Plcc Alliance

Home About Working Groups News & Events Resources Presentations Projects Publications

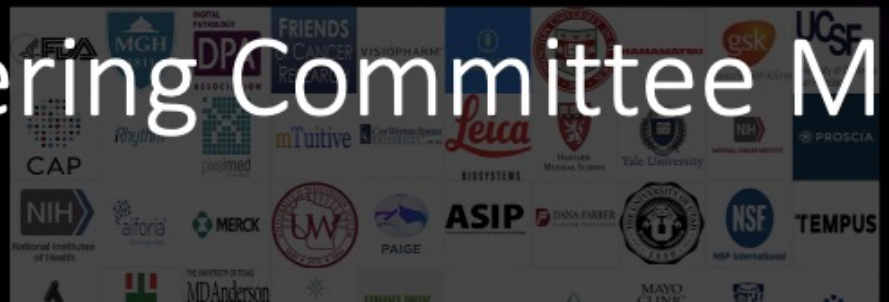
Join

Pathology Innovation Collaborative Community

Plcc

The Alliance for Digital Pathology

A collaborative community with FDA participation



Steering Committee Meeting

September 2023

FDA

Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research Real-World Evidence

CBER and CDER RWE Program

Real-World Evidence

Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research Real-World Evidence

On This Page:

Content current as of:
09/08/2023

Regulated Product(s)
Biologics
Drugs

Law(s) & Regulation(s)
21st Century Cures Act of 2016

As defined by FDA, real-world data (RWD) are the data relating to patient health status

Center for Biologics Evaluation and Research & Center for Drug Evaluation and Research Real-World Evidence

CBER and CDER RWE Program

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Guidance

- Framework for FDA's Real-World Evidence Program (2018)
- Use of Electronic Health Records in Clinical Investigations (2018)
- Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Data Standards for Drug and Biological Product Submissions Containing Real-World Data (2021)
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (2021)
- Digital Health Technologies for Remote Data Acquisition in Clinical Investigations (2022)
- Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics (2022)
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (2023)
- Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (2023)

Representative Publications

- July 2021: FDA approves new use of transplant drug based on RWE
- April 25, 2023: Emulation of Randomized Clinical Trials with Nonrandomized Database Analyses
- May 5, 2022: Real-World Evidence- Where Are We Now?
- Sep 2020: Randomized, observational, interventional, and real-world-What's in a name?
- Oct 2019: CTTI Recommendations: Use of Real-World Data to Plan Eligibility Criteria and Enhance Recruitment
- March 2019: The US FDA's Real-World Evidence Framework: A Commitment for Engagement and Transparency on Real-World Evidence
- Sep 2018: Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness

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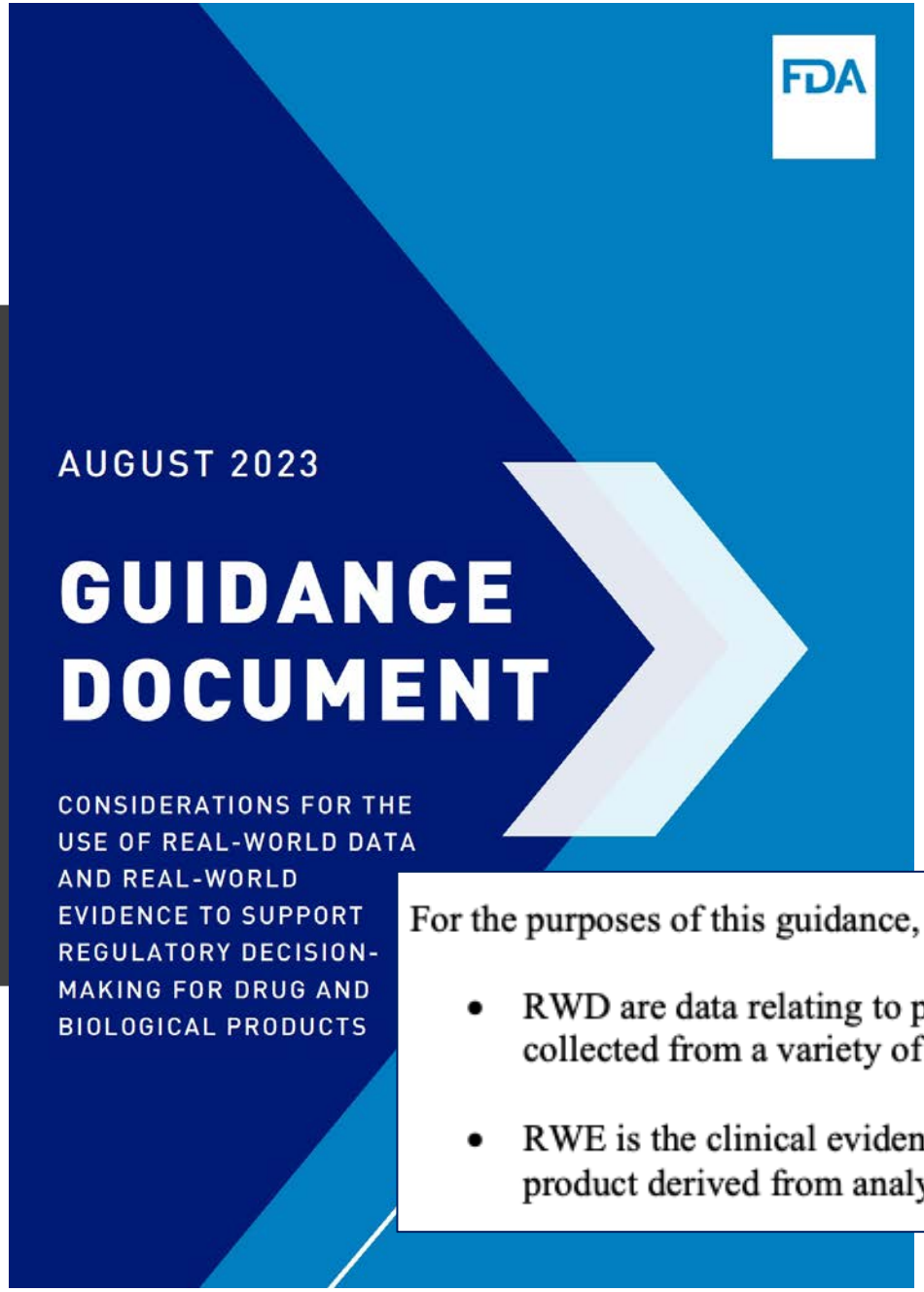
y FDA, real-world data (RWD) are the data relating to patient health status

Content current as of:
09/08/2023

Regulated Product(s)
Biologics
Drugs

Law(s) & Regulation(s)
21st Century Cures Act of 2016

Final guidance released



For the purposes of this guidance, FDA defines real-world data (RWD) and RWE as follows:

- RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Digital Health Frequently Asked Questions (FAQs)

Digital health technologies are advancing rapidly, and the Food and Drug Administration (FDA) regulatory landscape is evolving to continue helping developers bring safe, effective, and innovative technologies to market. The FDA encourages digital health developers to contact the Center for Devices and Radiological Health's (CDRH) Digital Health Center of Excellence (DHCoE) throughout the development process with questions about digital health regulatory considerations.

Do you have a Question About Digital Health Policy?

Before contacting us, please review our list of FAQs below and explore the FDA's many publicly available resources online to help answer your general questions. This will ensure we can provide valuable informal responses to your specific digital health policy questions in a timely manner.

Did you know the FDA has online education tools? Device Advice provides comprehensive regulatory education. Device Advice is CDRH's premier resource that explains medical device laws, regulations, guidances, and policies, across the entire product lifecycle. For more information read Device Advice: Comprehensive Regulatory Assistance.

Frequently Asked Questions (FAQs)

The FAQs below are intended to help you find resources quickly and suggest similar content that may interest you.

Q1: What regulatory requirements apply to my digital health or software product?

Content current as of:
09/15/2023

Regulated Product(s)
Medical Devices

Digital Health Frequently Asked Questions

Q1: What regulatory requirements apply to my digital health or software product?

Q2: What steps should I take to market my Software as a Medical Device (SaMD) or mobile medical app in the United States?

Q3: Is my product a Software as a Medical Device (SaMD)?

Q4: Can I contact staff in the Digital Health Center of Excellence (DHCoE) about my digital health product?

Q5: Where can I find a list of digital health devices the FDA has authorized?

Q6: Where can I learn more about DHCoE's work and resources on AI/ML-Enabled Devices?

Q7: What information should I review regarding clinical studies for my digital health device?

Q8: How do I know what other laws may be applicable to my mobile health app?

Q9: What is the best way to know about the latest digital health guidances or policies?

Q10: Is the Pre-Cert pilot still ongoing and can I participate?

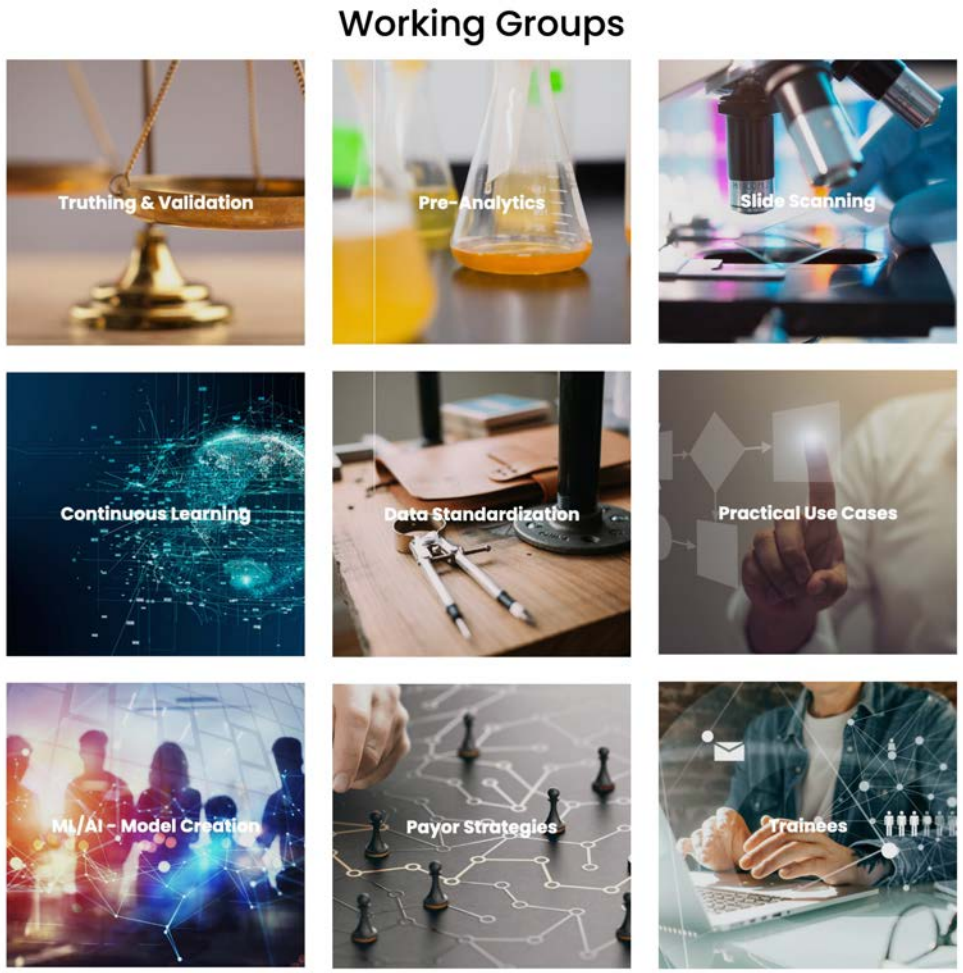
Q11: I am a manufacturer of software medical devices. Who do I contact about Establishment Registration and Device Listing?

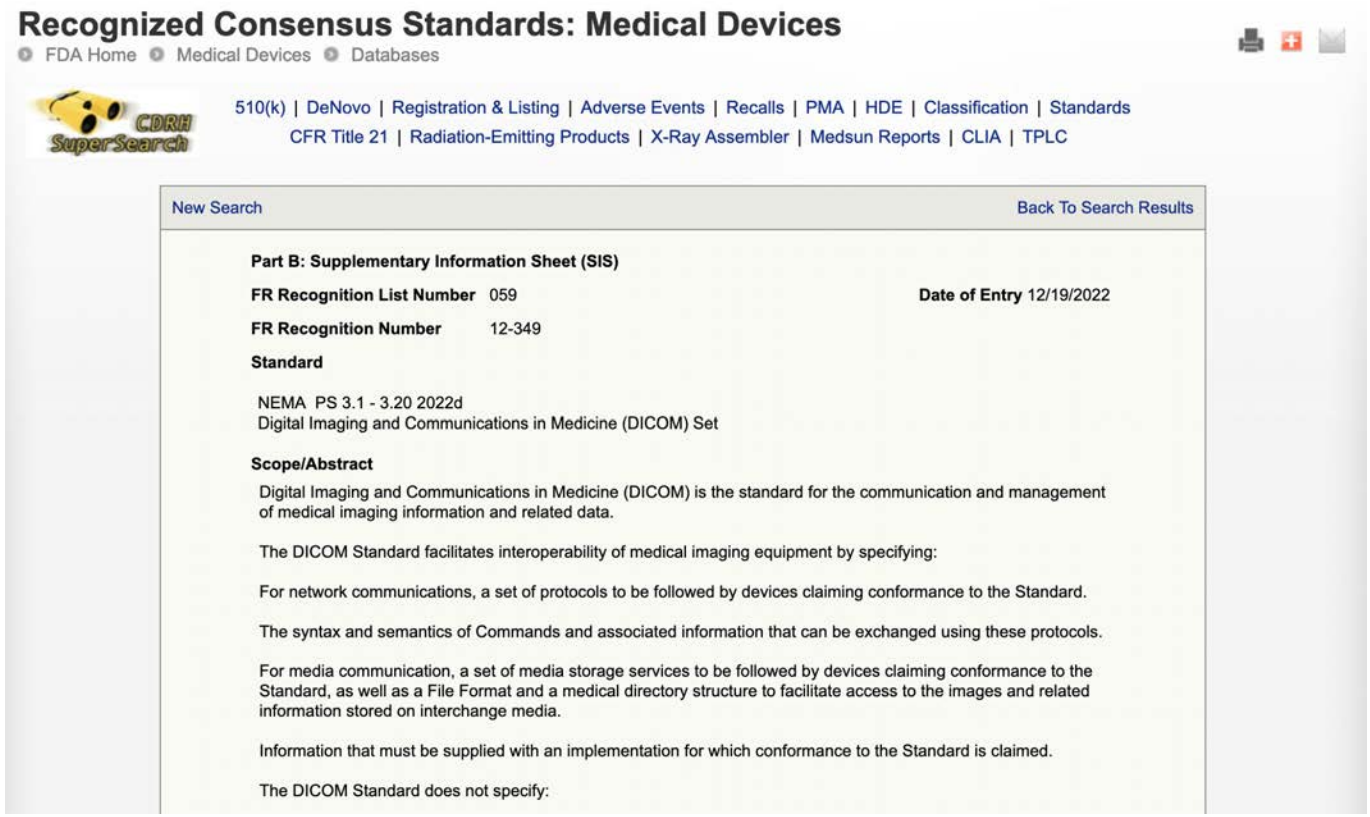
Q12: Can I subscribe to updates on digital health policies?

Content current as of:
09/15/2023

Regulated Product(s)
Medical Devices

DICOM for Digital Pathology highlighted on digital pathology products





Recognized Consensus Standards: Medical Devices

FDA Home | Medical Devices | Databases

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

New Search | Back To Search Results

Part B: Supplementary Information Sheet (SIS)

FR Recognition List Number 059 **Date of Entry** 12/19/2022

FR Recognition Number 12-349

Standard

NEMA PS 3.1 - 3.20 2022d
Digital Imaging and Communications in Medicine (DICOM) Set

Scope/Abstract

Digital Imaging and Communications in Medicine (DICOM) is the standard for the communication and management of medical imaging information and related data.

The DICOM Standard facilitates interoperability of medical imaging equipment by specifying:

For network communications, a set of protocols to be followed by devices claiming conformance to the Standard.

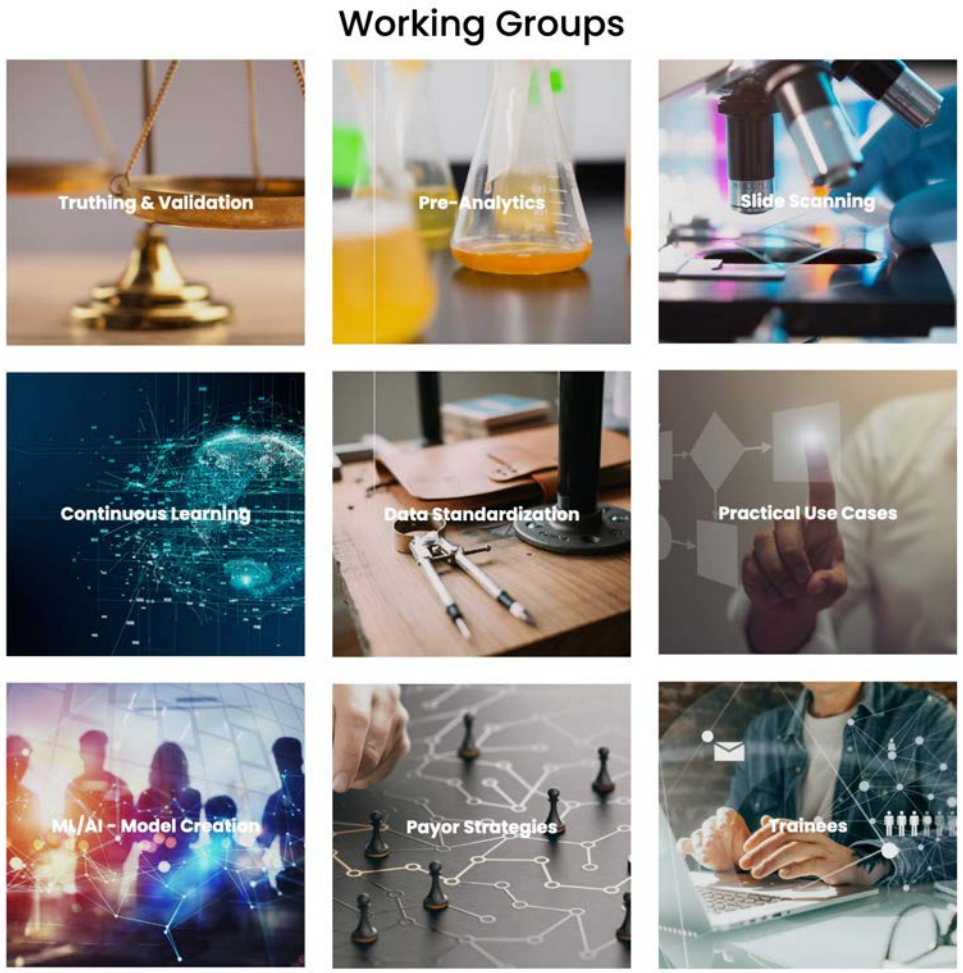
The syntax and semantics of Commands and associated information that can be exchanged using these protocols.

For media communication, a set of media storage services to be followed by devices claiming conformance to the Standard, as well as a File Format and a medical directory structure to facilitate access to the images and related information stored on interchange media.

Information that must be supplied with an implementation for which conformance to the Standard is claimed.

The DICOM Standard does not specify:

DICOM for Digital Pathology highlighted on digital pathology products



Transition Period

FDA recognition of NEMA PS 3.1 - 3.20 2021e [Rec# 12-342] will be superseded by recognition of NEMA PS 3.1 - 3.20 2022d [Rec# 12-349]. FDA will accept declarations of conformity, in support of premarket submissions, to [Rec# 12-342] until December 17, 2023. After this transition period, declarations of conformity to [Rec# 12-342] will not be accepted.

Public Law, CFR Citation(s) and Procode(s)*

Regulation Number	Device Name	Device Class	Product Code
§864.3700	Digital Pathology Image Viewing And Management Software	Class 2	QKQ
§864.3750	Software Algorithm Device To Assist Users In Digital Pathology	Class 2	QPN
§886.1120	Camera, Ophthalmic, Ac-Powered	Class 2	HKI
§886.1570	Tomography, Optical Coherence	Class 2	OBO
§886.1570	Ophthalmoscope, Laser, Scanning	Class 2	MYC
§886.1850	Biomicroscope, Slit-Lamp, Ac-Powered	Class 2	HJO
§886.1850	Device, Analysis, Anterior Segment	Class 2	MXK
§892.1680	Solid State X-Ray Imager (Flat Panel/Digital Imager)	Class 2	MQB
§892.1750	System, X-Ray, Tomography, Computed	Class 2	JAK
§892.2050	System, Image Processing, Radiological	Class 2	LLZ
§892.2050	System, Image Management, Ophthalmic	Class 2	NFJ

Relevant FDA Guidance and/or Supportive Publications*

Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Full Field Digital Mammography System. Issued March 2012.

Guidance for Industry and FDA Staff: Display Devices for Diagnostic Radiology. Issued October 2017.

Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Guidance for Industry and Food and Drug Administration Staff, issued September 2018.

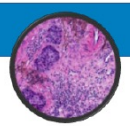
"AI–Enabled Medical Devices and Diagnostics: Statistical Challenges and Opportunities from a Regulatory Perspective"

Short easy read.

Outlines different AI use cases

Mentions few stat challenges

High Throughput Truthing Project



Recruiting Pathologists to Truth sTILs

Greetings! Researchers from the U.S. Food and Drug Administration, alongside academic, clinical and industry colleagues, are collecting pathologist annotations of stromal tumor infiltrating lymphocytes (sTILs) as data for AI/ML algorithm validation. Volunteer pathologists will receive training in the task through a continuing medical education course (3.00 CME credits) and interactive training on our digital data-collection platform. After training, participants will be assigned pivotal study collections (30-60 min per collection) according to their interest and availability. Through your involvement, you will be generating the reference standard for algorithm validation ensuring high quality commercial products with a faster FDA-pipeline to approval.

Learn More About the HTT Project!

Or visit: https://didsr.github.io/HTT.home/

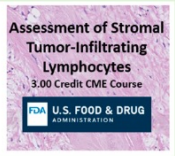
Background, Goals, Context, Methods

Publications and Accomplishments

Technologies and Training

Get Involved!

3.00 CME Credit Course



Create an account: https://ceportal.fda.gov/

Click on "Online Learning" tab

Scroll to "Assessment of Stromal Tumor-Infiltrating Lymphocytes"

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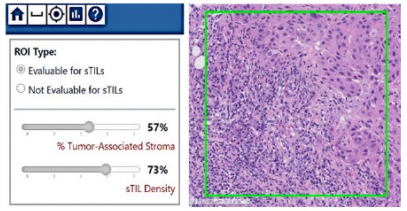
The Annotation Task



Annotation Fields

Region of Interest

Interactive Training Gives You Feedback!

After annotating an ROI the **Feedback Test** provides scores, comments and pitfalls from a panel of experts

Expert Panel Annotations:

ROI Type	% Tumor-Associated Stroma	% sTIL Density
Evaluable	70	85
Evaluable	60	70
Evaluable	50	75
Evaluable	70	85
Evaluable	60	80
Evaluable	60	60

Questions? Email the project management team:
https://didsr.github.io/HTT.home/assets/pages/team

SPi	Journal Code	Article ID	Dispatch: 11-SEP-23	CE:
	PATH	6208	No. of Pages: 7	ME:

Journal of Pathology
J Pathol 2023
Published online 00 Month 0000 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.6208

INVITED PERSPECTIVE

Initial interactions with the FDA on developing a validation dataset as a medical device development tool

Steven Hart[1], Victor Garcia[2], Sarah N Dudgeon[3], Matthew G Hanna[4], Xiaoxian Li[5], Kim RM Blenman[6,7], Katherine Elfer[2], Amy Ly[8], Roberto Salgado[9,10], Joel Saltz[11], Rajarsi Gupta[11], Evangelos Hytopoulos[12], Denis Larsimont[13], Jochen Lennerz[14] and Brandon D Gallas[2*]

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[2] *Division of Imaging, Diagnostics, and Software Reliability, Office Science and Engineering Laboratories, Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, MD, USA*
[3] *Computational Biology and Bioinformatics Program, Yale University, New Haven, CT, USA*
[4] *Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[5] *Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA, USA*
[6] *Department of Internal Medicine, Section of Medical Oncology, School of Medicine, Yale University, New Haven, CT, USA*
[7] *Department of Computer Science, School of Engineering and Applied Science, Yale University, New Haven, CT, USA*
[8] *Department of Pathology, Massachusetts General Hospital, Boston, MA, USA*
[9] *Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium*
[10] *Division of Research, Peter Mac Callum Cancer Centre, Melbourne, VIC, Australia*
[11] *Department of Biomedical Informatics, Stony Brook School of Medicine, Stony Brook, NY, USA*
[12] *iRhythm Technologies Inc., San Francisco, CA, USA*
[13] *Department of Pathology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*
[14] *Massachusetts General Hospital/Massachusetts General Hospital, Center for Integrated Diagnostics, Boston, MA, USA*

*Correspondence to: BD Gallas, Division of Imaging, Diagnostics, and Software Reliability, Office Science and Engineering Laboratories, Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, MD 20993, USA. E-mail: brandon.gallas@fda.hhs.gov

Hart et al., "Initial Interactions with the FDA on Developing a Validation Dataset as a Medical Device Development Tool," *J Pathol*, 2023-online, doi: https://pathsocjournals.onlinelibrary.wiley.com/doi/full/10.1002/path.6208.

LEGISLATIVE & FEDERAL UPDATES

US

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC)
NEXT GENERATION SEQUENCING (NGS) WORKGROUP

SUMMARY REPORT

Workgroup Charge

Provide input to CLIAC for consideration in developing recommendations to CDC, CMS, and FDA for assuring the quality of next generation sequencing based testing in clinical laboratory settings.

Workgroup Tasks

- Identify challenges in applying the existing regulatory framework
- Identify challenges and gaps in guidance
- Consider and suggest strategies to address the identified gaps and challenges
- Consider and suggest strategies for assuring workforce competency

Workgroup members used the following questions regarding the application of NGS-based tests for clinical practice to guide discussions. Workgroup members were asked to identify challenges/gaps and suggest strategies to address them.

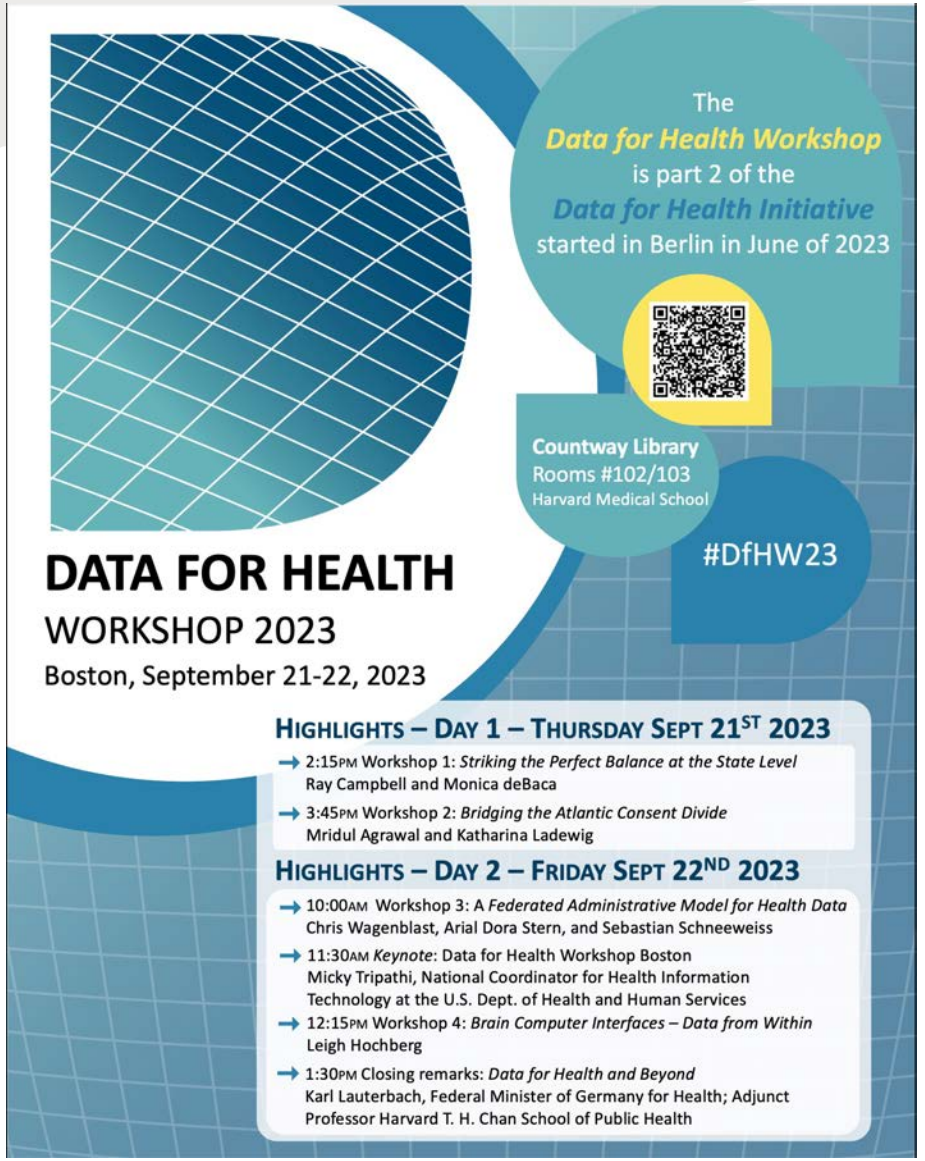
- SB 989, which was signed into law in May, states that **providers of health benefit plans must cover evidence-backed biomarker tests used to diagnose, treat, and manage or monitor an enrollee's condition**

LEGISLATIVE & FEDERAL UPDATES

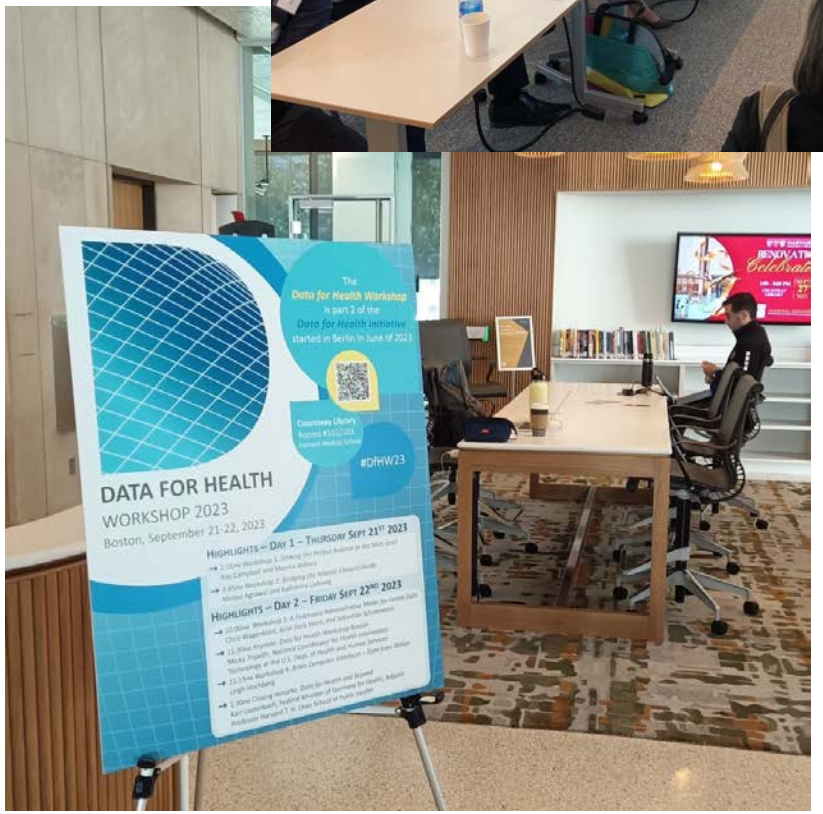
European perspective

Data for Health Initiative

- Follow up to the Data for Health conference hosted by German Federal Ministry of Health was hosted by Harvard T.H. Chan School of Public Health



Data for Health Workshop in Boston



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MEDICAL DEVICE INNOVATION CONSORTIUM

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MDIC Updates

https://mdic.org/

Join us at MXR2023!

Join MDIC, FDA, and top industry leaders in this exciting two-day regulatory science conference convening leaders in augmented and virtual reality! Learn about technological advances, current medical applications, drivers of innovation and adoption, and recent regulatory advances in the field of MXR.

Click here for registration and poster submissions

Contact MXR@mdic.org for Exhibition/Sponsorship opportunities

Early Bird Registration ends: August 31, 2023

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM
Align. Achieve. Accelerate.

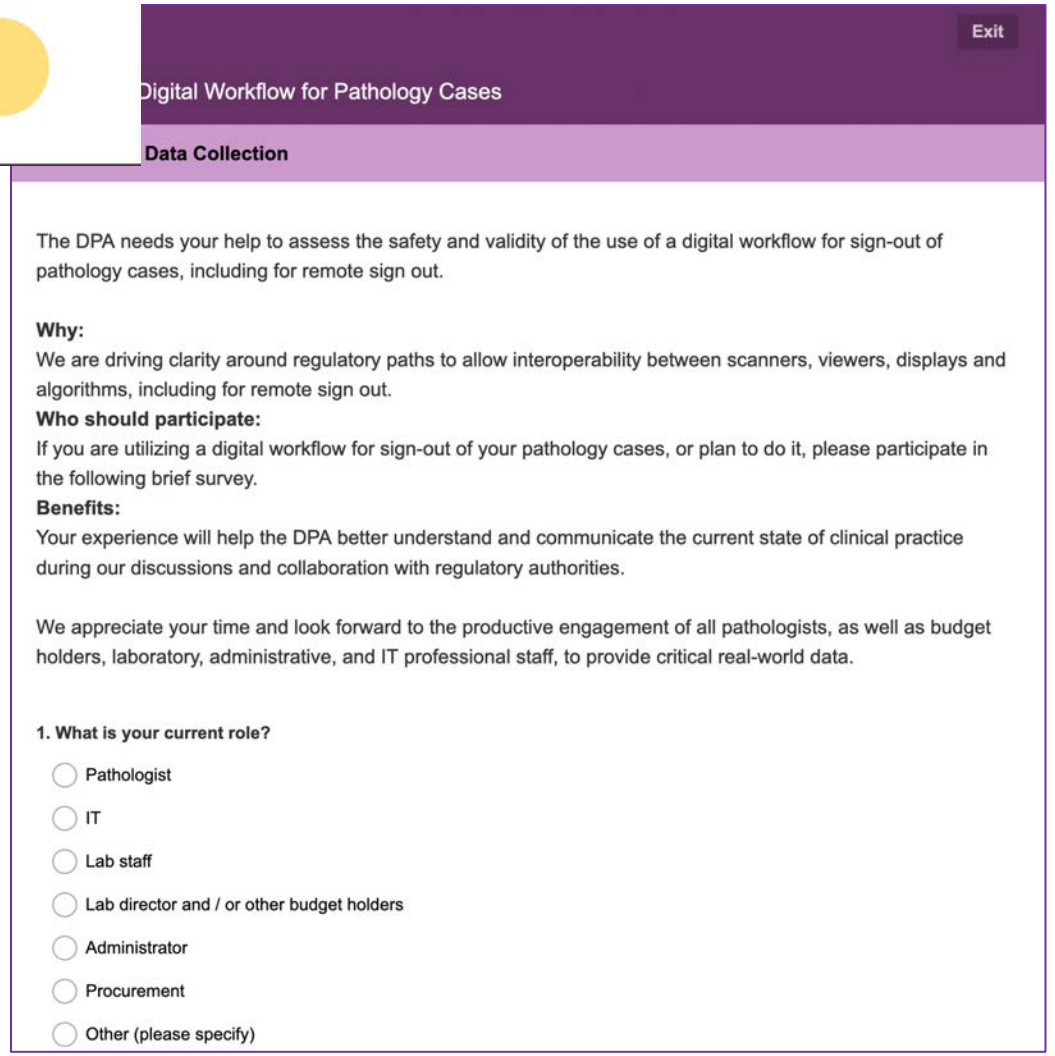
MXR Highlighted Speakers

Professional Societies

DPA DIGITAL PATHOLOGY ASSOCIATION

DPA => Survey of Digital Workflow for Pathology Cases

The DPA Regulatory and Standards Task Force is requesting your help to assess the safety and validity of the use of a digital workflow for sign-out of pathology cases. If you are utilizing a digital workflow for sign-out of your pathology cases, or plan to do it, please participate in the linked brief survey, by **Friday, October 6.**



Exit

Digital Workflow for Pathology Cases

Data Collection

The DPA needs your help to assess the safety and validity of the use of a digital workflow for sign-out of pathology cases, including for remote sign out.

Why:
We are driving clarity around regulatory paths to allow interoperability between scanners, viewers, displays and algorithms, including for remote sign out.
Who should participate:
If you are utilizing a digital workflow for sign-out of your pathology cases, or plan to do it, please participate in the following brief survey.
Benefits:
Your experience will help the DPA better understand and communicate the current state of clinical practice during our discussions and collaboration with regulatory authorities.

We appreciate your time and look forward to the productive engagement of all pathologists, as well as budget holders, laboratory, administrative, and IT professional staff, to provide critical real-world data.

1. What is your current role?

- Pathologist
- IT
- Lab staff
- Lab director and / or other budget holders
- Administrator
- Procurement
- Other (please specify)

Foundation for the National Institutes of Health Biomarkers Consortium

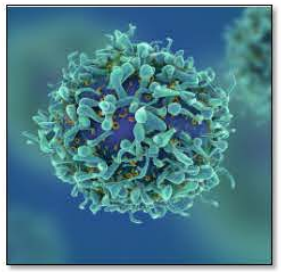
BIOMARKERS CONSORTIUM FNIH

Dr. Althea Lang, PhD, PMP

About the FNIH

Mission

The mission of the Foundation for the National Institutes of Health (FNIH) is to support the mission of the NIH. The FNIH creates and leads alliances and public-private partnerships that advance breakthrough biomedical discoveries and improve the quality of people's lives.



The FNIH was created by Congress in 1990 as a not-for-profit charitable organization. The Foundation began its work in 1996 to facilitate groundbreaking research at the U.S. National Institutes of Health (NIH) and worldwide.

Founded by Congress to:

- Attract and share resources
- Enable insight and innovation
- Establish standards
- Distribute expertise
- Create consensus
- Drive competitiveness in marketplace

FNIH

By the Numbers

$1.5B raised to date

$0.89 of every dollar spent directly supports programs

600+ programs supported since inception

~125 *active* research partnerships, scientific education/training, conferences/events, capital programs

17 years of outstanding Charity Navigator ratings

BIOMARKERS CONSORTIUM FNIH

Public Private Partnerships - the Role of the FNIH

Governance:

- Establishes and manages a variety of structures appropriate to each partnership

Policy Management:

- Provides a "safe harbor" for interactions between and among companies, government, academic entities
- Creates and implements policies that support NIH ethical and policy standards

Program Management:

- Drives consensus across all stakeholders about appropriate scientific selection and execution of projects

Fundraising and Relationship Management:

- Directly solicits contributions
- Stewards and manages donor funds

Project Management:

- Ensures projects meet established deliverables and "go/no go" milestones

Intellectual Property Management:

- Can provide "pre-competitive" structures for handling intellectual property, if needed

BIOMARKERS CONSORTIUM FNIH

FNIH Partnerships Cover a Spectrum of Designs

Funded exclusively by public organizations

ACTIV

Funded by both public and private organizations

LUNG-MAP

ADNI

Funded exclusively by private organizations

BIOMARKERS CONSORTIUM

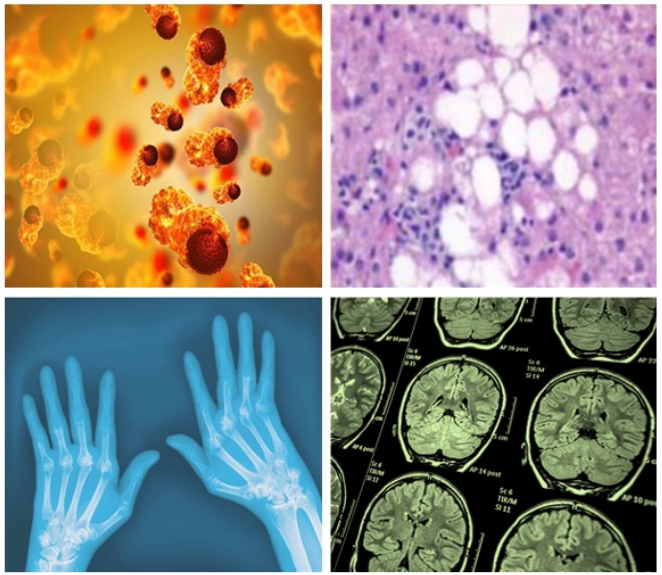
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

Grand Challenges in Global Health

Select FNIH Partnerships

ACTIV	**Accelerating COVID 19 Therapeutic Interventions and Vaccines (ACTIV)** NIH OD, BARDA, CDC, DOD, VA, EMA, OWS, FDA, 20 companies, 4 not-for-profit organizations	$1+ billion
	Accelerating Medicines Partnership® (AMP) NIH OD, 15 NIH ICs, 25 companies, 23 not-for-profit organizations	$733 million
PACT	**Partnership for Accelerating Cancer Therapies** NCI, PhRMA, 12 pharmaceutical companies	$220 million
ADNI	**Alzheimer's Disease Neuroimaging Initiative (ADNI)** NIA, NIBIB, 25+ companies, 3 not-for-profit organizations	$206 million
Grand Challenges in Global Health	**Grand Challenges in Global Health (GCGH)** Bill & Melinda Gates Foundation	$201 million
BIOMARKERS CONSORTIUM	**The Biomarkers Consortium** FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations	$107 million
LUNG-MAP	**LungMAP: Master Lung Protocol Trial** NCI (SWOG), FDA, Friends of Cancer Research, 10 companies to date	$42+ million

The Biomarkers Consortium



BIOMARKERS CONSORTIUM

IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

Biomarkers Consortium

Vision

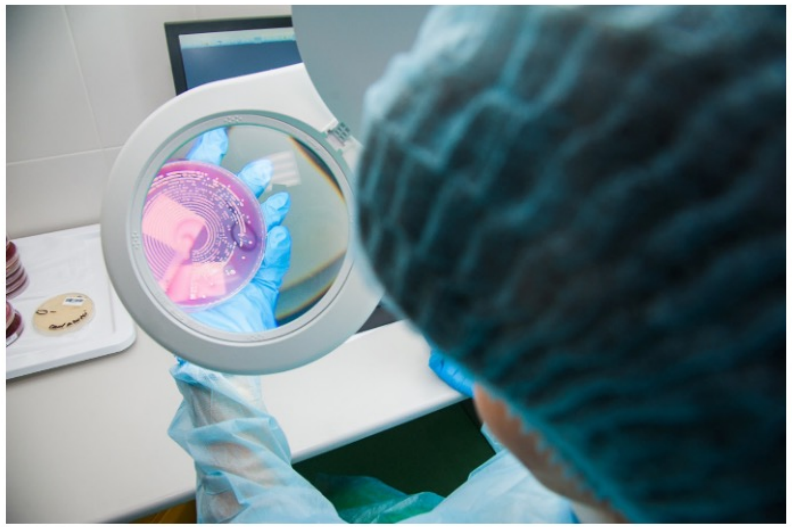
- Improving health through meaningful measurements

Mission

- To create and lead cross-sector efforts that validate and qualify biomarkers and other drug development tools to accelerate better decision making for the development of new therapeutics and health technologies.

Goals

- Facilitate the development and the seeking of regulatory approval for biomarkers using new and existing technologies;
- Develop evidence to help qualify biomarkers for specific applications in diagnosing disease, predicting therapeutic response or improving clinical practice;
- Generate information useful to inform regulatory decision making;
- Make consortium project results broadly available to the entire scientific community.



BIOMARKERS CONSORTIUM FNIH

Driving Principles of the Biomarkers Consortium

- BC projects bridge the gap between basic research and practical needs for advancing drug development and regulatory science.
- All work is pre-competitive, and results are released to the public as early as possible.
- Drug development tool projects are developed collaboratively with involvement from academic, government and industry scientists. Projects can be generated in any therapeutic area.
- All projects have specific, well-defined goals and are milestone-driven, including interim "go/no-go" funding gates.

>35+ projects have been approved and initiated since the founding of the Consortium in 2006

BIOMARKERS CONSORTIUM FNIH

Principles and Policies

- Specific policies and other information available at:
  https://fnih.org/our-programs/biomarkers-consortium/about

- Key governing policies negotiated prior to launch of Biomarkers Consortium with principals/legal counsel representing the FNIH, NIH, FDA, PhRMA and BIO:
  - Intellectual property (IP) and data sharing
  - Antitrust
  - Selection and award of grants/contracts
  - Confidentiality
  - Conflict of interest

BIOMARKERS CONSORTIUM FNIH

Biomarkers Consortium

15 years of collaboration, research, and progress

14 therapeutics advanced based on tools generated

9 clinical tools being used in drug development

5 FDA guidance documents supported by work of the BC

1 qualified composite biomarker

>50 publications

800+ citations

60+ member organizations

BIOMARKERS CONSORTIUM FNIH

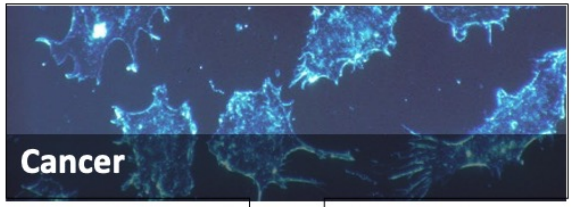
Biomarkers Consortium Private Sector Members (as of 23 August 2023)

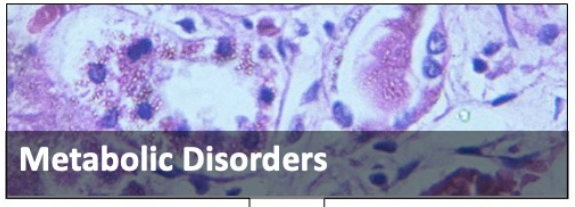
Represent large and small companies, trade groups and not-for-profit organizations

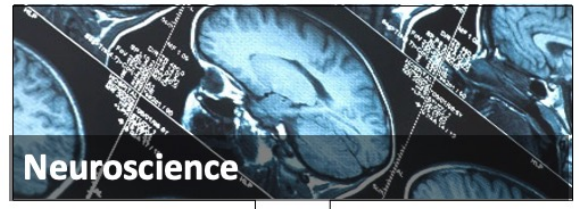
Biomarkers Consortium Governance

Executive Committee
NIH / FDA / CMS / Industry / FNIH

Steering Committees







Multiple Project Teams
Representatives from NIH, FDA, Industry, Non-Profits and Academia

Working Groups and Project Development Teams
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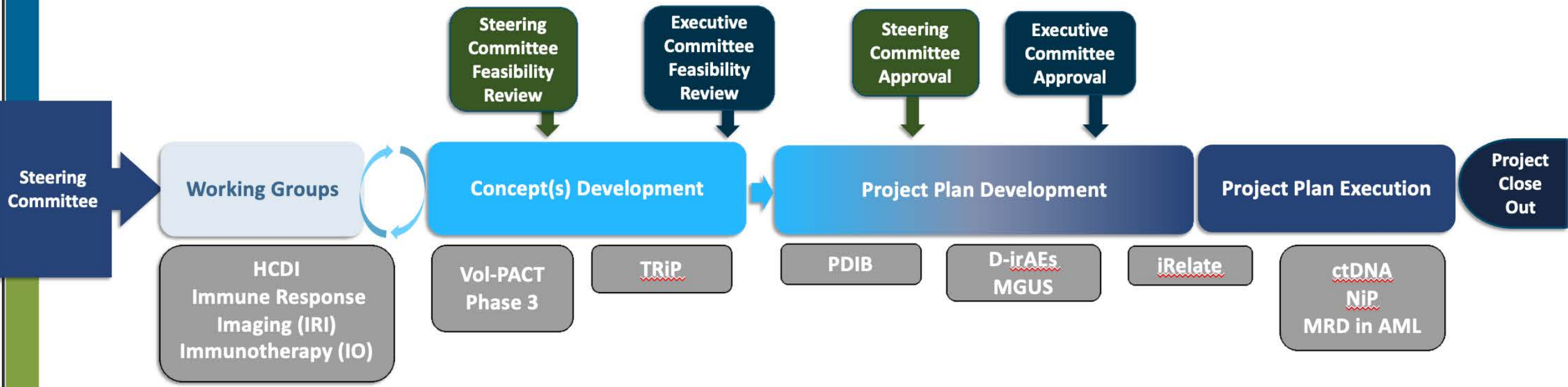
Project Development Pipeline



Completed Projects & Efforts

FDG-PET
MRD in ALL
HD-SCA
Vol-PACT
ChIIME
MRD in MM
Big Data Guidance

BIOMARKERS CONSORTIUM FNIH

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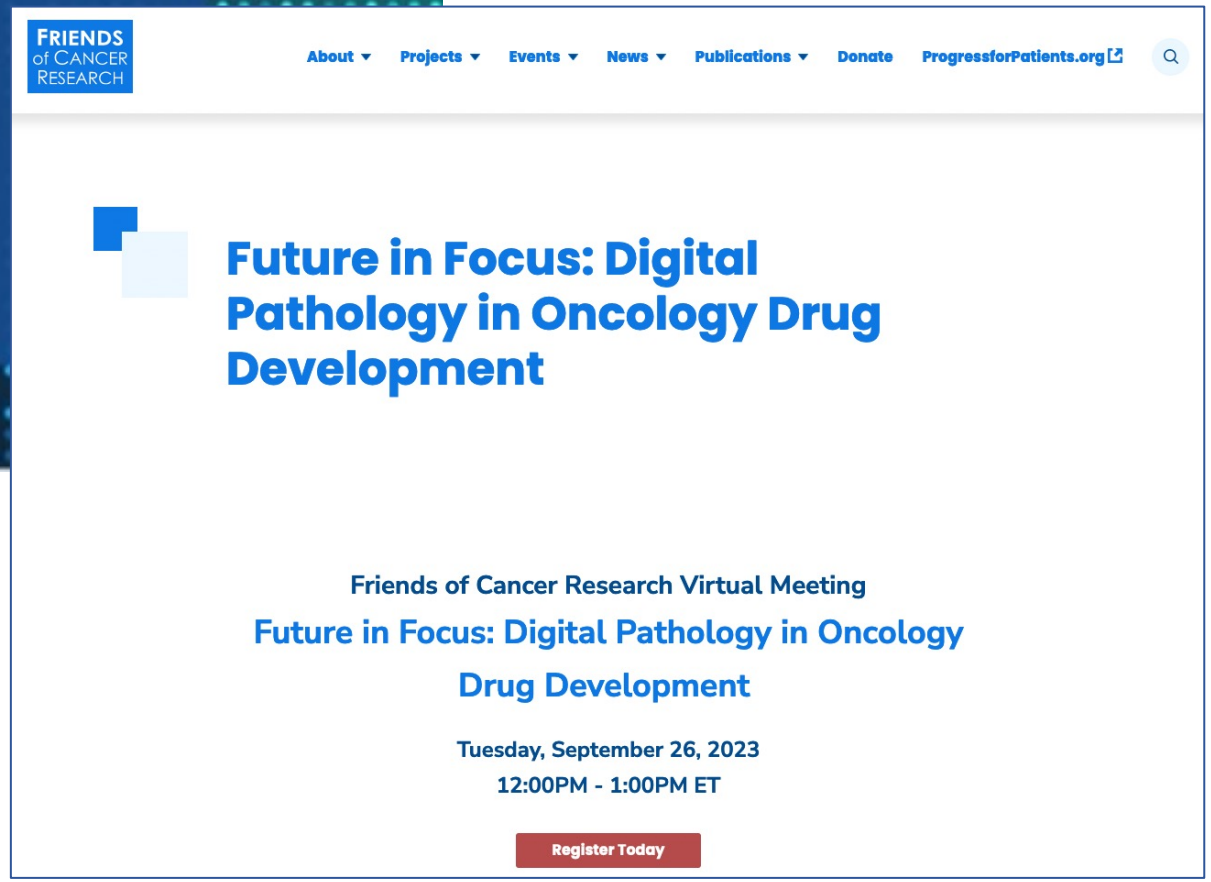
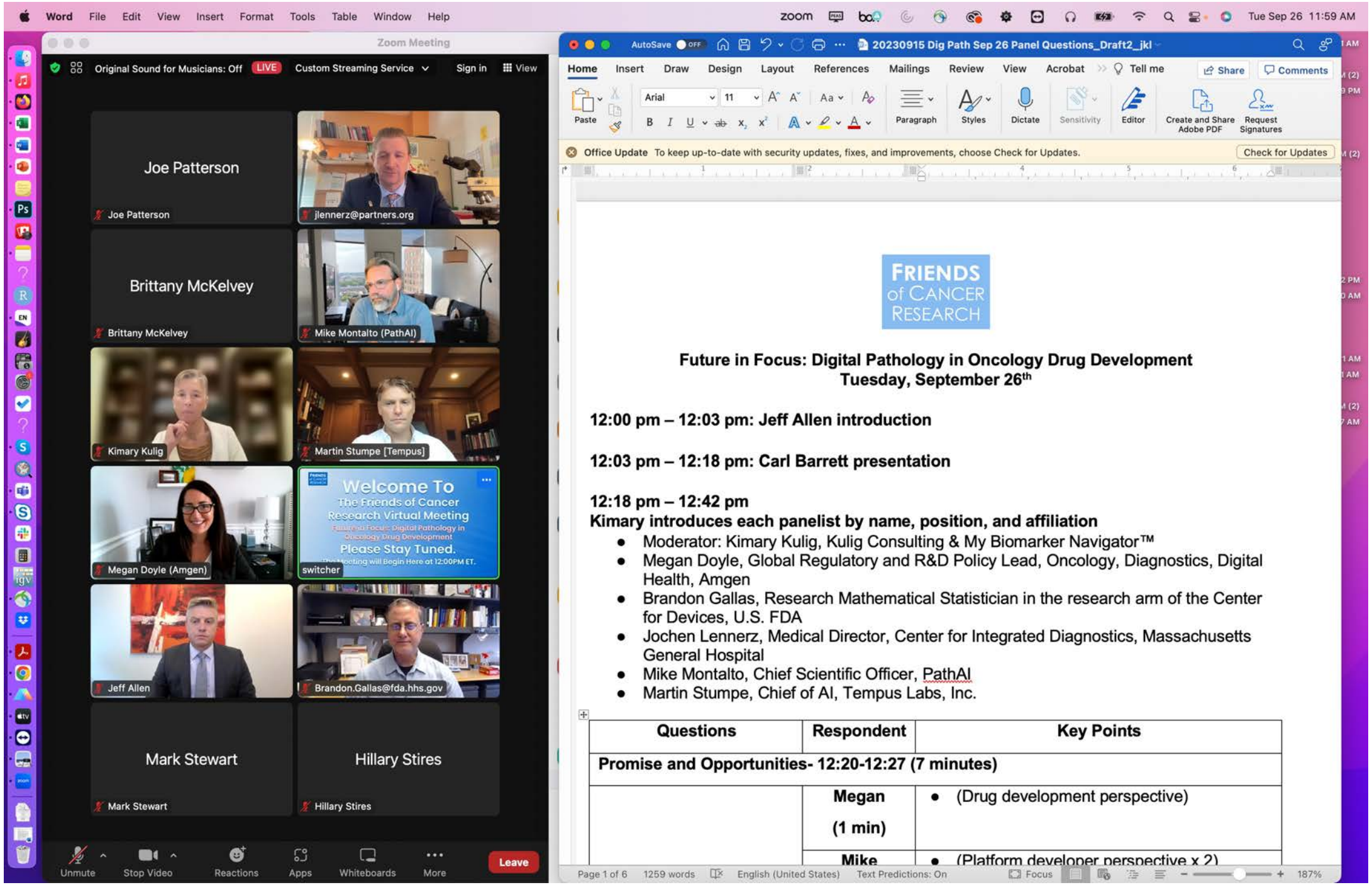
Patient advocacy



If you missed it, full webinar recording is available online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Joe Patterson
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jlennerz@partners.org
Brittany McKelvey
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Mike Montalto (PathAI)
Kimary Kulig
Martin Stumpe [Tempus]
Megan Doyle (Amgen)
Welcome To
The Friends of Cancer Research Virtual Meeting
Please Stay Tuned.
switcher
Jeff Allen
Brandon.Gallas@fda.hhs.gov
Mark Stewart
Hillary Stires
Unmute
Stop Video
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Office Update To keep up-to-date with security updates, fixes, and improvements, choose Check for Updates.
Check for Updates
FRIENDS of CANCER RESEARCH
Future in Focus: Digital Pathology in Oncology Drug Development
Tuesday, September 26th
12:00 pm – 12:03 pm: Jeff Allen introduction
12:03 pm – 12:18 pm: Carl Barrett presentation
12:18 pm – 12:42 pm
Kimary introduces each panelist by name, position, and affiliation
Moderator: Kimary Kulig, Kulig Consulting & My Biomarker Navigator™
Megan Doyle, Global Regulatory and R&D Policy Lead, Oncology, Diagnostics, Digital Health, Amgen
Brandon Gallas, Research Mathematical Statistician in the research arm of the Center for Devices, U.S. FDA
Jochen Lennerz, Medical Director, Center for Integrated Diagnostics, Massachusetts General Hospital
Mike Montalto, Chief Scientific Officer, PathAI
Martin Stumpe, Chief of AI, Tempus Labs, Inc.
Questions
Respondent
Key Points
Promise and Opportunities- 12:20-12:27 (7 minutes)
Megan
(1 min)
(Drug development perspective)
Mike
(Platform developer perspective x 2)
Page 1 of 6
1259 words
English (United States)
Text Predictions: On
Focus
187%

FRIENDS of CANCER RESEARCH

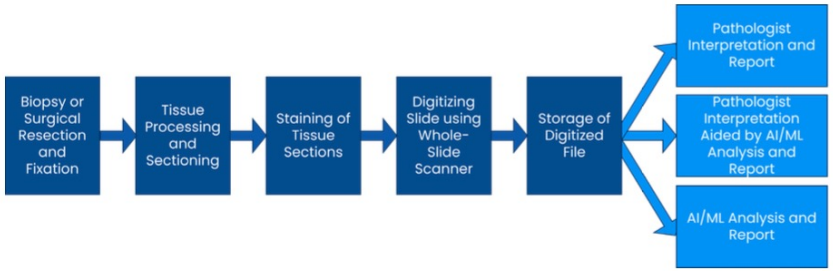
A FRIENDS OF CANCER RESEARCH WHITE PAPER

Supporting the Application of Computational Pathology in Oncology

Introduction

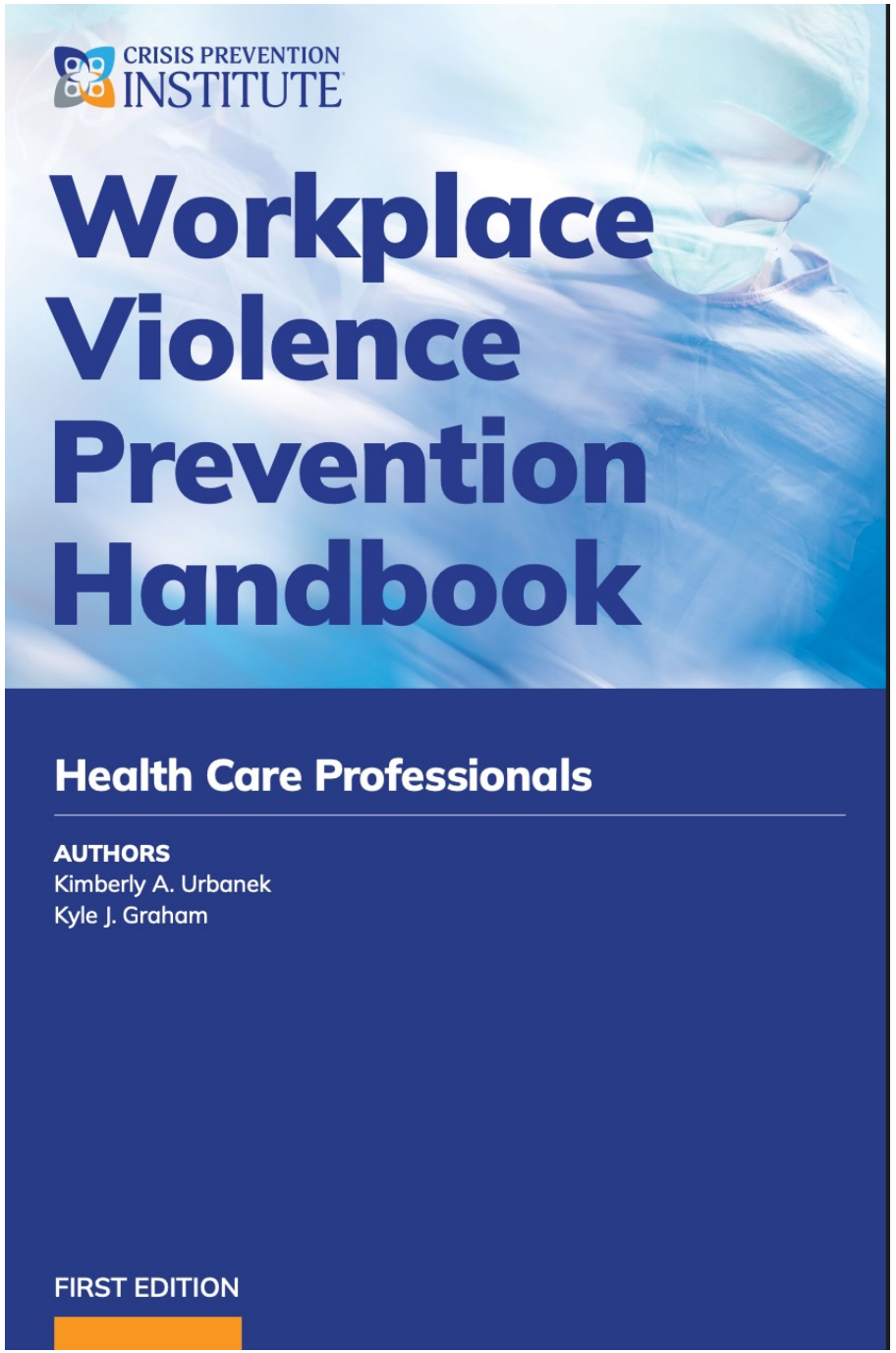
Biological heterogeneity of cancers causes tumors to respond differently to the same treatments. Thus, there is a compelling need to appropriately diagnose patients and identify relevant biomarkers for oncology treatments in both clinical practice and trials. Digital pathology is an emerging application in oncology drug development and clinical care, which allows for whole-slide image creation for storage, viewing, analyses, and interpretation. Digitized images are used directly by pathologists for biomarker interpretation, cellular annotation, and diagnosis. These images can also be used to support development of computational pathology platforms that utilize techniques such as artificial intelligence (AI) and machine learning (ML) to analyze and measure specific image elements, such as subvisual morphological patterns and phenotypes, identify features, and generate reproducible and structured data. These AI and ML platforms referred to in aggregate as computational pathology, may establish novel biomarkers, aid in quantifying prognostic and predictive biomarkers currently assessed or categorized by a pathologist, and expedite diagnosis or pathological scoring, all of which may go towards identifying and selecting patients for oncology treatments. Digital and computational pathology encompass several linked workflow components including both the digitization of the whole slides as well as the platforms for analysis (**Figure 1**).

Figure 1: Workflow Components of Digital and Computational Pathology



White Paper

Diversity Equity & Inclusion


CRISIS PREVENTION INSTITUTE
Workplace Violence Prevention Handbook
Health Care Professionals
AUTHORS
Kimberly A. Urbanek
Kyle J. Graham
FIRST EDITION

Resources

Radiology: Artificial Intelligence

ORIGINAL RESEAR

The Subgroup Imperative: Chest Radiograph Classifier Generalization Gaps in Patient, Setting, and Pathology Subgroups

Monish Ahluwalia, MD, MSc • Mohamed Abdalla, PhD • James Sanayei, MD • Laleh Seyyed-Kalantari, PhD • Mohannad Hussain, HBSc • Amna Ali, HBSc • Benjamin Fine, SM, MD

From the Kingston Health Sciences Centre, Queen's U
Policy, Management and Evaluation (M. Ahluwalia), D
Toronto, Toronto, Ontario, Canada; Vector Institute fo
Department of Diagnostic Imaging (A.A., B.F.), Trillium
1B8; Department of Medicine, Royal University Hospit
versity, Toronto, Ontario, Canada (L.S.K.); and Techie M
received June 6; accepted June 22. **Address corresponde**

Supported by Digital Supercluster Canada.

Conflicts of interest are listed at the end of this article.

Purpose: To externally test four chest radiograph classifiers on a large, diverse, real-world dataset with robust subgroup analysis.

Materials and Methods: In this retrospective study, adult posteroanterior chest radiographs (January 2016–December 2020) and associated radiology reports from Trillium Health Partners in Ontario, Canada, were extracted and de-identified. An open-source natural language processing tool was locally validated and used to generate ground truth labels for the 197 540-image dataset based on the associated radiology report. Four classifiers generated predictions on each chest radiograph. Performance was evaluated using accuracy, positive predictive value, negative predictive value, sensitivity, specificity, F1 score, and Matthews correlation coefficient for the overall dataset and for patient, setting, and pathology subgroups.

Results: Classifiers demonstrated 68%–77% accuracy, 64%–75% sensitivity, and 82%–94% specificity on the external testing dataset. Algorithms showed decreased sensitivity for solitary findings (43%–65%), patients younger than 40 years (27%–39%), and patients in the emergency department (38%–60%) and decreased specificity on normal chest radiographs with support devices (59%–85%). Differences in sex and ancestry represented movements along an algorithm's receiver operating characteristic curve.

Conclusion: Performance of deep learning chest radiograph classifiers was subject to patient, setting, and pathology factors, demonstrating that subgroup analysis is necessary to inform implementation and monitor ongoing performance to ensure optimal quality, safety, and equity.

Supplemental material is available for this article.

JAMA Internal Medicine | Review

Assessing the Clinical Utility of Liquid Biopsies Across 5 Potential Indications From Therapy Selection to Population Screening

A Review

David J. Carr, MD; H. Gilbert Welch, MD, MPH

IMPORTANCE There has been great enthusiasm for the emerging technology of molecular-based tests to detect and quantify tumor DNA circulating in the bloodstream, colloquially known as a liquid biopsy. However, less attention has been given to how their clinical utility depends on the indication for testing, which includes a range of clinical situations, each presenting unique challenges.

OBSERVATIONS Five indications for circulating tumor DNA (ctDNA) blood testing were considered. (1) For therapy selection, ctDNA tests can identify genetic alterations in patients with cancer amenable to targeted therapy, but most patients do not have a targetable alteration. (2) For response to therapy, the absence of residual tumor DNA following cancer surgery could reduce the use of adjuvant chemotherapy, but it is unclear that this will happen in practice. (3) For disease surveillance following cancer treatment, ctDNA tests may well detect cancer recurrence before symptoms appear, yet earlier intervention may have no effect on mortality. (4) For diagnosis of suspected cancer, ctDNA tests are able to identify some symptomatic cancers, but how they add to the conventional diagnostic evaluation is unknown. (5) For screening for cancer, multicancer tests can detect many types of cancer, but their low sensitivity for early-stage tumors raises questions as to whether screening can help patients live longer or live better.

CONCLUSIONS AND RELEVANCE Circulating tumor DNA tests are being promoted for multiple indications. Numerous studies are ongoing, but randomized clinical trials of their effect on patient-centered outcomes are rare. While these tests have the potential to improve care in selected indications, this must be proven, as they will add cost, complexity, and unintended adverse effects for patients.

JAMA Intern Med. doi:10.1001/jamainternmed.2023.3603
Published online August 28, 2023.

Table 2. Harms of Screening

Harm	Description	No. of individuals affected	Effect on individual
Overdiagnosis	Patients are diagnosed and treated for a cancer not destined to progress to cause symptoms or death. Some experience complications of treatment.	Few	Large
Earlier detection of aggressive cancer and/or no change in death	Patients live longer with the knowledge they have a deadly cancer and experience interventions and their toxic effects at a time they would otherwise be asymptomatic.	Few	Large
Financial toxicity of subsequent evaluation	While screening itself typically has few out-of-pocket costs, it can trigger subsequent diagnostic evaluations with substantial out-of-pocket costs.	Several	Moderate
False alarm	People with abnormal screening test results generally do not have cancer, but before they are pronounced "cancer free," many have to go through multiple tests. Throughout the process, many will worry about whether they have cancer. Some will never be reassured that they are, in fact, healthy.	Many	Small

Author Affiliations: Department of Pathology, Detroit Medical Center University Laboratories, Wayne State University School of Medicine, Detroit, Michigan (Carr); Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, Massachusetts (Welch).

Corresponding Author: David J. Carr, MD, Wayne State University, 4707 St Antoine, Detroit, MI 48201 (dcarr@med.wayne.edu).

nature reviews drug discovery

COMMENT | 08 September 2023

Defining rare conditions in the era of personalized medicine

The total number of rare conditions is debated, partly because of the variety of definitions of what constitutes rare. A broader consensus view of what rare means, bas on improved understanding of individual group and patient clinicopathological characteristics, will help maximize the impact of technological advances in therapeuti development programmes.

COMMENT | 08 September 2023

Defining rare conditions in the era of personalized medicine

The total number of rare conditions is debated, partly because of the variety of definitions of what constitutes rare. A broader consensus view of what rare means, based on improved understanding of individual group and patient clinicopathological characteristics, will help maximize the impact of technological advances in therapeutic development programmes.

Daniel J. O'Connor ✉, Michela Gabaldo, Annemieke Aartsma-Rus & Anneliene Hechtelt Jonker

Rare conditions have been defined and categorized in a variety of ways. Traditionally, rare conditions have been described with specific clinical features and in some cases named after their discoverer. Through a panel of experts and in collaboration with the World Health Organization, an operational description of rare diseases has been proposed by Rare Diseases International: a medical condition with a specific pattern of clinical signs, symptoms and findings that affects fewer than or equal to 1 in 2,000 persons living in any World Health Organization-defined region of the world. Numerous other similar and overlapping definitions exist, including those from regulatory authorities, governments, not-for-profit organizations and patients' organizations[1]. In these definitions, it is generally accepted that rare diseases are defined by their low prevalence, that patients with rare diseases face specific challenges in their diagnostic and treatment journeys, and that these patients should have the same opportunities for health care as patients with more common conditions.

Despite these consensus features, there is currently no common global agreement on the impact and widespread application of advances in molecular sciences and pathology on the definition of a rare condition. Here, we discuss the impact of defining rare conditions in the era of personalized medicine, including subsetting of common conditions, subsetting of rare conditions, individualized treatment options and shared molecular entity conditions.

How are rare conditions currently defined?

Most definitions for rare conditions are based on low prevalence, such as the definition in the European Union, in which a rare condition is one that affects no more than 5 in 10,000 people. In addition, definitions may include qualitative indicators, such as

nature communications

Article

https://doi.org/10.1038/s41467-023-40336-4

Delayed gut microbiota maturation in the first year of life is a hallmark of pediatric allergic disease

Received: 23 February 2023

Accepted: 19 July 2023

Published online: 29 August 2023

Check for updates

Courtney Hoskinson[1,2], Darlene L. Y. Dai[1], Kate L. Del Bel[1], Allan B. Becker[3], Theo J. Moraes[4], Piushkumar J. Mandhane[5], B. Brett Finlay[2,6,7], Elinor Simons[3], Anita L. Kozyrskyj[5], Meghan B. Azad[3,8,9], Padmaja Subbarao[4,10,11], Charisse Petersen[1,12] & Stuart E. Turvey[1,12]

Allergic diseases affect millions of people worldwide. An increase in their prevalence has been associated with alterations in the gut microbiome, i.e., the microorganisms and their genes within the gastrointestinal tract. Maturation of the infant immune system and gut microbiota occur in parallel; thus, the conformation of the microbiome may determine if tolerant immune programming arises within the infant. Here we show, using deeply phenotyped participants in the CHILD birth cohort ($n = 1115$), that there are early-life influences and microbiome features which are uniformly associated with four distinct allergic diagnoses at 5 years: atopic dermatitis (AD, $n = 367$), asthma (As, $n = 165$), food allergy (FA, $n = 136$), and allergic rhinitis (AR, $n = 187$). In a subset with shotgun metagenomic and metabolomic profiling ($n = 589$), we discover that impaired 1-year microbiota maturation may be universal to pediatric allergies (AD $p = 0.000014$; As $p = 0.0073$; FA $p = 0.00083$; and AR $p = 0.0021$). Extending this, we find a core set of functional and metabolic imbalances characterized by compromised mucous integrity, elevated oxidative activity, decreased secondary fermentation, and elevated trace amines, to be a significant mediator between microbiota maturation at age 1 year and allergic diagnoses at age 5 years ($\beta_{indirect} = -2.28$; $p = 0.0020$). Microbiota maturation thus provides a focal point to identify deviations from normative development to predict and prevent allergic disease.

Allergic diseases affect hundreds of millions of children worldwide and continue to increase in prevalence[1–4]. These rising rates have coincided with social and environmental changes that have had an intergenerational impact on the stably colonizing microbes and their collective genes that make up our microbiota and microbiome, respectively[5,6].

Established during infancy, the nascent microbiota's initial expansion and fluctuation are particularly sensitive to external

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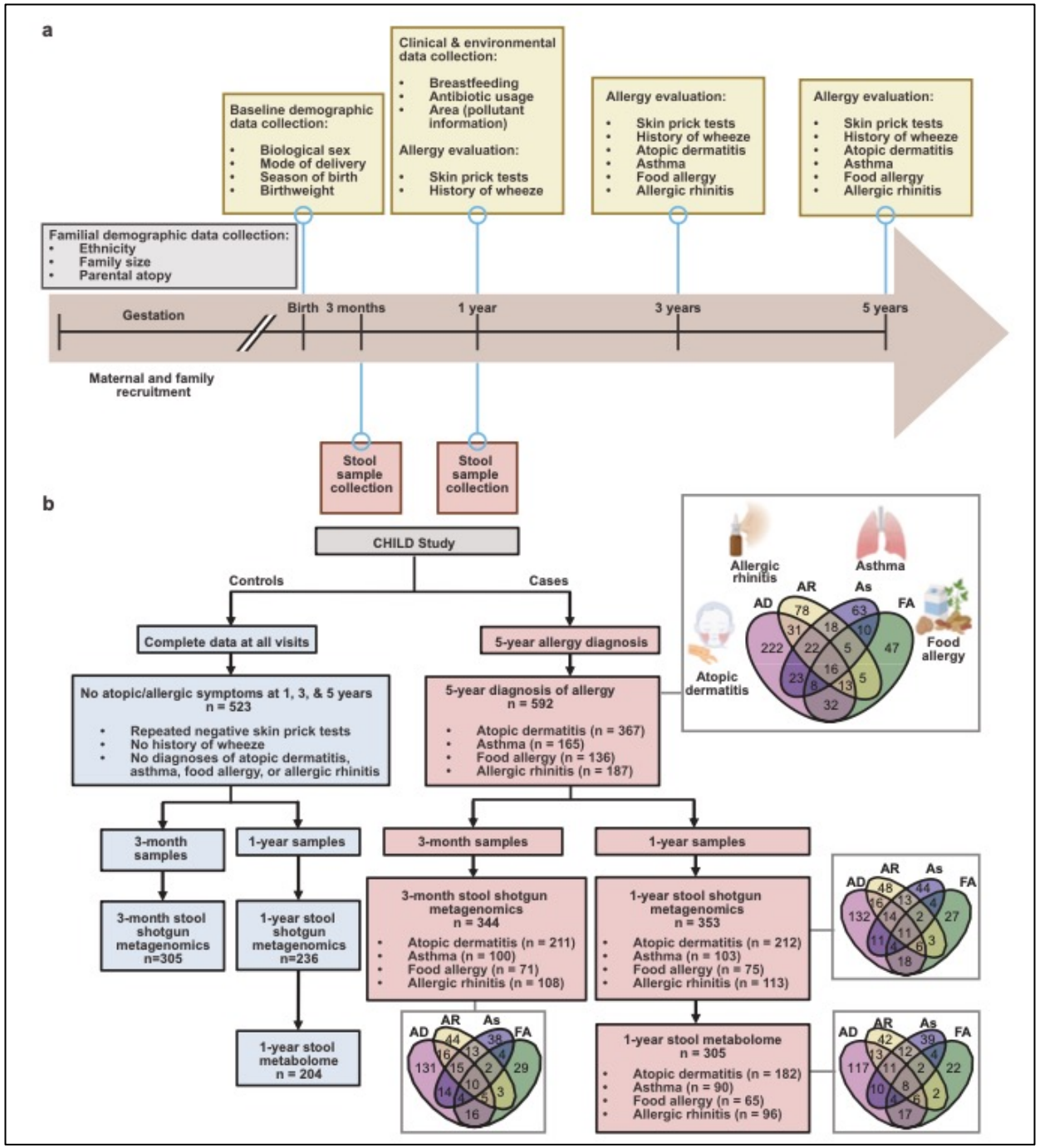


Radiology: Artificial Intelligence

The AI Generalization Gap: One Size Does Not Fit All

Merel Huisman, MD, PhD • Gerjon Hannink, PhD

Merel Huisman, MD, PhD, is a radiologist at Radboud University Medical Center in Nijmegen, the Netherlands. Her clinical subspecialty interest is cardiothoracic and musculoskeletal radiology. She is a clinical epidemiologist by training, a European Society of Medical Imaging Informatics board member, and involved in several national and international initiatives concerning artificial intelligence in health care.

Gerjon Hannink, PhD, is a clinical epidemiologist and biostatistician at Radboud University Medical Center in Nijmegen, the Netherlands. His research interests focus on clinical prediction models, artificial intelligence, and medical decision-making.

was a proprietary third-party classifier, while the rest were open source and trained on well-known, large, publicly available datasets (ie, CheXpert, MIMIC-CXR, and Chest X-ray-14). The classifiers were tested on a large dataset of chest radiographs consecutively collected at their regional teaching hospital from patients with temporally, geographically, and demographically different makeup (n = 197 540 adults with a posteroanterior chest radiograph; age range, 18–105 years; 50% males; 67% with ancestry from "greater Europe"). The primary outcome was binary (normal or abnormal) with algorithm composition and operating thresholds "as-is"; for example, the overall prevalence of abnormalities was 49% of cases versus 91% in CheXpert.

Subgroup analysis was conducted by patient setting (eg, emergency), age categories, sex, and name-based ancestry. A pragmatic, natural language processing–based, semisupervised method to establish ground truth was chosen and locally validated. Overall sensitivity ranged from 50% to 72%; the third-party classifier had the highest overall performance. We could not find the intended performance of the studied classifiers in the article nor in the literature, but we assume that the overall performance

Learning under Concept Drift: A Review

Jie Lu, *Fellow, IEEE,* Anjin Liu, *Member, IEEE,* Fan Dong, Feng Gu, João Gama, and Guangquan Zhang

Abstract—Concept drift describes unforeseeable changes in the underlying distribution of streaming data over time. Concept drift research involves the development of methodologies and techniques for drift detection, understanding and adaptation. Data analysis has revealed that machine learning in a concept drift environment will result in poor learning resu
researchers identify which research topics are significant and how to apply related techniques in
that a high quality, instructive review of current research developments and trends in the concept
due to the rapid development of concept drift in recent years, the methodologies of learning unde
noticeably systematic, unveiling a framework which has not been mentioned in literature. This pa
publications in concept drift related research areas, analyzes up-to-date developments in method
establishes a framework of learning under concept drift including three main components: concep
understanding, and concept drift adaptation. This paper lists and discusses 10 popular synthetic
benchmark datasets used for evaluating the performance of learning algorithms aiming at handli
related research directions are covered and discussed. By providing state-of-the-art knowledge, t
researchers in their understanding of research developments in the field of learning under concep

Index Terms—concept drift, change detection, adaptive learning, data streams

1 Introduction

Governments and companies are generating huge amounts of streaming data and urgently need efficient data analytics and machine learning techniques to support them making predictions and decisions. However, the rapidly changing environment of new products, new markets and new customer behaviors inevitably results in the appearance of concept drift problem. Concept drift means that the statistical properties of the target variable, which the model is trying to predict, change over time in unforeseen ways [1]. If the concept drift occurs, the induced pattern of past data may not be relevant to the new data, leading to

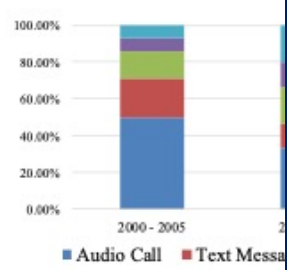


Fig. 1. Concept drift in mob
demonstration only)

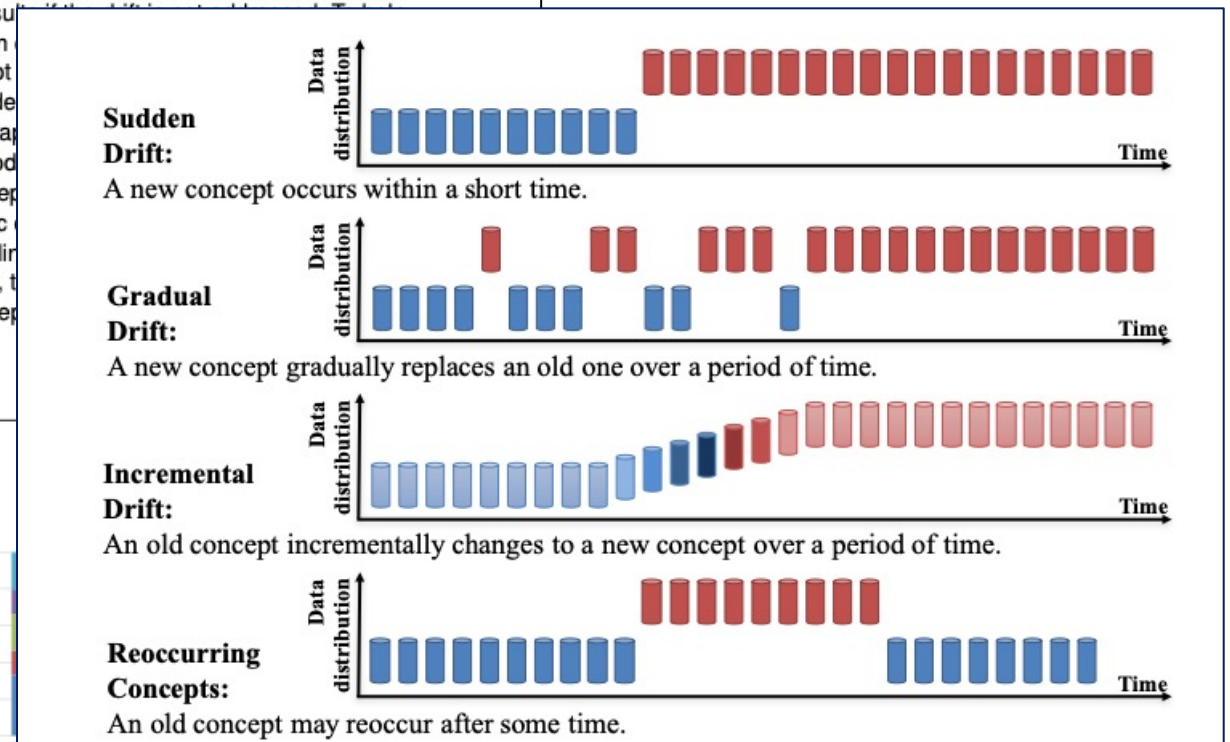


Fig. 4. An example of concept drift types.

Radiology Research Alliance

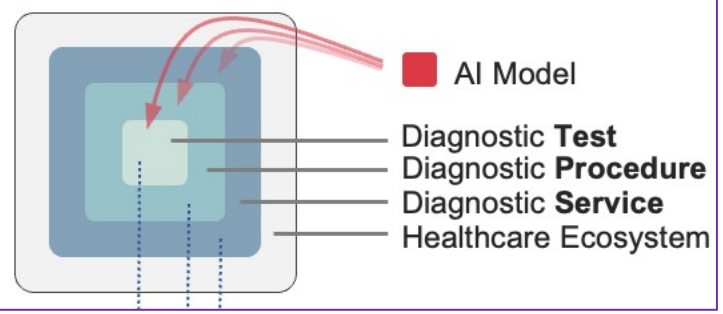
Noninterpretive Uses of Artificial Intelligence in Radiology

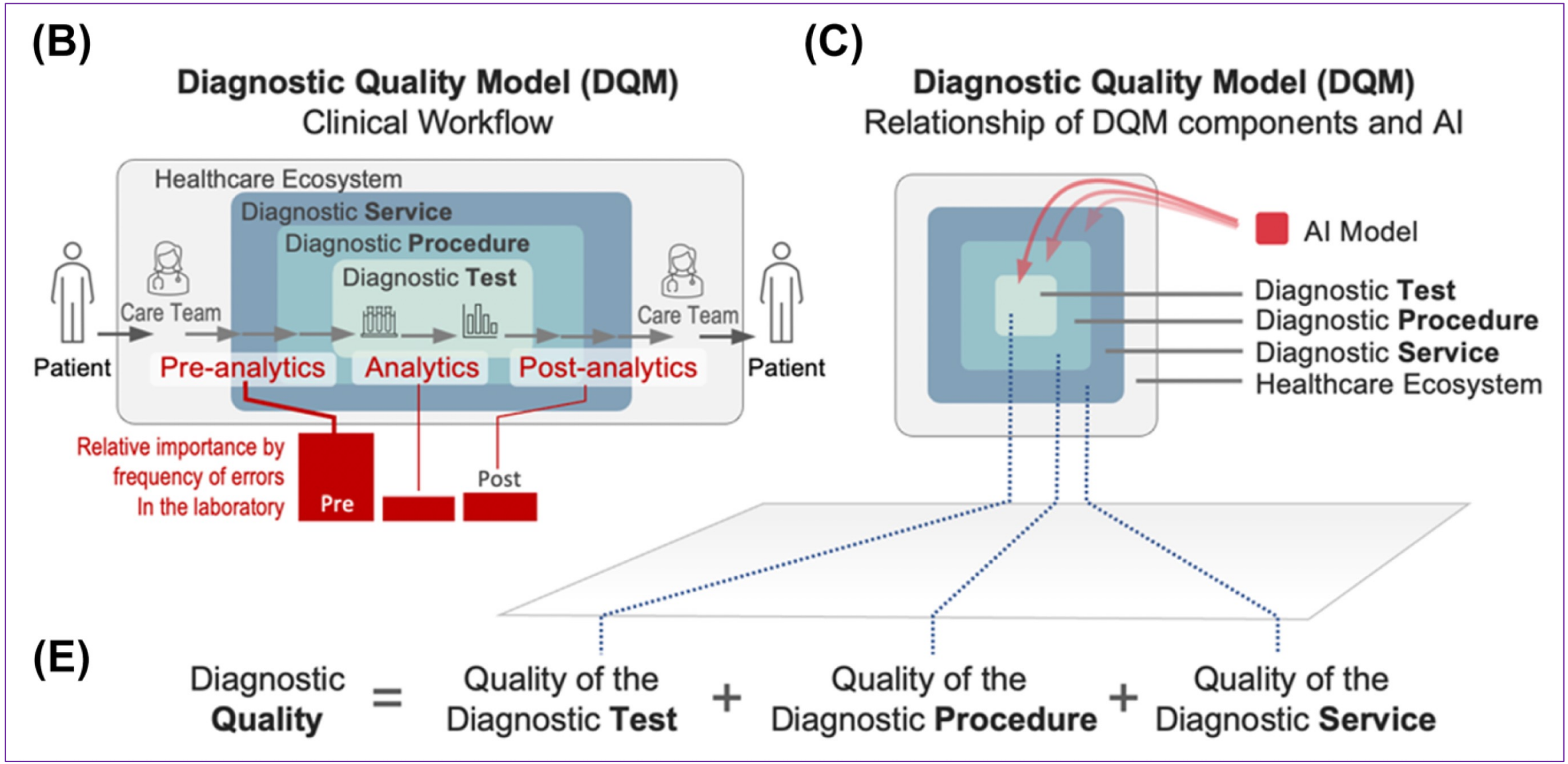
Michael L. Richardson, MD, Elisabeth R. Garwood, MD, Yueh Lee, MD, Matthew D. Li, MD, Hao S. Lo, MD, MBA, Arun Nagaraju, MD, Xuan V. Nguyen, MD, PhD, Linda Probyn, MD, Prabhakar Rajiah, MD, Jessica Sin, MD, Ashish P. Wasnik, MD, Kali Xu, MD

We deem a computer to exhibit artificial intelligence (AI) when it performs a task that would normally require intelligent action by a human. Much of the recent excitement about AI in the medical literature has revolved around the ability of AI models to recognize anatomy and detect pathology on medical images, sometimes at the level of expert physicians. However, AI can also be used to solve a wide range of noninterpretive problems that are relevant to radiologists and their patients. This review summarizes some of the newer noninterpretive uses of AI in radiology.

Key Words: Artificial intelligence; Deep learning; Radiology applications; Radiology education.

Diagnostic Quality Model (DQM)
Relationship of DQM components and AI




(B)
Diagnostic Quality Model (DQM)
Clinical Workflow
Healthcare Ecosystem
Diagnostic Service
Diagnostic Procedure
Diagnostic Test
Care Team
Care Team
Patient
Patient
Pre-analytics
Analytics
Post-analytics
Relative importance by
frequency of errors
In the laboratory
Pre
Post
(C)
Diagnostic Quality Model (DQM)
Relationship of DQM components and AI
AI Model
Diagnostic Test
Diagnostic Procedure
Diagnostic Service
Healthcare Ecosystem
(E)
Diagnostic
Quality
=
Quality of the
Diagnostic Test
+
Quality of the
Diagnostic Procedure
+
Quality of the
Diagnostic Service

Radiology Research Alliance

Noninterpretive Uses of Artificial Intelligence in Radiology

Michael L. Richardson, MD, Elisabeth R. Ga
Hao S. Lo, MD, MBA, Arun Nagaraju, MD
Prabhakar Rajiah, MD, Jess

We deem a computer to exhibit artificial intelligence (AI) when it performs a
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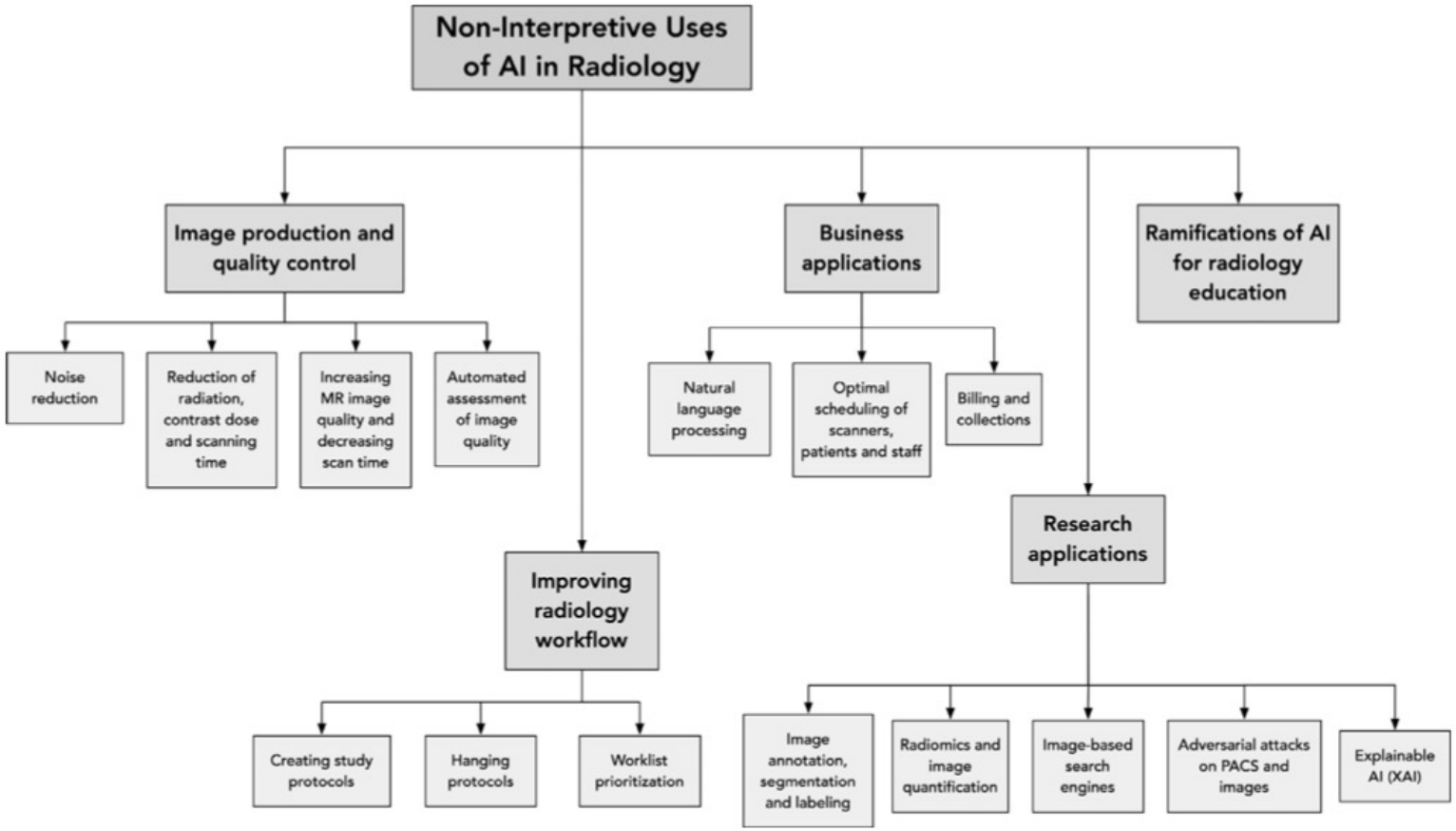


Figure 1. Flowchart of topics covered in this review.

RESEARCH ARTICLE SUMMARY

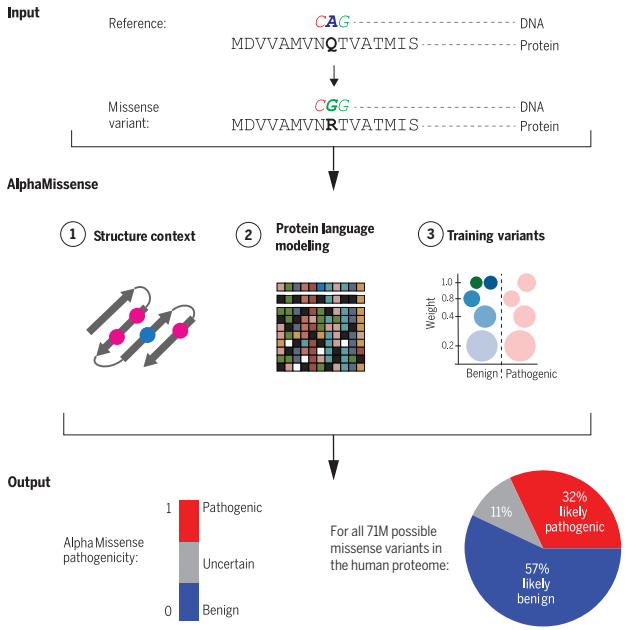
MACHINE LEARNING

Accurate proteome-wide missense variant effect prediction with AlphaMissense

Jun Cheng*, Guido Novati, Joshua Pan†, Clare Bycroft†, Akvilė Žemgulytė†, Taylor Applebaum†, Alexander Pritzel, Lai Hong Wong, Michal Zielinski, Tobias Sargeant, Rosalia G. Schneider, Andrew W. Senior, John Jumper, Demis Hassabis, Pushmeet Kohli*, Žiga Avsec*

INTRODUCTION: Genome sequencing has revealed extensive genetic variation in human populations. Missense variants are genetic variants that alter the amino acid sequence of proteins. Pathogenic missense variants disrupt protein function and reduce organismal fitness, while benign missense variants have limited effect.

RATIONALE: Classifying these variants is an important ongoing challenge in human genetics. Of more than 4 million observed missense variants, only an estimated 2% have been clinically classified as pathogenic or benign, while the vast majority of them are of unknown clinical significance. This limits the diagnosis of rare diseases, as well as the development or application of clinical treatments that target the underlying genetic cause. Machine learning approaches could close the variant interpretation gap by exploiting patterns in biological data to predict the pathogenicity of unannotated variants. Specifically, AlphaFold, which accurately predicts pro… structure from protein sequence, may be … as a foundation to predict the pathogenicity of variants on proteins.



AlphaMissense pathogenicity prediction. AlphaMissense takes as input a missense variant and predicts its pathogenicity. We fine-tuned AlphaFold on human and primate variant population frequency data and calibrated the confidence on known disease variants. AlphaMissense predicts the probability of a missense variant being pathogenic and classifies it as either likely benign, likely pathogenic, or uncertain. We provide predictions for all possible human missense variants as a resource for the community.

RESULTS: We developed AlphaMissense to leverage advances on multiple fronts: (i) unsupervised protein language modeling to learn amino acid distributions conditioned on sequence context; (ii) incorporating structural context by using an AlphaFold-derived system; and (iii) fine-tuning on weak labels from population frequency data, thereby avoiding bias from human-curated annotations. AlphaMissense achieves state-of-the-art missense pathogenicity predictions in clinical annotation, de novo disease variants, and experimental assay benchmarks without explicitly training on such data. As a resource to the community, we provide a database of predictions for all possible single amino acid substitutions in the human proteome. We classify 32% of all missense variants as likely pathogenic and 57% as likely benign using a cutoff yielding 90% precision on the ClinVar dataset, thereby providing a confident prediction for most human missense variants.

We show how this resource can be used to accelerate research in multiple fields. Molecular biologists could use the database as a starting point for designing and interpreting experiments that probe saturating amino acid substitutions across the human proteome. Human geneticists could combine gene-level AlphaMissense predictions with population cohort–based approaches to quantify the functional significance of genes, especially for shorter human genes where cohort-based approaches lack statistical power. Finally, clinicians could benefit from the boost in coverage of confidently classified pathogenic variants when prioritizing de novo variants for rare disease diagnostics, and AlphaMissense predictions could inform studies of complex trait genetics that use annotations of rare, likely deleterious variants.

CONCLUSION: AlphaMissense predictions may illuminate the molecular effects of variants on protein function, contribute to the identification of pathogenic missense mutations and previously unknown disease-causing genes, and increase the diagnostic yield of rare genetic diseases. AlphaMissense will also foster further development of specialized protein variant effect predictors from structure prediction models. ■

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RESEARCH ARTICLE

MACHINE LEARNING

Accurate proteome-wide missense variant effect prediction with AlphaMissense

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The vast majority of missense variants observed in the human genome are of unknown clinical significance. We present AlphaMissense, an adaptation of AlphaFold fine-tuned on human and primate variant population frequency databases to predict missense variant pathogenicity. By combining structural context and evolutionary conservation, our model achieves state-of-the-art results across a wide range of genetic and experimental benchmarks, all without explicitly training on such data. The average pathogenicity score of genes is also predictive for their cell essentiality, capable of identifying short essential genes that existing statistical approaches are underpowered to detect. As a resource to the community, we provide a database of predictions for all possible human single amino acid substitutions and classify 89% of missense variants as either likely benign or likely pathogenic.

Events

Next steering committee meeting

October 25
3PM

PIcc + EMPAIA at ASCP meeting

How can You Contribute to Overcome Hurdles for Application of AI in Routine Clinical Care?

empaia

ecosystem for pathology diagnostics
with AI assistance

Big props to Norman Zerbe (EMPAIA) for joining

live in Long Beach on **Thursday, October 19th** at **2:30pm**