Ethiek van autonome kunstmatige intelligentie in de gezondheidszorg

Michael D. Abràmoff, MD, PhD

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Professor of Electrical and Computer Engineering, and Biomedical Engineering
University of Iowa

Founder and Executive Chairman, Digital Diagnostics

Chair, FDA's Foundational Principles of Algorithmic Interpretation WG

DIGITAL DIAGNOSTICS
AI the right way.

CCOI

Support: Digital Diagnostics, National Eye Institute R01 EY019112, EY018853, EY017066, NovaGo AG
Conflicts of Interest: Digital Diagnostics – Founder, Executive Chairman, Director, Patents and Investor.

Artificial Intelligence: Autonomous vs Assistive

Autonomous

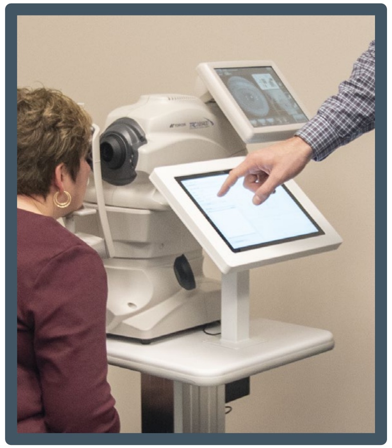
Medical decision by AI

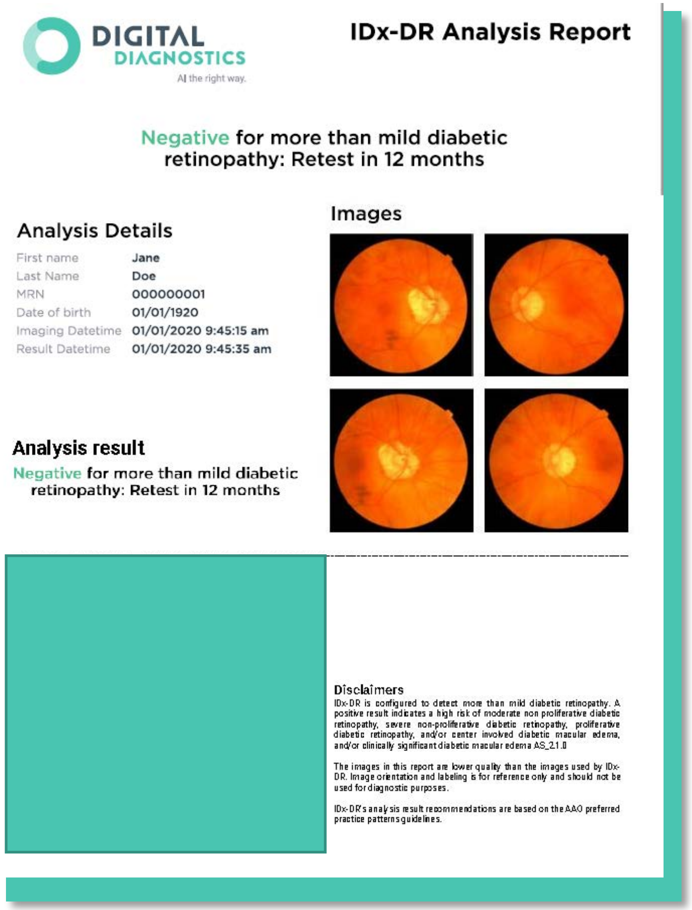
No human oversight

Instantaneous

Point of Care

Liability for creator





DIGITAL DIAGNOSTICS
AI the right way.

IDx-DR Analysis Report

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

Analysis Details

First name	Jane
Last Name	Doe
MRN	000000001
Date of birth	01/01/1920
Imaging Datetime	01/01/2020 9:45:15 am
Result Datetime	01/01/2020 9:45:35 am

Images

Analysis result

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

Disclaimers

IDx-DR is configured to detect more than mild diabetic retinopathy. A positive result indicates a high risk of moderate non proliferative diabetic retinopathy, severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, and/or center involved diabetic macular edema, and/or clinically significant diabetic macular edema AS_2.1.0

The images in this report are lower quality than the images used by IDx-DR. Image orientation and labeling is for reference only and should not be used for diagnostic purposes.

IDx-DR's analysis result recommendations are based on the AAO preferred practice patterns guidelines.

Assistive

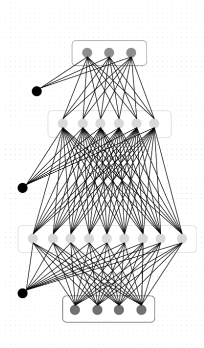
Clinician needed

Medical decision by clinician

Liability for clinician

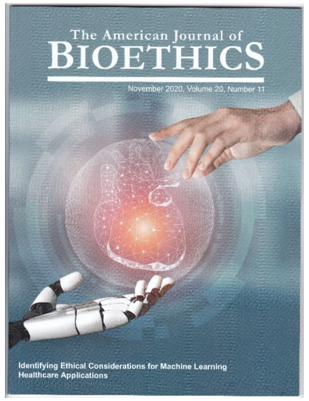
Creation of a new industry: Autonomous AI in healthcare

'diagnostic AI algorithm'



300+ papers
(2008)

Foundation in Ethics


The American Journal of
BIOETHICS
November 2020, Volume 20, Number 11
Identifying Ethical Considerations for Machine Learning Healthcare Applications

Ethical Foundations
(2020)

Clinical trial design / Regulatory Approval

First FDA de novo clearance (2018)

Second FDA clearance with 510k
(2020)

Standards of Care

Standards of Medical Care in Diabetes
(2020)

Reimbursement

First ever CPT Code 92229
(2019)

Coverage
$55.66
(2020)

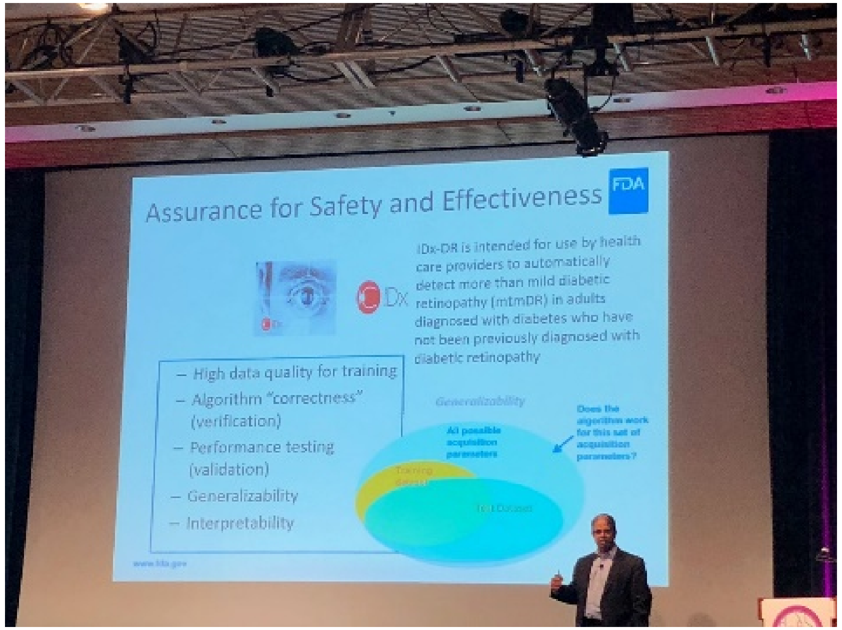
Affect patient outcomes/ Address health disparities

Preventing blindness and visual loss

Abramoff et al. Lessons Learned About Autonomous AI: Finding a Safe, Efficacious, and Ethical Path Through the Development Process. Am J Ophthalmol. 2020;214(1):134-42.
Char, Abràmoff, Feudtner. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020;20(11):7-17.
American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes – 2020. Diabetes Care; 43(Supplement 1): S135-S151, 2020.
https://www.ncqa.org/wp-content/uploads/2020/07/20200701_Summary_Table_of_Measures_Product_Lines_and_Changes.pdf
https://www.ama-assn.org/practice-management/digital/ophthalmologist-doing-health-care-ai-right-way

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”



FDA U.S. FOOD & DRUG ADMINISTRATION

Home / News & Events / FDA Newsroom / Press Announcements / 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

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Press Announcements

For Immediate Release: April 11, 2018

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.

U.S. Food & Drug Administration (FDA). FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm604357.htm

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. Abràmoff[1,2,3,4], Philip T. Lavin[5], Michele Birch[6], Nilay Shah[7] and James C. Folk[1,2,3]

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 enrolled 900 subjects, with no history of DR at primary care clinics, by comparing to Wisconsin Fundus Photograph Reading Center (FPRC) widefield stereoscopic photography and macular Optical Coherence Tomography (OCT), by FPRC certified photographers, and FPRC grading of Early Treatment Diabetic Retinopathy Study Severity Scale (ETDRS) and Diabetic Macular Edema (DME). More than mild DR (mtmDR) was defined as ETDRS level 35 or higher, and/or DME, in at least one eye. AI system operators underwent a standardized training protocol 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 mtmDR. 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%) (>82.5%), 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 health care 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

npj Digital Medicine (2018)1:39 ; doi:10.1038/s41746-018-0040-6

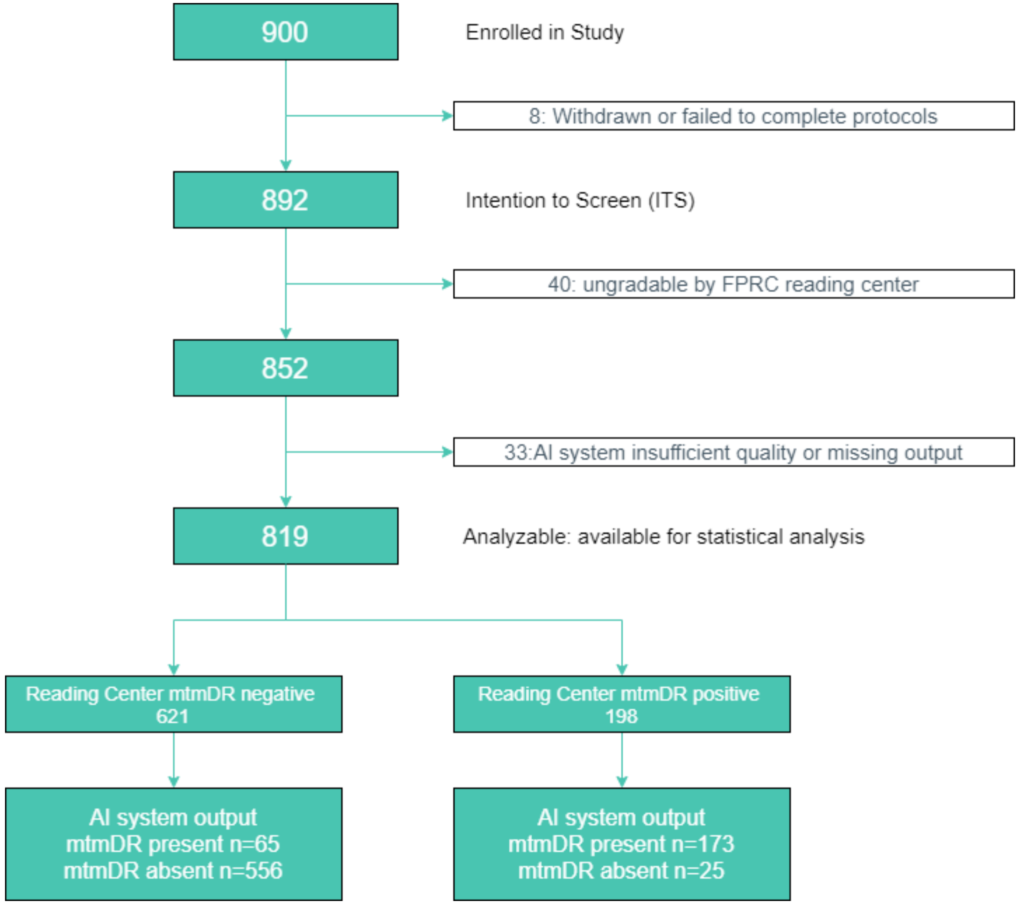
INTRODUCTION

People with diabetes fear visual loss and blindness more than any other complication.[1] 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.[2,3] Adherence to regular eye examinations is necessary to diagnose DR at an early stage, when it can be treated with the best prognosis,[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] and adherence has not increased over the last 15 years despite large-scale efforts to increase it.[8] To increase adherence, retinal imaging in or close to primary care offices followed by remote evaluation using telemedicine has also been widely studied.[9–11]

Artificial intelligence (AI)-based algorithms to detect DR from

care, and consistent diagnostic accuracy across age, race and ethnicity.[12,13,18,19] 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.

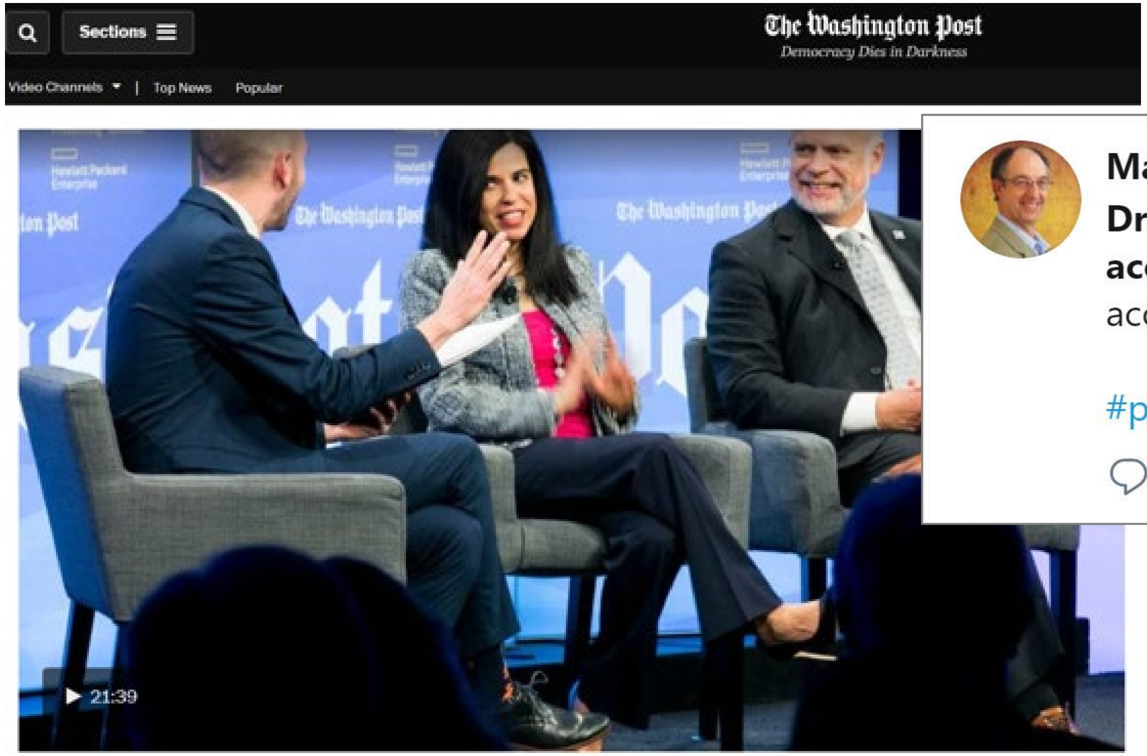
The Wisconsin Fundus Photograph Reading Center (FPRC) has historically been the gold standard for trials that require grading of the severity of DR, including the Epidemiology of Diabetes Interventions and Complications/Diabetes Control and Complications Trial (EDIC/DCCT), Diabetic Retinopathy Clinical Research Network (DRCR.net) studies, as well as pivotal phase III studies.[20,21] The FPRC 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 45–60°, equivalent to the area of the retina covered by the older, modified 7-field stereo film protocol.[22,23] Traditionally, the presence of Diabetic Macular



Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. Nature Dig Med 2018;1:39ff

2019: Solving Autonomous AI liability

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



(Erica Jones/The Washington Post)

Matthew Loxton @mloxton · Jan 10, 2019

Dr. Abramoff takes a very interesting, bold, and **ethical position on accountability** - states that as the vendor for an autonomous AI, they take accountability if it messes up and a patient suffers harm

#postlive

1 2

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

https://www.ama -assn.org/system/files/2019 -08/ai-2018-board-policy-summary.pdf

2020: First Standard of Care supporting Autonomous AI

American Diabetes Association. Diabetes Care

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Position Statements

11. Microvascular Complications and Foot Care: *Standards of Medical Care in Diabetes–2020*

American Diabetes Association

Diabetes Care 2020 Jan; 43(Supplement 1): S135-S151.
https://doi.org/10.2337/dc20-S011

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Article | Figures & Tables | Info & Metrics | PDF

Abstract

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee

American Diabetes Association®

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). […]

115. Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. NPJ Digit Med 2018;1:39

American Diabetes Association. 11. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes – 2020. Diabetes Care; 43(Supplement 1): S135-S151, 2020.
https://care.diabetesjournals.org/content/43/Supplement_1/S135

2020: First Autonomous AI cost -effectiveness analysis

Research

JAMA Ophthalmology | **Original Investigation**

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

Supplemental content

Author Affiliations: Department of Pediatrics, Division of Pediatric Endocrinology, Johns Hopkins School of Medicine, Baltimore, Maryland (Wolf); Department of Ophthalmology, Baylor College of Medicine, Houston, Texas (Channa); Department of Ophthalmology and

JOHNS HOPKINS
MEDICINE

Wolf, Channa, Abramoff Lehmann. Cost-effectiveness of Autonomous Point-of-Care Diabetic Retinopathy Screening for Pediatric Patients With Diabetes.JAMA Ophthalmol. Published online September 03, 2020

2020: First Autonomous AI payment

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

- Discounted human cost

Abramoff et al, US Senate Committee on Finance. Briefing on Autonomous AI and Reimbursement, May 28, 2019

2020: US Medicare (OPPS): $55/exam for Autonomous AI

Federal Register / Vol. 85, No. 248 / Monday, December 28, 2020 / Rules and Regulations **84629**

h advanced fibrosis and
10 are at high risk for
ns and costly care, allowing
uccessful outpatient
1. Commenters
ed that Fibroscan
ent should be increased, not
which will allow expanded
and access for more GI
providing more widespread
ffective and non-invasive

Comment: Several commenters stated that Medicare and commercial payor utilization data for CPT code 91200 demonstrate that the usage of FibroScan in the physician office setting is well below 50 percent. Commenters stated that at a 50 percent usage rate, each FibroScan would generate 6,250 exams per year, or 24 per day, resulting in 3,656,250 total national exams per year but the Medicare database identifies

CPT code 92228 includes work, accounting for the physician at the reading site. For both CPT codes 92227 and 92228, direct PE pays for the clinical staff at both sites.

The AMA CPT Editorial Panel also created CPT code 92229 (*Imaging of retina for detection or monitoring of disease; with point-of-care automated analysis with diagnostic report; unilateral or bilateral*) for point-of-care

CENTERS FOR MEDICARE & MEDICAID SERVICES

“[…]**IDx-DR technology** received a new CPT code effective January 1st, 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

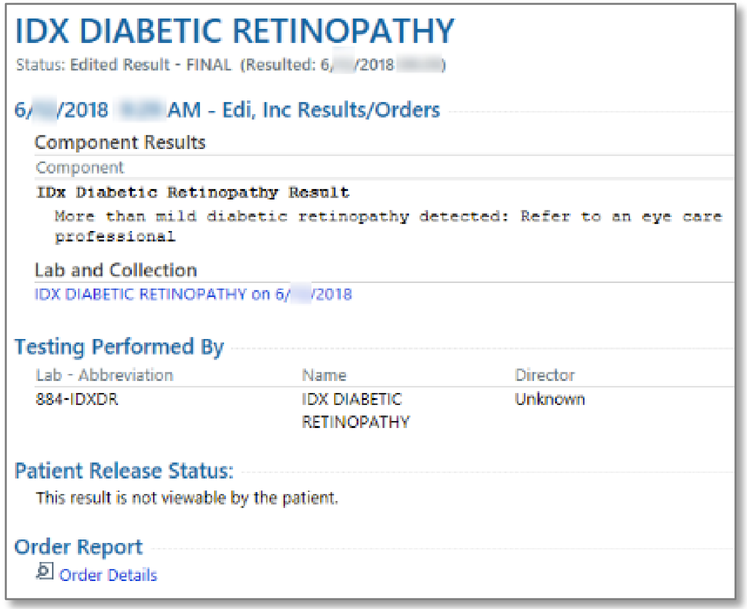
MPFS states “We are considering CPT code 92229 to be a diagnostic service under the PFS.”

CY 2021 Payment Policies under the Physician Fee Schedule and Other Changes to Part B Payment Policies, available at https://public-inspection.federalregister.gov/2020-26815.pdf (“2021 MPFS”)
Page 271-272 in https://www.cms.gov/files/document/cms-1734-p-pdf.pdf
Pages 450-453 in https://public-inspection.federalregister.gov/2020-26815.pdf
Pages 290-295 in https://www.cms.gov/files/document/12220-opps-final-rule-cms-1736-fc.pdf

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



IDX DIABETIC RETINOPATHY

Status: Edited Result - FINAL (Resulted: 6/ /2018)

6/ /2018 AM - Edi, Inc Results/Orders

Component Results

Component

IDx Diabetic Retinopathy Result

More than mild diabetic retinopathy detected: Refer to an eye care professional

Lab and Collection

IDX DIABETIC RETINOPATHY on 6/ /2018

Testing Performed By

Lab - Abbreviation	Name	Director
884-IDXDR	IDX DIABETIC RETINOPATHY	Unknown

Patient Release Status:

This result is not viewable by the patient.

Order Report

Order Details

Diabetic Eye Exams in Grocery Store

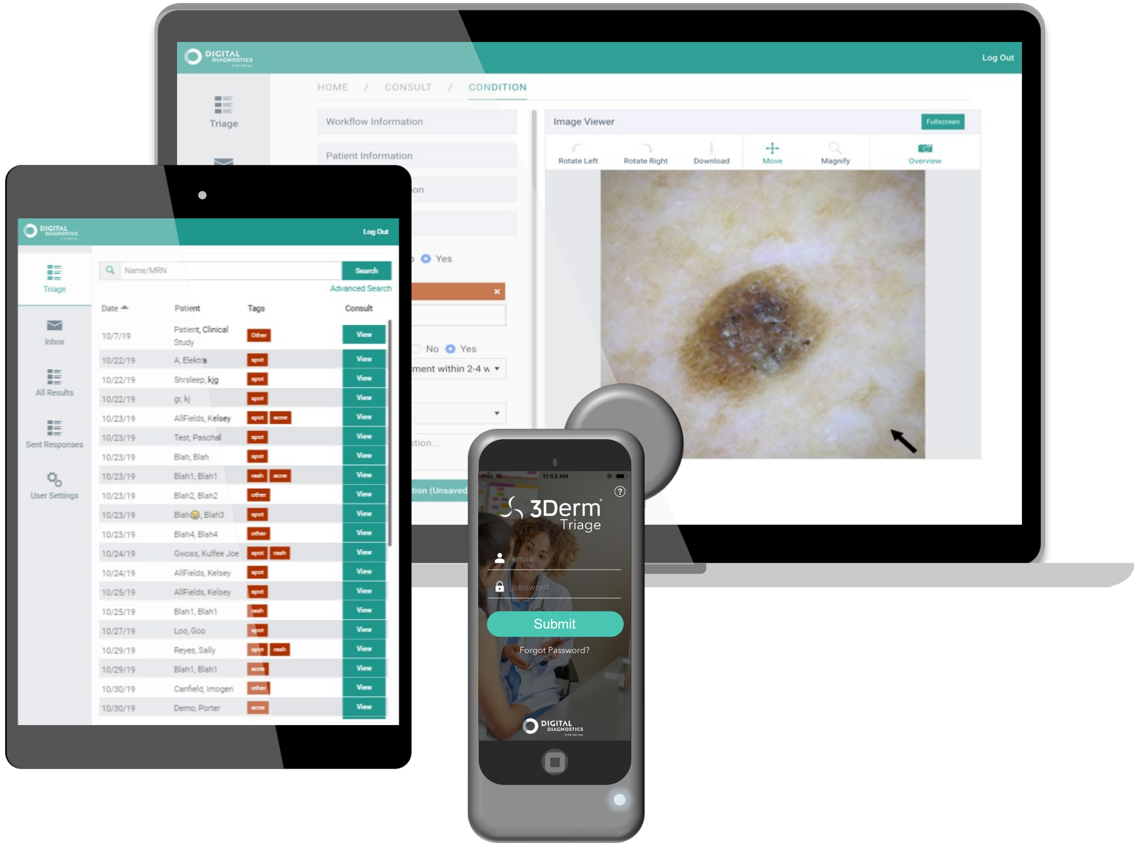
- Safeway retail has primary care clinics in store
- Full-service primary care clinics with primary care MD
- Autonomous AI for diabetic eye exam in diabetes management workflow
- Coordinated Diabetes Care

OUS Adoption– partnership with Orbis – Flying Eye Hospital

https://cybersight.org/portfolio/lecture -autonomous-ai-finding-a-safe-efficacious-and-ethical-path-to-increasing-healthcare-productivity/

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

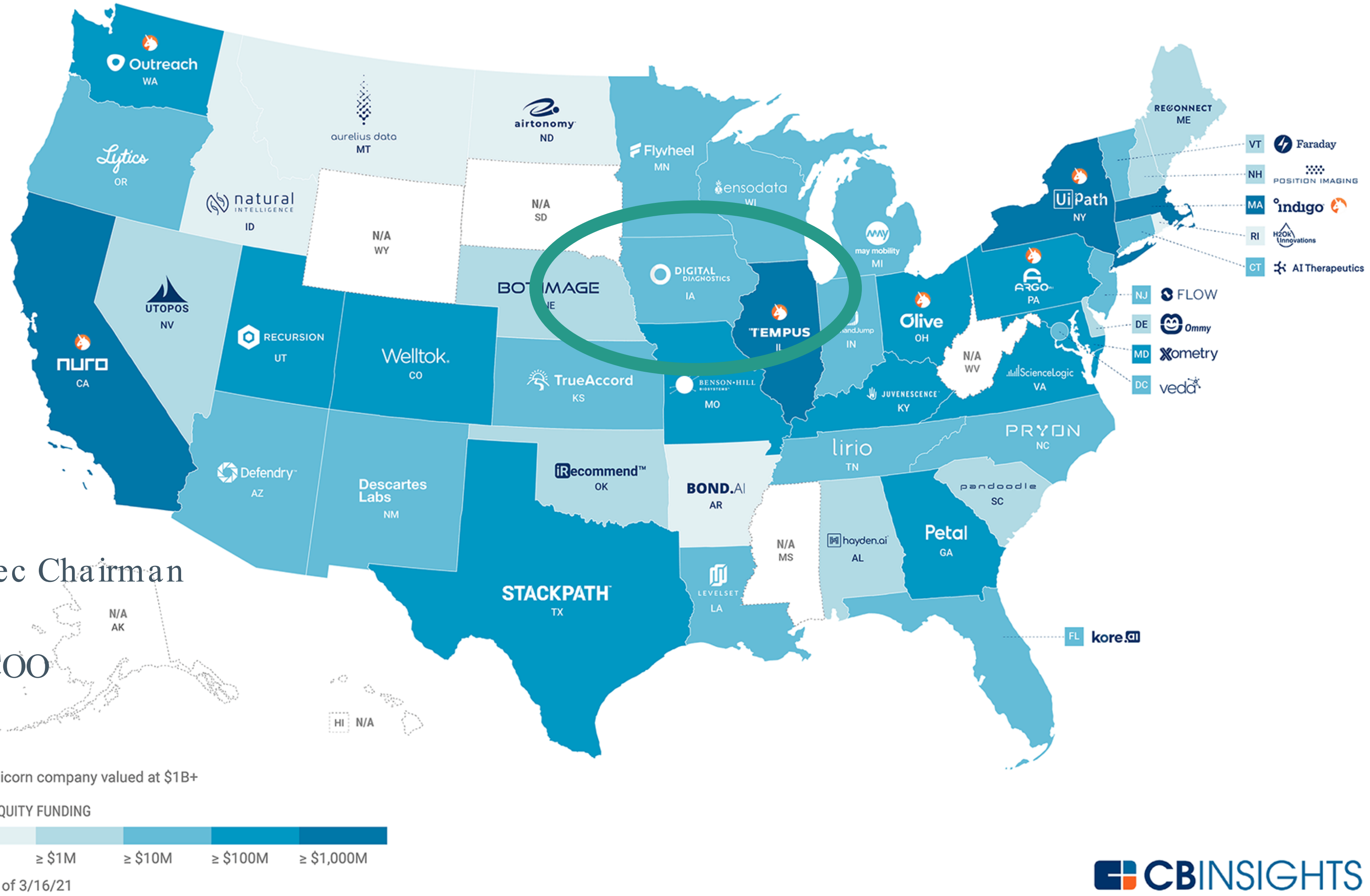
DIGITAL DIAGNOSTICS
AI the right way.

THE UNITED STATES OF ARTIFICIAL INTELLIGENCE

The most well-funded AI startups by state. Our analysis ranks companies based on total disclosed equity funding and only considers AI companies that have raised an equity round since 2016.

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



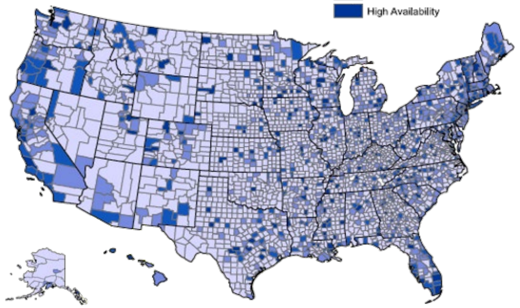
https://www.cbinsights.com/research/artificial -intelligence-startup-us-map/

CB INSIGHTS

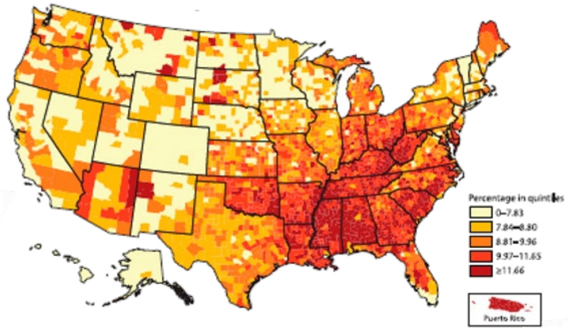
Healthcare problems to be solved by Autonomous AI

Health disparities - Access

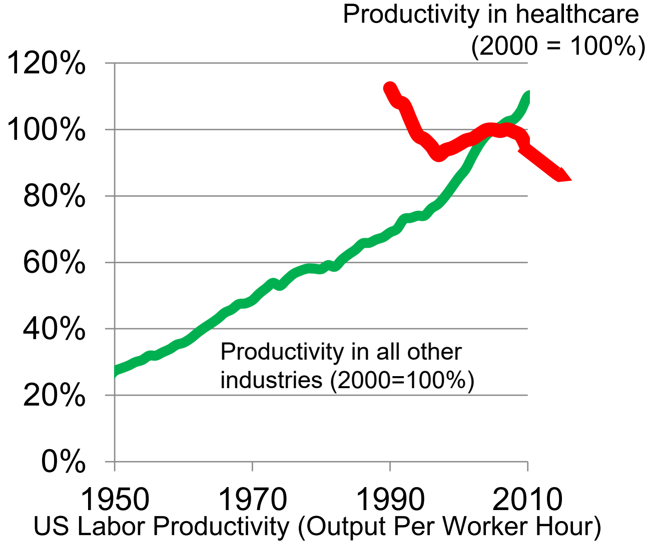
Eye care availability



Eye care need



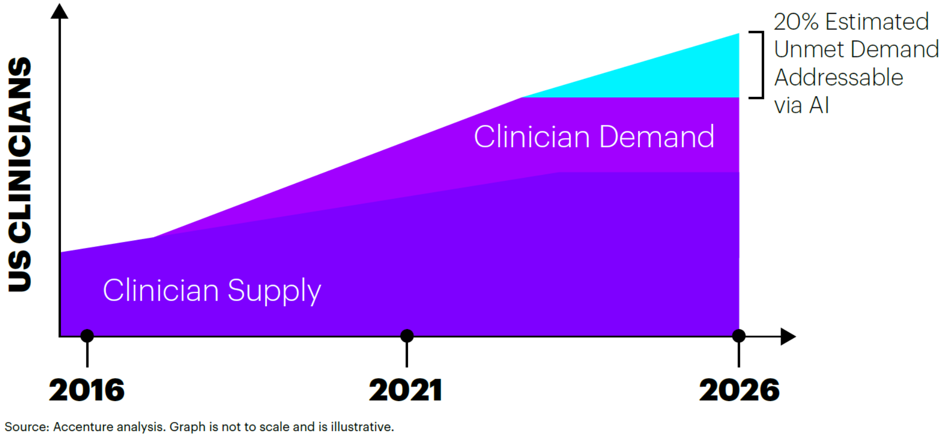
Healthcare Cost - Productivity



Other industries decades of steady improvement

Outpatient continues to decline

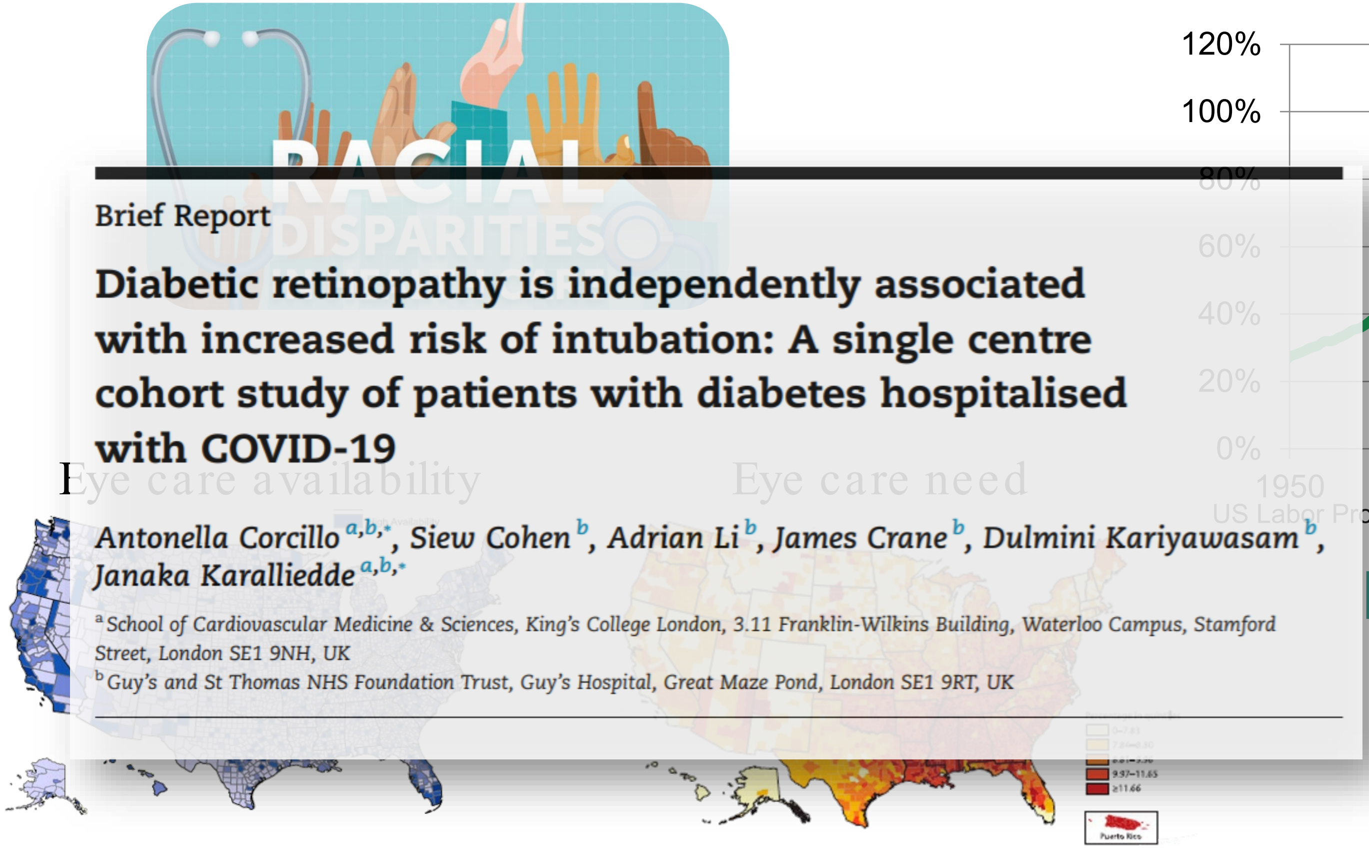
Healthcare demand - workforce gap



1. US Bureau Labor Statistics, 2010
Lam et al, The effect of electronic health records adoption on patient visit volume at an academic ophthalmology department BM Health Serv Res, 2016
2. Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice, J AAPOS 2014
3. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care. 2003;26(1):226-229.
4. Centers for Disease Control and Prevention. Diabetes Report Card 2012. Atlanta, GA: U.S. Department of Health and Human Services;2012
5. U.S. Centers for Disease Control level distribution of diagnosed diabetes among US adults aged 20 or older, 2013. https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf

Healthcare problems to be solved by Autonomous AI

Health disparities - Access



Brief Report

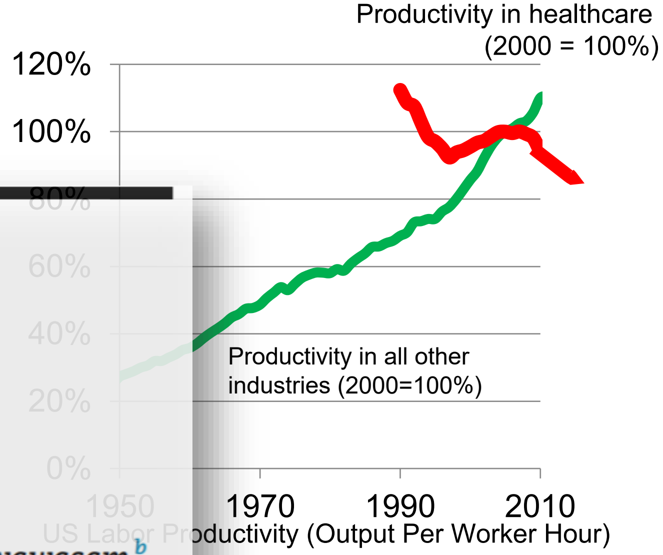
Diabetic retinopathy is independently associated with increased risk of intubation: A single centre cohort study of patients with diabetes hospitalised with COVID-19

Antonella Corcillo [a,b,], Siew Cohen [b], Adrian Li [b], James Crane [b], Dulmini Kariyawasam [b], Janaka Karalliedde [a,b,*]*

[a] School of Cardiovascular Medicine & Sciences, King's College London, 3.11 Franklin-Wilkins Building, Waterloo Campus, Stamford Street, London SE1 9NH, UK

[b] Guy's and St Thomas NHS Foundation Trust, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK

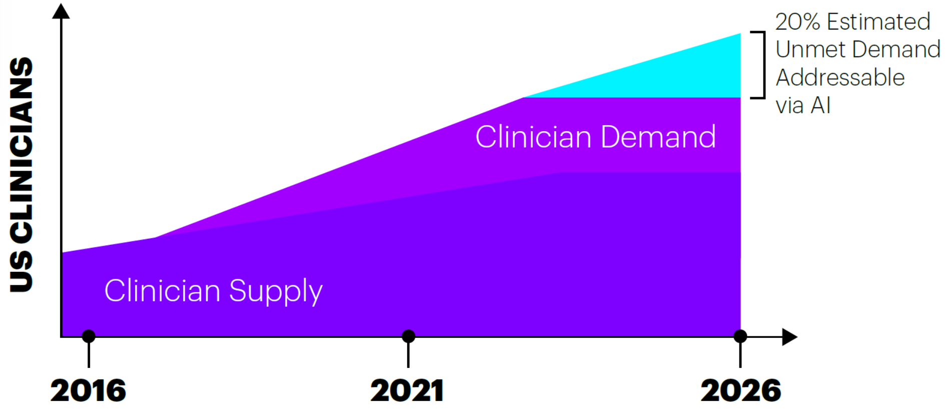
Healthcare Cost - Productivity



Other industries decades of steady improvement

Outpatient Demand continues to decline

Healthcare demand - workforce gap



Source: Accenture analysis. Graph is not to scale and is illustrative.

1. US Bureau Labor Statistics, 2010
   Lam et al, The effect of electronic health records adoption on patient visit volume at an academic ophthalmology department BM Health Serv Res, 2016
2. Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice AAPOS 2014
3. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care. 2003;26(1):226.
4. Centers for Disease Control and Prevention. Diabetes Report Card 2012. Atlanta, GA: U.S. Department of Health and Human Serv, 2012
5. U.S. Centers for Disease Control level distribution of diagnosed diabetes among US adults aged 20 or older, 2013.
   https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017_-508.pdf

A brief history of (autonomous) AI in healthcare

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

```
--------PATIENT-538--------
 1) Patient's  name:
 **  PT538
 2) Age:
 **  34 YEARS
 3)  Sex:
 **  MAEL
                                              M YC IN respells the user's answer
=MALE
 4) Race:
 **  CAUCASIAN

                                              Several questions are skipped.

 14) Has Pt.538 recently had symptoms of persistent headache or other
     abnormal neurologic symptoms (dizziness, lethargy, etc.)?
 **  YES
 15) Has Pt538 recently had objective evidence of abnormal neurologic
     signs (nuchal rigidity, coma, seizures, etc.) documented by physician
     observation or examination?
 **  YES

                                              Note that M YCIN 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.

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

 .

 23) For how many days has Pt538 had abnormal neurologic signs?
```

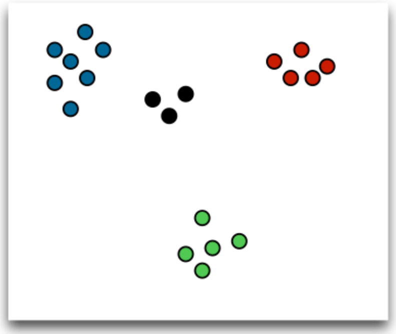
Shortliffe EH, Davis R, Axline SG, Buchanan BG, Green CC, Cohen SN. Computer-based consultations in clinical therapeutics: explanation and rule acquisition capabilities of the MYCIN system. Comput Biomed Res. 1975;8(4):303-20. http://www.ncbi.nlm.nih.gov/pubmed/1157471
Rumelhart DE, McClelland JL, University of California San Diego. PDP Research Group. Parallel distributed processing : explorations in the microstructure of cognition. Cambridge, Mass.: MIT Press; 1986.

Inputs – images - for Autonomous AI

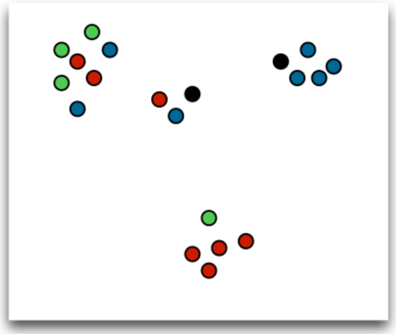
Key Characteristics

- Objective sensors
  - Secondary role for GPU / neurosimilar 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

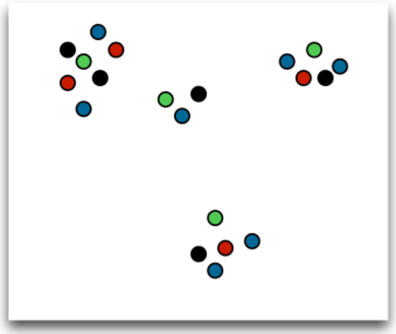
Positive



None



Negative



Abramoff, Garvin, Sonka. Retinal imaging and image analysis. IEEE Rev Biomed Eng. 2010;3:169-208. doi:10.1109/RBME.2010.2084567

Autonomous AI is different

Key Constraints on AI in healthcare

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

kl Abramoff, Ton Coolen, George Wieneke 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. These 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 attentio various disciplines (Amit, 1989). This study illustrates the use of a neura ork for simulating the temporal organization of speech in relation t ering. More specifically, it addresses the question, whether the network ca nfluenced in such a way that behavior resembling stuttering will result. ification of the original Hopfield type neural network was chosen to simulat temporal aspects of motor systems. By introducing delays in th ections between the neurons, sequences of patterns can be stored an oduced at a later time (Coolen & Gielen, 1988). It is assumed that eac rn in a sequence represents the information necessary for producin ulatory movements from one phoneme to the next (Braamhof, 1989).

al network

Generally a neuronal network consists of a collection of neurons,which ar connected by axons ending in synapses on dendrites. In the Hopfield typ ork these parts are all represented rather simply (Hopfield, 1982). Neuron discrete on/off threshold units. That is to say, a neuron only fires if th nation of all of its inputs is higher than some threshold. All neurons ar

Long Path from Science, to Algorithm, to Patient

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

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nation of all of its inputs is higher than some th

15 ABSTRACTS

LOW LEVEL SCREENING OF EXSUDATES AND HAEMORRAGHES IN BACKGROUND DIABETIC RETINOPATHY

M.D. Abramoff[1,2,3], MD MSc, J.J. Staal[2,3], MSc, M.S. Suttorp[1], MD PhD, B.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
I2 Engineering, Amstelveen, Netherlands

Purpose: to develop a fast and reliable method to screen fundus images on exsudates and haemorraghes 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-mydriatic fundus camera, 800x600pixels, 24 bit JPEG decompressed). Using this operator the eigenvalues of the Hessian and the structure tensor were mapped nonlinearly to a multidimensional probability measure

$$f_i = prob[\Gamma_i(H_\sigma\{\lambda_1 \ldots \lambda_n\}, G_\sigma\{\lambda_1 \ldots \lambda_n\})]$$

The operator is constructed in such a way that reddish and white-yellowish ellipsoid structures (20-520µm) give optimal response.
Results: 500 images were used for optimization. The features detected

Long Path from Science, to Algorithm, to Patient

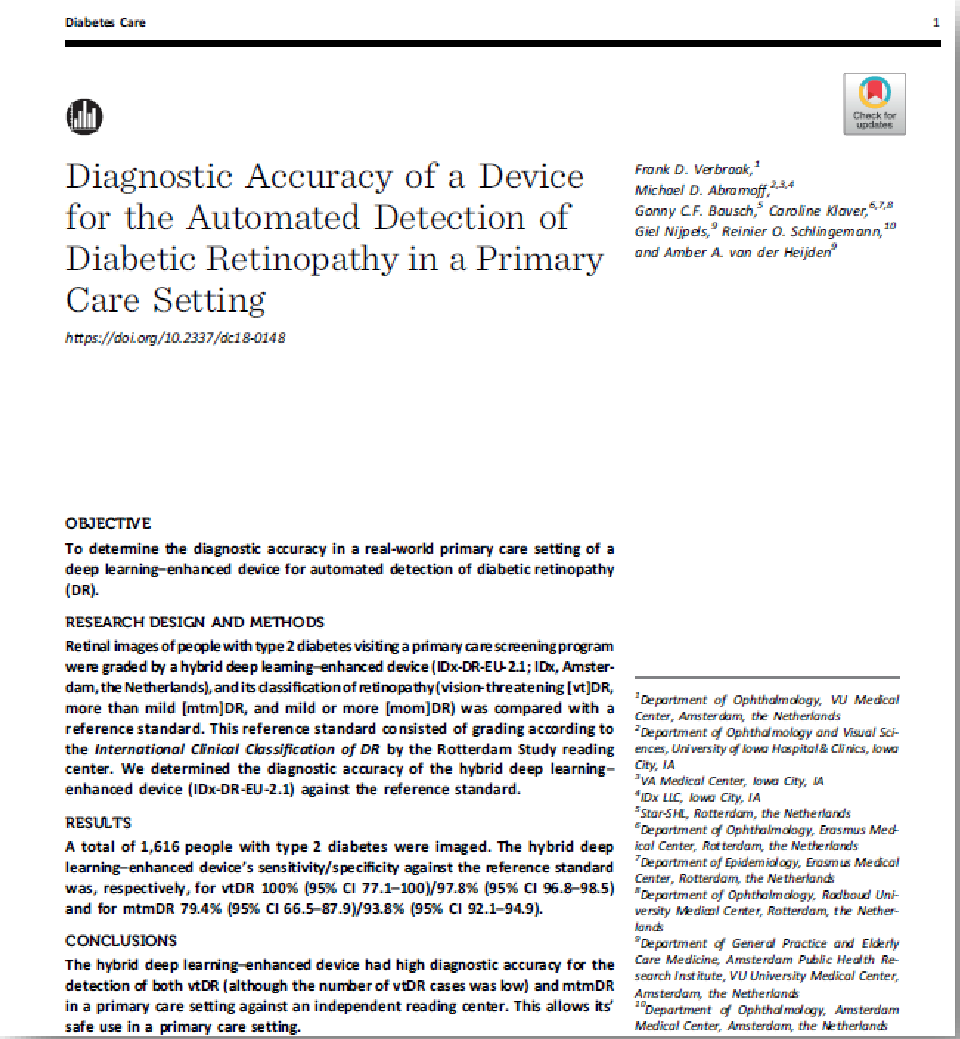
1988: Machine learning using artificial neural networks
2000: AI Detection of retinopathy lesions
2003+: *Many* more lesion detection publications

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

US Patent 10,140,699. 2018. “Optimal, User-Friendly, Object Background Separation in Images”.
US Patent 7,474,775. 2009. "Automatic Detection of Red Lesions in Digital Color Fundus Photographs”.
US Patent 7,712,898. 2010. “Methods and Systems for Optic Nerve Head Segmentation”.
US Patent 8,194,936. 2012. “Optimal Registration of Multiple Deformed Images Using a Physical Model of the Imaging Distortion”.
US Patent 8,616,702. 2013. “Hybrid Laser Ophthalmoscope”.
US Patent 8,358,819 2018. “System and Methods for Image Segmentations in N-Dimensional Space”.
US Patent 9,155,465. 2015. “Snapshot spectral domain optical coherence tomographer”.
US Patent 8,340,437. 2014. "Methods and Systems for Determining Optimal Features for Classifying Patterns or Objects in Images".
US Patent 9,545,196. 2017. “Automated Assessment of Glaucoma Loss from Optical Coherence Tomography”.
US Patent 9,782,065. 2017. “Parallel Optical Coherence Tomography Apparatuses, Systems, and Related Methods”.
US Patent 9,814,386. 2017. “Systems and Methods for Alignment of the Eye for Ocular Imaging”,
US Patent 9,924,867. 2018. “Automated Determination of Arteriovenous Ratio in Images of Blood Vessels”.
US Patent 10,410,355. 2019. “Methods and systems for image analysis using non-Euclidean deformed graphs”.
US Patent 10,115,194. 2018. “Systems and Methods for Feature Detection in retinal Images”.
US Patent 10,360,672. 2019 “Automated Separation of Binary Overlapping Trees”. Inventors:
US Patent 10,694,945. 2020 “Systems and methods for alignment of the eye for ocular imaging”.
US Patent 10,783,639. 2020. “System and methods for n-dimensional image segmentation using convolutional neural networks”.

How do we get such an AI to patients here



Diabetes Care 1

Diagnostic Accuracy of a Device for the Automated Detection of Diabetic Retinopathy in a Primary Care Setting

https://doi.org/10.2337/dc18-0148

Frank D. Verbraak,[1] Michael D. Abramoff,[2,3,4] Gonny C.F. Bausch,[5] Caroline Klaver,[6,7,8] Giel Nijpels,[9] Reinier O. Schlingemann,[10] and Amber A. van der Heijden[9]

OBJECTIVE

To determine the diagnostic accuracy in a real-world primary care setting of a deep learning–enhanced device for automated detection of diabetic retinopathy (DR).

RESEARCH DESIGN AND METHODS

Retinal images of people with type 2 diabetes visiting a primary care screening program were graded by a hybrid deep learning–enhanced device (IDx-DR-EU-2.1; IDx, Amsterdam, the Netherlands), and its classification of retinopathy (vision-threatening [vt]DR, more than mild [mtm]DR, and mild or more [mom]DR) was compared with a reference standard. This reference standard consisted of grading according to the *International Clinical Classification of DR* by the Rotterdam Study reading center. We determined the diagnostic accuracy of the hybrid deep learning–enhanced device (IDx-DR-EU-2.1) against the reference standard.

RESULTS

A total of 1,616 people with type 2 diabetes were imaged. The hybrid deep learning–enhanced device's sensitivity/specificity against the reference standard was, respectively, for vtDR 100% (95% CI 77.1–100)/97.8% (95% CI 96.8–98.5) and for mtmDR 79.4% (95% CI 66.5–87.9)/93.8% (95% CI 92.1–94.9).

CONCLUSIONS

The hybrid deep learning–enhanced device had high diagnostic accuracy for the detection of both vtDR (although the number of vtDR cases was low) and mtmDR in a primary care setting against an independent reading center. This allows its' safe use in a primary care setting.

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[10]Department of Ophthalmology, Amsterdam Medical Center, Amsterdam, the Netherlands

Abramoff MD, Folk JC, Han DP, et al. Automated analysis of retinal images for detection of referable diabetic retinopathy. JAMA Ophthalmol. Mar 1 2013;131(3):351-7. doi:10.1001/jamaophthalmol.2013.1743

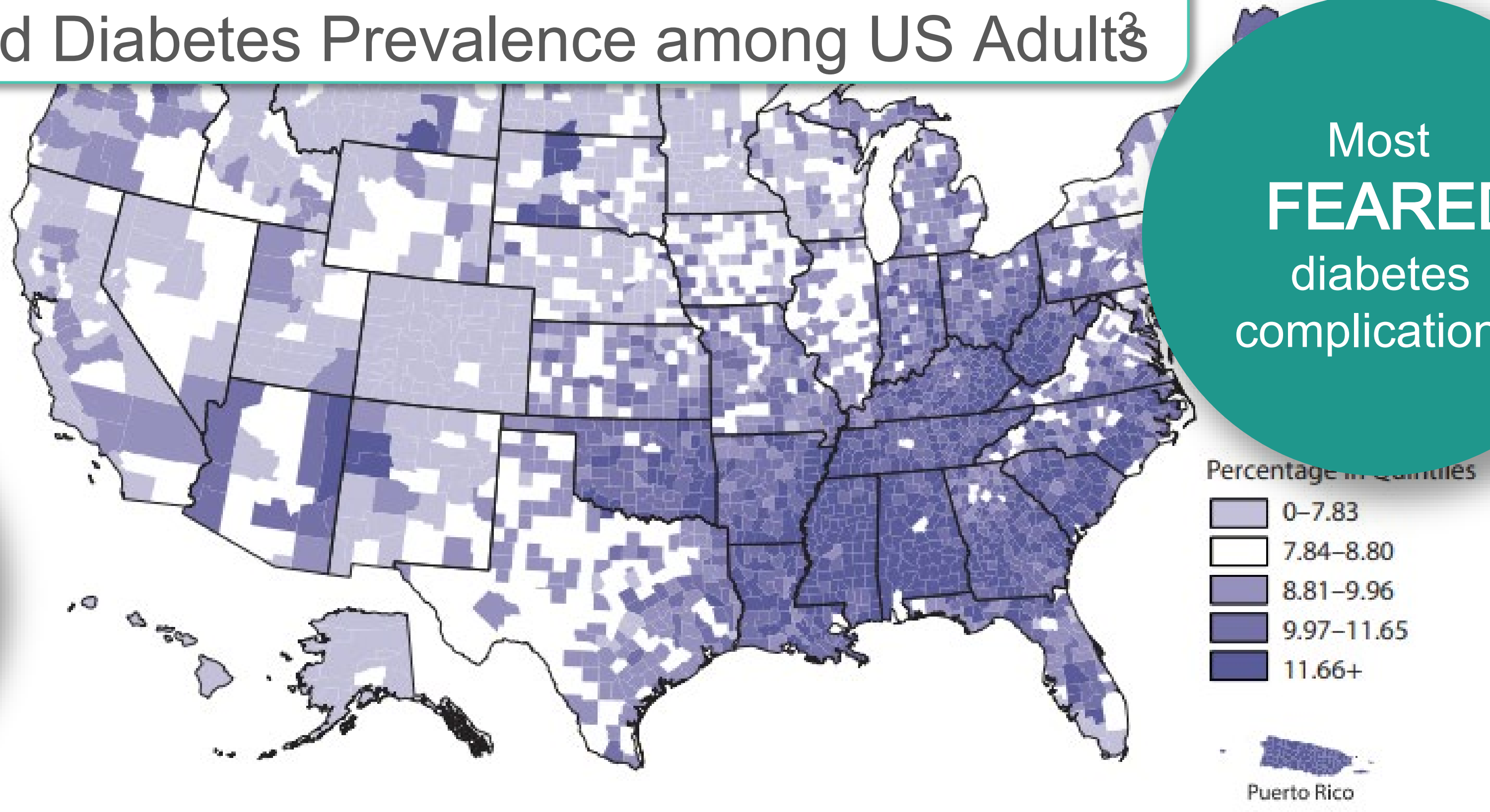
Diabetes is a large and growing problem in the US.[1,2]

60,000
Americans blind every year

34.2
million people have diabetes[1,2]

Blindness from diabetes is preventable.

Diagnosed Diabetes Prevalence among US Adults[3]



Most **FEARED** diabetes complication[4]

1. Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. *Diabetes Care* 2003;26(1):226-229.
2. Centers for Disease Control and Prevention. *Diabetes Report Card 2012.* Atlanta, GA: U.S. Department of Health and Human Services; 2012
3. U.S. Centers for Disease Control level distribution of diagnosed diabetes among US adults aged 20 or older, 2013. https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf
4. Hendricks LE, Hendricks RT. Greatest fears of type 1 and type 2 patients about having diabetes: implications for diabetes educators. Diabetes Educ. 1998;24(2):168-173.

Image from: CDC Infographics. A Snapshot: Diabetes in the United States. https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html Accessed June 18, 2020

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

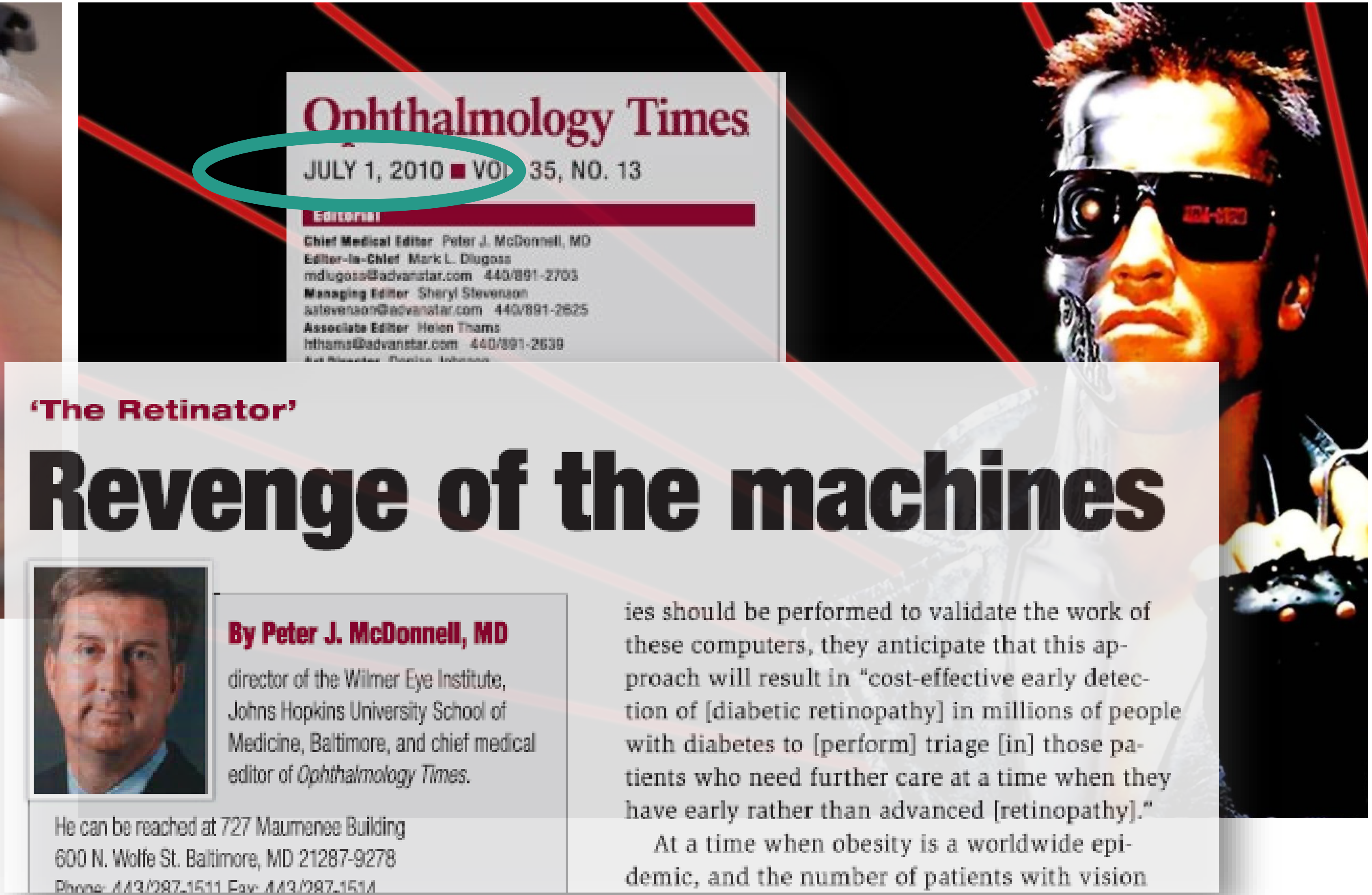
» Use existing staff
  - Operable by existing staff (high school diploma)
  - Robotic camera with assistive AI

» Automatic claims, billing and care gap closure
  - Real time, immediate claims and ICD-10 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?

'The Retinator'



Ophthalmology Times

JULY 1, 2010 ■ VOL 35, NO. 13

Editorial

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'The Retinator'

Revenge of the machines

By Peter J. McDonnell, MD

director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of *Ophthalmology Times.*

He can be reached at 727 Maumenee Building
600 N. Wolfe St. Baltimore, MD 21287-9278

ies should be performed to validate the work of these computers, they anticipate that this approach will result in "cost-effective early detection of [diabetic retinopathy] in millions of people with diabetes to [perform] triage [in] those patients who need further care at a time when they have early rather than advanced [retinopathy]."

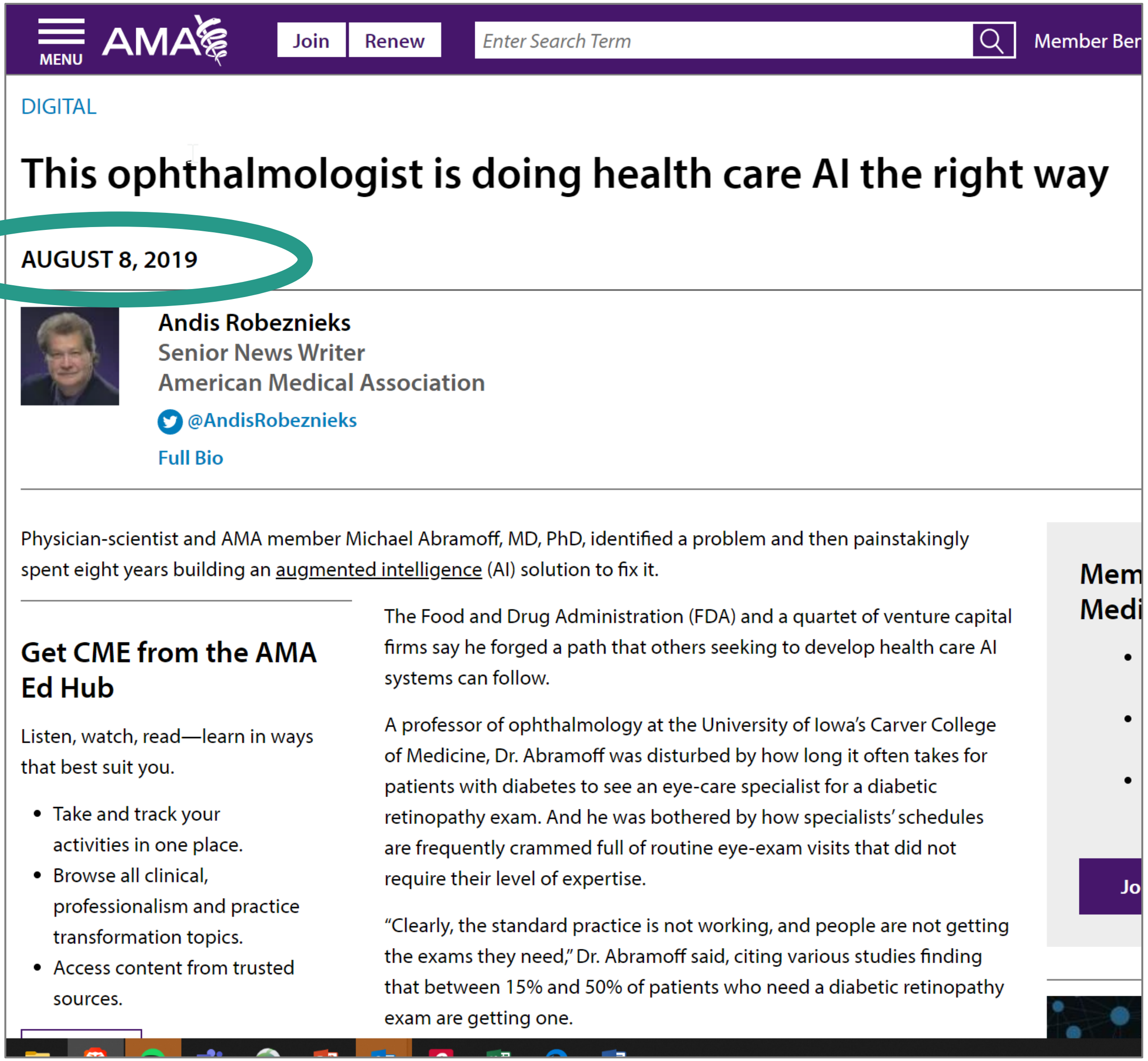
At a time when obesity is a worldwide epidemic, and the number of patients with vision

McDonnell PJ. 'The Retinator': revenge of the machines. *Ophthalmology Times*. 2010;35(13):4.

10 years later, turning it around

DIGITAL DIAGNOSTICS

AI the right way.



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DIGITAL

This ophthalmologist is doing health care AI the right way

AUGUST 8, 2019

Andis Robeznieks
Senior News Writer
American Medical Association
@AndisRobeznieks
Full Bio

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.

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.

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https://www.ama -assn.org/practice-management/digital/ophthalmologist -doing-health-care-ai-right-way

The risk of backlash

Historical example: Gene therapy

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

nature

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nature > news > article

Published: 07 October 1999

Virus treatment questioned after gene therapy death

Sally Lehrman

Nature **401**, 517–518(1999) | Cite this article

4086 Accesses | **437** Citations | **12** Altmetric | Metrics

San Francisco

Researchers at the University of Pennsylvania are investigating the first death in a gene therapy experiment, which was revealed last week. Their enquiries centre on the adenovirus vector used to deliver potentially therapeutic DNA to the liver.

Jesse Gelsinger, an 18-year-old, high-school graduate from Arizona, developed a fever and blood clots throughout his body within hours of treatment to correct partial ornithine transcarbamylase (OTC) deficiency, a rare metabolic disease that can cause a dangerous build-up of ammonia in the body. He died four days later.

Chandler RJ, Venditti CP. Gene Therapy for Metabolic Diseases. Transl Sci Rare Dis. 2016;1(1):73-89.
Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017;390(10097):849-860.

The risk of backlash for AI is real

HEALTH TECH

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

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

THE WALL STREET JOURNAL.

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TECH

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

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

THE NEW YORKER

A REPORTER AT LARGE OCTOBER 22, 2018 ISSUE

"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

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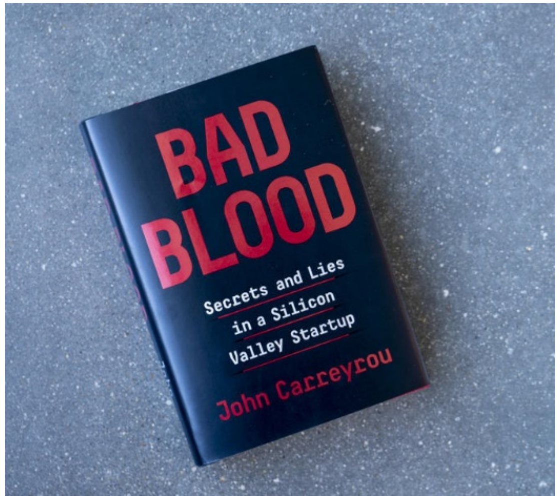
RESEARCH ARTICLE

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

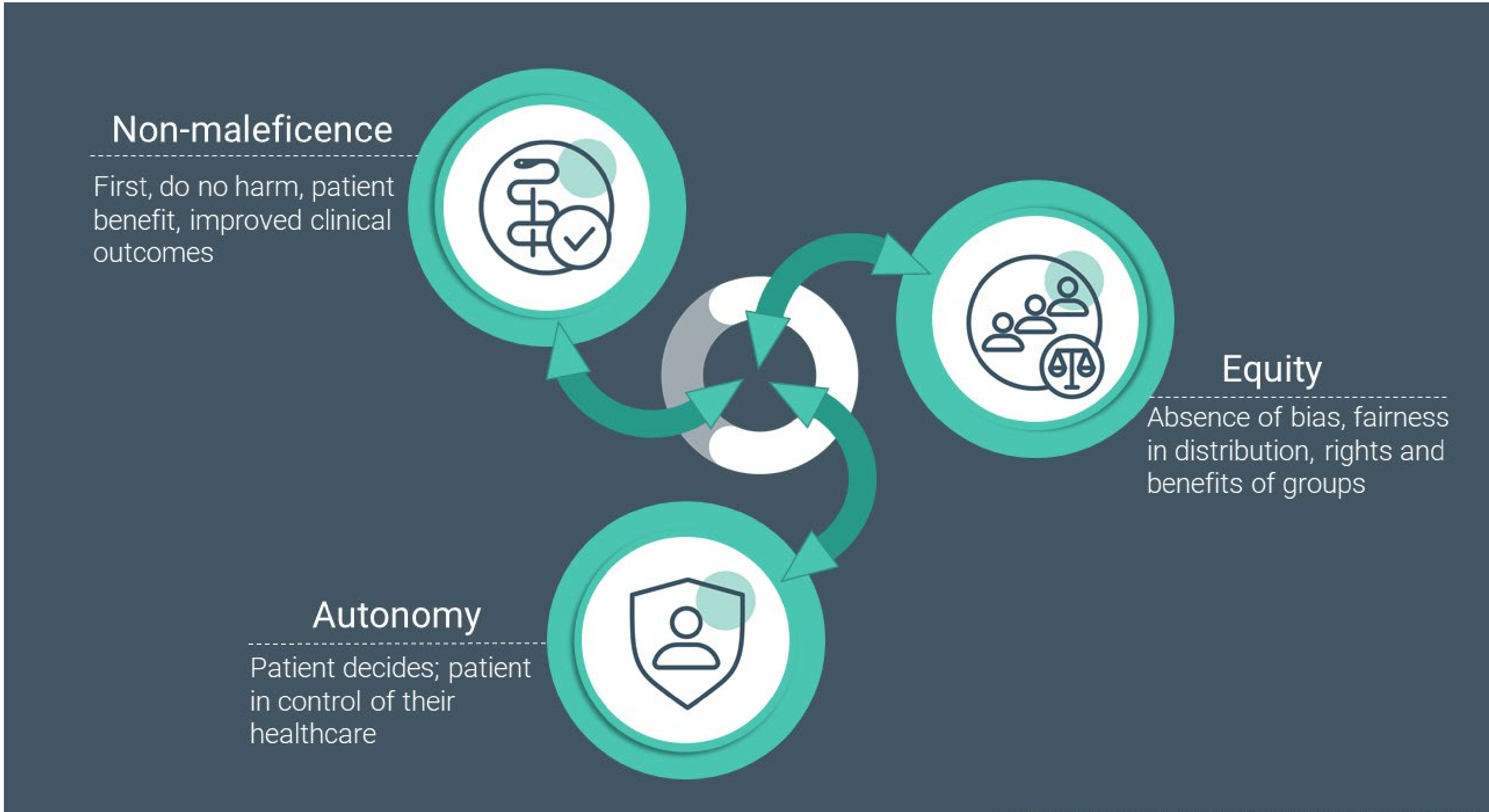


Higgins et al, Tesla, Uber Deaths Raise Questions About the Perils of Partly Autonomous Driving https://www.wsj.com/articles/tesla-uber-deaths-raise-questions-about-the-perils-of-partly-autonomous-driving-1522661400 WSJ, April 2, 2018
Obermeyer Z, Powers B, Vogeli C, Mullainathan S. Dissecting racial bias in an algorithm used to manage the health of populations. Science. Oct 25 2019;366(6464):447-453. doi:10.1126/science.aax2342
Robbins, Ross, HHS to probe whether Google's 'Project Nightingale' followed federal privacy law, STAT+, 2019 https://www.statnews.com/2019/11/13/hhs-probe-google-ascension-project-nightingale/

AI's Ethics Iron Triangle

Ethical principles

- Non-maleficence
- Autonomy
- Equity



Abramoff MD, Tobey D, Char DS. Lessons Learned About Autonomous AI: Finding a Safe, Efficacious, and Ethical Path Through the Development Process. Am J Ophthalmol. 2020;214(1):134-142.
Char DS, Abràmoff MD, Feudtner C. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020(21):7-17.

AI's Ethics framework

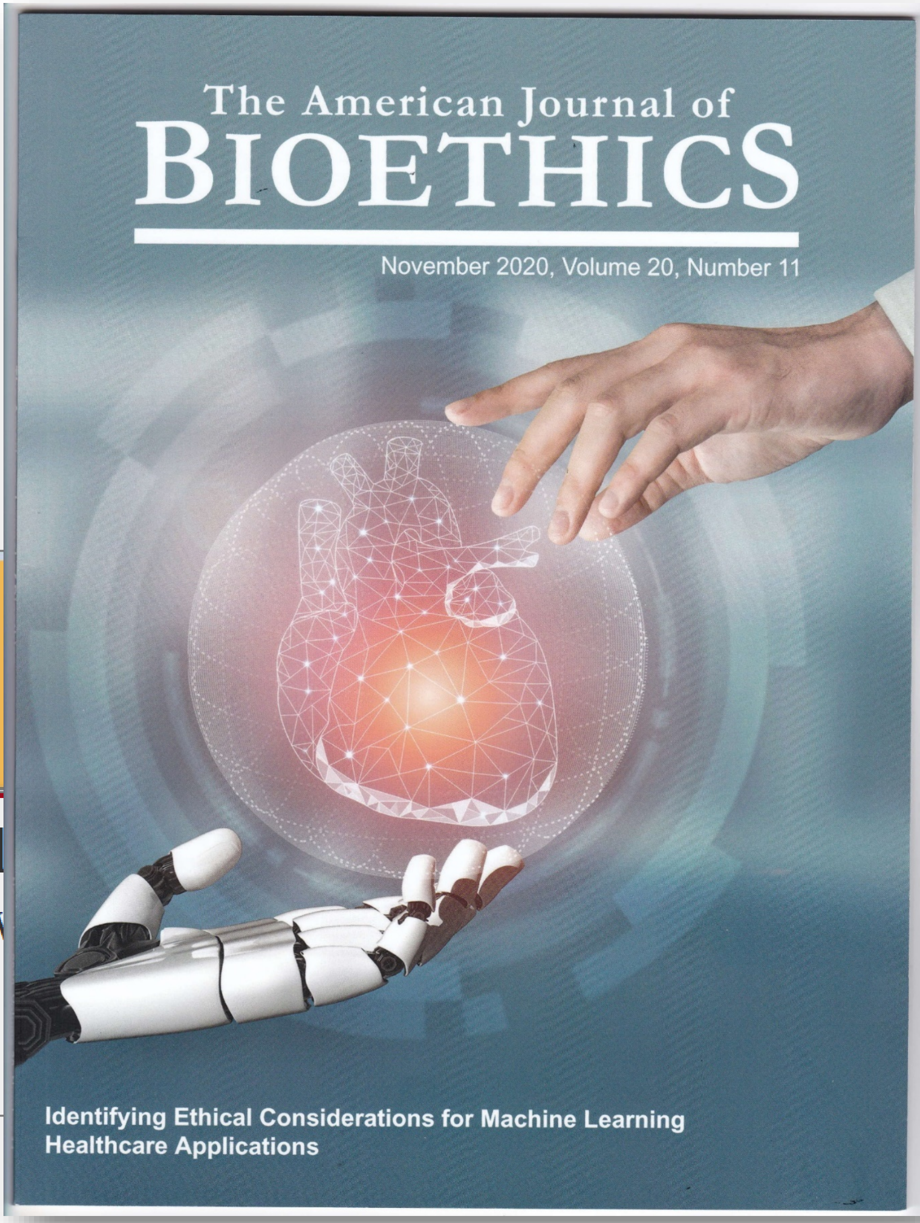
Ethical principles

- Non-maleficence
- Autonomy
- Equity

AMERICAN JOURNAL OF OPHTHALMOLOGY®

Lessons Learned About Autonomous AI: Find
Efficacious, and Ethical Path Through the Dev
Process

Michael D. Abràmoff[a,b,*], Danny Tobey[c], Danton S. Char[d,e]



Abramoff, Tobey Char. Lessons Learned About Autonomous AI: Finding a Safe, Efficacious, and Ethical Path Through the Development Process. Am J Ophthalmol. 2020;214(1):134-142.
Char, Abràmoff , Feudtner. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020;20(11):7-17.

AI Ethical Requirements

- Respect autonomy by **maximally protecting data security and privacy**
- **Improve patient outcome 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

Harvard AI Symposium on AI and Bias
https://www.youtube.com/watch?v=nuC6A1ZWRvA

1. Abramoff MD, Tobey D, Char DS. Lessons Learned About Autonomous AI: Finding a Safe, Efficacious, and Ethical Path Through the Development Process. Am J Ophthalmol. 2020;214(1):134-42.
2. Char DS, Abràmoff MD, Feudtner C. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020(21):7-17.

AI Ethical Requirements

- Respect autonomy by maximally protecting data security and privacy

- Improve patient outcome shown by direct evidence or linked clinical literature

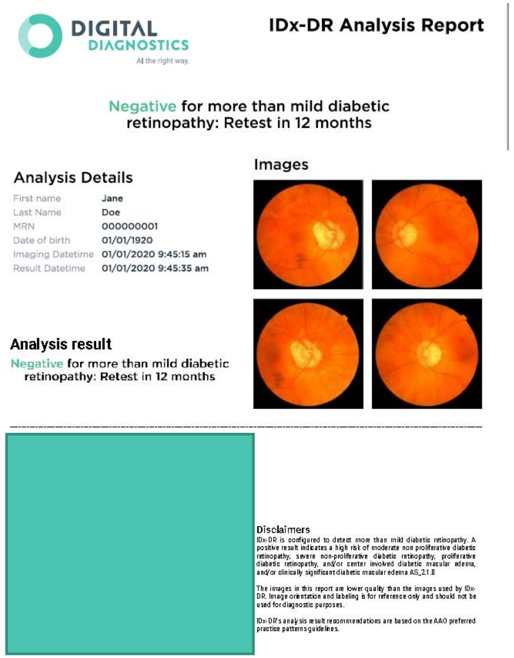
Improve patient outcome by linkage to AI Outputs

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 years, 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 years, if untreated



<u>In other words, if patient is left untreated, and has AI + output:</u>

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

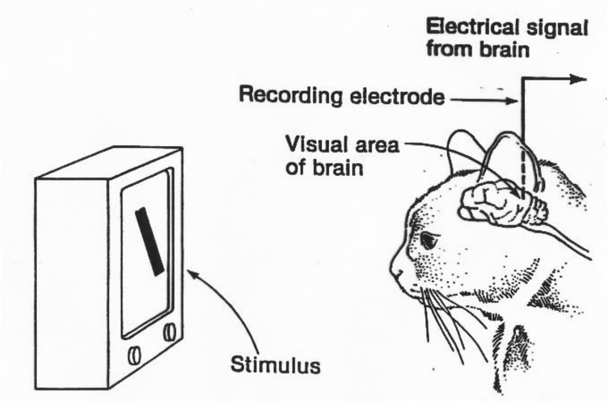
Not possible if AI validated against clinicians

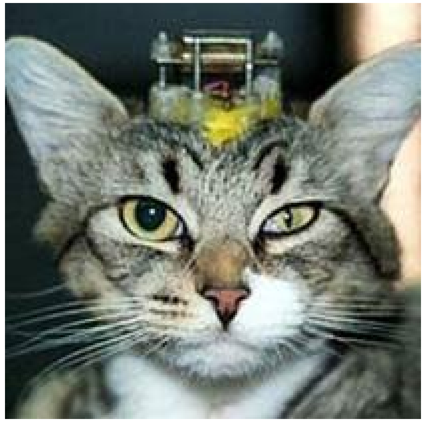
Abramoff, Blodi, Folk,, 2021 Macula Society. Autonomous AI for diabetic retinopathy and macular edema confers patient level outcome prognsis

AI Ethical Requirements

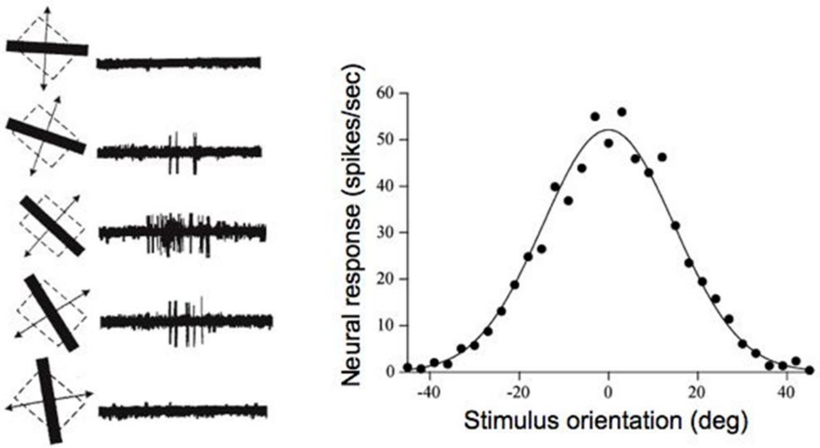
Design AI algorithms so they are maximally reducible to human clinician cognition

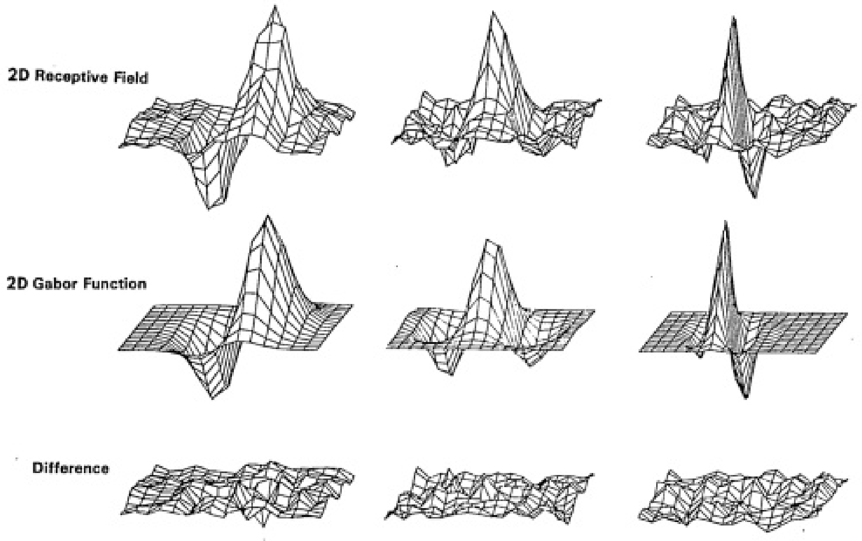
AI Design: how does the clinician brain solve this

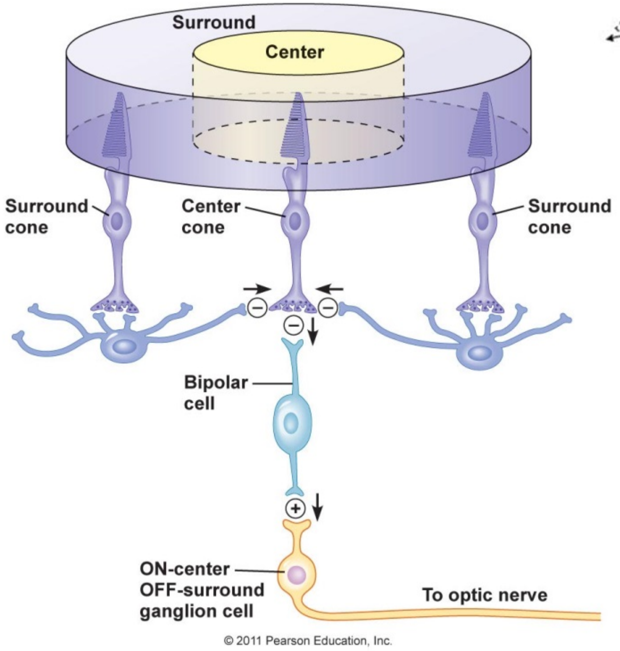




V1 physiology: orientation selectivity

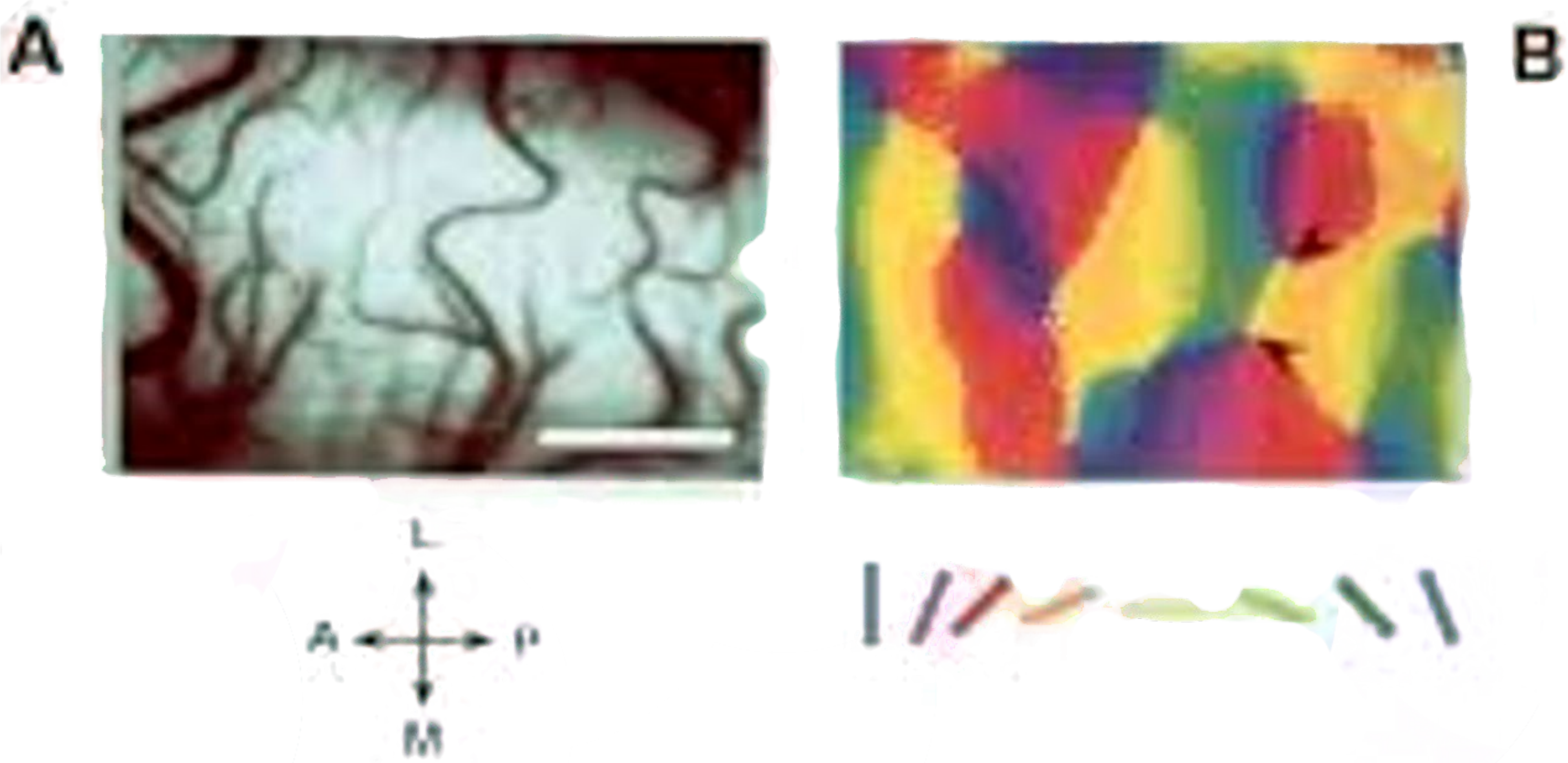






Hubel and Wiesel, 1959, 1962
Daugman, 1980, 1985

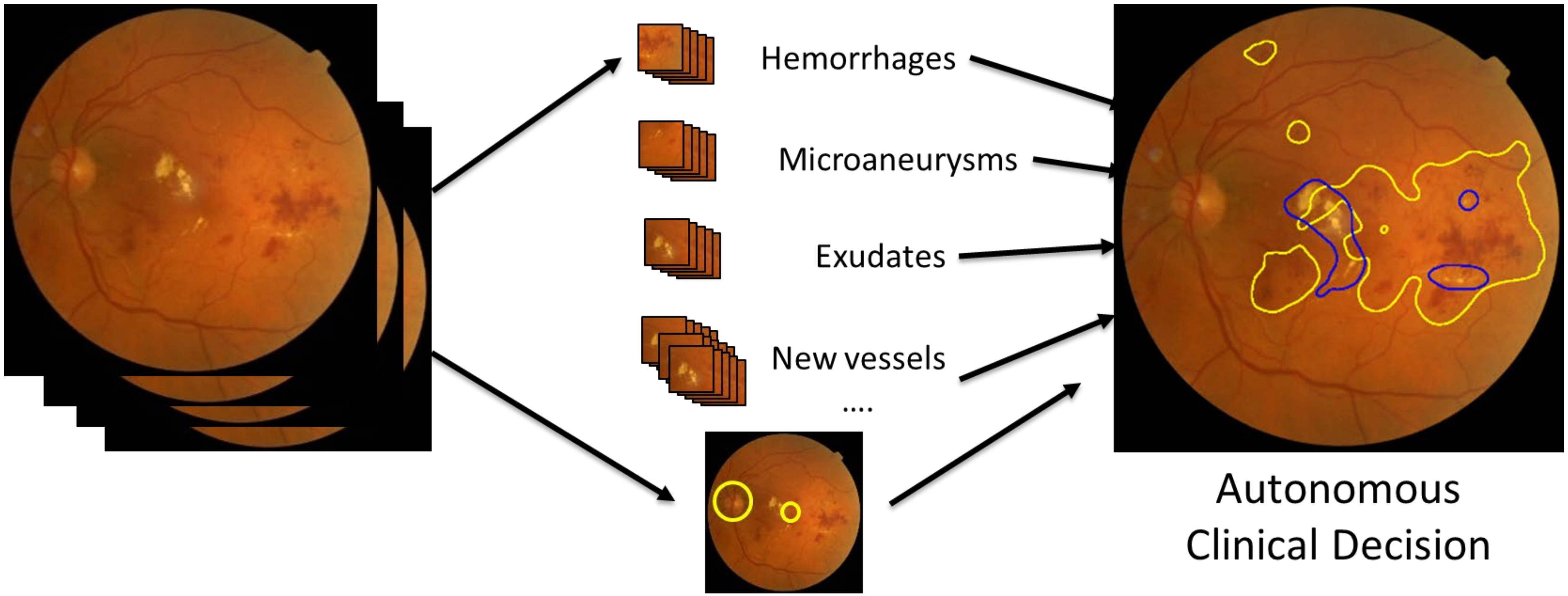
AI Design: Detectors are partially dependent in Cortex V1



Bonhoeffer, Grinvald. Nat. 1991

Mimic cortical processing of clinicians as much as possible

Partially dependent detectors



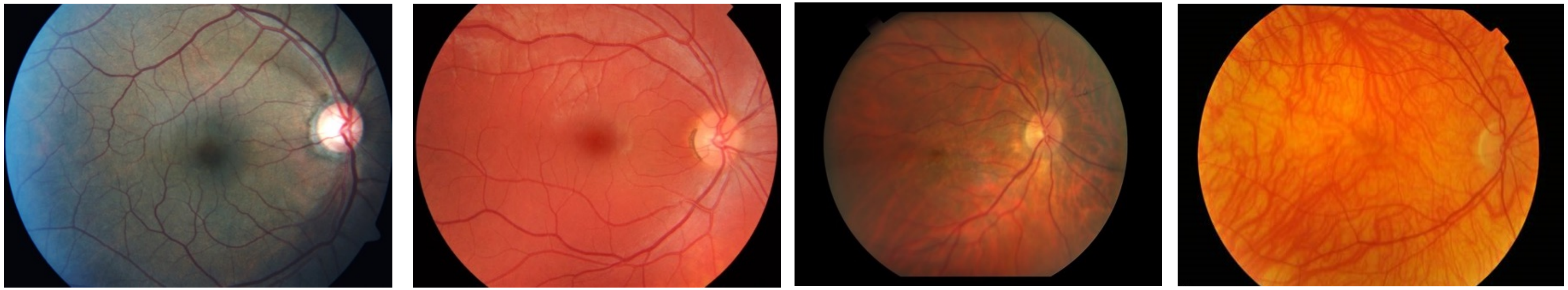
Robust against
catastrophic failure

Robust against
racial / ethnic / sex / age bias

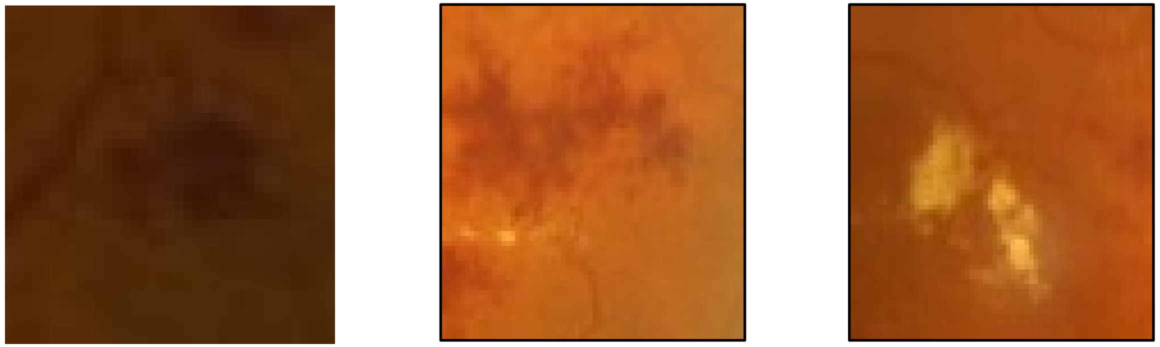
1.Abramoff et al, IOVS 2007
2.Lynch et al, ARVO 2018
3.Finlayson et al, Science, 2019
Nat Dig Med 2018
Shah et al, Proc ISBI 2018
Larrazabal et al,, PNAS 2020

AI Design aligned with human clinician cognition

Image based training of convolutional neural networks



Biomarker based multiple partially redundant detectors



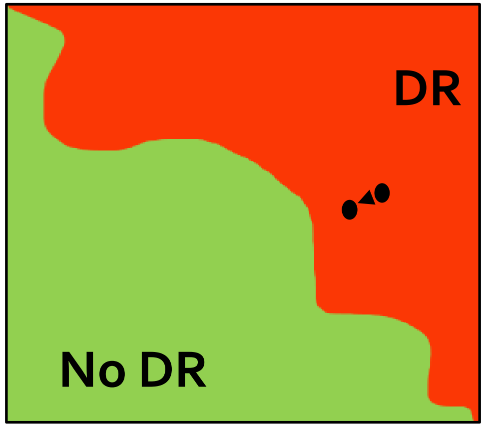
1. Abramoff et al, IOVS 2007, Abramoff et al, Nat Dig Med, 2018, Abramoff et al, IOVS 2016
2. Lynch et al, ARVO 2017, Shah et al, Proc ISBI 2018
3. Finlayson et al, Science, 2019
4. Larrazabal et al, Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis, PNAS 2020

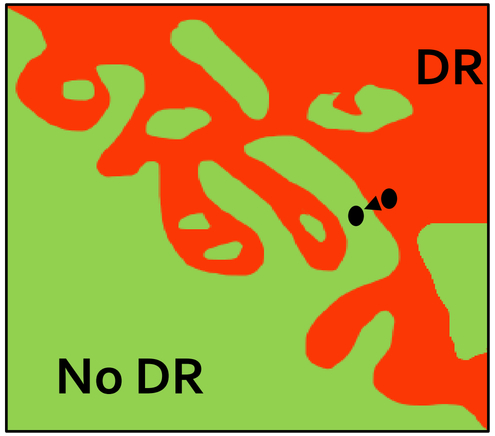
Black boxes and Catastrophic Failure

Real image

<1% changed

Correctly detect DR	
Biomarker-based AI: 99%	Biomarker-based AI: 99%
CNN (Black Box): 99%	CNN (Black Box): 3%





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

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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 1988 and May 1989 were asked to participate. Patients with diabetes identified from a laboratory list of elevated serum glucose values we…

RE… exam by the phy… and positive and … 9, 72, 0.67; photographs without pharmacological dilation 0.61, 0.85, 4.1, 0.46; dilated photographs 0.81, 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 seven 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 ophthalmoscopic 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 commitment and lack of readily available ophthalmological exams as a result of patient or institutional financial constraint (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

33% Sensitivity

The Sensitivity and Specificity of Single-field Nonmydriatic Monochromatic Digital Fundus Photography With Remote Image Interpretation for Diabetic Retinopathy Screening: A Comparison With Ophthalmoscopy and Standardized Mydriatic Color Photography

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• PURPOSE: To evaluate single-field digital monochromatic nonmydriatic fundus photography as an adjunct in the screening of diabetic retinopathy.
• DESIGN: Prospective, comparative, observational case ser…
• M… me… dif… nonmydriatic photography; dilated ophthalmoscopy by an ophthalmologist; and seven Early Treatment Diabetic

• RESULTS: There was highly significant agreement (κ = 0.97, P = .0001) between the degree of retinopathy detected by a single nonmydriatic monochromatic digital photograph and that seen in seven standard 35-mm color … mydriatic fields. The sensitivity of digital … compared with color photography was 78%, … ficity of 86%. Agreement was poor (κ = … .0001) between mydriatic ophthalmoscopy and the seven-field standard 35-mm color photographs. Sensitivity of ophthalmoscopy compared with color pho-

34% Sensitivity

1. Lin et al, 2002
2. Pugh et al, 1993
3. Sussmann et al, JAMA, 1982
4. Lawrence et al, Trans AMO 2004

Rigorous validation : Clinicians differ systematically

Wisconsin Reading Center
Prognostic standard 'truth'

Physicians in Amsterdam

Physicians at Iowa

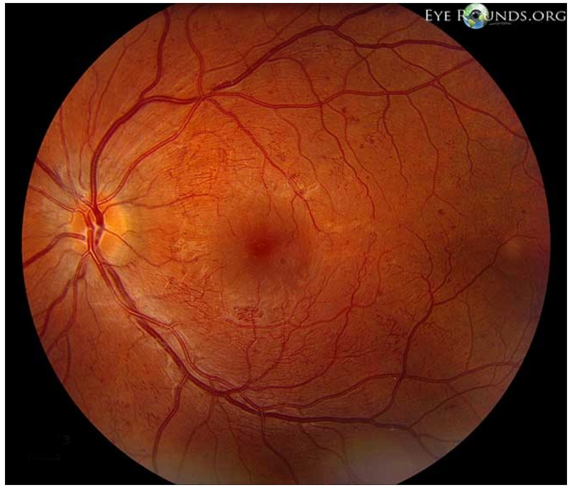
AI system

Physicians at Michigan

Abramoff et al, 2016
Abramoff et al, 2018

Highest Prognostic Standard

- 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
- ALL DR management and treatment based on this reference standard



<u>Surrogate outcome</u>:

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 ci-DME

- No benefit from treatment

1. ETDRS report number 9. Ophthalmology 98, 767-785 (1991).
2. ETDRS report number 10. Ophthalmology 98, 786-806 (1991).
3. ETDRS report number 12. Ophthalmology 98, 823-833 (1991).
4. DCCT Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 102, 647-661 (1995).
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).
6. Browning et al., Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. Ophthalmology 115, 1366-1371, 1371 e1361 (2008).
7. DRCR, Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. Arch Ophthalmol 127, 245-251 (2009).
8. Glassman et al., Comparison of optical coherence tomography in diabetic macular edema, with and without reading center manual grading from a clinical trials perspective. Invest Ophthalmol Vis Sci 50, 560-566 (2009).

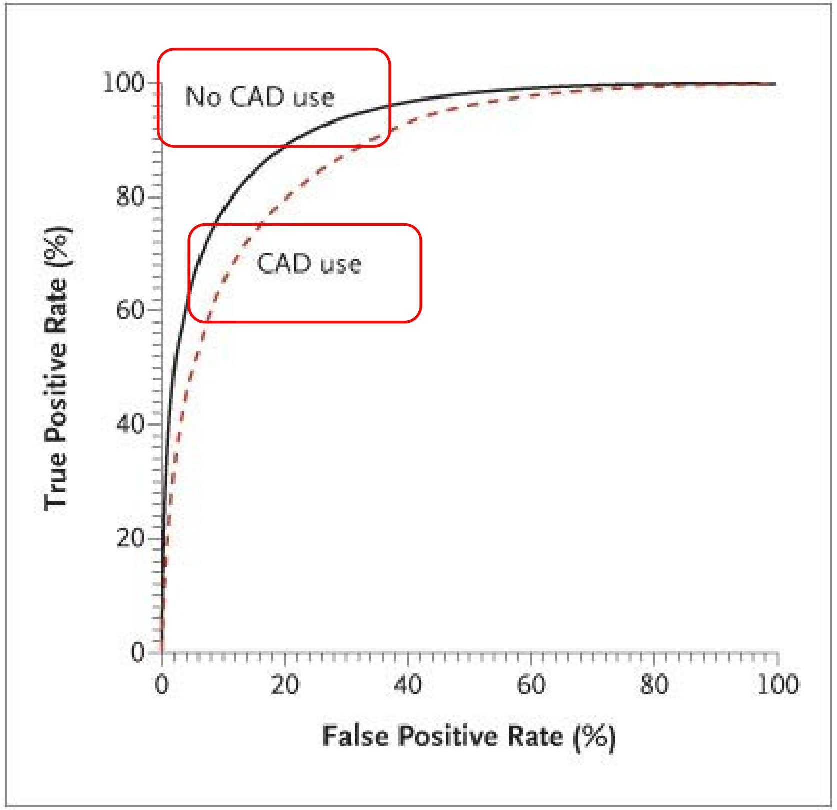
Validate in Workflow

Lessons from the Fenton study

Mammography

» FDA approved breast cancer assistive /
» 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

	FDA Superiority Endpoint	IDx-DR(n=819)	Remote Reading Network / Telemedicine	Board Certified Ophthalmologist in Clinic
Sensitivity	85%	87%[1] (81% - 91%)	72% (65%-79%)[6]	33%[2]-34[3]%
Specificity	82%	90%[1] (88% - 93%)	97% (95%-99%)[6]	99%[2]-100[3]%
Repeatability		99%	<80%[6]	60%[4]
Reproducibility		99%[5]		83%[4]
Equity: No significant effects for sex, race, ethnicity, HbA1C, lens status, or site			All other AI, remote readers, and clinician studies do not use surrogate outcome as the standard, and onlycompare to unvalidated clinicians (who may or may not correspond to outcome markers)	

Abràmoff MD, Lavin PT, Birch M, Shah N, Folk JC. Pivotal trial of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. Nature Digit Med 2018;1:39
Pugh JA, Jacobson JM, Van Heuven WA, et al. Screening for diabetic retinopathy. The wide-angle retinal camera. Diabetes Care. 1993;16(6):889-895.
Lin DY, Blumenkranz MS, Brothers RJ, Grosvenor DM. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpretation for diabetic retinopathy screening: a comparison with ophthalmoscopy and standardized mydriatic color photography. Am J Ophthalmol. 2002;134(2):204-213. Liu et al, 2018
Lynch et al, IOVS, 2018
Abramoff et al, Improved Automated Detection of Diabetic Retinopathy Through Integration of Deep Learning, IOVS, 2016. Compared to 3 retina specialists.
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

CONFIDENTIAL final draft 0.5
Under review, Ophthalmology

Foundational Considerations for Artificial Intelligence utilizing ophthalmic images

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1. https://www.cc -oi.org/