The Intersection of Health and Innovation

Michael D. Abràmoff, MD, PhD

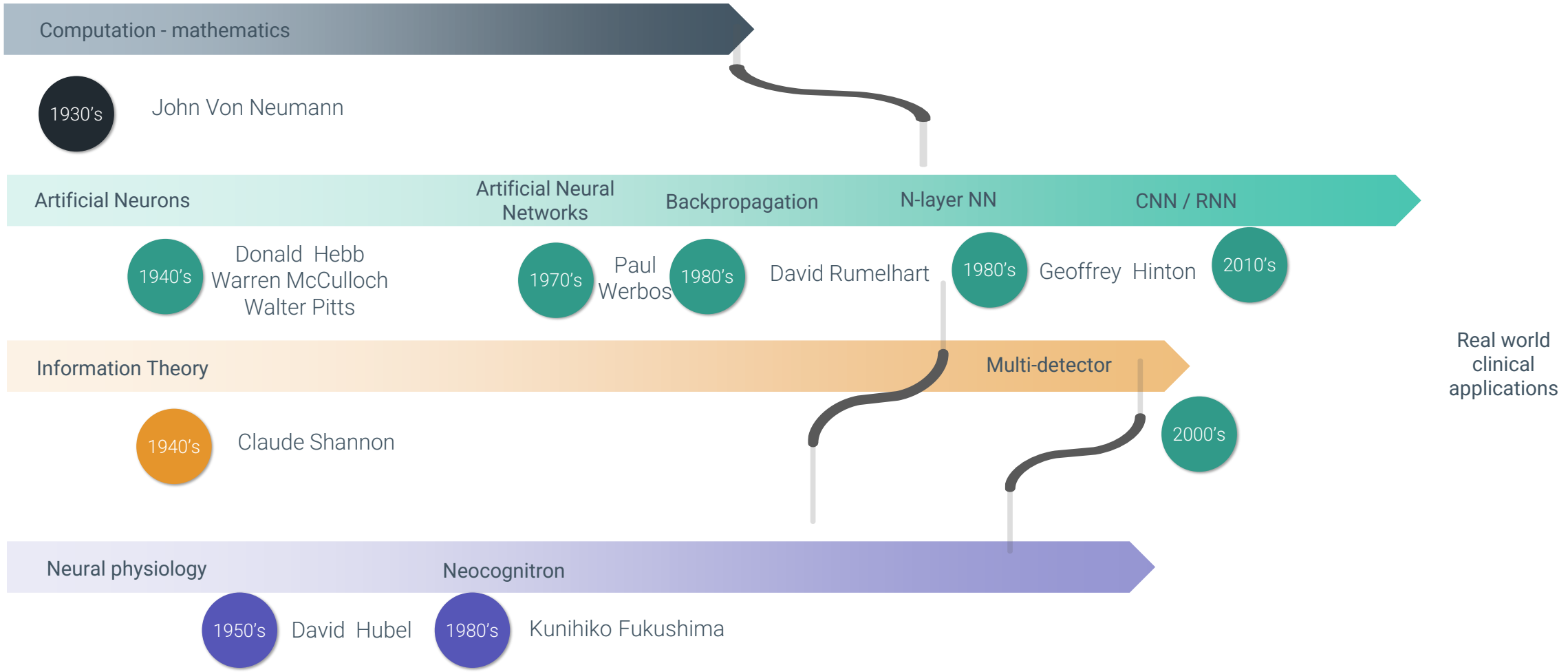
Gold Fellow ARVO, ***Fellow*** IEEE,
Retina Service
The Watzke Professor of Ophthalmology, Electrical & Computer, and Biomedical Engineering
University of Iowa

founder and executive chairman, Digital Diagnostics Inc, Coralville, IA
Founder & Chair, Healthcare AI Coalition, Washington DC
Member, Executive Committee, CCOI

Conflicts of Interest disclosure

- Digital Diagnostics, Inc, Coralville, Iowa: Founder, Investor, Director, Consultant, Patents and Patent applications University of Iowa: Patents and Patent applications
- Chair, Healthcare AI Coalition, Washington DC
- Member, Collaborative Community for Ophthalmic Imaging
- member, American Academy of Ophthalmology (AAO) AI Committee
- member, AI Workgroup Digital Medicine Payment Advisory Group (DMPAG) of the American Medical Association.

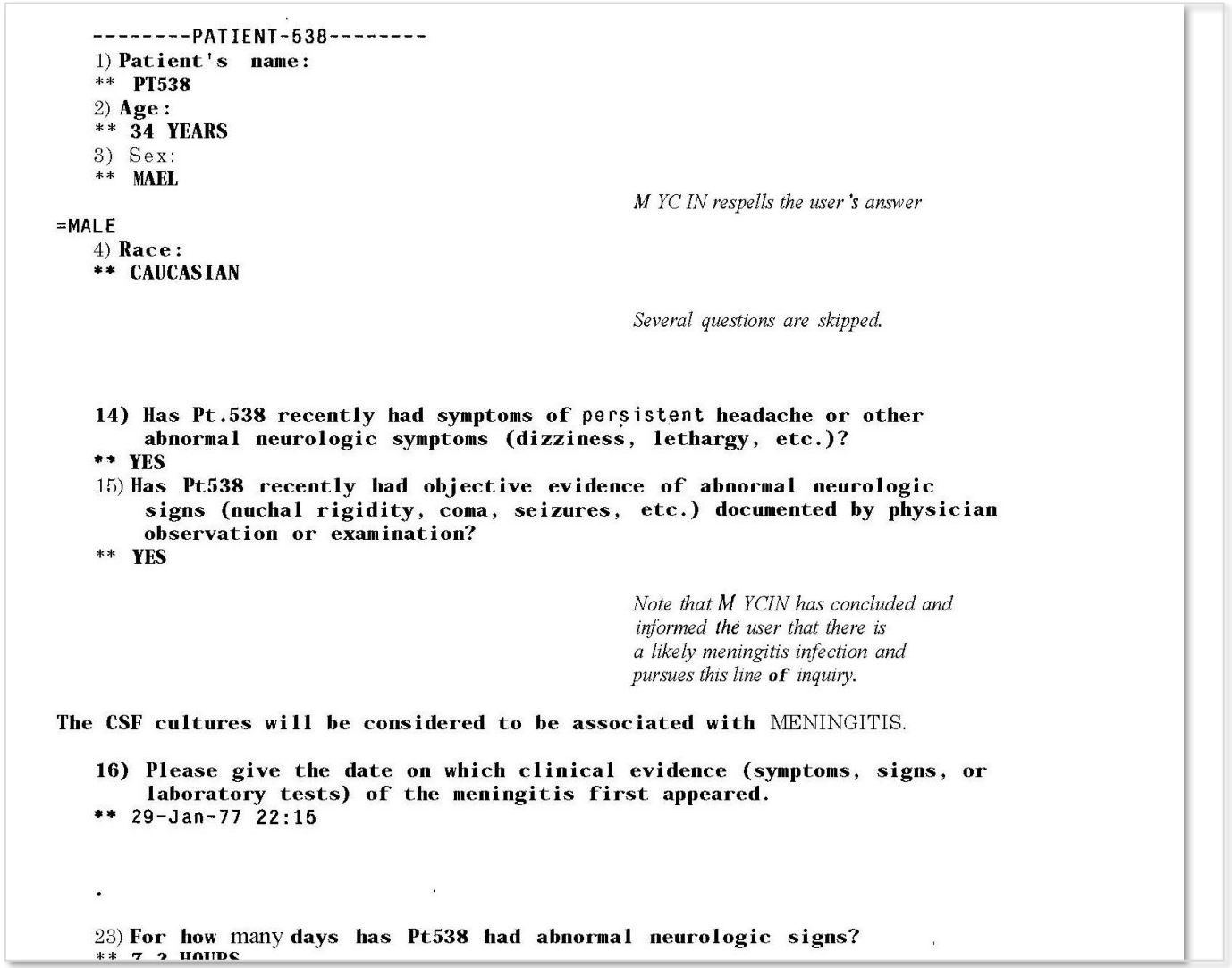
A Brief AI History



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. 2010's: 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?
** 7.2 HOURS

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.

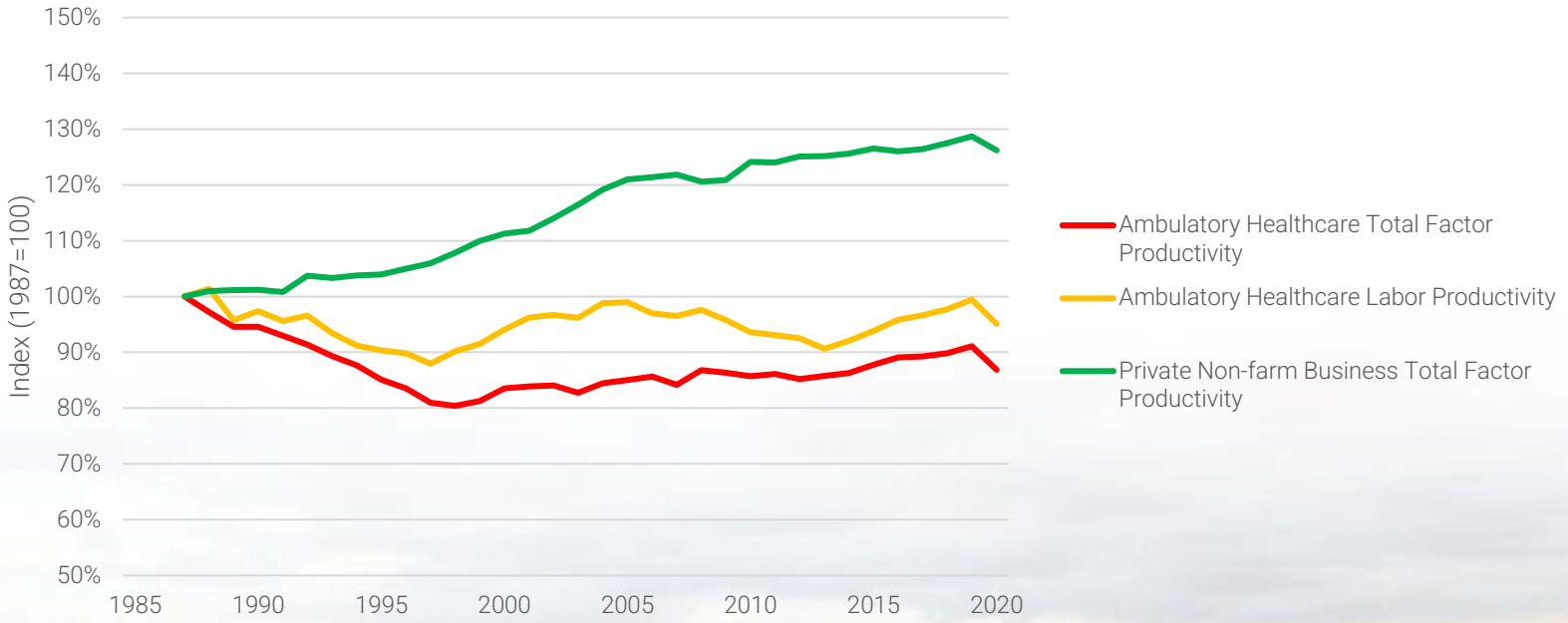
Key Constraints on AI in healthcare

- **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 reference standard = 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
- **Hiqh quality environment / high expertise operators are scarce**
  - Inputs require high quality images in specific settings and use cases
  - High expertise operators are scarce

Hypothesis: productivity is central problem

- **Ever increasing cost**
- **Lower access**
- **Health inequity**

- **Healthcare has the potential to be ubiquitous**



IT often lowers healthcare productivity

Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice

Travis K. Redd, BS,[a,b] Sarah Read-Brown, BA,[a] Dongseok Choi, PhD,[a,b,c] Thomas R. Yackel, MD,[d] Daniel C. Tu, MD PhD,[a,c] and Michael F. Chiang, MD[a,d]

PURPOSE To measure the effect of electronic health record (EHR) implementation on productivity and efficiency in the pediatric ophthalmology division at an academic medical center.

METHODS Four established providers were selected from the pediatric ophthalmology division at the Oregon Health & Science University Casey Eye Institute. Clinical volume was compared before and after EHR implementation for each provider. Time elapsed from chart open to completion (OTC time) and the proportion of charts completed during business hours were monitored for 3 years following implementation.

RESULTS Overall there was an 11% decrease in clinical volume following EHR implementation, which was not statistically significant ($P = 0.18$). The mean OTC time ranged from 5.5 to 28.3 hours among providers in this study, and trends over time were variable among the four providers. Forty-four percent of all charts were closed outside normal business hours (30% on weekdays, 14% on weekends).

CONCLUSIONS EHR implementation was associated with a negative impact on productivity and efficiency in our pediatric ophthalmology division. (J AAPOS 2014;18:584-589)

Electronic health records (EHRs) are becoming an ... physicians in the United States, less than 50% have adop-

Lam *et al. BMC Health Services Research* (2016) 16:7
DOI 10.1186/s12913-015-1255-8

BMC Health Services Research

RESEARCH ARTICLE Open Access

The effect of electronic health records adoption on patient visit volume at an academic ophthalmology department

Jocelyn G. Lam, Bryan S. Lee and Philip P. Chen*

Abstract

Background: Electronic health records (EHRs) have become a mandated part of delivering health care in the United States. The purpose of this study is to report patient volume before and after the transition to EHR in an academic outpatient ophthalmology practice.

Methods: Review of patient visits per half-day and number of support staff for established faculty ophthalmologists between July and October for five consecutive years beginning the year before EHR implementation.

Results: Eight physicians met inclusion criteria for the study. The number of patient visits was lower in each year after EHR adoption compared to baseline $p \leq 0.027$). Patient volume per provider was reduced an average of 16.9 % over the 4 years (range 15.3–18.5 %), and during the final year studied, no provider had returned to the pre-EHR number of patients per clinic session. Support staffing was unchanged ($p > 0.2$).

Conclusions: Adoption of EHR was associated with a significantly reduced number of patient visits per clinic session in an academic setting in which support staffing remained stable. Maintaining clinic volume and access in similar settings may require use of additional staffing.

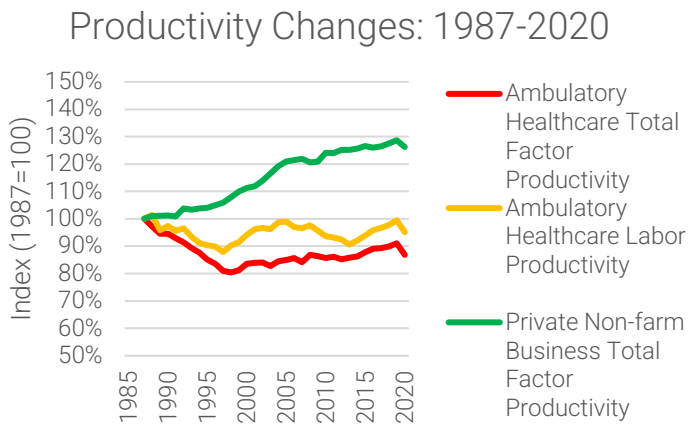
Keywords: Ophthalmology, Electronic health record, Electronic medical record, Health information technology, Medical informatics, Health care delivery, Health law

7/17/2018 CMS Administrator Varma:
We believe that you should be able to focus on delivering care to patients, not sitting in front of at a computer screen. […] Electronic Health Records were supposed to make it easier for you to record notes, and the government spent $30 billion to encourage their uptake. But the inability to exchange records between systems – and the increasing requirements for information that must be documented – has turned this tool into a serious distraction from patient care.

Healthcare Problems Solvable by Autonomous AI

Health inequity - Access

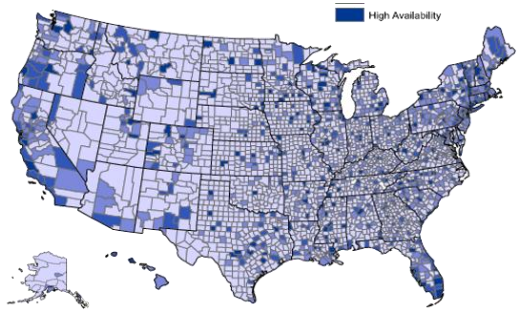
Healthcare cost - Productivity



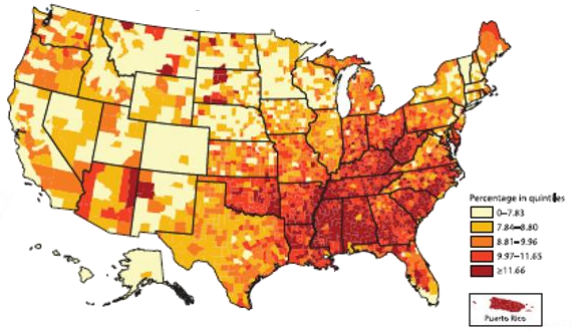
Other industries decades of steady improvement

Outpatient continues to decline

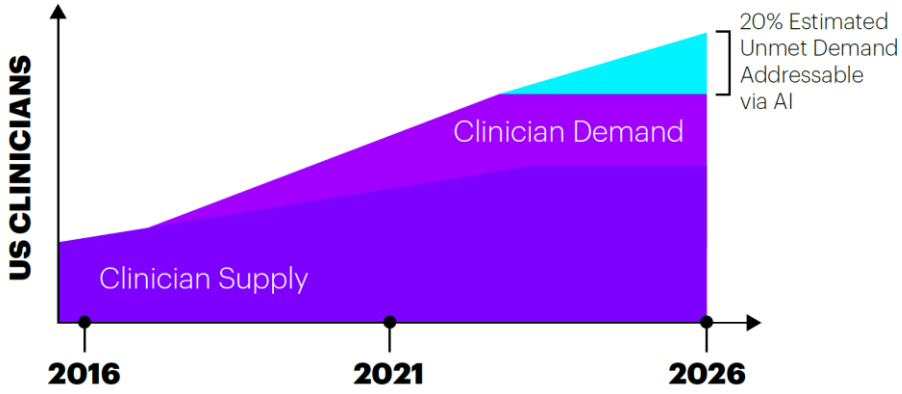
Eye care availability



Eye care need



Healthcare demand - workforce gap



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

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
Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice, JAAPOS 2014
Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care. 2003;26(1):226-229.
Centers for Disease Control and Prevention. Diabetes Report Card 2012. Atlanta, GA: U.S. Department of Health and Human Services;2012
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 Solvable by Autonomous AI

Health inequity - Access

npj | digital medicine

www.nature.com/npjdigitalmed

PERSPECTIVE OPEN

Check for updates

Considerations for addressing bias in artificial intelligence for health equity

Michael D. Abràmoff[1], Michelle E. Tarver[2], Nilsa Loyo-Berrios[2], Sylvia Trujillo[3], Danton Char[4,5], Ziad Obermeyer[6], Malvina B. Eydelman[2], Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group of the Collaborative Community for Ophthalmic Imaging Foundation, Washington, D.C.* and William H. Maisel[2]

Health equity is a primary goal of healthcare stakeholders: patients and their advocacy groups, clinicians, other providers and their professional societies, bioethicists, payors and value based care organizations, regulatory agencies, legislators, and creators of artificial intelligence/machine learning (AI/ML)-enabled medical devices. Lack of equitable access to diagnosis and treatment may be improved through new digital health technologies, especially AI/ML, but these may also exacerbate disparities, depending on how bias is addressed. We propose an expanded Total Product Lifecycle (TPLC) framework for healthcare AI/ML, describing the sources and impacts of undesirable bias in AI/ML systems in each phase, how these can be analyzed using appropriate metrics, and how they can be potentially mitigated. The goal of these "Considerations" is to educate stakeholders on how potential AI/ML bias may impact healthcare outcomes and how to identify and mitigate inequities; to initiate a discussion between stakeholders on these issues, in order to ensure health equity along the expanded AI/ML TPLC framework, and ultimately, better health outcomes for all.

npj Digital Medicine (2023)6:170 ; https://doi.org/10.1038/s41746-023-00913-9

US Bureau Labor Statistics, 2010
Lam et al, The effect of electronic health records adoption on patient visit volume at an academic ophthalmology department B
Redd et al, Electronic health record impact on productivity and efficiency in an academic pediatric ophthalmology practice, JAA
Fong DS, Aiello L, Gardner TW, et al. Diabetic retinopathy. Diabetes Care. 2003;26(1):226-229.
Centers for Disease Control and Prevention. Diabetes Report Card 2012. Atlanta, GA: U.S. Department of Health and Human Ser
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/diabetesreportcard2012-508.pdf

Healthcare cost - Productivity

npj | digital medicine

Explore content About the journal Publish with us

nature > npj digital medicine > articles > article

Article | Open Access | Published: 04 October 2023

Autonomous artificial intelligence increases real-world specialist clinic productivity in a cluster-randomized trial

Michael D. Abramoff, Noelle Whitestone, Jennifer L. Patnaik, Emily Rich, Munir Ahmed, Lutful Husain, Mohammad Yeadul Hassan, Md. Sajidul Huq Tanjil, Dena Weitzman, Tinglong Dai, Brandie D. Wagner, David H. Cherwek, Nathan Congdon & Khairul Islam

npj Digital Medicine **6**, Article number: 184 (2023) | Cite this article

Metrics

Abstract

Autonomous artificial intelligence (AI) promises to increase healthcare productivity, but real-world evidence is lacking. We developed a clinic productivity model to generate testable hypotheses and study design for a preregistered cluster-randomized clinical trial, in which we tested the hypothesis that a previously validated US FDA-authorized AI for diabetic eye exams increases clinic productivity (number of completed care encounters per hour per specialist physician) among patients with diabetes. Here we report that 105 clinic days are cluster

gap

Autonomous vs Assistive AI

Assistive

- Medical decision by clinician
- Liability for clinician
- Patient already in care workflow
- Real world value:

~ outcome improvement for existing patients

Autonomous

- Medical decision by “computer”
- Liability for AI creator
- Point of Care and Immediate
- Can be ‘added’ wherever patient is
- Real world value:

~ outcome improvement for patients & populations – i.e. address health inequity

Abramoff, Cunningham, Patel, Eydelman, et al. "Foundational Considerations for Artificial Intelligence ", Ophthalmology (2021). https://www.aaojournal.org/article/S0161-6420(21)00643-6/fulltext.

LLMs: everybody can build an autonomous AI now

write the exact python script to download a diabetic retinopathy detection training set, get it to github repository, and then write the commands I need to use to train and test it it with an input image set

There are several ways to download a diabetic retinopathy detection training set in Python. One way is to use TensorFlow Datasets1. You can install TensorFlow Datasets using pip by running pip install tensorflow-datasets. Once installed, you can use the following code snippet to download the dataset:

```
import tensorflow_datasets as tfds
dataset_name = 'diabetic_retinopathy_detection'
ds_train = tfds.load(name=dataset_name, split='train[:80%]', shuffle_files=True)
ds_test = tfds.load(name=dataset_name, split='train[80%:]', shuffle_files=True)
```

This code will download the dataset and split it into training and testing sets.

To push this dataset to a GitHub repository, you can use Git commands. First, you need to create a new repository on GitHub and then clone it locally using the following command:

```
git clone https://github.com/USERNAME/REPOSITORY.git
```

Then you can add your files to the repository using the following commands:

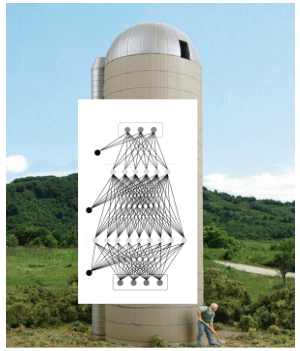
```
cd REPOSITORY
git add .
git commit -m "Initial commit"
git push origin main
```

To train and test your model with an input image set, you can use TensorFlow2. Here's an example of how you can train a model using TensorFlow:

```
import tensorflow as tf

model = tf.keras.Sequential([
    tf.keras.layers.Conv2D(32, (3, 3), activation='relu', input_shape=(28, 28, 1)),
    tf.keras.layers.MaxPooling2D((2, 2)),
    tf.keras.layers.Flatten(),
    tf.keras.layers.Dense(10, activation='softmax')
])

model.compile(optimizer='adam',
              loss='sparse_categorical_crossentropy',
              metrics=['accuracy'])

model.fit(ds_train,
          epochs=10,
          validation_data=ds_test)
```

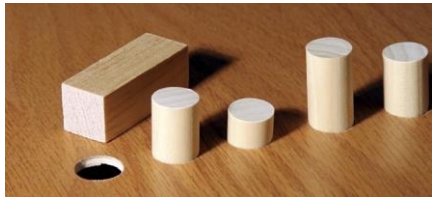
This code will train a simple convolutional neural network on the diabetic retinopathy detection dataset.

Two approaches to develop healthcare AI



- Start with AI algorithm / tech solution
- Look for a clinical problem

- Start with optimal outcome for patient / population
- Which role if any can AI play
- Build that



Diabetes is a Giant Source of Health Inequity

34.2 million people have diabetes [3,4]

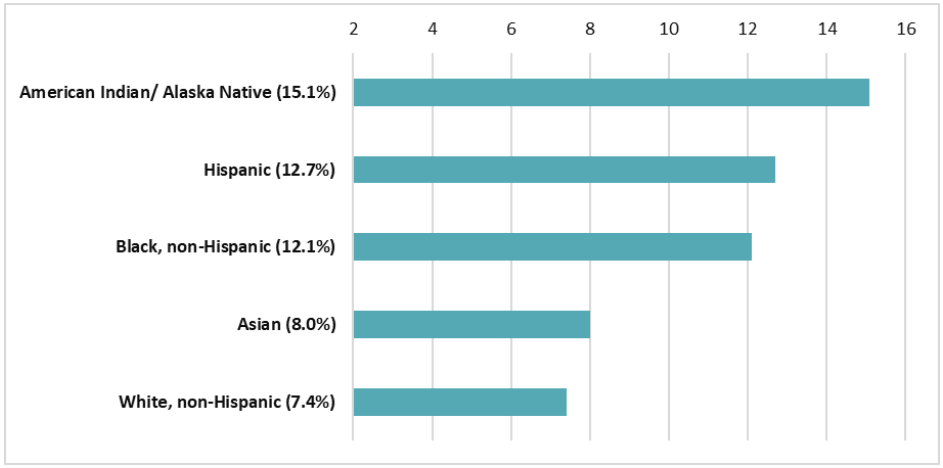
60k Americans go blind from diabetes every year [7,8]

44% Medicaid Managed Care Members do not get annual eye exam [6]

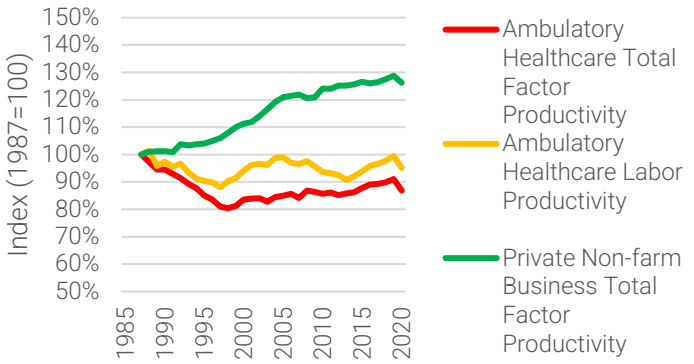
Visual loss almost entirely preventable if caught before symptoms

85% Adults living with diabetes do not get annual eye exam [6]

Health Disparities in Diabetes[5]



Productivity Changes: 1987-2020



Cumulation of inequities

- Higher risk for getting diabetes
- More severe diabetic retinopathy
- Higher risk of diabetic retinopathy
- Lower access issues to care

1 Vision Health Initiative. https://www.cdc.gov/visionhealth/basics/ced/index.html Accessed June 18, 2020
2 National Eye Institute. https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/diabetic-retinopathy-data-and-statistics Accessed June 18, 2020
3 CDC Infographics. A Snapshot: Diabetes in the United States. https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html Accessed June 18, 2020
4 County level distribution of diagnosed diabetes among US adults aged 20 or older, 2013. https://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2017-508.pdf. Accessed June 18, 2020.
5 U.S. Centers for Disease Control, "Addressing Health Disparities in Diabetes," *2017 Diabetes Score Card* (2017) available at https://www.cdc.gov/diabetes/disparities.html
6 Benoit SR, Swenor B, Geiss LS, Gregg EW, Saaddine JB. Eye Care Utilization Among Insured People With Diabetes in the U.S., 2010-2014. Diabetes Care. 2019;42(3):427-433.
7. Varma R, Vajaranant TS, Burkemper B, Wu S, Torres M, Hsu C, Choudhury F, McKean-Cowdin R. Visual Impairment and Blindness in Adults in the United States: Demographic and Geographic Variations From 2015 to 2050. JAMA Ophthalmol 2016;134:802-809
8. Bourne RRA, Jonas JB, Bron AM, Cicinelli... Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe in 2015: magnitude, temporal trends and projections. The British journal of ophthalmology 2018;102:575-585

Autonomous AI for the Diabetic Eye Exam

FDA De Novo Authorized, which like FDA Premarket Approval (PMA), requires a pre-registered clinical trial at arms length.

Fully autonomous AI

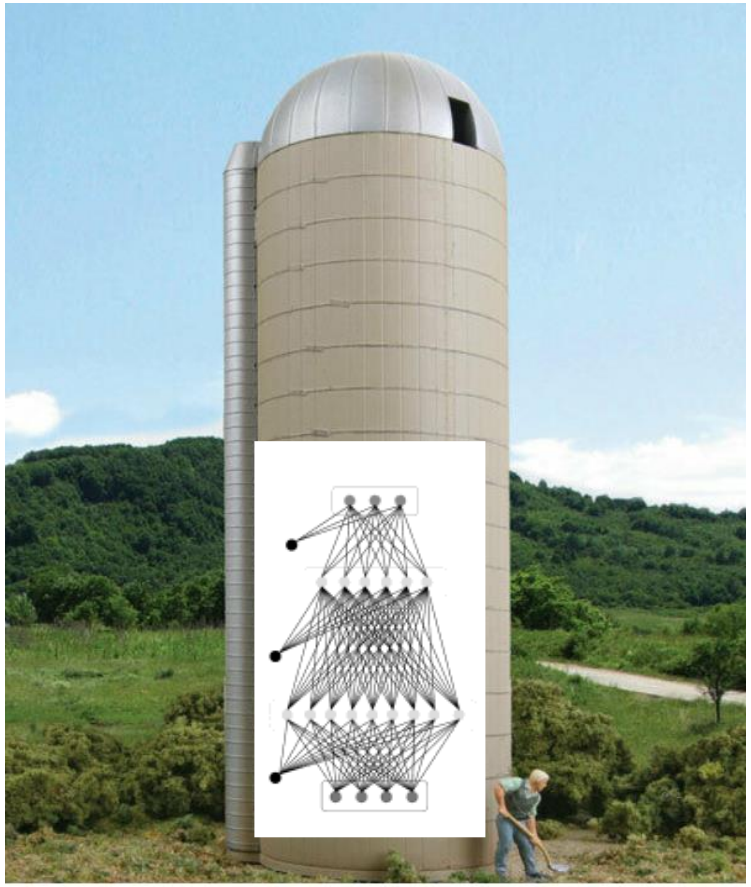
- ✓ Diagnoses diabetic retinopathy and all forms of diabetic macular edema
- ✓ Proven to have no racial/ ethnic bias
- ✓ More accurate than retina specialists
- ✓ No specialist overread or reading network required
- ✓ Medical liability with the creator

Designed & validated in primary care

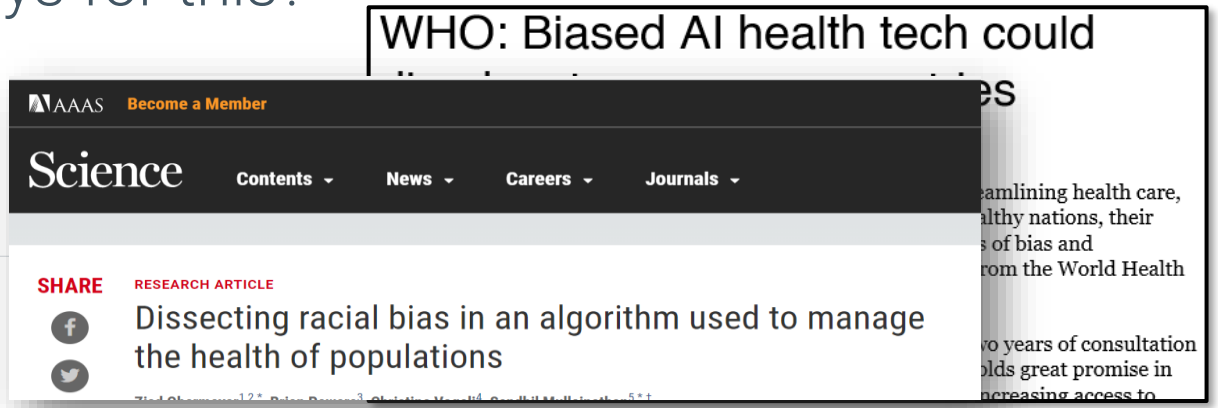
- ✓ Assistive AI guides operator with image quality
- ✓ Robotic retinal camera
- ✓ Diagnostics results provided real time
- ✓ 88% diagnosability without dilation[1]
- ✓ Maintains integrity of patient centered medical home (PCMH)

Abramoff et al. Pivotal trail of an autonomous AI-based diagnostic system for detection of diabetic retinopathy in primary care offices. Npj Digital Medicine. (2018)1:39; doi:10.1038/s41746-018-0040-6.

Proactively Address Concerns About Healthcare AI



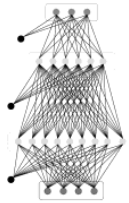
- Will it benefit me as a patient?
- Will it exacerbate health disparities?
- What happens to my data?
- Is there racial, ethnic bias?
- Who is liable for errors?
- Who pays for this?



DIGITAL DIAGNOSTICS

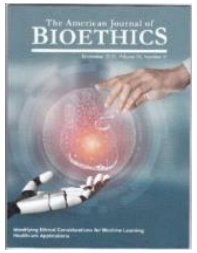
Creating the Guardrails for Autonomous AI in Healthcare

'Diagnostic AI Algorithm'



300+ papers (2008)

Foundation in Ethics



Ethical Foundations (2020)

Regulatory framework

Clinical trial design / Regulatory Clearance

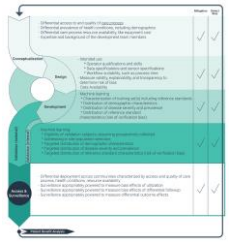
First FDA de novo clearance (2018)

Second FDA clearance with 510k (2020)

Solving liability

AMA AI Policy 2019

(Racial) bias mitigation



Concept to validation

Standards of Care

American Diabetes Association.

Standards of Medical Care in Diabetes (2019)

Quality measures

NCQA

HEDIS-MIPS care gap closure with autonomous AI

Reimbursement

AMA CMS

AMERICAN ACADEMY OF OPHTHALMOLOGY

First ever CPT Code 92229 (2019)

Nationwide Medicare Payment

Blended rate ~$79

RCT evidence

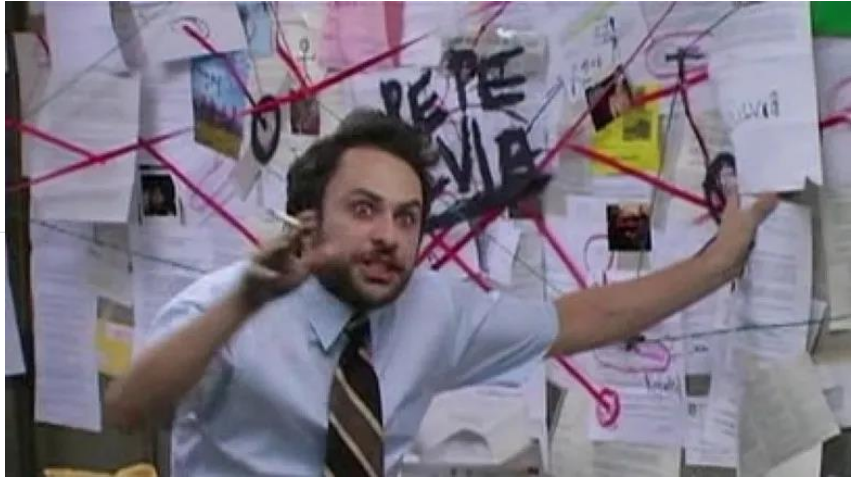
Improvement and elimination of disparities

Increase in physician productivity

Scalable prevention of blindness and visual loss

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
https://www.aaojournal.org/article/S0161-6420(21)00643-6/fulltext

Healthcare AI Stakeholders



- **Patients**
  - **& their organizations**: American Diabetes Association
- **Populations**
  - **& their organizations: civil rights organizations (NAACP, CBC, RCAC, NRHA)**
- **Physicians and other providers**
  - **Professional organizations**: AAO, AMA, NHMA, NMA
- **AI-creators**: researchers and manufacturers
- **Bio-ethicists**
- **Regulators**: FDA, FTC
- **Value based care authorities and organizations**: NCQA, PCORI, USPSTF
- **Payors:** CMS, State Medicaid, Commercial payors
- **Investors:** VC and Growth Equity
- **Legislators and executive branches of Federal and State governments**
  - 21st Century Cures Act and related amendments to the Social Security Act,

AMERICAN ACADEMY OF OPHTHALMOLOGY®

AMA

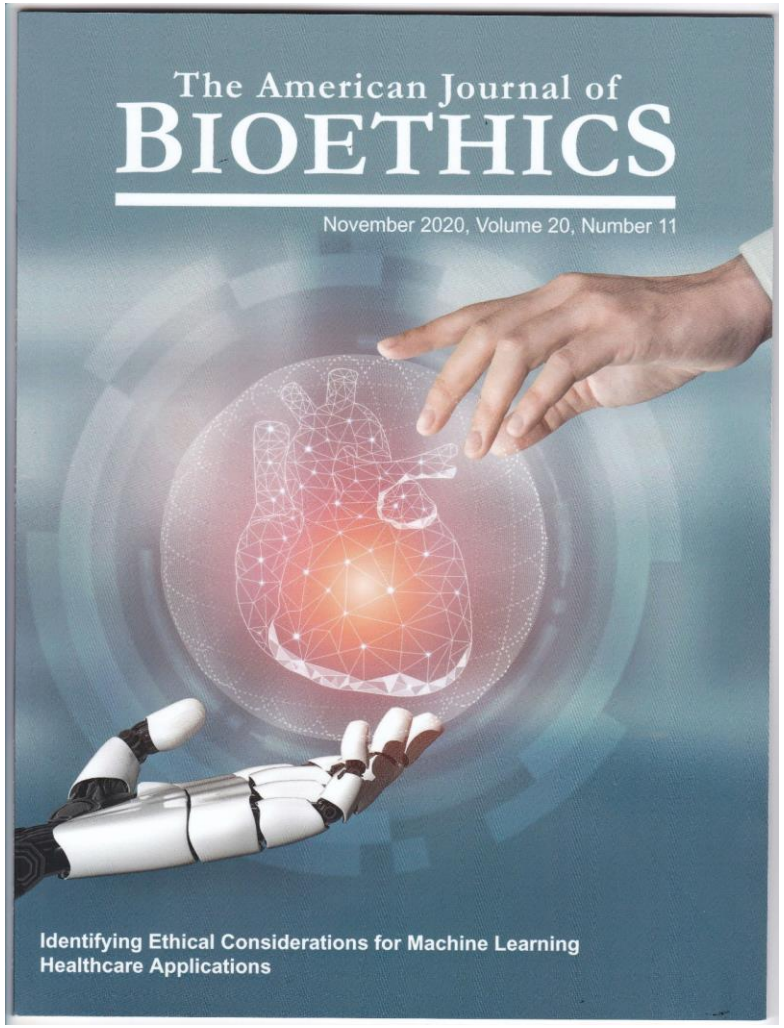
NHMA
National Hispanic Medical Association

NMA National Medical Association
Since 1895

Michael D. Abramoff[1,], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein, Anitra S. Graves[6] Michael X. Repka[7] Ezequiel "Zeke" Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med in press.

Ethical Framework for AI

» Bioethical principles
  - Non-maleficence
  - Autonomy
  - Justice
  - Responsibility



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.
Char DS, Abràmoff MD, Feudtner C. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020;20(11):7-17.

Ethics and AI Creators

- Model A: “ethical experts” dictate what and what not to do from the outside looking in
- Model B: **metrics for ethics** integral to engineering & operations

Google fires second AI ethics researcher following internal investigation

/ Margaret Mitchell and Timnit

Illustrati

Bloomberg the Company & Its Products | Bloomberg Terminal Demo Request | Bloomberg Anywhere Remote Login | Bloomberg Customer Support

Bloomberg

US Edition | Sign I

Live Now | Markets | Economics | Industries | **Technology** | Politics | Wealth | Pursuits | Opinion | Businessweek | Equality | Green | CityLa

Subscriber Only

Technology

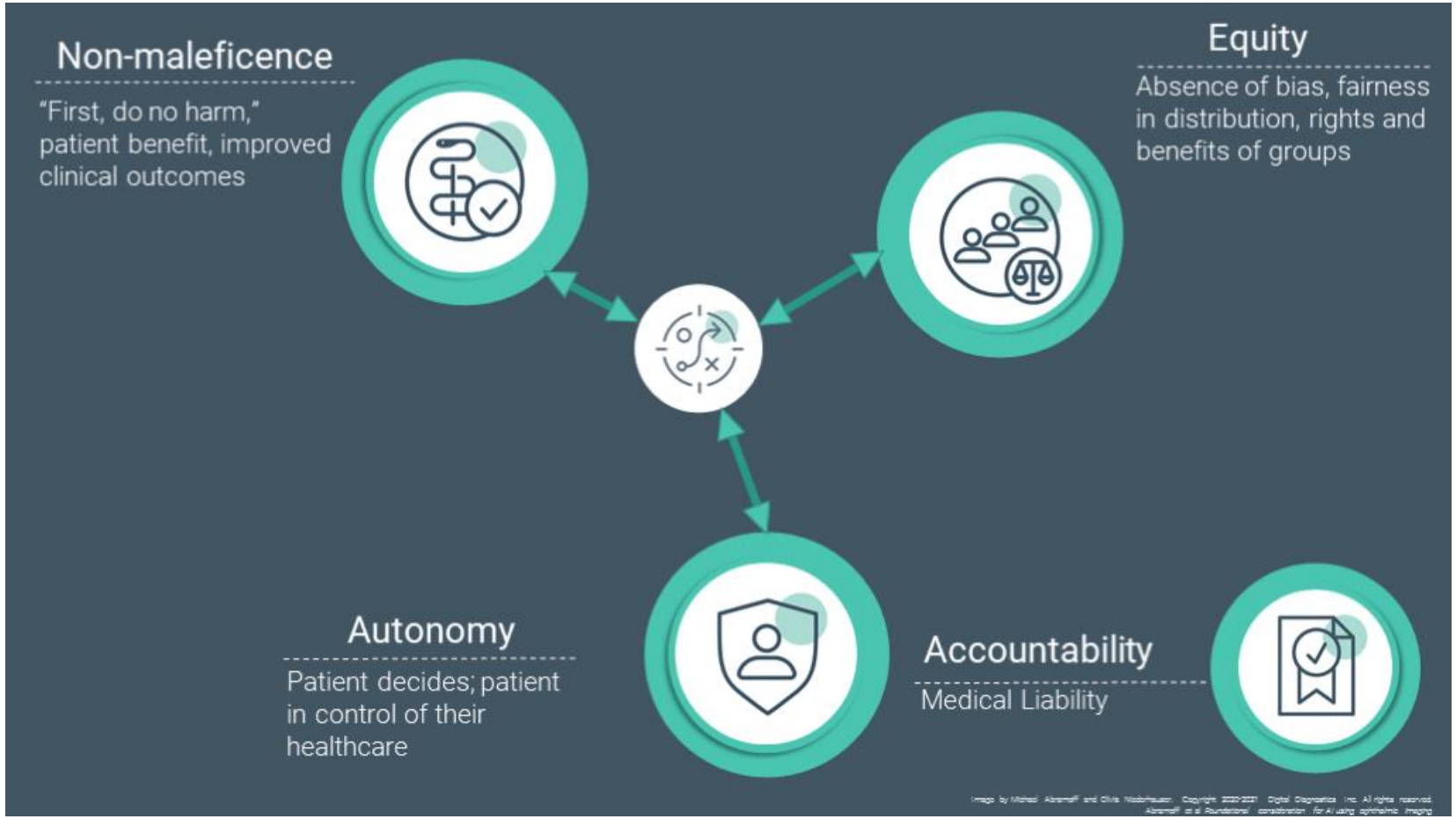
Two of Google's Ethical AI Staffers Leave to Join Ousted Colleague's Institute

- Research scientist and software engineer resign on Wednesday

Image Credits: Jean-Luc Ichard / Getty Images

Metrics for Ethics Concept

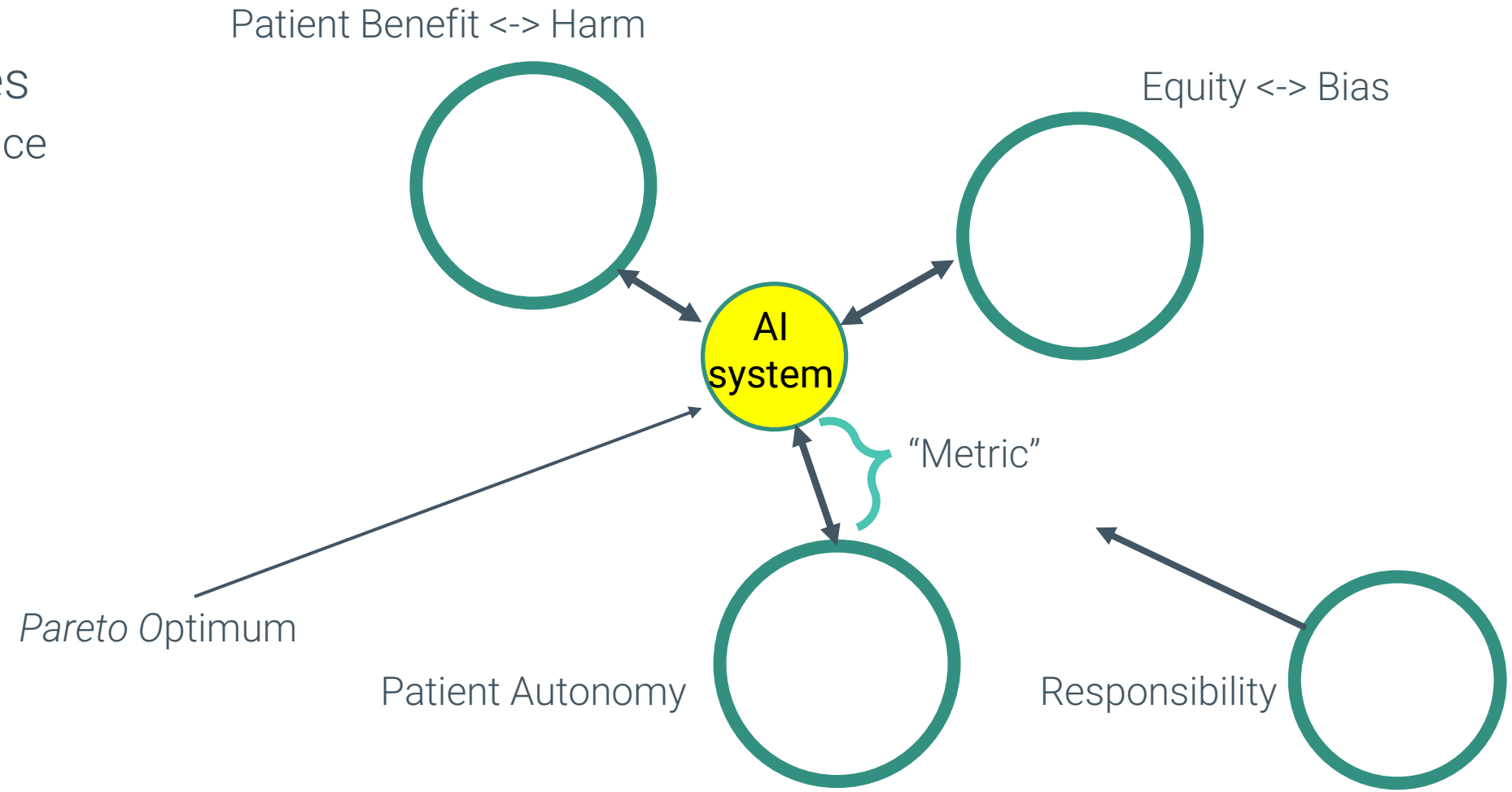
- Bioethical principles
  - Non-maleficence
  - Autonomy
  - Justice / Equity
  - Responsibility
- None can be met 100%



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.
Char DS, Abràmoff MD, Feudtner C. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020;20(11):7-17.

Metrics for Ethics

» Ethical principles
- Non-maleficence
- Autonomy
- Equity
- Responsibility



» 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.
» Char DS, Abràmoff MD, Feudtner C. Identifying Ethical Considerations for Machine Learning Healthcare Applications. The American Journal of Bioethics. 2020;20(11):7-17.

Ethical Foundation: AI safety, mitigating AI Bias and AI Reimbursement

Ophthalmology

AMERICAN ACADEMY OF OPHTHALMOLOGY

FULL LENGTH ARTICLE | ARTICLES IN PRESS

Foundational Considerations for Artificial Intelligence Utilizing Ophthalmic Images

Michael D. Abramoff • Brad Cunningham • Bakul Patel • ... Michael F. Chiang • Danton Char •
on behalf of the Collaborative Community on Ophthalmic Imaging Executive Committee and Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group • •
Show all authors • Show footnotes

Published: August 31, 2021 • DOI: https://doi.org/10.1016/j.ophtha.2021.08.023

IMPORTANCE

The development of Artificial Intelligence (AI) and other machine diagnostic systems, also known as Software as a Medical Device (SaMD), and its recent introduction into clinical practice, requires a deeply-rooted foundation in bioethics, for consideration by regulatory agencies and other stakeholders around the globe.

OBJECTIVES

Initiate a dialogue on the issues to consider when developing a bioethically sound foundation for AI in medicine, based on images of eye structures, for discussion with all stakeholders.

npj | digital medicine

www.nature.com/npjdigitalmed

COMMENT OPEN

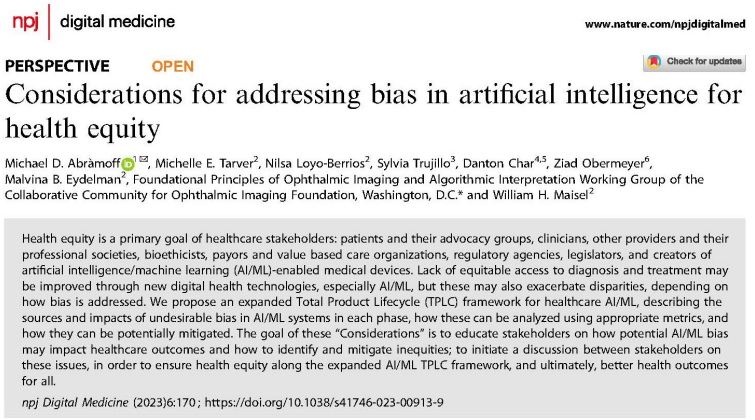
Check for updates

A reimbursement framework for Artificial Intelligence in Healthcare

Michael D. Abramoff[1,2,3], Cybil Roehrenbeck [2,4], Sylvia Trujillo[5], Juli Goldstein[3], Anitra S. Graves[6], Michael X. Repka[7], Ezequiel "Zeke" Silva III [8,9]

Abstract

Responsible adoption of healthcare artificial intelligence (AI) requires that AI systems which benefit patients and populations, including autonomous AI systems, are incentivized financially at a consistent and sustainable level. We present a framework for establishing reimbursement for such healthcare AI, by analytically determining value and cost of each unique AI service. It aligns with existing ethical frameworks for AI, focuses on outcomes and reducing cost per patient, while leading to predictable sustainable financial incentives for AI creators. Its processes involve affected stakeholders, including patients, providers, legislators, payors, and AI creators, in order to find an optimum balance among ethics, workflow, cost, and value as identified by each of these stakeholders. We use an example for a specific autonomous AI service, for the diabetic retinal exam, to show that the framework allows AI systems that have been shown to be safe, effective, and where potential bias has been mitigated, and developed under an ethical framework, to be priced and reimbursed at a sustainable level, resulting in predictable financial incentives for AI creators, and continued research. It puts in place multiple "guardrails" for the AI system implementation that are overseen by all stakeholders to enforce the ethical principles. The present financial incentive framework may be helpful to guide development of sustainable reimbursement for future AI services, while ensuring quality of care, healthcare equity, and mitigation of potential bias, and thereby contribute to realize the potential of AI to improve clinical outcomes for patients and populations, remove disparities, lower cost, and improve access.



npj | digital medicine

www.nature.com/npjdigitalmed

PERSPECTIVE OPEN

Check for updates

Considerations for addressing bias in artificial intelligence for health equity

Michael D. Abràmoff[1], Michelle E. Tarver[2], Nilsa Loyo-Berrios[2], Sylvia Trujillo[3], Danton Char[4,5], Ziad Obermeyer[6], Malvina B. Eydelman[7], Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group of the Collaborative Community for Ophthalmic Imaging Foundation, Washington, D.C.* and William H. Maisel[2]

Health equity is a primary goal of healthcare stakeholders: patients and their advocacy groups, clinicians, other providers and their professional societies, bioethicists, payors and value based care organizations, regulatory agencies, legislators, and creators of artificial intelligence/machine learning (AI/ML)-enabled medical devices. Lack of equitable access to diagnosis and treatment may be improved through new digital health technologies, especially AI/ML, but these may also exacerbate disparities, depending on how bias is addressed. We propose an expanded Total Product Lifecycle (TPLC) framework for healthcare AI/ML, describing the sources and impacts of undesirable bias in AI/ML systems in each phase, how these can be analyzed using appropriate metrics, and how they can be potentially mitigated. The goal of these "Considerations" is to educate stakeholders on how potential AI/ML bias may impact healthcare outcomes and how to identify and mitigate inequities; to initiate a discussion between stakeholders on these issues, in order to ensure health equity along the expanded AI/ML TPLC framework, and ultimately, better health outcomes for all.

npj Digital Medicine (2023)6:170 ; https://doi.org/10.1038/s41746-023-00913-9

1. Michael D. Abramoff[1], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein, Anitra S. Graves[6] Michael X. Repka[7] Ezequiel "Zeke" Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med 2022
2. Abramoff, M.D., B. Cunningham, B. Patel, M.B. Eydelman, T. Leng, T. Sakamoto, R. M. Wolf, A.K. Manrai, J.M. Ko, and M.F. Chiang. "Foundational Considerations for Artificial Intelligence ", Ophthalmology [in press] (2021). https://www.aaojournal.org/article/S0161-6420(21)00643-6/fulltext.
3. Abràmoff, M.D., Tarver, M.E., Loyo-Berrios, N. et al. Considerations for addressing bias in artificial intelligence for health equity. npj Digit. Med. 6, 170 (2023). https://doi.org/10.1038/s41746-023-00913-9

Applying the Ethical Framework to Regulation Foundational Principles for AI

Collaborative Community for Ophthalmic Imaging

Co-authored with FDA and FTC

Ophthalmology

AMERICAN ACADEMY OF OPHTHALMOLOGY

FULL LENGTH ARTICLE | ARTICLES IN PRESS

Foundational Considerations for Artificial Intelligence Utilizing Ophthalmic Images

Michael D. Abramoff • Brad Cunningham • Bakul Patel • ... Michael F. Chiang • Danton Char •

on behalf of the Collaborative Community on Ophthalmic Imaging Executive Committee and Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group * •

Show all authors • Show footnotes

Published: August 31, 2021 • DOI: https://doi.org/10.1016/j.ophtha.2021.08.023

Abstract

IMPORTANCE

The development of Artificial Intelligence (AI) and other machine diagnostic systems, also known as Software as a Medical Device (SaMD), and its recent introduction into clinical practice, requires a deeply-rooted foundation in bioethics, for consideration by regulatory agencies and other stakeholders around the globe.

OBJECTIVES

Initiate a dialogue on the issues to consider when developing a bioethically sound foundation for AI in medicine, based on images of eye structures, for discussion with all stakeholders.

FDA

PROTECTING AMERICA'S CONSUMERS

Abramoff, M.D., B. Cunningham, B. Patel, M.B. Eydelman, T. Leng, T. Sakamoto, R. M. Wolf, A.K. Manrai, J.M. Ko, and M.F. Chiang. "Foundational Considerations for Artificial Intelligence ", Ophthalmology [in press] (2021). https://www.aaojournal.org/article/S0161-6420(21)00643-6/fulltext.

Ethical Foundation for Mitigating AI Bias

npj | digital medicine

www.nature.com/npjdigitalmed

PERSPECTIVE OPEN

Check for updates

Considerations for addressing bias in artificial intelligence for health equity

Michael D. Abràmoff[1] ✉, Michelle E. Tarver[2], Nilsa Loyo-Berrios[2], Sylvia Trujillo[3], Danton Char[4,5], Ziad Obermeyer[6], Malvina B. Eydelman[2], Foundational Principles of Ophthalmic Imaging and Algorithmic Interpretation Working Group of the Collaborative Community for Ophthalmic Imaging Foundation, Washington, D.C.* and William H. Maisel[2]

Health equity is a primary goal of healthcare stakeholders: patients and their advocacy groups, clinicians, other providers and their professional societies, bioethicists, payors and value based care organizations, regulatory agencies, legislators, and creators of artificial intelligence/machine learning (AI/ML)-enabled medical devices. Lack of equitable access to diagnosis and treatment may be improved through new digital health technologies, especially AI/ML, but these may also exacerbate disparities, depending on how bias is addressed. We propose an expanded Total Product Lifecycle (TPLC) framework for healthcare AI/ML, describing the sources and impacts of undesirable bias in AI/ML systems in each phase, how these can be analyzed using appropriate metrics, and how they can be potentially mitigated. The goal of these "Considerations" is to educate stakeholders on how potential AI/ML bias may impact healthcare outcomes and how to identify and mitigate inequities; to initiate a discussion between stakeholders on these issues, in order to ensure health equity along the expanded AI/ML TPLC framework, and ultimately, better health outcomes for all.

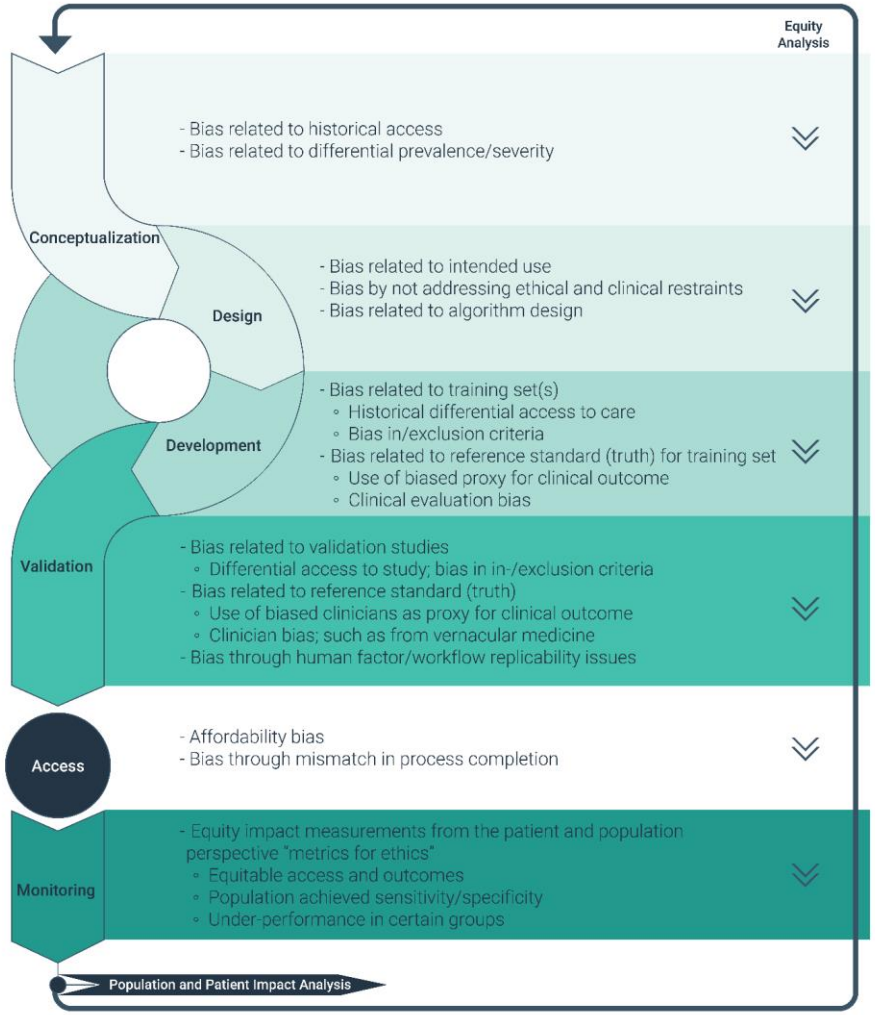
npj Digital Medicine (2023)6:170 ; https://doi.org/10.1038/s41746-023-00913-9

INTRODUCTION

devices being currently developed. While the vast majority of AI

Michael D. Abramoff[1,], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein, Anitra S. Graves[6] Michael X. Repka[7] Ezequiel "Zeke" Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med 2022

Health Equity and AI Bias: Ethical Framework to AI Total Product Life-Cycle



	Beneficence	Justice/Equity	Autonomy
Concept			
Design			
Development			
Validation			
Access & Marketing			
Monitoring			
Population and Patient Impact Analysis			

Reimbursement Framework for AI Charge

npj | digital medicine

www.nature.com/npjdigitalmed

COMMENT OPEN

Check for updates

A reimbursement framework for Artificial Intelligence in Healthcare

Michael D. Abramoff[1,2,3], Cybil Roehrenbeck [2,4], Sylvia Trujillo[5], Juli Goldstein[3], Anitra S. Graves[6,] Michael X. Repka[7], Ezequiel "Zeke" Silva III [8,9]

Abstract

Responsible adoption of healthcare artificial intelligence (AI) requires that AI systems which benefit patients and populations, including autonomous AI systems, are incentivized financially at a consistent and sustainable level. We present a framework for establishing reimbursement for such healthcare AI, by analytically determining value and cost of each unique AI service. It aligns with existing ethical frameworks for AI, focuses on outcomes and reducing cost per patient, while leading to predictable sustainable financial incentives for AI creators. Its processes involve affected stakeholders, including patients, providers, legislators, payors, and AI creators, in order to find an optimum balance among ethics, workflow, cost, and value as identified by each of these stakeholders. We use an example for a specific autonomous AI service, for the diabetic retinal exam, to show that the framework allows AI systems that have been shown to be safe, effective, and where potential bias has been mitigated, and developed under an ethical framework, to be priced and reimbursed at a sustainable level, resulting in predictable financial incentives for AI creators, and continued research. It puts in place multiple "guardrails" for the AI system implementation that are overseen by all stakeholders to enforce the ethical principles. The present financial incentive framework may be helpful to guide development of sustainable reimbursement for future AI services, while ensuring quality of care, healthcare equity, and mitigation of potential bias, and thereby contribute to realize the potential of AI to improve clinical outcomes for patients and populations, remove disparities, lower cost, and improve access.

Michael D. Abramoff[1,], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein, Anitra S. Graves[6] Michael X. Repka[7] Ezequiel "Zeke" Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med 2022

How does an AI creator set their charge?

- **Marginal cost**
  - cost of a single additional patient's service, - incremental cost for one more patient
  - Not sustainable business model
- **Total cost of ownership**
  - sum of investment in R&D, including training the AI, validation of safety, and efficacy, as well as the ongoing marginal costs mentioned above
  - Advantages giant systems over small practices
- **Cost-effective value**
  - cost benefit analyses (CBA) or cost effectiveness analyses (CEA).
  - extra expenditures if a service is not provided, compared to when the service is provided
  - Many assumptions
- **Substitution value**
  - Current value – willingness to pay
  - No cost savings
- **'Equity maximizing' value**
  - Willingness to pay scaled to entire population -> v_e
  - From 30% for $170 each to 100% for $55 each

$$e_c = v_c \, n \, c,$$
$$v_e = v_c \, c$$

Michael D. Abramoff[1], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein,~ Anitra S. Graves[6] Michael X. Repka[7] Ezequiel "Zeke" Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med 2022

Implementation of Equity Enhancing Charge v_e

- Meet ‘guardrails’ for all stakeholders, such as
  - Safety, efficacy
  - Racial Bias mitigation
  - Liability and data usage
  - Outcomes research

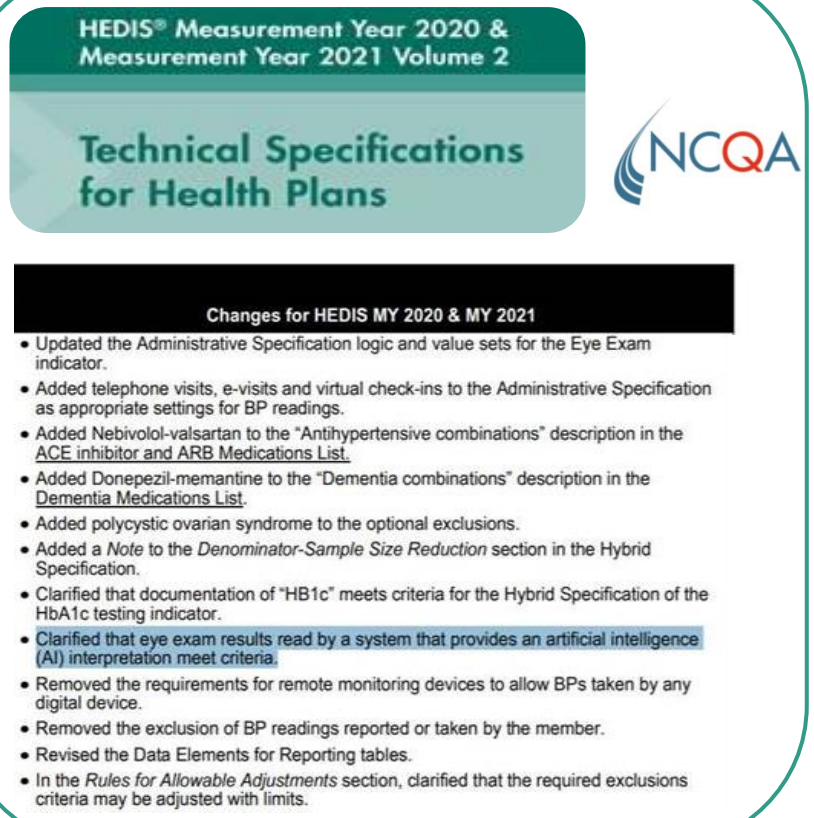
- Work with all stakeholders to ensure alignment
  - (AI creators)
  - Ethicists
  - Regulators
  - Physicians and other providers
  - Payors
  - Patients / populations
  - Investors
  - Legislators

Michael D. Abramoff[1], Cybil Roehrenbeck , Sylvia Trujillo, Juli Goldstein, Anitra S. Graves[6] Michael X. Repka[7] Ezequiel “Zeke” Silva III: A reimbursement framework for Artificial Intelligence in Healthcare. Nature Dig Med, 2022

HEDIS / MIPS with Autonomous AI

HEDIS | MIPS Care Gaps

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). […]



Automated Eye Exam	2.16.840.1.113883.3.464.1004.2251	2021-03-31	92229		CPT	2.16.840.1.113883.6.12	2021.2.20AB

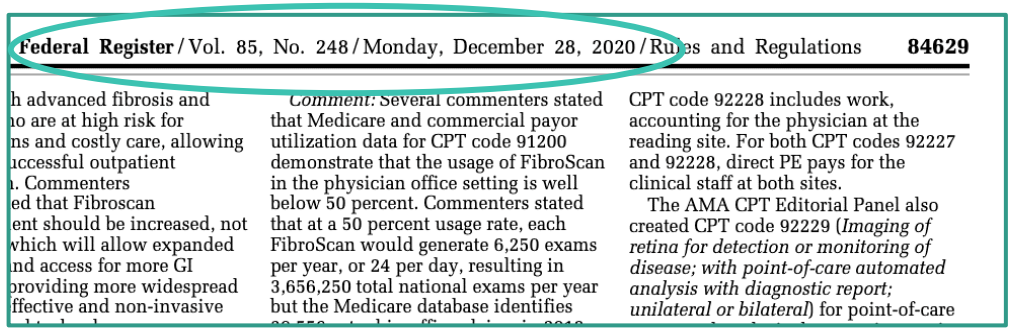
NCQA Updated for lab

CMS Reimbursement Update

» In the CY 2021 Medicare Payment Rules, CMS:

Decided to reimburse for new **CPT® Category 1 Code 92229** (formerly 9225X) – **first-ever** Medicare reimbursement of **AI**

Affirmed CPT **92229** to be a **diagnostic service**



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

h advanced fibrosis and
ıo are at high risk for
ns and costly care, allowing
ıccessful outpatient
ı. Commenters
ed that Fibroscan
ent should be increased, not
which will allow expanded
nd access for more GI
oroviding 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

AMERICAN ACADEMY OF OPHTHALMOLOGY®

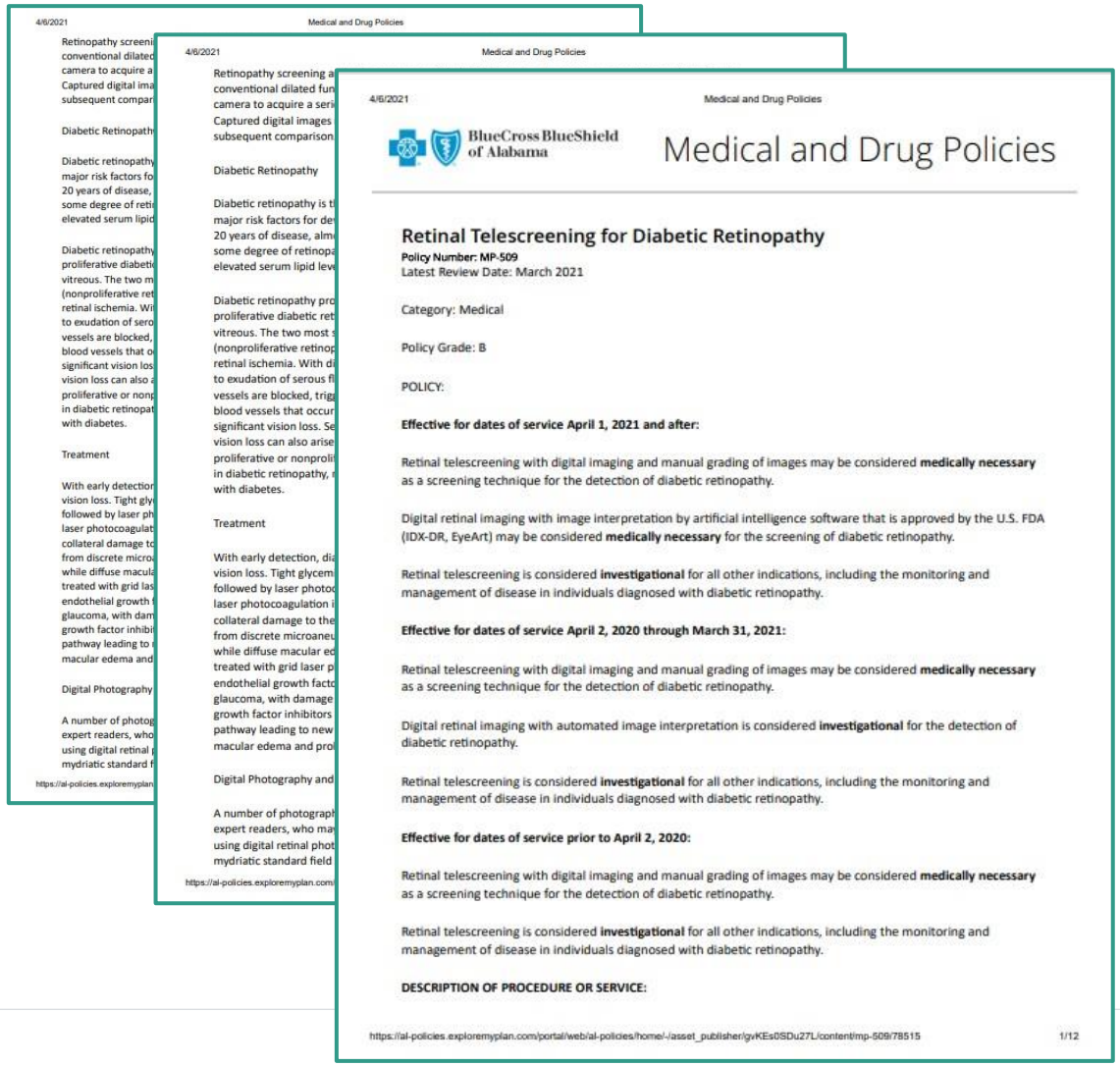
AMA

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

"[…]**IDx-DR [now known as LumineticsCore] 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
MPFS states "We are considering CPT code 92229 to be a diagnostic service under the PFS."

Payer Coverage and Partnerships



4/6/2021 Medical and Drug Policies

BlueCross BlueShield of Alabama

Medical and Drug Policies

Retinal Telescreening for Diabetic Retinopathy

Policy Number: MP-509
Latest Review Date: March 2021

Category: Medical

Policy Grade: B

POLICY:

Effective for dates of service April 1, 2021 and after:

Retinal telescreening with digital imaging and manual grading of images may be considered **medically necessary** as a screening technique for the detection of diabetic retinopathy.

Digital retinal imaging with image interpretation by artificial intelligence software that is approved by the U.S. FDA (IDX-DR, EyeArt) may be considered **medically necessary** for the screening of diabetic retinopathy.

Retinal telescreening is considered **investigational** for all other indications, including the monitoring and management of disease in individuals diagnosed with diabetic retinopathy.

Effective for dates of service April 2, 2020 through March 31, 2021:

Retinal telescreening with digital imaging and manual grading of images may be considered **medically necessary** as a screening technique for the detection of diabetic retinopathy.

Digital retinal imaging with automated image interpretation is considered **investigational** for the detection of diabetic retinopathy.

Retinal telescreening is considered **investigational** for all other indications, including the monitoring and management of disease in individuals diagnosed with diabetic retinopathy.

Effective for dates of service prior to April 2, 2020:

Retinal telescreening with digital imaging and manual grading of images may be considered **medically necessary** as a screening technique for the detection of diabetic retinopathy.

Retinal telescreening is considered **investigational** for all other indications, including the monitoring and management of disease in individuals diagnosed with diabetic retinopathy.

DESCRIPTION OF PROCEDURE OR SERVICE:

https://al-policies.exploremyplan.com/portal/web/al-policies/home/-/asset_publisher/gvKEs0SDu27L/content/mp-509/78515 1/12

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

United Healthcare

BlueCross BlueShield

Anthem

Humana

aetna

Cigna

CPT® 92229 (*imaging of retina for detection of monitoring of disease; point-of-care automated analysis with diagnostic report; unilateral or bilateral)*: Payment on MPFS Beginning CY22

FEDERAL REGISTER

The Daily Journal of the United States Government

This document is scheduled to be published in the Federal Register on 11/19/2021 and available online at federalregister.gov/d/2021-23972, and on govinfo.gov

<RULE>

<PREAMB>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Parts 403, 405, 410, 411, 414, 415, 423, 424, and 425

[CMS-1751-F]

RIN 0938-AU42

Medicare Program; CY 2022 Payment Policies under the Physician Fee Schedule and Other Changes to Part B Payment Policies; Medicare Shared Savings Program Requirements; Provider Enrollment Regulation Updates; and Provider and Supplier Prepayment and Post-payment Medical Review Requirements.

AGENCY: Centers for Medicare & Medicaid Services (CMS), Health and Human Services (HHS).

ACTION: Final rule.

SUMMARY: This major final rule addresses: changes to the physician fee schedule (PFS); other changes to Medicare Part B payment policies to ensure that payment systems are updated to reflect changes in medical practice, relative value of services, and changes in the statute; Medicare Shared Savings Program requirements; updates to the Quality Payment Program;

"Rapid advances in innovative technology are having a profound effect on every facet of the economy, including the delivery of health care. Emerging and evolving technologies are introducing advances in treatment options that have the potential to increase access to care for Medicare beneficiaries, improve outcomes and reduce overall costs to the program…"

Preamble to Establishment of Payment for Remote Retinal Imaging (CPT® Code 92229)

Effectiveness Model of Autonomous AI

npj | digital medicine

Explore content ⌄ About the journal ⌄ Publish with us ⌄

nature › npj digital medicine › perspectives › article

Perspective | Open Access | Published: 27 March 2023

Effectiveness of artificial intelligence screening in preventing vision loss from diabetes: a policy model

Roomasa Channa, Risa M. Wolf, Michael D. Abràmoff & Harold P. Lehmann

npj Digital Medicine **6**, Article number: 53 (2023) | Cite this article

797 Accesses | **4** Altmetric | Metrics

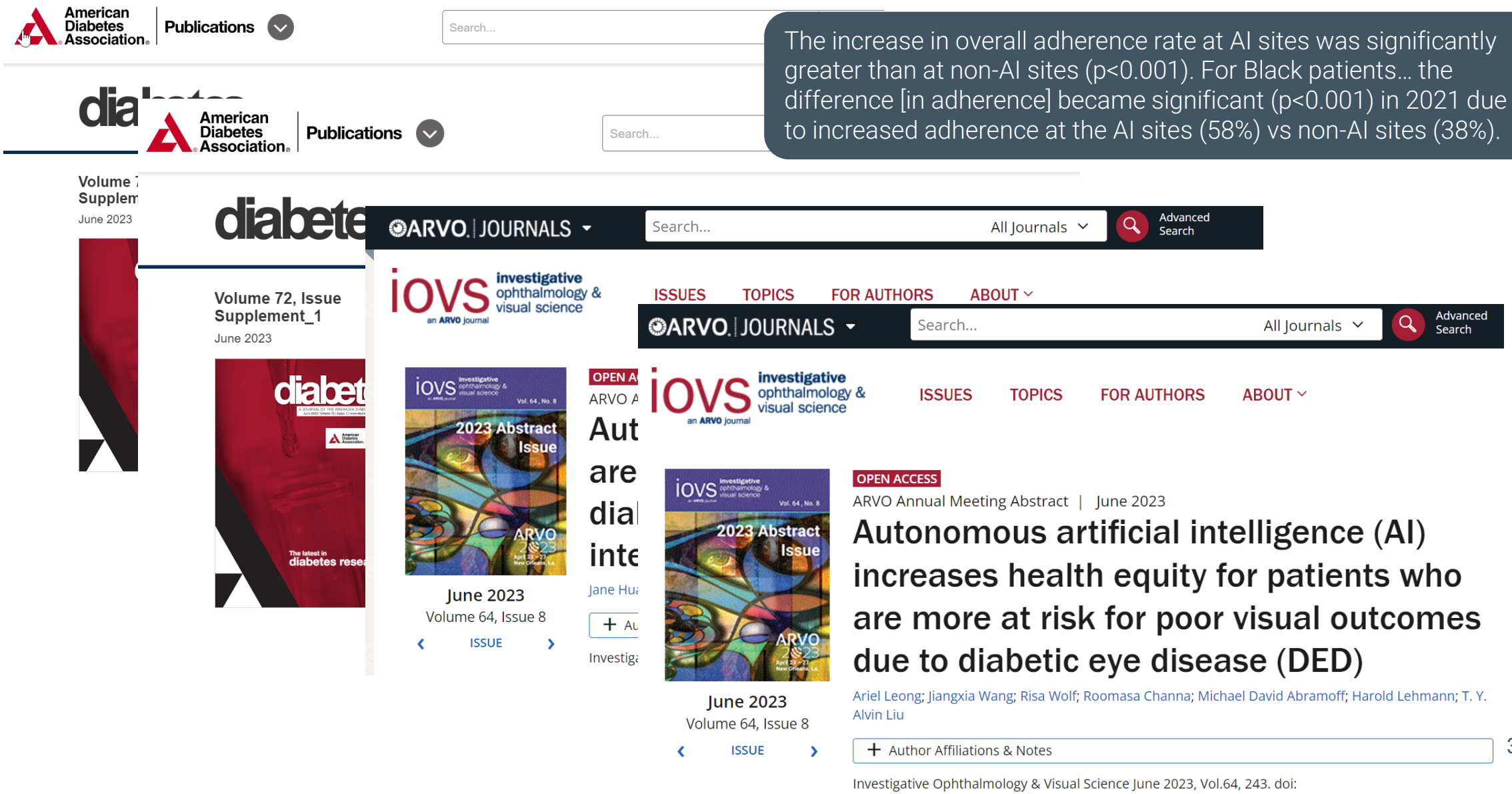
Abstract

The effectiveness of using artificial intelligence (AI) systems to perform diabetic retinal exams ('screening') on preventing vision loss is not known. We designed the Care Process for

https://www.nature.com/articles/s41746-023-00785-z
Channa R, Wolf RM, Abràmoff MD, Lehmann HP. Effectiveness of artificial intelligence screening in preventing vision loss from diabetes: a policy model. NPJ Digit Med. 2023 Mar 27;6(1):53. doi: 10.1038/s41746-023-00785-z. PMID: 36973403; PMCID: PMC10042864.

Scientific Evidence from RCTs Shows Autonomous AI is Improving Health Equity Among Minority Populations

The increase in overall adherence rate at AI sites was significantly greater than at non-AI sites (p<0.001). For Black patients… the difference [in adherence] became significant (p<0.001) in 2021 due to increased adherence at the AI sites (58%) vs non-AI sites (38%).



RCT of Outcomes and Impact on Productivity

npj | digital medicine

Explore content ▾ About the journal ▾ Publish with us ▾

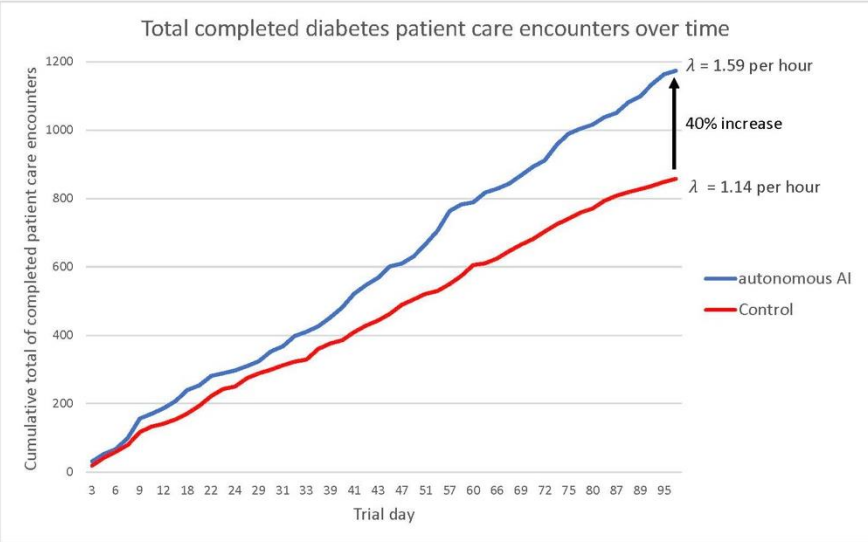
nature › npj digital medicine › articles › article

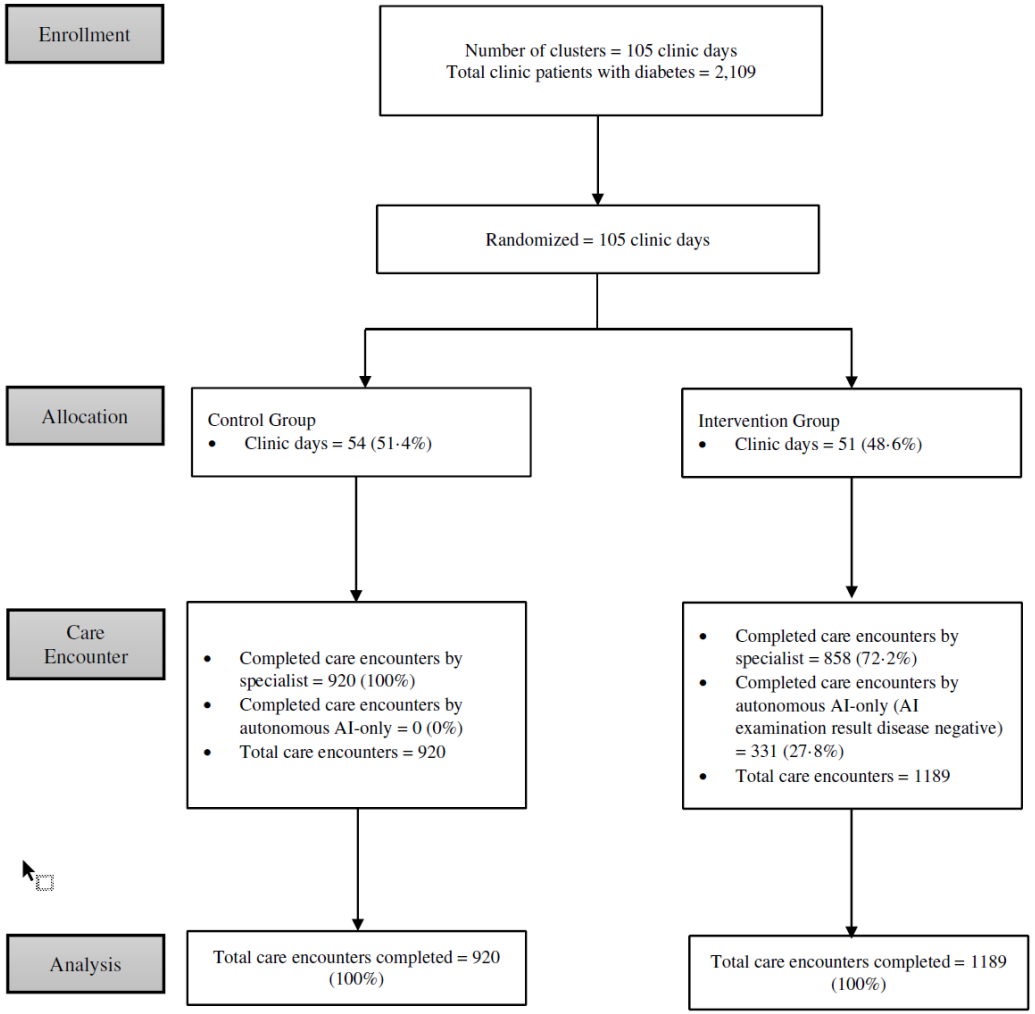
Article | Open Access | Published: 04 October 2023

Autonomous artificial intelligence increases real-world specialist clinic productivity in a cluster-randomized trial

Michael D. Abramoff, Noelle Whitestone, Jennifer L. Patnaik, Emily Rich, Munir Ahmed, Lutful Husain, Mohammad Yeadul Hassan, Md. Sajidul Huq Tanjil, Dena Weitzman, Tinglong Dai, Brandie D. Wagner, David H. Cherwek, Nathan Congdon & Khairul Islam

npj Digital Medicine **6**, Article number: 184 (2023) | Cite this article





https://clinicaltrials.gov/ct2/show/NCT05182580?term=%28B-PRODUCTIVE%29&draw=2&rank=1

Design to Mitigate Bias

Design so operations are maximally reducible to characteristics aligned with scientific knowledge of human clinician cognition

Mitigating bias through AI design

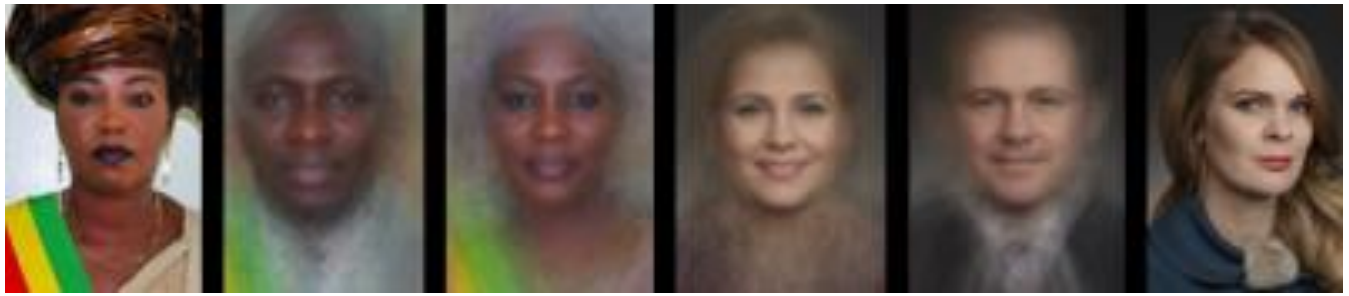
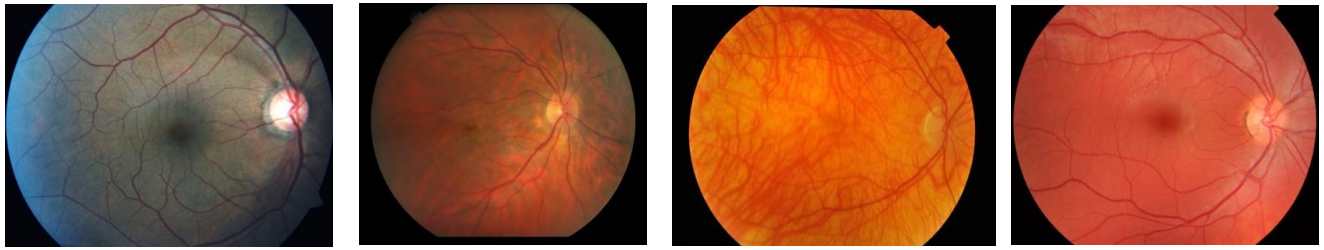


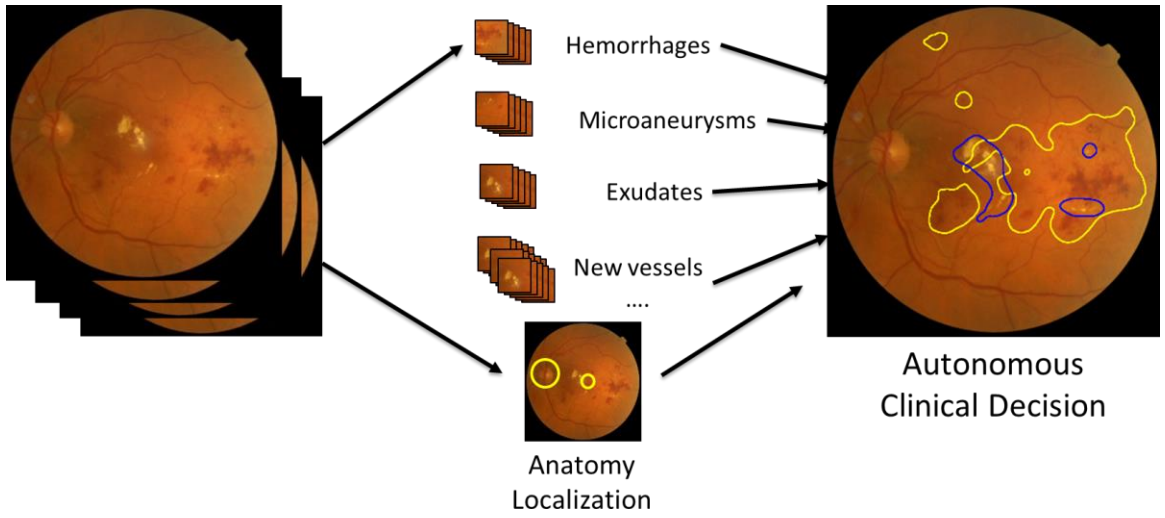
Image based training of convolutional neural networks



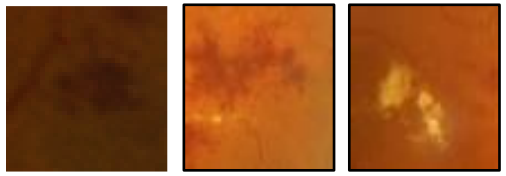
High risk of (racial) bias

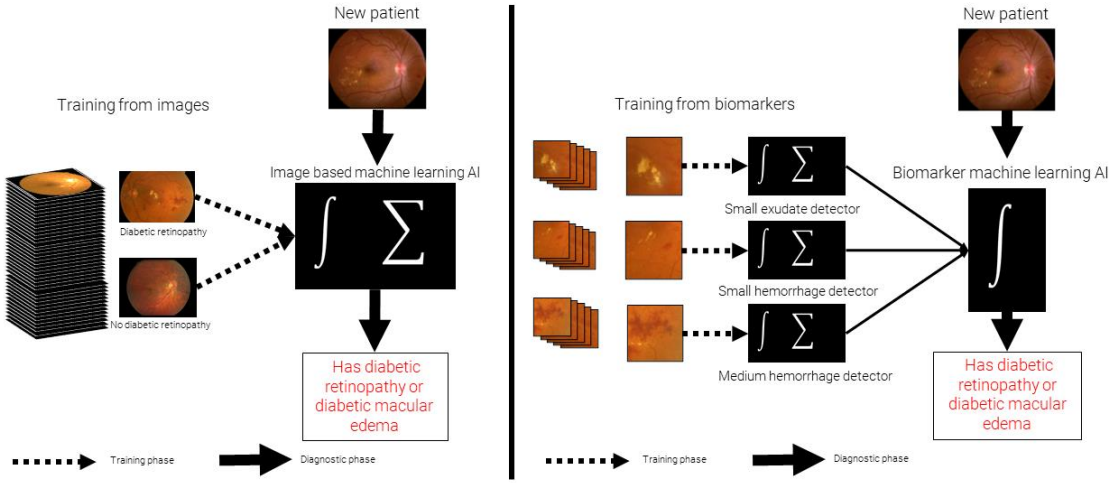
Abramoff et al, IOVS 2007, Abramoff et al, Nat Dig Med, 2018, Abramoff et al, IOVS 2016
Lynch et al, ARVO 2017, Shah et al, Proc ISBI 2018
Finlayson et al, Science, 2019
Larrazabal et al, Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis, PNAS 2020

Autonomous AI Requirement: Design



Detector based design – lesion specific
Racially invariant detectors





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

Link AI Output to Patient Outcome

Improve patient outcome

Improve patient outcome shown by direct evidence or linked clinical literature; aligned with evidence based clinical standards of care/practice patterns, accounting for safety, efficacy and equity

- Autonomous AI: 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
- Autonomous AI: 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
- 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

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

Establishing the Reference Standard

Improve patient outcome shown by direct evidence or linked clinical literature; aligned with evidence based clinical standards of care/practice patterns, accounting for safety, efficacy and equity

Level I Reference Standard

» A reference standard that either is a clinical outcome or a previously agreed surrogate outcome . If the surrogate outcome is derived from an independent reading center, validation against outcome is required, as is published evidence of temporal drift, reproducibility, and repeatability metrics.

Level II Reference Standard

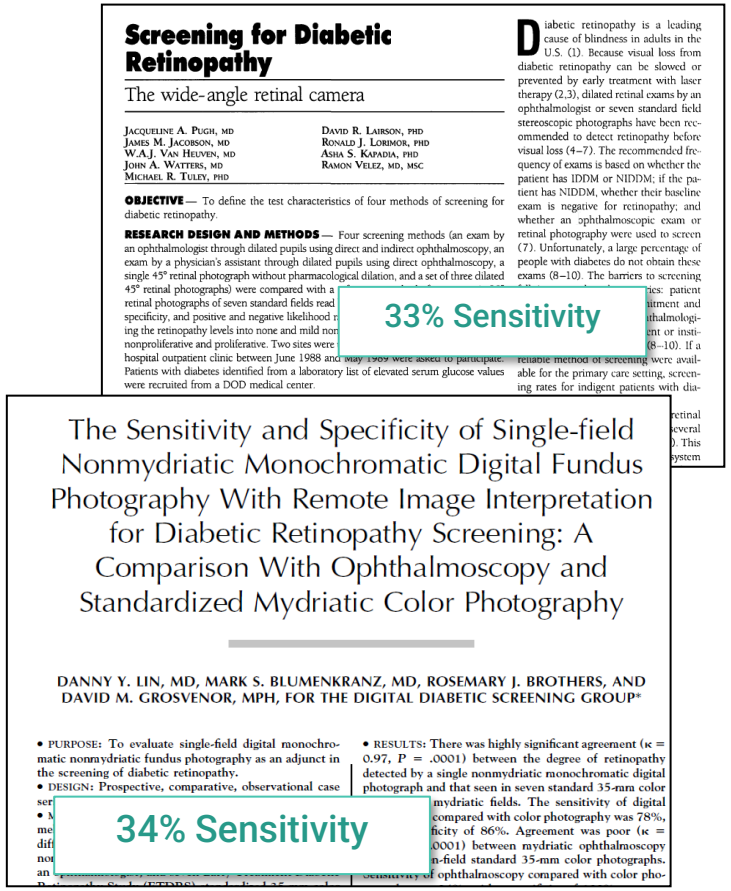
» A reference standard established by an independent reading center with published temporal drift, reproducibility, and repeatability metrics. A level II reference standard has not been validated to correlate to a clinical outcome.

Level III Reference Standard

» A reference standard created from the same modality as used by the AI, by adjudicating or voting of multiple independent expert readers, documented to be masked, with published reproducibility and repeatability metrics. A level III reference standard has not been established an independent reading center and has not been validated to correlate with a clinical outcome.

Level IV Reference Standard

» All other reference standards, created by single readers or non-expert readers, without an established protocol. A level IV reference standard has not been derived from an independent reading center, has not been validated to correlate with a clinical outcome, and there are no published reproducibility and repeatability metrics.



Screening for Diabetic Retinopathy

The wide-angle retinal camera

JACQUELINE A. PUGH, MD; JAMES M. JACOBSON, MD; W.A.J. VAN HEUVEN, MD; JOHN A. WATTERS, MD; MICHAEL R. TULEY, PHD; DAVID R. LARSON, PHD; RONALD J. LORIMOR, PHD; ASHA S. KAPADIA, PHD; RAMON VELEZ, MD, MSC

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

33% Sensitivity

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

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

DANNY Y. LIN, MD, MARK S. BLUMENKRANZ, MD, ROSEMARY J. BROTHERS, AND DAVID M. GROSVENOR, MPH, FOR THE DIGITAL DIABETIC SCREENING GROUP*

• PURPOSE: To evaluate single-field digital monochromatic nonmydriatic fundus photography as an adjunct in the screening of diabetic retinopathy.

• DESIGN: Prospective, comparative, observational case

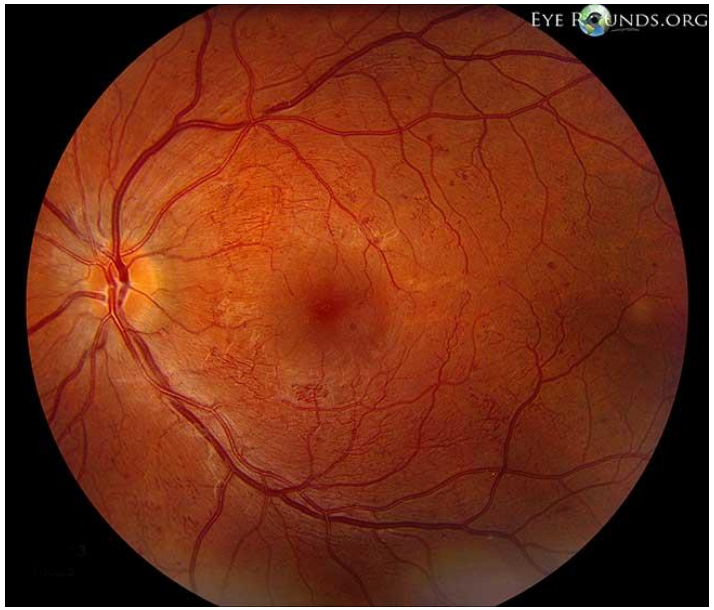
• RESULTS: There was highly significant agreement (κ = 0.97, P = .0001) between the degree of retinopathy detected by a single nonmydriatic monochromatic digital photograph and that seen in seven standard 35-mm color mydriatic fields. The sensitivity of digital compared with color photography was 78%,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

34% Sensitivity

» FDA's "Foundational Principles of ophthalmic Imaging and Algorithmic Interpretation" workgroup draft best practices. Presented at the first CCOI meeting, Spet 2020, Stanford University, https://www.cc-oi.org/2020-ccoi-conference

Level I Prognostic reference standard

- Clinical trials
  - Diabetic Retinopathy Study (DRS)
    - 1972-1975
    - randomized clinical trial n~2000
  - Diabetes Control & Complications Trial (DCCT – EDIC)
    - 1983-ongoing
    - n~1400
  - Early Treatment of Diabetic Retinopathy Study (ETDRS)
    - 1979-1985
    - RCT n~3700
- ETDRS Reference Standard is Prognostic:
  - Predicts untreated outcome
  - Wisconsin Fundus photograph Reading Center w known reproducibility etc
  - ETDRS Severity Scale
  - Cannot be repeated today ethically
- Almost all evidence for patient management and treatment based on this reference standard



Example ETDRS level 43 & 0 CI-DME

1 year risk of early PDR 26.3%

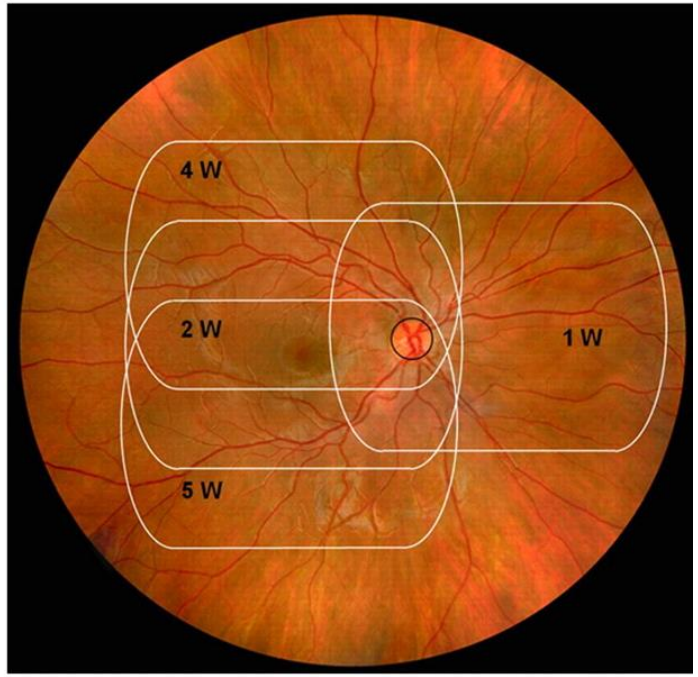
1 year risk of high risk PDR: 8.1%

1 year risk of CI-DME < 1.7%

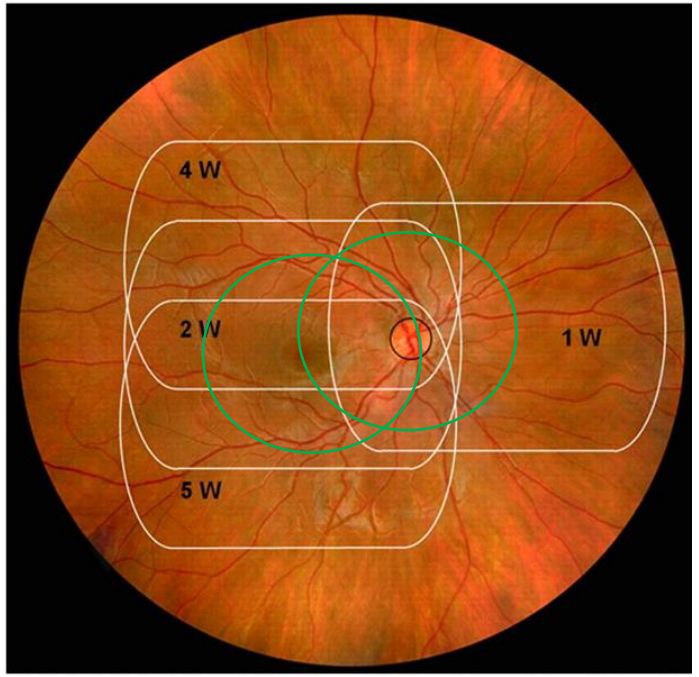
Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):823-833.
Klein R. The epidemiology of diabetic retinopathy: findings from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Int Ophthalmol Clin. 1987;27:230-238.
Varma R, Choudhury F, Klein R, et al. Four-year incidence and progression of diabetic retinopathy and macular edema: the Los Angeles Latino Eye Study. Am J Ophthalmol. 2010;149(5):752-761 e751-753.

ETDRS Imaging + macular OCT

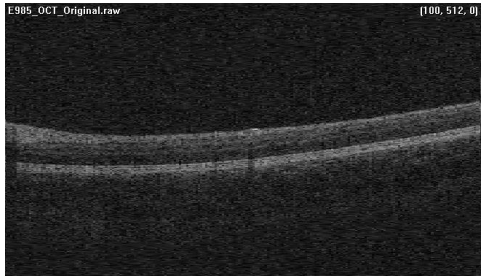
Reference Standard: 4 widefield stereo (in white)



AI system: 2 field mono (green)



Reference Standard: Macular OCT (SDOCT)



Autonomous AI Pivotal Trial Design

n = 900 subjects with diabetes

10 Primary Care clinics around US

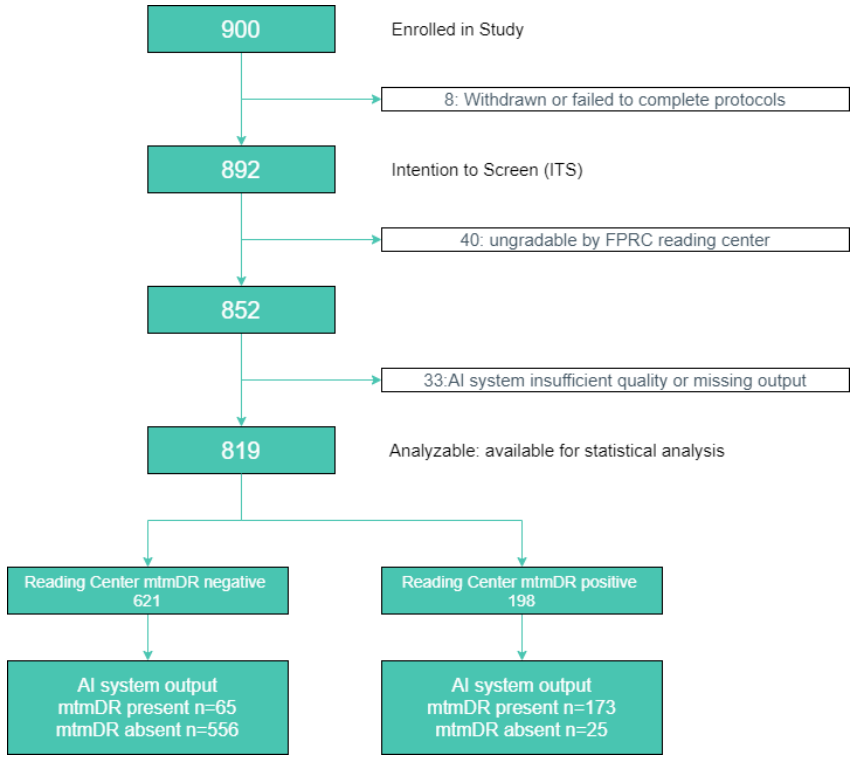
- Existing clinic staff w minimal training

Compared to surrogate outcome

- ETDRS / DRCR by FPRC
- Required full ETDRS stereo color protocol and macular OCT

Endpoints finalized before study

- Sensitivity (superiority endpoint 85.0%)
- Specificity (superiority endpoint 82.5%)
- Diagnosability (85.0%)
- Repeatability and reproducibility



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

Autonomous AI Pivotal Trial

npj | Digital Medicine

www.nature.com/npjdigitalmed

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

AI Consideration: Validate Rigorously

	FDA Superiority Endpoint	Autonomous AI in Primary Care (n=819)**	Remote Reading Network / Telemedicine	Board Certified Ophthalmologist in Clinic
Sensitivity	85.0%	87.2%*,[1] (81.8% - 91.2%)	72% (65%-79%) [6]	33%[2]-34.3%
Specificity	82.5%	90.7%*,[1] (88.3% - 92.7%)	97% (95%-99%)[6]	99%[2]-100.3%
Diagnosability (reflexive)	82.5%	96%*,[1] (94.0% - 96.8%)		N/A
Reproducibility		99%[5]		83%[4]
Equity		**No significant effects for sex, race, ethnicity**	Unknown	Unknown

Autonomous AI study and board-certified studies conducted separately, both by **University of Wisconsin's Fundus Photography Reading Center

All other AI, telemedicine, and clinician studies do not use surrogate outcome as the standard, and only compare to unvalidated clinicians (who may or may not correspond to outcome markers)

1. 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;1:39off 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
2. 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.
3. 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. AmJOphthalmol. 2002;134(2):204-213. Liu et al, 2018
4. Lynch et al, IOVS, 2018
5. Abramoff et al, Improved Automated Detection of Diabetic Retinopathy Through Integration of Deep Learning, IOVS, 2016. Compared to 3 retina specialists.
6. Fransen SR, Leonard-Martin TC, Feuer WJ, Hildebrand PL. Clinical evaluation of patients with diabetic retinopathy: accuracy of the Inoveon diabetic retinopathy-3DT system. Ophthalmology. 2002;109(3):595-601.
7. Wolf et al, Cost-effectiveness of using autonomous point of care diabetic retinopathy screening in a pediatric diabetes clinic: the family perspective, Diabetes Care [under review].
8. Not preregistered study, no OCT imaging to diagnose for center-involved macular edema

*This side by side is not a comparison, as the performance numbers were obtained in different studies. Studies 1,2,3,5 used the same surrogate outcome reference standard, the ETDRS 7-widefield stereo equivalent reference standard. Study 4 used single retina specialist reference standard. Study 5 used a three retina specialists reference standard.