
** 2 days
Inputs – images - for Autonomous AI

Key Characteristics

» Objective sensors
  • Secondary role for GPU / neuro similar processing hardware
  • Focus on Image based sensors

» Images are quantifications of
  • Physical processes
  • Pathological processes

» Both processes exhibit
  • spatial coherence (autocorrelation), see right
  • temporal coherence
  • Foundational assumptions are to which degree

» AI exploits spatial/temporal coherences
  • Neural networks exploit coherences through local nonlinearities

Autonomous AI is different

Key Constraints on AI in healthcare

» High quality data is scarce
  • Risk of harm to patients from obtaining data
    o Radiation, light damage
  • Many diseases are rare, making cases scarce
    o Ocular melanoma 1:1,000,000 = only n=300 in whole US
  • Control cases (no disease) hard to obtain
    o Ethical issues with exposing non patients to harm to obtain data

» High quality truth is scarce
  • Highly qualified and expensive experts (clinicians, pathologists etc)
  • Health outcomes may be years away in chronic disease
  • Scarcity of valid surrogate outcomes

» Challenging environments, when AI is deployed
  • Inputs require high quality images in specific settings and use cases
  • Low proficiency operators
From Science, to Algorithm, to Patient Benefit

1988: Machine learning using artificial neural networks

Id Abramoff, Ton Coolen, George Wismeije and Peggy Janssen

This pilot study is based on the assumption that stuttering is a disorder of speech motor control. Parameters of a neural network were varied in order to produce simulations resembling stuttering behavior. A Hopfield network with temporal delays was used and a sequence of ten patterns was learned. Those patterns were supposed to represent the control of muscles for an articulatory movement. The following parameters of the network were varied systematically: noise in the simulated neurons and the ratio (v) between the delay in the neural connection and the duration during which the patterns were realized in the network in the learning phase. Moreover the similarity between the patterns was varied. Abnormalities in the network output were found for certain combinations of parameter values. However, these abnormalities showed no clear resemblance to stuttering behavior. Noise had only a very moderate effect. When the subsequent patterns were correlated, an increase in the value of the parameter v resulted in increased temporal variability and increased duration of the production of a cycle of ten patterns.

Recently, artificial neural networks have received a great deal of attention from various disciplines (Ami, 1988). This study illustrates the use of a neural network for simulating the temporal organization of speech in relation to stuttering. More specifically, it addresses the question, whether the network can influence such a way that behavior resembling stuttering will result. Simulation of the original Hopfield type neural network was chosen to simulate temporal aspects of motor systems. By introducing delays in the connections between the neurons, sequences of patterns can be stored and retrieved at a later time (Coolen & Gelen, 1988). It is assumed that each in a sequence represents the information necessary for producing transitional movements from one phoneme to the next (Braamhod, 1989).

Artificial network

Generally a neuronal network consists of a collection of neurons which are connected by axons ending in synapses on dendrites. In the Hopfield type of network these parts are all represented rather simply (Hopfield, 1982). Neurons have discrete on/off threshold units. That is to say, a neuron only fires if the sum of all of its inputs is higher than some threshold. All neurons are connected to all other neurons in the network, and the strength of connection between two neurons is represented by the weight of the connection. Neurons send signals to other neurons via axons, which are the projections of the cell body. These signals are impulses, which travel through the axon and along the dendrites of other neurons, where they can excite or inhibit the neuron. The strength of the connection between two neurons is represented by the weight of the connection. The weight of a connection can be positive or negative, depending on whether the signal transmitted by the axon of one neuron excites or inhibits the neuron it is connected to.

dxs.ai | 22
Long Path from Science, to Algorithm, to Patient

1988: Machine learning using artificial neural networks
2000: AI Detection of retinopathy lesions

This pilot study is based on the assumption that stuttering is a disorder of speech motor control. Parameters of a neural network were varied in order to produce simulations resembling stuttering behavior. A Hopfield network with temporal delays was used and a sequence of ten patterns was to be represented. The following parameters of the network were varied systematically: the ratio (r) between the delay time and the duration during which the patterns were repeated; the learning phase. Moreover, the similarity between the abnormalities in the network output were found for different parameter values. However, these abnormalities showed a stuttering behavior. Noise had only a very moderate effect. Patterns were correlated, an increase in the value of the parameter r increased temporal variability and increased duration of the pattern.

Recently, artificial neural networks have received widespread interest in various disciplines (Ami, 1989). This study illustrates how artificial neural networks can be used to simulate the temporal organization of stuttering. More specifically, it addresses the question of whether behavior can be influenced in such a way that behavior resembling stuttering can be elicited from the original Hopfield type neural network after input of temporally organized movement patterns from one phoneme to the next.

A neural network consists of a collection of neurons connected by axons ending in synapses on dendrites. These parts are all represented rather simply within the discrete on/off threshold units. This is to say, a neuron fires if the sum of all its inputs is higher than some threshold value.

LOW LEVEL SCREENING OF EXUDATES AND HAEMORRHAGES IN BACKGROUND DIABETIC RETINOPATHY

M.D. Abramoff1,2, MD MSc, J.J. Staal3, MSc, M.S. Suttrop1, MD PhD, D.C.P. Polak, MD PhD, M.A. Viergever, PhD

Dept. of Ophthalmology and Diabetes Center, Vrije Universiteit University Hospital, Amsterdam, Netherlands
Image Sciences Institute, University Hospital, Utrecht, Netherlands

Purpose: To develop a fast and reliable method to screen fundus images for exudates and haemorrhages in early background diabetic retinopathy.

Methods: A differential topology based, scale and color space indexed operator was used to obtain geometrical features in digital fundus images (Canon non-mydratic fundus camera, 800x800 pixels, 24 bit JPEG decompressed). Using this operator the eigenvalues of the Hessian and the structure tensor were mapped nonlinearly to a multidimensional probability measure.

The operator is constructed in such a way that red blood cells and white blood cell structures (20-520 µm) give optimal responses. Results: 500 images were used for optimization. The features detected...
Long Path from Science, to Algorithm, to Patient

1988: Machine learning using artificial neural networks
2000: AI Detection of retinopathy lesions
2003+: Many more lesion detection publications

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Long Path from Science, to Algorithm, to Patient

1988: Machine learning using artificial neural networks
2000: AI Detection of retinopathy lesions
2003+: Many more lesion detection publications
17+ patents on retinal image analysis/imaging
How do we get such an AI to patients here
Diabetes is a large and growing problem in the US.¹,²

34.2 million people have diabetes¹,²

60,000 Americans blind every year

Most FEARED diabetes complication ⁴

Blindness from diabetes is preventable.
Diagnosed Diabetes Prevalence among US Adults³


First: Autonomous AI clinical requirements

» Make medical decision without human oversight
  • Autonomous AI
  • Creator assumes liability
  • Easy-to-understand diagnostic output

» Minimal changes to clinic/lab workflow
  • Make diagnosis within minutes
  • Minimal footprint to fit clinic space, power outlet only requirement
  • High diagnosability

» Use existing staff
  • Operable by existing staff (high school diploma)
  • Robotic camera with assistive AI

» Automatic claims, billing and care gap closure
  • Real time, immediate claims and ICD10 generation
  • Aligned w Standards of Care and Preferred Practice Patterns
Many concerns about AI in Healthcare

• Will it benefit me as a patient?
• What happens to my data?
• Is there racial, ethnic bias?
• Who is liable for errors?
• Who pays for it?
• Will doctors lose their jobs?
10 years later, turning it around

This ophthalmologist is doing health care AI the right way

AUGUST 8, 2019

Andis Robeznieks
Senior News Writer
American Medical Association

Physician-scientist and AMA member Michael Abramoff, MD, PhD, identified a problem and then painstakingly spent eight years building an augmented intelligence (AI) solution to fix it.

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The Food and Drug Administration (FDA) and a quartet of venture capital firms say he forged a path that others seeking to develop health care AI systems can follow.

A professor of ophthalmology at the University of Iowa's Carver College of Medicine, Dr. Abramoff was disturbed by how long it often takes for patients with diabetes to see an eye-care specialist for a diabetic retinopathy exam. And he was bothered by how specialists' schedules are frequently crammed full of routine eye-exam visits that did not require their level of expertise.

“Clearly, the standard practice is not working, and people are not getting the exams they need,” Dr. Abramoff said, citing various studies finding that between 15% and 50% of patients who need a diabetic retinopathy exam are getting one.
The risk of backlash

Historical example: Gene therapy

- Poorly overseen gene Rx trials
- **Early 2000s**: effective moratorium
  - closure of research institutions
  - no more funding
- **2017**: FDA approval of Gene Rx for RPE65 variant of LCA

The risk of backlash for AI is real

HHS to probe whether Google’s ‘Project Nightingale’ followed federal privacy law

By REBECCA ROBBINS @rebeccadrobbins and CASEY ROSS @caseymross / NOVEMBER 13, 2019

Tesla, Uber Deaths Raise Questions About the Perils of Partly Autonomous Driving

Humans were behind the wheel in fatal crashes, raising questions of complacency

“"If it is your job to advance technology, safety cannot be your No. 1 concern," Levandowski told me. “If it is, you’ll never do anything. It’s a trade-off. You have to do a lot of things without being perfect.”

Dissecting racial bias in an algorithm used to manage the health of populations


AI’s Ethics Iron Triangle

Ethical principles

- Non-maleficence
- Autonomy
- Equity

Non-maleficence
First, do no harm, patient benefit, improved clinical outcomes

Autonomy
Patient decides; patient in control of their healthcare

Equity
Absence of bias, fairness in distribution, rights and benefits of groups

AI’s Ethics framework

Ethical principles

• Non-maleficence
• Autonomy
• Equity


AI Ethical Requirements

• Respect autonomy by **maximally protecting data security and privacy**
• Improve patient outcomes shown by **direct evidence** or linked clinical literature
• Design **AI algorithms so they are maximally reducible to human clinician cognition**
• Validate rigorously for safety, efficacy and equity **AI against clinical outcome**, in clinical workflow
• Mitigate **Bias** along the entire workstream
• Assume **liability** for performance

American Journal of Bioethics – Panel on ethics in AI
[https://www.youtube.com/watch?v=Irg3jGxa6HM](https://www.youtube.com/watch?v=Irg3jGxa6HM)

Harvard AI Symposium on AI and Bias
[https://www.youtube.com/watch?v=nuC6A1ZWRvA](https://www.youtube.com/watch?v=nuC6A1ZWRvA)
AI Ethical Requirements

• **Respect autonomy** by maximally protecting data security and privacy

• **Improve patient outcome** shown by direct evidence or linked clinical literature
Improve patient outcome by linkage to AI Outputs

IDx-DR: *diabetic retinopathy or macular edema present*

- 18.5% likelihood of PDR in 3 years, if untreated
- 17.7% likelihood of DME in 1 year, if untreated

IDx-DR: *diabetic retinopathy or macular edema absent:*

- 1.8% likelihood of PDR in 3 years, if untreated
- 2.4% likelihood of DME in 1 year, if untreated

In other words, if patient is left untreated, and has AI + output:

- **10x** PDR risk in 3 years
- **7x** DME risk in 1 year

Not possible if AI validated against clinicians
AI Ethical Requirements

Design AI algorithms so they are maximally reducible to human clinician cognition.
AI Design: how does the clinician brain solve this

Hubel and Wiesel, 1959, 1962
Daugman, 1980, 1985
AI Design: Detectors are partially dependent in Cortex V1

Bonhoeffer, Grinvald. Nat. 1991
Mimic cortical processing of clinicians as much as possible

Partially dependent detectors

Robust against catastrophic failure

Autonomous Clinical Decision

Robust against racial / ethnic / sex / age bias

Anatomy Localization

Hemorrhages

Microaneurysms

Exudates

New vessels

1. Abramoff et al, IOVS 2007
2. Lynch et al, ARVO 2018
3. Finlayson et al, Science, 2019
4. Shah et al, Proc ISBI 2018
5. Larrazabal et al., PNAS 2020
AI Design aligned with human clinician cognition

Image based training of convolutional neural networks

Biomarker based multiple partially redundant detectors
Black boxes and Catastrophic Failure

Real image    <1% changed

<table>
<thead>
<tr>
<th>Correctly detect DR</th>
<th>Biomarker-based AI: 99%</th>
<th>Biomarker-based AI: 99%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNN (Black Box):</td>
<td>99%</td>
<td>3%</td>
</tr>
</tbody>
</table>

1. Lynch et al, ARVO 2017
2. Shah et al, Proc ISBI 2018
3. Finlayson et al, Science 2019
AI Ethical Requirements

- Validate rigorously for safety, efficacy and equity AI against clinical outcome, in clinical workflow
Validate against what? Clinicians do not do so well against clinical outcome

**Screening for Diabetic Retinopathy**

The wide-angle retinal camera

- **Jacqueline A. Pugh, MD**
- **David R. Lawson, MD**
- **James M. Jackson, MD**
- **W.A.J. Van Herpen, MD**
- **John A. Watter, MD**
- **Michael R. Teel, MD**

**OBJECTIVE** — To define the test characteristics of four methods of screening for diabetic retinopathy.  

**RESEARCH DESIGN AND METHODS** — Four screening methods (an exam by an ophthalmologist through dilated pupils using direct and indirect ophthalmoscopy, an exam by a physician's assistant through dilated pupils using direct ophthalmoscopy, a single 45° retinal photograph without pharmacological dilation, and a set of three dilated 45° retinal photographs) were compared with a reference standard of stereoscopic 30° retinal photographs of seven standard fields read by a central reading center. Sensitivity, specificity, and positive and negative likelihood ratios were calculated after dichotomizing the retinopathy levels into none and mild nonproliferative versus moderate to severe nonproliferative and proliferative. Two sites were used. All patients with diabetes in a VA hospital outpatient clinic between June 1998 and May 1999 were asked to participate. Patients with diabetes identified from a laboratory list of elevated serum glucose values were included.  

**RESULTS** — The wide-angle retinal camera had the highest test characteristics: 33% sensitivity, 72%, 0.67; photographs without pharmacological dilation 0.61, 0.63, 4.1, 0.95; dilated photographs 0.91, 0.97, 24, 0.19; and physician's assistant 0.14, 0.99, 12, 0.87.

Diabetic retinopathy is a leading cause of blindness in adults in the U.S. (1). Because visual loss from diabetic retinopathy can be slowed or prevented by early treatment with laser therapy (2,3), dilated retinal exams by an ophthalmologist or three standard field stereoscopic photographs have been recommended to detect retinopathy before visual loss (4–7). The recommended frequency of exams is based on whether the patient has IDDM or NIDDM, if the patient has NIDDM, whether their baseline exam is negative for retinopathy, and whether an ophthalmologist exam or retinal photography were used to screen (7). Unfortunately, a large percentage of people with diabetes do not obtain these exams (8–10). The barriers to screening fall into two broad categories: patient lack of knowledge or commitments and lack of readily available ophtalmologic tests as a result of patient or institutional financial constraints (8–10). If a reliable method of screening were available for the primary care setting, screening rates for indigent patients with diabetes might increase.

Use of the wide-angle retinal camera has been explored in several studies and clinical reports (11–19). This camera has an infrared focusing system.
Rigorous validation: Clinicians differ systematically

Wisconsin Reading Center
Prognostic standard ‘truth’

Physicians at Iowa

Physicians in Amsterdam

Physicians at Michigan

AI system

80% agree
50% agree
20% agree

Abramoff et al, 2016
Abramoff et al, 2018
Highest Prognostic Standard

1. Evidence based markers for diabetic retinopathy
   - Studies from 70s and 80s and today
   - Highly reproducible and consistent over decades
   - Used today for FDA drug trials: ETDRS, DRS and DRCR
   - Cannot be created again ethically
   - Clinicians not validated against this standard
     - Low diagnostic accuracy and diagnostic drift
     - Lack of consistency
2. ALL DR management and treatment based on this reference standard

Surrogate outcome:
Stereo imaging: ETDRS level 43
- 1-year risk of early PDR 26.3%
- 1-year risk of high-risk PDR: 8.1%
OCT: DRCR level no DME
- No benefit from treatment

References:
5. DCCT The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44, 968-983 (1995).
Mammography
» FDA approved breast cancer assistive AI
» N = 222,135 women
» N = 2351 biopsy confirmed BC
» Women diagnosed by either:
  • Radiologist + AI (‘CAD use’)
  • Radiologist alone (‘No CAD use’)
» Safety not improved
» 20% more biopsies

» Outcomes worse for AI

1. Fenton et al, NEJM, 2007
## Validation of AI against prognostic standard

<table>
<thead>
<tr>
<th></th>
<th>FDA Superiority Endpoint</th>
<th>IDx-DR(n=819)</th>
<th>Remote Reading Network / Telemedicine</th>
<th>Board Certified Ophthalmologist in Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>85%</td>
<td>87%(^1) (81%-91%)</td>
<td>72% (65%-79%)(^6)</td>
<td>33%-34%^3%</td>
</tr>
<tr>
<td>Specificity</td>
<td>82%</td>
<td>90%(^1) (88%-93%)</td>
<td>97% (95%-99%)(^6)</td>
<td>99%^2-100%^3%</td>
</tr>
<tr>
<td>Repeatability</td>
<td></td>
<td>99%</td>
<td>&lt;80%(^6)</td>
<td>60%^4</td>
</tr>
<tr>
<td>Reproducibility</td>
<td></td>
<td>99%(^5)</td>
<td></td>
<td>83%^4</td>
</tr>
</tbody>
</table>

**Equity:** No significant effects for sex, race, ethnicity, HbA1C, lens status, or site

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4. Liu et al, 2018
5. Lynch et al, IOVS, 2018
7. Folk et al, Macula Society. Accuracy of the diabetic eye exam by ophthalmologists, as well as telemedicine by retina specialists and reading center, against a validated outcome standard.
AI Bias mitigation

**Mitigate Bias** along the entire development process

» Intended use
  • Consider patient population and its potential effects

» Design
  • Maximize use of biomarkers where possible
  • Consider training data distributions

» Validation
  • In full workflow
  • Unbiased clinical outcome
  • Account for entire patient population

» Implementation
  • Where and how it is implemented
  • How is it paid for
Patient centric autonomous AI

- Evidence of improving patient outcome
- Rigorous validation against prognostic standards
- Maximal protection of patient data security and privacy
- Design maximally reducible to human clinician cognition
- Liability for creator

Foundational Considerations for Artificial Intelligence utilizing ophthalmic images

Authors: Michael D. Abramoff,1 Brad Cunningham,2 Bakul Patel,3 Malvina B. Eydelman,4 Theodore Leng,5 Taiji Sakamoto,5,6 Barbara Blodi,7 S. Marlene Grenon,8 Risa Wolf,9 Arjun K. Manrai,10 Justin M. Ko,12 Michael F. Chiang,13 Danton Char,14,15 on behalf of the Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group*

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