Pathology Innovation Collaborative Community
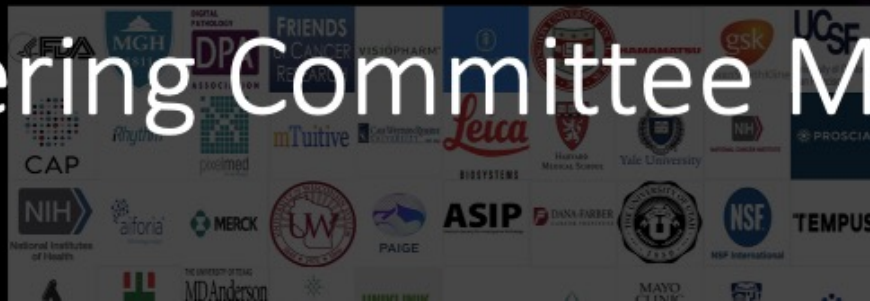
PIcc

The Alliance for Digital Pathology

A collaborative community with FDA participation

Steering Committee Meeting | November 2022

FDA

Spotlight: Digital Health Regulatory Science Research Opportunities

Release Date: October 27, 2022

Digital Imaging

Digitization of medical imaging in diagnostic and therapeutic applications across many clinical areas has the potential to improve the quality and efficiency of care. Traditional radiology modalities are currently harnessing the power of AI/ML to enhance tasks like lesion detection, computer-aided-diagnosis, and image reconstruction or segmentation. Digital pathology is an emergent area within digital health that visualizes, analyzes, and interprets digitized specimen slides, typically in a diagnostic application. Additionally, clinical areas like ophthalmology and dermatology are also rapidly integrating AI/ML into workflows to enhance tasks like informing diagnoses. Overall, digital imaging is an important component of health care of the future. Since digital imaging relies heavily on AI/ML, many of the research gaps presented in the AI/ML section of this document are also relevant.

Digital Imaging-Related Research Areas

Near-Term	Longer-Term
• Technical and clinical verification and validation of a digital imaging modality • Simulation and/or phantom development to assist with digital imaging modality characterization • Reproducibility evaluation across different systems, operators, or sites • Generalizability of AI/ML algorithms across multiple manufacturers, models, or versions of a digital imaging modality	• Performance standards and assessments for different clinical applications • Interoperability of components of digital imaging modalities • Digital imaging modalities integration into existing clinical workflows to optimize efficiency

www.fda.gov/digitalhealth
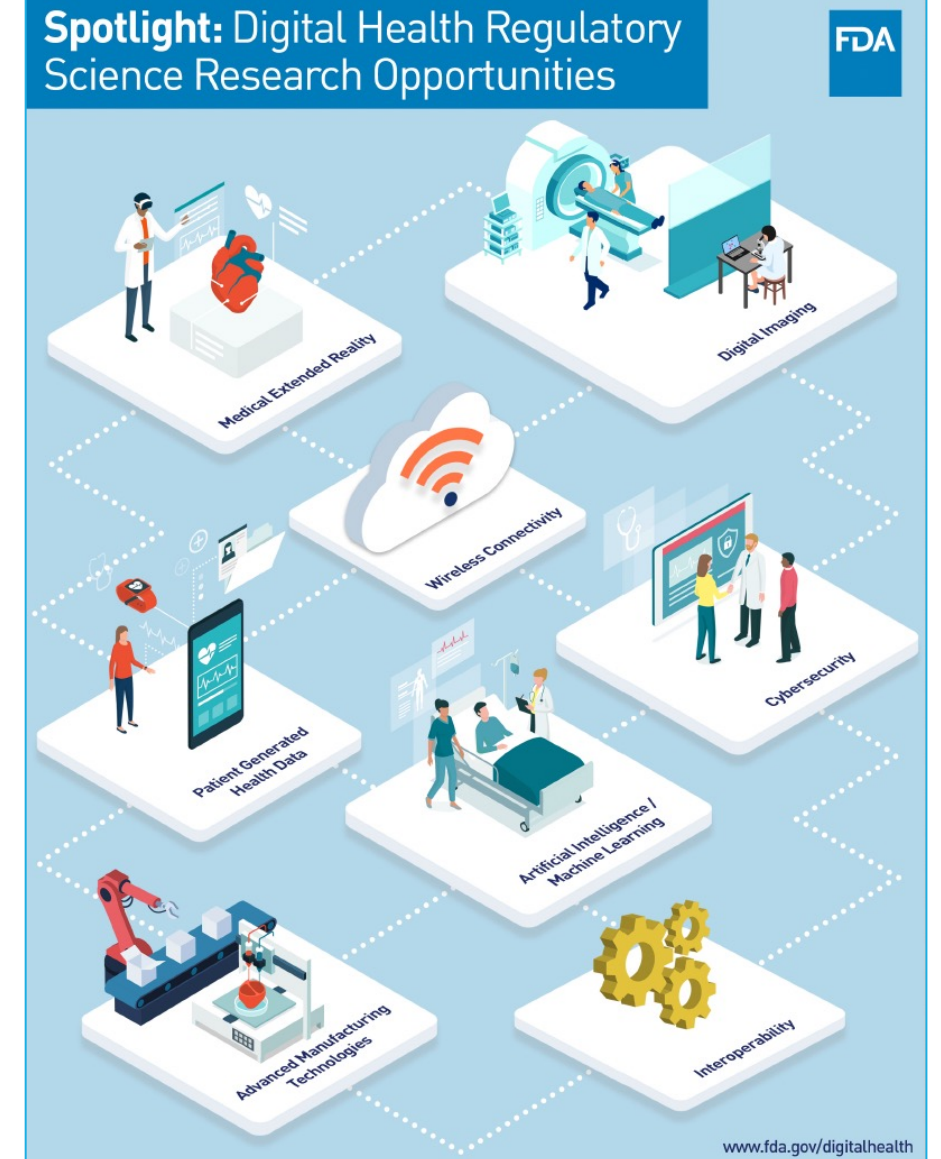
2022 CC Townhall
November 10, 2022, 10:05 – 11:25 AM

Panel #1—Harnessing the Power of Artificial Intelligence and Machine Learning (AI/ML)

1. Pathology Innovation Collaborative Community (PIcc)
   - Convenor Representative: Jochen Lennerz, MD, PhD
   - CDRH Liaison: Brandon Gallas, PhD
2. Case for Quality Collaborative Community
   - Convenor Representative: Paul Sumner
   - CDRH Liaison: Cisco Vicenty
3. Heart Valve Collaboratory
   - Convenor Representative: Martin Leon, MD
   - CDRH Liaison: Changfu Wu, PhD
4. Wound Care Collaborative Community
   - Convenor Representative: Vickie Driver, DPM, MS, FACFAS
   - CDRH Liaison: Cynthia Chang, PhD
5. National System for health Technology Coordinating Center (NESTcc) Collaborative Community
   - Convenor Representative: Richard Smith, MBA
   - CDRH Liaison: Daniel Caños, PhD, MPH
6. Collaborative Community on Ophthalmic Imaging (CCOI)
   - Convenor Representative: Mark Blumenkranz, MD, MMS
   - CDRH Liaison: Malvina Eydelman, MD

FDA

Modeling & Simulation at FDA

FDA scientists routinely use M&S approaches for scientific research and regulatory decision-making
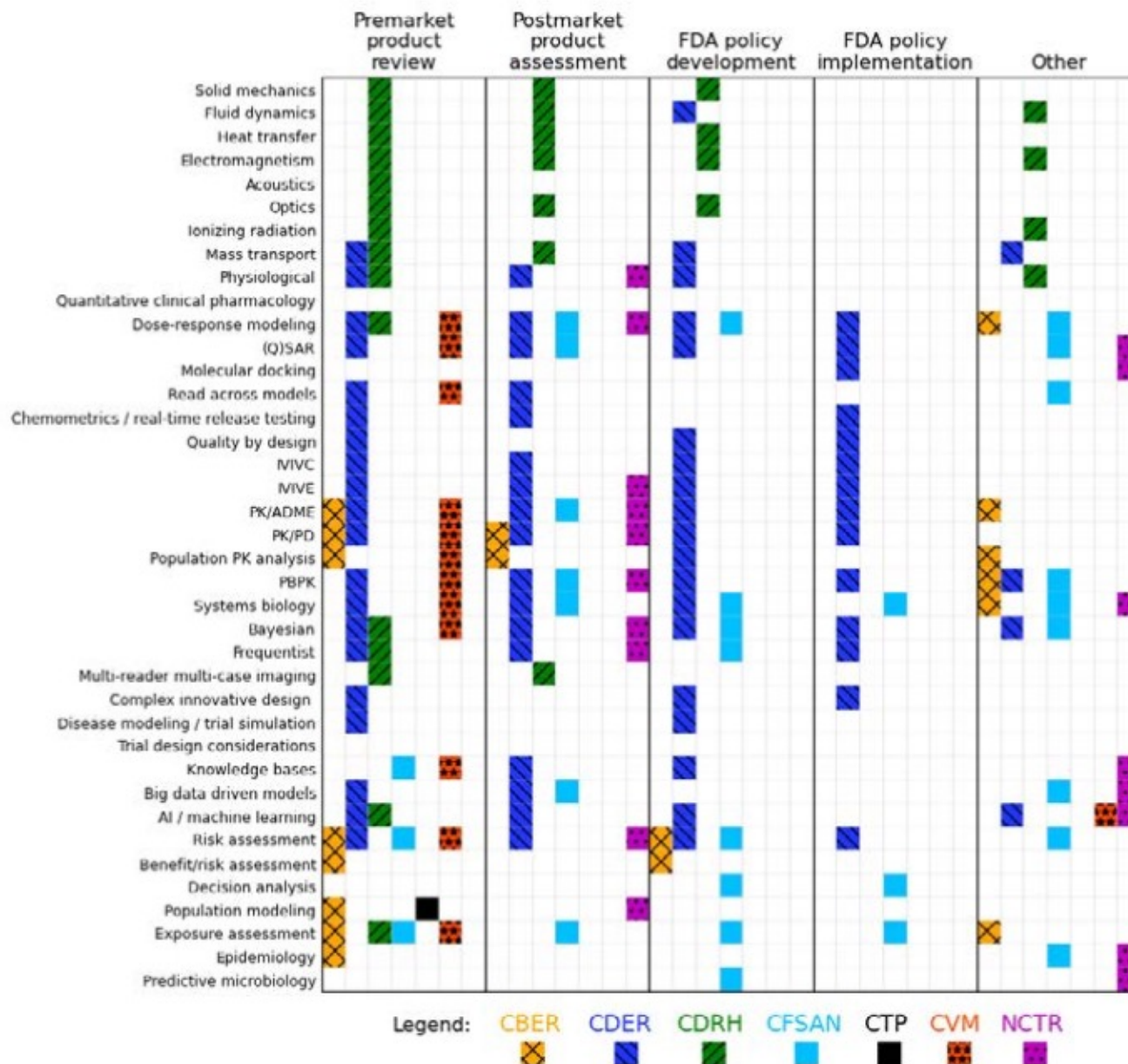
MDDT Program

Medical Device Development Tools (MDDT)

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The FDA's Medical D...
device development...

Tool (Link to SEBQ)	Product Area(s)	MDDT Category	Date Qualified
CHemical RISk Calculator (CHRIS) - Color Additives	Toxicology, Biocompatibility	Non-clinical Assessment Model	11/28/2022
FACE-Q | Aesthetics	Plastic Surgery, Dermatology	Clinical Outcome Assessment	04/26/2022
Virtual MRI Safety Evaluations of Medical Devices	Imaging	Non-clinical Assessment Model	11/16/2021
Patient-Reported Outcomes with LASIK Symptoms and Satisfaction (PROWL-SS)	Ophthalmology	Clinical Outcome Assessment	06/17/2021
IMAnalytics with MRIxViP1.5T/3.0T And BCLib	Active implanted medical devices (AIMDs)	Nonclinical Assessment Model	05/20/2021
Rubric for Applying CVSS to Medical Devices	Cybersecurity	Nonclinical Assessment Model	10/20/2020
BREAST-Q Reconstruction Module	Plastic Surgery	Clinical Outcome Assessment	08/20/2020
Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE) Questionnaires	Automated Insulin Dosing (AID)	Clinical Outcome Assessment	06/24/2020
Tissue Mimicking Material (TMM) for Preclinical Acoustic Performance Characterization of High Intensity Therapeutic Ultrasound (HITU) Devices	Imaging	Nonclinical Assessment Model	07/10/2019
OSIRIX CDE Software Module	Neurology	Biomarker Test	03/12/2019
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Cardiology	Clinical Outcome Assessment	03/19/2018
Kansas City Cardiomyopathy Questionnaire (KCCQ)	Cardiology	Clinical Outcome Assessment	10/19/2017

MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR CHEMICAL RISK CALCULATOR (CHRIS) – COLOR ADDITIVES

BACKGROUND

MDDT NAME: CHemical RISk calculator (CHRIS) – COLOR ADDITIVES
SUBMISSION NUMBER: U210555
DATE OF SUBMISSION: DECEMBER 14, 2021
CONTACT: David M. Saylor, PhD
OFFICE OF SCIENCE AND ENGINEERING LABORATORIES
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
U.S. FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MD 20993
PHONE: 301-796-2626
DAVID.SAYLOR@FDA.HHS.GOV

TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

CHemical RISk calculator (CHRIS) – Color Additives is a Nonclinical Assessment Model (NAM) to conduct screening level risk assessments to aid in the biocompatibility
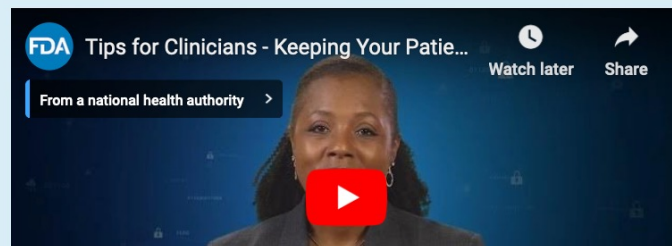
Cybersecurity

November 15, 2022 – In collaboration with MITRE, the FDA updated the *__Medical Device Cybersecurity Regional Incident Preparedness and Response Playbook__* ⧉, a resource to help health care organizations prepare for cybersecurity incidents. The playbook focuses on preparedness and response for medical device cybersecurity issues that impact device functions.

Updates to the playbook include:

- Emphasizing the need to have a diverse team participating in cybersecurity preparedness and response exercises – including clinicians, health care technology management professionals, IT, emergency response, and risk management and facilities staff.

- Highlighting considerations for widespread impacts and extended downtimes during cybersecurity incidents which benefit from the use of regional response models and partners.

- Adding a resource appendix making it easier to find tools, references, and other resources to help health care organizations prepare for and respond to medical device cybersecurity incidents (including ransomware).

A Playbook Quick Start Companion Guide is also available. The guide is a shorter version of the playbook that discusses preparedness and response activities health care organizations might want to start with as they are developing their medical device incident response program.

October 7, 2022 - The FDA released a new video, Tips for Clinicians - Keeping Your Patients' Connected Medical Devices Safe to help clinicians discuss cybersecurity of connected medical devices with patients. These tips focus on communicating with patients and aim to increase clinician comfort in approaching this topic.

- [Cybersecurity News and Updates](#)

- [Mitigating Cybersecurity Risks](#)

- [Cybersecurity Reports and White Papers](#)

- [Cybersecurity Guidances](#)

- [Cybersecurity Safety Communications and Other Alerts](#)

- [Reporting Cybersecurity Issues](#)

- [MOUs on Cybersecurity in Medical Devices](#)

- [Workshops and Webinars on Cybersecurity](#)

- [Other Collaborations on Cybersecurity](#)

- [FDA Cybersecurity New Releases](#)

FDA looks to bypass cancer drugs' companion diagnostics with new pilot program: Pazdur

By **Angus Liu** • Nov 18, 2022 09:17am

Richard Pazdur   Robert Califf   U.S. FDA   Cancer

Share

Existing cancer companion diagnostics are bundled with the specific cancer drugs they're approved for. But the FDA is looking to get around this one-drug-one-test situation by looking at "minimal performance criteria" of tests, Pazdur said.

The concept of a minimal performance criteria, Pazdur said, would allow doctors to use any test that meets those standards, rather than having to stick to specific tests. But the idea doesn't preclude testmakers from developing and selling drug-specific diagnostics, he added.

The FDA's medical device regulators are working on a pilot program to implement that proposal, Pazdur said. The director of the Oncology Center of Excellence made the comment during a discussion with FDA Commissioner Robert Califf, M.D., at the Friends of Cancer Research annual meeting on Thursday.

Digital Health Center of Excellence

November 16, 2022

Digital health is driving a revolution in health care and the U.S Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) is setting the stage for these advances. As an important step in promoting the advancement of digital health technology, CDRH established the Digital Health Center of Excellence (DHCoE) in 2020.

The Digital Health Center of Excellence recent milestones include:

• Engaging with patients to discuss their views on augmented reality/virtual reality in health care;

• Updating the FDA's list of artificial intelligence/machine learning-enabled medical devices (which now includes more than 500 authorized devices); and

• Completing FDA's Software Precertification Pilot and sharing in a final report.

As year-end approaches, the Digital Health Center of Excellence looks the stage for the advancement of digital health to help protect and prom

Promote consistent application of digital health policies

Launched a Tool to Help Stakeholders Navigate Digital Health Policies

On September 27, 2022, the FDA launched the Digital Health Policy Navigator to help stakeholders with navigating the FDA's digital health policies. This tool guides users through a series of questions based on published digital health policies, to provide general information to help a user assess whether a particular software function meets the device definition and, if so, whether it is the focus of FDA's oversight as a device. The tool directs users to the appropriate policies to learn more. View the Digital Health Policy Navigator.

Issued the Final Guidance: Clinical Decision Support Software

On September 28, 2022, the FDA issued the final guidance on Clinical Decision Support Software. The final guida the scope of the FDA's oversight of clinical decision (CDS) software intended for health care profession devices. This guidance further clarifies that the FD. digital health policies continue to apply to software that meet the definition of a medical device, includi that provides decision support and is used by patie caregivers. Read the Final Guidance.

The FDA has also developed a graphic to provide overview of certain policies described in the guidar examples of non-device CDS functions and device functions for illustrative purposes. View the graphic.

The FDA hosted a webinar for industry, health care providers, and others interested more about the final guidance. View Webinar Details.
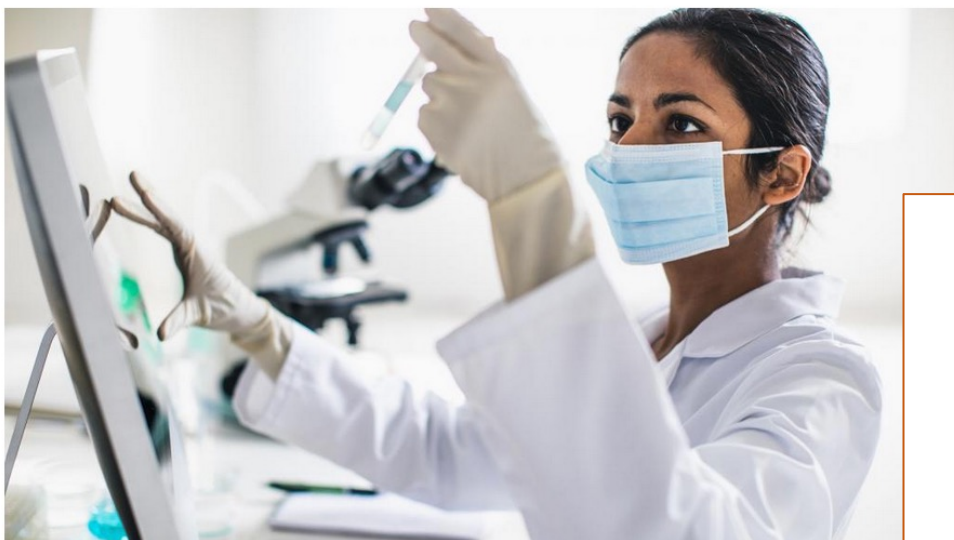
Catalog of Regulatory Science Tools to Help Assess New Medical Devices

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Content current
09/28/2022

Regulated Produ...
Medical Devices

This catalog collates a variety of regulatory science tools that the FDA's Center for Devices and Radiological Health's (CDRH) Office of Science and Engineering Labs (OSEL) developed and plans to expand as new tools become available.

On this page:

- Regulatory science tools
- About the catalog of regulatory science tools
- Additional resources

FDA, Veterans Health Administration Collaborate to Help Accelerate Medical Device Innovation and Advancement of Care

The FDA and the Veterans Health Administration (VHA) are announcing a collaboration

Regulatory science tools

Types of tools in the catalog include:

- Phantoms (physical and virtual)
- Methods (lab methods and clinical outcome assessments)
- Computational models and simulations (models and datasets)

Search: pathology   Export Excel

Name	Description	Type	Areas	Reference
eeDAP: Evaluation Environment for Digital and Analog Pathology	A software and hardware platform for designing and executing digital and analog pathology studies.	Model	Digital pathology	GitHub ↗
HIMSPEC: Pixel-wise spectral transmittance dataset of histological glass slides of human organs	The HIMSPEC dataset contains pixel-wise spectral transmittance of human organs tissue microarray slides measured with a hyperspectral imaging microscopy system (HIMS). It provides the reference color truth for evaluating color performance of whole-slide imaging scanners used in digital pathology.	Dataset	Digital pathology	GitHub ↗ Article ↗

Showing 1 to 2 of 2 entries (filtered from 117 total entries)

Digital Health Policy Navigator

A tool to help in determining whether your product's software functions are potentially the focus of the FDA's oversight

What is a software "function"?

If you are developing a digital health or software product, it may contain software functions that are considered devices as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and are subject to FDA's oversight as devices. Section 201(h) of the FD&C Act defines "device" as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related

CDRH Learn

Welcome to CDRH Learn, the FDA Center for Devices and Radiological Health's (CDRH) web page for multimedia industry education. CDRH Learn is our innovative educational tool, which consists of learning modules describing many aspects of medical device and radiation emitting product regulations, covering both premarket and postmarket topics. This tool is intended to provide industry with information that is comprehensive, interactive, and easily accessible. Modules are provided in various formats, including videos, audio recordings, and slide presentations. CDRH will determine the most appropriate format for the particular topic being presented and will post the learning module on this site to help meet your educational needs.

Tips for Viewing Modules

Modules should be compatible with most devices (computers, tablets, smart phones). We recommend you use Mozilla Firefox or Google Chrome to view modules. If you encounter a viewing error, we suggest you try another browser.

Medical Device Regulatory Science Research Programs Conducted by OSEL

These Research Programs aim to ensure that patients have access to high-quality, safe and

HTT Project Updates
Dr. Gallas

HTT

- installing the WSI viewer caMicroscope on precision FDA for data collection
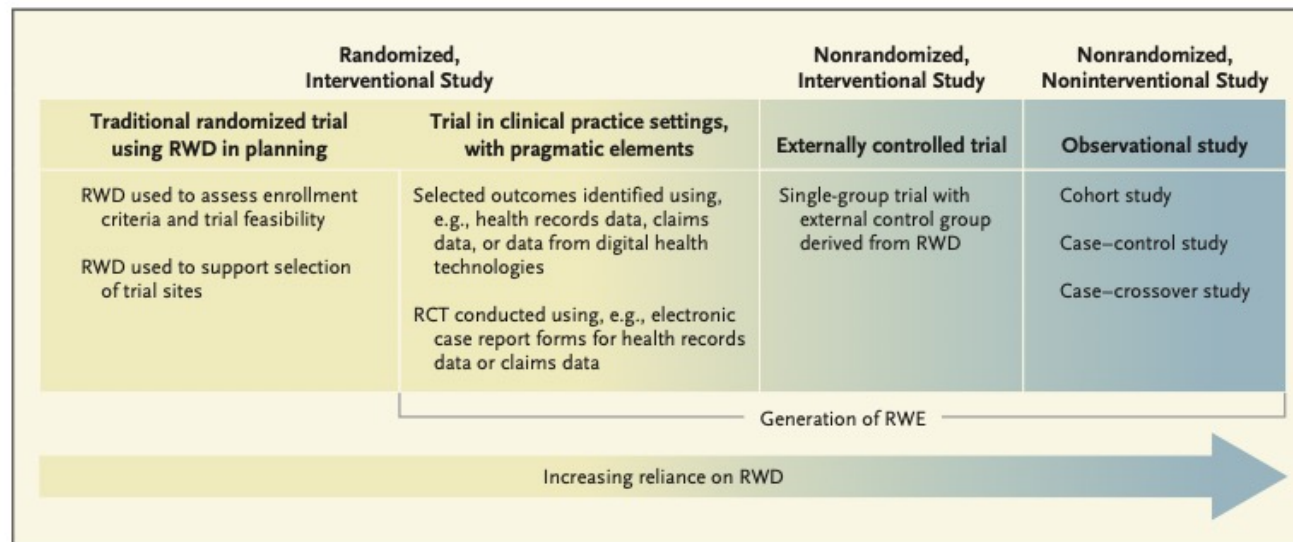
PERSPECTIVE

REAL-WORLD EVIDENCE

Real-World Evidence — Where Are We Now?

John Concato, M.D., M.P.H., and Jacqueline Corrigan-Curay, J.D., M.D.

Randomized, Interventional Study		Nonrandomized, Interventional Study	Nonrandomized, Noninterventional Study
Traditional randomized trial using RWD in planning	**Trial in clinical practice settings, with pragmatic elements**	**Externally controlled trial**	**Observational study**
RWD used to assess enrollment criteria and trial feasibility RWD used to support selection of trial sites	Selected outcomes identified using, e.g., health records data, claims data, or data from digital health technologies RCT conducted using, e.g., electronic case report forms for health records data or claims data	Single-group trial with external control group derived from RWD	Cohort study Case–control study Case–crossover study

Generation of RWE

Increasing reliance on RWD

Reliance on RWD in Representative Types of Study Design.

RCT denotes randomized, controlled trial; RWD real-world data; and RWE real-world evidence.

Original research

Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks

Art Sedrakyan [ID],[1] Danica Marinac-Dabic,[2] Bruce Campbell,[3] Suvekshya Aryal,[1] Courtney E Baird,[4] Philip Goodney [ID],[5] Jack L Cronenwett,[5] Adam W Beck,[6] Elizabeth W Paxton,[7] Jim Hu [ID],[8] Ralph Brindis,[9] Kevin Baskin,[10] Terrie Cowley,[11] Jeffery Levy,[12] David S Liebeskind,[13] Benjamin K Poulose,[14] Charles R Rardin,[15] Frederic S Resnic [ID],[16] James Tcheng,[17] Benjamin Fisher,[2] Charles Vivi...[?] Vincent Devlin,[2] Murray Sheldon,[2] Jens Eldrup-Jorgensen,[18,19] Jesse A [?] Joseph Drozda [ID],[21] Michael E Matheny,[22] Sanket S Dhruva [ID],[23] Timothy Feeney,[24] Kristi Mitchell,[25] Gregory Pappas [ID][26]

were based on a previous IMDRF report[17] that was led by a number of coauthors of that study. There are seven domains:

1. Promotion of unique device identification.
2. Improving data collection efficiency.
3. Advancing data quality for regulatory decision-making.
4. Considering TPLC research.
5. Establishing governance and ensuring sustainability.
6. Leveraging registries as quality systems.
7. Incorporation of patient-generated data and PROs.

In this study, we used the Delphi method for reaching consensus to develop and refine the framework from

APPENDIX A1: MATURITY FRAMEWORK

1. Promotion of unique device identification (UDI): the precise identification of medical devices is essential for evaluating the performance over time. Currently, most registries use manufacturer names, device names or billing codes for product identification, but this is mostly inadequate for unique product identification. Both regulators and MDEpiNet now advocate use of Unique Device Identification (UDI) system.[a] The FDA UDI rules require manufacturers to assign unique identifiers to their marketed devices and submit required device attributes to a UDI Database. In the U.S., the FDA's AccessGUDID, a public portal of the Global Unique Device Identification Database (GUDID), serves this purpose.[b] By providing a unique numeric or alphanumeric code for each device model and an identifier that includes the production information for that specific device (eg, serial number, manufacturing date), the UDI delivers the most accurate way to identify and track medical devices.

Device Identification domain describes the registry's ability to uniquely identify a device. Ideally, the UDI would be included; however, when unavailable, the registry should capture a combination of identifiers that enables unique identification of the device (eg, catalogue number, manufacturer, brand or generic name, device description).	Level 1 Early Learner	The registry or a linkable database in a CRN is capturing device information that is available under CPT, ICD, or other generic coding for the device-based procedure.[i]
	Level 2 Making Progress	The registry or a linkable database in a CRN is capturing device information using at least manufacturer and specific device names and leverages relevant CPT, ICD, or other generic coding system.[i]
	Level 3 Defined Path to Success	Building from level two achievements, the CRN has conducted large scale demonstration project to include manufacturer's product catalogue numbers or UDI that included at least five percent of annual patient enrollment.
	Level 4 Well Managed	The registry or a linkable database in a CRN is routinely capturing device information with manufacturer's product catalogue numbers or UDI that can identify devices and mapped to attributes/features needed for research and surveillance.
	Level 5 Optimised	The registry or a linkable database in a CRN is routinely capturing device information with UDI and mapping to attributes/features needed for research and surveillance. UDI information is seamlessly and efficiently integrated with the registry or CRN operations.

[i] Level 1 and level two achievements can be sufficient if only one device and few devices are on the market and if such coding would appropriately identify the device. In all other instances, catalogue numbers and ideally UDIs are required.

[a] Gross TP, Crowley J. Unique device identification in the service of public health. *The New England journal of medicine.* 2012;367(17):1583-1585.

[b] Unique Device Identification System. In: FDA, ed. *21 CFR § 16, 801, 803, 806, 810, 814, 820, 821, 822, 830.* Vol 0910-AG312013:58785-58828.

WHO/IARC updates

BMJ Open

Understanding the use of evidence in the WHO Classification of Tumours: a protocol for an evidence gap map of the classification of tumours of the lung

Javier del Aguila Mejía ●,[1] Subasri Armon,[1] Fiona Campbell ●,[2] Richard Colling,[3] Magdalena Chechlinska,[4] Magdalena Kowalewska,[4] Marina Pollán ●,[5,6] Stefan Holdenrieder,[7] Puay Hoon Tan,[8] Ian Cree,[1] Blanca Iciar Indave Ruiz ●[1]

Viewpoint

Barriers in access to oncology drugs – a global crisis

Carlos Barrios, Gilberto de Lima Lopes, Mastura Md Yusof, Fidel Rubagumya, Piotr Rutkowski & Manju Sengar

World Health Organization

| | Health Topics ˅ | Countries ˅ | Newsroom ˅ | Emergencies ˅ | Data ˅ |

WHO Model Lists of Essential Medicines

The WHO Model Lists of Essential Medicines are updated every two years by the Expert Committee on Selection and Use of Essential Medicines.

The first Essential Medicines List was published in 1977, and the first Essential Medicines List for Children was published in 2007.

The current versions, updated in September 2021, are the 22nd Essential Medicines List (EML) and the 8th Essential Medicines List for Children (EMLc).

WHO Electronic EML

Short description: The eEML is a information on essential medicin

WHO AWaRe

Short description: WHO framewo Reserve – which all together for

WHO Global EML

Short description: Database of th

World Health Organization

Health Topics ∨   Countries ∨   Newsroom ∨   Emergencies ∨

WHO publishes new Essential Diagnostics List and urges countries to prioritize investments in testing

SPECIAL REPORT

IARC Perspective on Oral Cancer Prevention

Véronique Bouvard, Ph.D., Suzanne T. Nethan, M.D.S., Deependra Singh, Ph.D.,
Saman Warnakulasuriya, Ph.D., Ravi Mehrotra, M.D., Ph.D., Anil K. Chaturvedi, M.P.H., Ph.D.,
Tony Hsiu-Hsi Chen, Ph.D., Olalekan A. Ayo-Yusuf, M.P.H., Ph.D., Prakash C. Gupta, Ph.D.,
Alexander R. Kerr, D.D.S., Wanninayake M. Tilakaratne, Ph.D., Devasena Anantharaman, Ph.D.,
David I. Conway, D.P.H., Ph.D., Ann Gillenwater, M.D., Newell W. Johnson, F.Med.Sci.,
Luiz P. Kowalski, M.D., Ph.D., Maria E. Leon, Ph.D., Olena Mandrik, Ph.D.,
Toru Nagao, D.D.S., Ph.D., D.M.Sc., Vinayak M. Prasad, M.B., B.S., Ph.D.,
Kunnambath Ramadas, M.D., Ph.D., Felipe Roitberg, M.D., Pierre Saintigny, M.D.,
Rengaswamy Sankaranarayanan, M.D., Alan R. Santos-Silva, D.D.S., Ph.D., Dhirendra N. Sinha, Ph.D.,
Patravoot Vatanasapt, M.D., Rosnah B. Zain, M.D.C., and Béatrice Lauby-Secretan, Ph.D.

Table 2. Evaluation of the Evidence of Interventions and Strategies for the Prevention of Oral Cancer.

Intervention	Evaluation
Primary prevention*	
Cessation of exposure to risk factor	
Tobacco smoking	Sufficient
Use of smokeless tobacco	Inadequate
Use of areca nut (including betel) with or without tobacco	Sufficient
Alcohol consumption	Sufficient
Cessation intervention for smokeless tobacco	
Behavioral intervention	Sufficient in adults; limited in youths
Pharmacologic intervention	Limited
Combined behavioral and pharmacologic interventions	Limited
Secondary prevention†	
Clinical oral examination in high-risk populations	Group B

* According to the criteria described in the preamble of the *IARC Handbooks* for primary prevention,[7] "sufficient evidence" indicates that a causal preventive association between the intervention and cancer in humans has been established; "limited evidence" indicates that a causal preventive association between the intervention and cancer in humans is plausible; "inadequate evidence" indicates that the current body of evidence does not enable a conclusion to be drawn about the presence or absence of a preventive association between the intervention and cancer in humans.

† According to the criteria described in the preamble of the *IARC Handbooks* for secondary prevention,[8] Group B indicates that a causal preventive association between the use of the screening method and cancer incidence or death is credible, but chance, bias, or confounding as explanations for the association could not be ruled out with reasonable confidence.

LEGISLATIVE UPDATES

White House Sets Sights on New Healthcare Cybersecurity Standards

Anne Neuberger said that the creation of additional healthcare cybersecurity standards and guidance would be an upcoming area of focus for the White House.

VALID Act

- The story continue

- Likely attached (in modification) to the "end of year spending bill"

Califf: FDA may use rulemaking for diagnostics reform if VALID isn't passed

Regulatory News | 25 October 2022 | By Ferdous Al-Faruque

BOSTON, MA – The US Food and Drug Administration (FDA) may look to notice and comment rulemaking to implement diagnostics reform if Congress fails to act, according to FDA Commissioner Robert Califf.

Janet Trunzo, AdvaMed senior executive vice president for technology and regulatory affairs, spoke to Califf on 25 October at the group's annual Medtech Conference to talk about his vision for the agency. She asked the chief regulator what he planned to do if US lawmakers fail to pass the *Verifying Accurate Leading-edge IVCT Development (VALID) Act* as part of the December omnibus spending bill. (RELATED: *AdvaMed seeks diagnostics reform in December budget bill, Regulatory Focus* 13 October 2022)

"That's a tough question," said Califf. "You know, it's not something we want to do because having a clear law passed leads to the best situation."

Janet Trunzo (left) and Robert Califf (right)

Improving Diagnosis and Treatment Through Personalized Medicine

This briefing will explore the potential of policies designed to encourage physicians to target treatments to only those who will benefit.

By Personalized Medicine Coalition   82 followers`   [Follow]
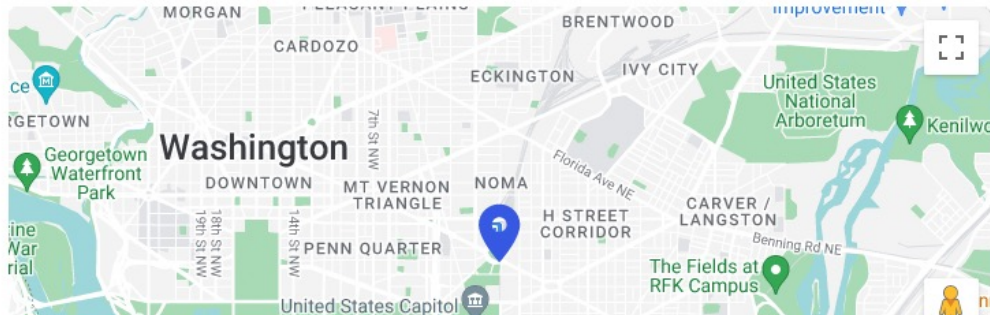
When and where

Date and time
Mon, December 5, 2022,
12:00 PM – 1:00 PM EST

Location
U.S. Capitol Visitor Center First
Street NE Room 217 Washington, DC
20515

Hide map ⌃

On Monday, December 5th, the Personalized Medicine Coalition is hosting a congressional educational briefing titled Improving Diagnosis and Treatment Through Personalized Medicine, in collaboration with the co-chairs of the Congressional Personalized Medicine Caucus.

AGENDA

Welcome & Introductions

- Congressional Personalized Medicine Caucus Co-Chairs (invited)

Panel Discussion

- Moderator: Cynthia A. Bens, Senior Vice President, Public Policy, Personalized Medicine Coalition
- Carolyn "Bo" Aldigé, Founder, Prevent Cancer Foundation
- Sam Asgarian, M.D., Chief Medical Officer, Scipher Medicine
- Brock Schroeder, Ph.D., Vice President, Market Access, Illumina
- Dylan Simon, Director of Policy, EveryLife Foundation for Rare Diseases
- Jeffrey Trent, Ph.D., President, Research Director, Translational Genomics Research Institute (TGen), an Affiliate of City of Hope
- Tiffany Westrich-Robertson, CEO, AiArthritis

Organized by the Personalized Medicine Coalition in cooperation with the Congressional Personalized Medicine Caucus.

This briefing is a widely attended event that conforms to House and Senate ethics rules.

Better lab test standards can ensure precision medicine is truly precise

By Jeff Allen and Lisa Lacasse   Nov. 30, 2022

Reprints

SAUL LOEB/AFP/GETTY IMAGES

Cancer is becoming less deadly in America.

According to the recently released Annual Report to the Nation on the Status of Cancer, overall cancer death rates have continued to decline by about 2% per year over the last several years for Americans of all ages, races, and genders. The decline in cancer death rates is clearly welcome news and coincides with a significant shift in cancer treatment through the development of new targeted therapies and accompanying diagnostic tests that guide their use.

For decades, most cancers have been treated with toxic, cell-killing treatments that had limited ability to distinguish between cancerous and normal cells. While this approach often worked, it came with significant side effects and made treatment difficult to tolerate.

A growing number of new cancer therapies, however, use precision medicine to tailor treatment to the patient and target only cancer cells. But these targeted treatments must be matched to specific genetic markers, which can be detected only with lab tests known as biomarker tests.

Biomarker tests can help determine what an individual's prognosis might be and which drugs would work best to treat their disease. For example, tests that detect certain genetic characteristics in breast, lung, and skin cancer can indicate who should — or should not — be treated with specialized classes of targeted drugs.

With the advent of targeted therapies, the accuracy of a diagnostic test is critical. Yet oversight of such tests has not kept pace with innovation.

The Food and Drug Administration currently regulates and ensures only the accuracy of tests used in multiple laboratories or health care facilities. Those designated laboratory-developed tests (LDTs), are left to meet less-stringent of lab tests, including those used to determine cancer treatment without assurances that they work.

An example of the potential damage of faulty and poorly regulated a consumer health care startup that claimed to be able to of blood. The company's touted technology never worked, for a number of serious conditions. The company's founder more than 11 years in prison for fraud.

In an earlier example, from 2008, a company claimed a lab cancers but could, in fact, detect only 1 in 15 (7%) of cases positive results and may have pursued unnecessary, invasive healthy uteruses, fallopian tubes, and ovaries, which could them into early menopause.

Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics

John D. Pfeifer, MD, PhD,[1] Robert Loberg, PhD,[2] Catherine Lofton-Day, PhD,[3] and Barbara A. Zehnbauer, PhD[4]

From the [1]Department of Pathology, Washington University School of Medicine, St Louis, MO, USA; [2]Clinical Biomarkers and Diagnostics and [3]In Vitro Diagnostics, Amgen, Thousand Oaks, CA, USA; and [4]Department of Pathology, Emory University School of Medicine, Atlanta, GA, USA.

ABSTRACT

KEY POINTS

- Engineered cell lines and in silico mutagenized sequence files are complementary reference materials that can be used to assess the accuracy of clinical next-generation sequencing (NGS) test results.

- The accuracy of detection of genetic variants differed among the laboratory-developed tests (LDTs) performed by different laboratories.

- The varied accuracy suggests that different LDTs may identify different subsets of oncology patients as candidates for targeted therapy.

A recent study published in the American Journal of Clinical Pathology reported that LDTs offered for the same intended use as an FDA-approved test had significant variability in their results. Errors in tests, including false negatives (when the test inaccurately states the genetic marker is not present) may impede patients' access to safe and effective treatments for their cancers.

The VALID Act (S. 2209 and H.R. 4128), currently before Congress, provides an opportunity to set a clear, modernized regulatory framework to ensure that any test, no matter where it is developed, meets the same quality and performance standards. It also allows for continued innovation by providing detailed flexibilities that will ensure labs can still meet individual patient needs without delaying patient care.

VALID is a flexible, bipartisan bill that is the result of years of collaborative work between various stakeholders. The bill is good for industry, laboratories, providers and, most importantly, patients. An individual's best chance to fight cancer should never be affected by something as easily preventable as a faulty diagnostic test. Congress has the opportunity today to do what is right for patients.

VALID-related
Device vs. Technology

Referencing the Definition of "Device" in the Federal Food, Drug, and Cosmetic Act in Guidance, Regulatory Documents, Communications, and Other Public Documents

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 14, 2022.

The draft of this document was issued on December 16, 2021.

For questions about this document regarding CDRH-regulated devices, contact the CDRH Guidance Program in the Office of Policy at CDRH-Guidance@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

(h)(1) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

(A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(C) intended to affect the structure or any function of the body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on t... ...olized for t... ...nclude soft...

(2) T...

B.   Future References to the Term "Device"

Following enactment of the Safeguarding Therapeutics Act, FDA aims to follow certain conventions when referencing the terms "device" and "counterfeit device." For consistency with prior documents, we will generally continue to reference section 201(h) of the FD&C Act for the definition of "device." For example, a future FDA guidance might read:

Section 3060(a) of the 21st Century Cures Act amended the FD&C Act to add section 520(o), which excludes certain software functions from the definition of device in section 201(h) of the FD&C Act.

In certain instances, FDA and others may utilize the more precise reference to section 201(h)(1) of the FD&C Act. Instances in which FDA may opt to reference paragraph (1) of subsection (h) specifically include quoting the definition of "device" in part or in its entirety, referring to statements contained in subparagraphs (A) through (C), or maintaining consistency with other definitions in the same document.[9]

For example, when referring to the structure/function prong of the "device" definition, FDA may cite to subparagraph (C) of section 201(h)(1) of the FD&C Act for precision:

FDA considers needle penetration beyond the stratum corneum as a result of the design or technology of a microneedling product as evidence that it may be "intended to affect the structure or any function of the body" under section 201(h)(1)(C) of FD&C Act.

SWISS MEDTECH

POLITICIANS DECIDE IN FAVOUR OF PATIENT CARE

Pragmatism and speed are now essential

Bern, 28 November 2022 – Swiss Medtech welcomes Parliament's instructions to the Federal Council to adapt national laws – enabling Switzerland to accept medical devices with FDA approval for the welfare of its own population. Until now, healthcare providers and patients in Switzerland have only had access to medical devices with an EU certificate. It is essential that the order be implemented swiftly and pragmatically. Waiting cannot be an option if patient safety is at risk.

Voluntary Alternative Pathway: FDA Floats Legislation for Agile Regulation

SHARE | in LINKEDIN | TWEET | EMAIL | BOOK

2022 Medtech Conference

Shuren floats voluntary alternative pathway for digital device premarket review

By Mark McCarty   Oct. 27, 2022

According to Shuren, VAP would allow FDA to tailor regulatory oversight to the realities of new technologies—in particular, the very rapid iteration of digital health products.

"The idea that we are going to have a system where you are constantly [reviewing] every one of these changes, even out of the gate, and that is going to take months and months, isn't good," Shuren said. "It actually puts patients at risk—you need a lot of these changes so that your product remains safe...and secure." Embedded in the legislative proposal, though, are assurances that any approach adopted by CDRH would meet essential principles of safety and effectiveness.

MDIC Updates

MDIC Updates

- New Approach to Clinical Trial Design Helps Medical Devices Better Meet Patient Needs and Priorities
  - https://mdic.org/news/new-approach-to-clinical-trial-design-helps-medical-devices-better-meet-patient-needs-and-priorities/

    https://mdic-spi.org/category/bayesian-decision-analysis-bda-framework/
- Cybersecurity Threat-modeling Virtual Bootcamps: 12/12-12/16, 2022 and 3/13-3/17, 2023
  - https://mdic.org/project/2022-threat-modeling-bootcamps/
- Medical Device Cybersecurity Maturity: MDIC Industry Benchmarking Report 2022 has been released
  - https://mdic.org/resource/cybersecurity-benchmarking-report/
- **Coming Soon:**
  - AI/ML in IVDs: Framework for a Predetermined Change Control Plan (PCCP) for AI/ML-Enabled IVDs, including both Software as a Medical Device (SaMD) and Software in a Medical Device (SiMD)
  - 5G-enabled Healthcare Technologies: MDIC Landscape Report (Coming December 2022)
  - Computational Modeling & Simulation (CM&S) in Medical Device & Diagnostics: Case Studies and Landscape Analysis (Coming December 2022)
- Please contact Noor Falah nfalah@mdic.org or Jithesh Veetil jveetil@mdic.org with any questions about MDIC initiatives

Professional Societies

ASSOCIATION FOR MOLECULAR PATHOLOGY

**Proposal for Modernization of CLIA Regulations
for Laboratory Developed Testing Procedures (LDPs)**

Transparency. Quality. Innovation.

Desired Outcomes:

- Patients receive the most appropriate test(s) for their clin[...]
- Laboratory tests are accurate, precise, clinically relevant,

LDP Oversight Summary:

Low Risk	• Laboratory validates and puts into service • LDPs subject to inspection in the normal course of the laboratory inspection process
Moderate Risk	• LDP information submitted at least 30 days before the LDP is offered to the public • LDP reviewed (time limit) • Grandfathering provision
High Risk	• LDP information submitted at least 90 days before the LDP is offered to the public • LDP reviewed (time limit) • Lab must reveal proprietary information, e.g., algorithm; alternative is FDA submission

Councils and Committees

Council on Informatics and Pathology Innovation

- Artificial Intelligence (AI) Committee
- Cancer Committee
- Digital and Computational Pathology Committee
- Informatics Committee
- Pathology Electronic Reporting (PERT) Committee

Council on Informatics and Pathology Innovation
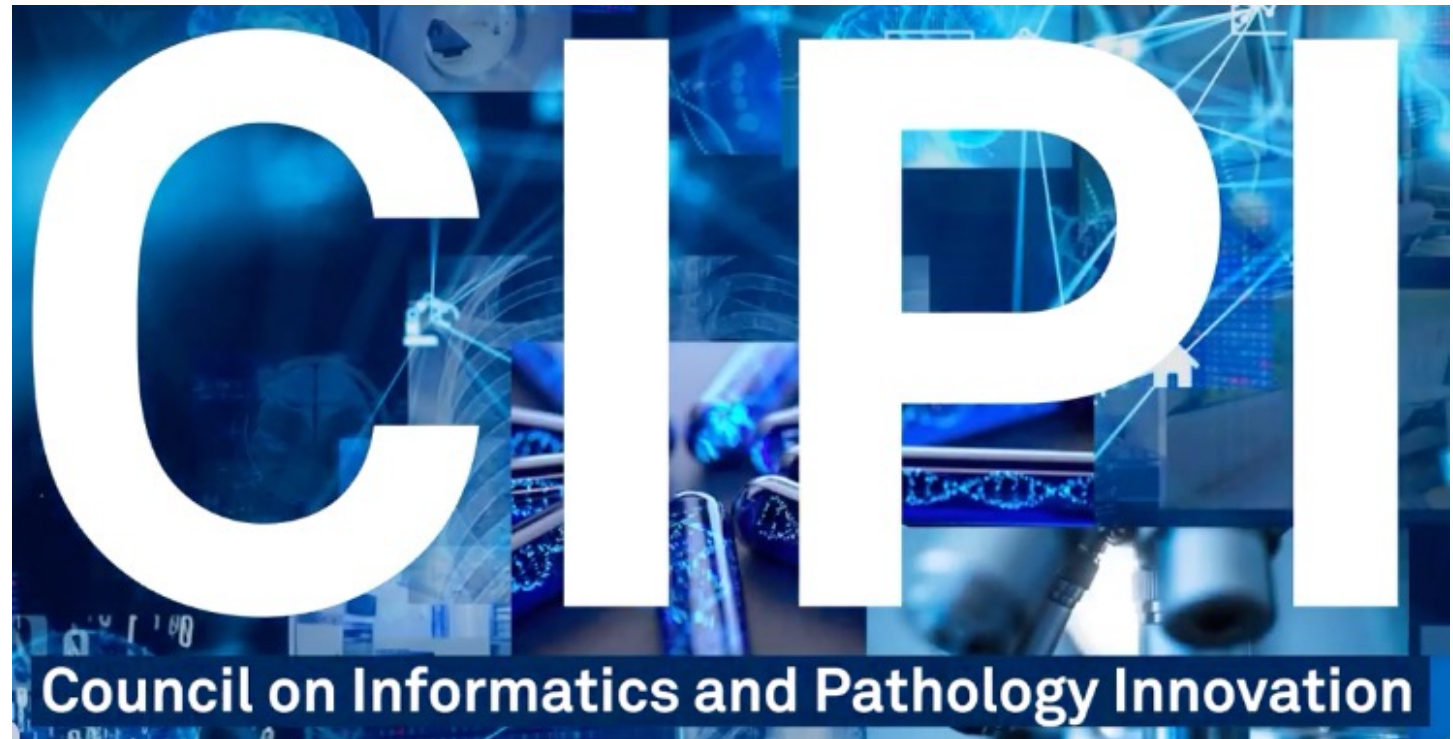
To identify and recommend strategic direction on current and emerging medical information science, data science, and computational technologies that could impact the practice of pathology; provide informatics domain information and expertise to the CAP in furtherance of its programs and mission; and support appropriate engagement with external stakeholders.

Latest News 🔊

College of American Pathologists (CAP) multidisciplinary team receives a $1 million contract from the US Food and Drug Administration (FDA)

04-NOV-2022

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Friends of Cancer Research

Molecular Characterization of Circulating Tumor DNA in Pediatric Rhabdomyosarcoma: A Feasibility Study

Olivia Ruhen, PhD[1]; Nathalie S.M. Lak, MD[2,3]; Janine Stutterheim, MD, PhD[2,3]; Sara G. Danielli, MSc[4]; Mathieu Chicard, PhD[5]; Yasmine Iddir, PhD[5]; Alexandra Saint-Charles, PhD[5]; Virginia Di Paolo, PhD[6]; Lucia Tombolan, PhD[7]; Susanne A. Gatz, PhD[1,8]; Ewa Aladowicz, PhD[1]; Paula Proszek, MSc[1,9]; Sabri Jamal, PhD[1,9]; Reda Stankunaite, MSc[1,9,10]; Deborah Hughes, PhD[1,9]; Paul Carter, PhD[1,9]; Elisa Izquierdo, PhD[1,9]; Ajla Wasti, MD[11]; Julia C. Chisholm, MD, PhD[11,12]; Sally L. George, MD, PhD[1,11]; Erika Pace, PhD[11,13]; Louis Chesler, MD, PhD[1,11]; Isabelle Aerts, MD[5]; Gaelle Pierron, PhD[5]; Sakina Zaidi, MSc[14]; Olivier Delattre, MD, PhD[14]; Didier Surdez, PhD[14,15]; Anna Kelsey, MD[16]; Michael Hubank, PhD[1,9]; Paolo Bonvini, PhD[7]; Gianni Bisogno, MD, PhD[17]; Angela Di Giannatale, MD, PhD[6]; Gudrun Schleiermacher, MD, PhD[5,18]; Beat W. Schäfer, PhD[4]; Godelieve A.M. Tytgat, MD, PhD[2,3]; and Janet Shipley, PhD[1]

ML/AI • 3/9/22

Project AI Grand Challenges

Read More

Can AI Grand-Challenge
Regulatory Science in A

When AI meets the TILs: results from the TIGER challenge

Published 24 Oct. 2022

"It's the beginning of a new phase".

This is what the organizers of the challenge on Tumor Infiltrating Lymphocytes in breast cancer (TIGER) stated during the closing event of the challenge, which was held online on August 30.

organized by researchers from the Radboud University Medical Center (Netherlands), in n with an international network of clinical and academic partners, and sponsored by AWS, which oth the computing power to run the challenge and the credits to award the best methods in the Ve have covered the TIGER challenge in a previous post, check it out if you want to know more about ion and the goal of this challenge.

Survival (Final) Evaluation Leaderboard

#↑↓	User (Team)	Algorithm	Created	C-Index↑↓
1st	sungdukcho_vuno (VUNO)	TIGER L2 Final LB	22 June 2022	0.6388
2nd	mart.vanrijthoven	Tiger baseline v2-1	23 June 2022	0.6338
3rd	a.tsakiroglou (Spotlight Pathology)	TIGER L1	28 June 2022	0.6224
4th	大胖胖墩	tiger_til	20 June 2022	0.6120
5th	arian.arab (FDA-CDRH-OSEL-DIDSR)	DIDSR-TiGER-Final	23 June 2022	0.6034
6th	vishweshramanathan (SRI)	TIL-test7	19 June 2022	0.5996
7th	mart.vanrijthoven	Tiger Survival Baseline Model	9 June 2022	0.5903
8th	adamshephard (TIAger)	TIAger L2 EUN Re	28 June 2022	0.5879
9th	Biototem (Biototem)	Bio-Totem-Tiger-Breast-v1-tryout	24 June 2022	0.5793

Toxicologic Pathology

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Volume 50 Issue 7, October 2022

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Special Issue: Proceedings of the STP 41st Annual Symposium: Toxicologic Pathology of the Hematopoietic System

Guest Editor: Michelle C. Cora   Guest Editor: Basel T. Assaf

Ethics
Diversity
&
Inclusion

Do we need a Hippocratic Oath for artificial intelligence scientists?

Nikolaos M. Siafakas

University of Crete

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Abstract

Artificial intelligence (AI) has been beneficial for humanity, improving many human activities. However, there are now significant dangers that may increase when AI reaches a human level of intelligence or superintelligence. It is paramount to focus on ensuring that AI is designed in a manner that is robustly beneficial for humans. The ethics and personal responsibilities of AI scientists could play an important role in continuing the constructive use of AI in the future. Lessons can be learnt from the long and successful history of medical ethics. Therefore, a Hippocratic Oath for AI scientists may increase awareness of the potential lethal threats of AI, enhance efforts to develop safe and beneficial AI to prevent corrupt practices and manipulations and invigorate ethical codes. The Hippocratic Oath in medicine, using simple universal principles, is a basis of human ethics, and in an analogous way, the proposed oath for AI scientists could enhance morality beyond biological consciousness and spread ethics across the universe.

COMMENT   **OPEN**

Check for updates

Emerging approaches to redressing multi-level racism and reproductive health disparities

Bethany Golden[1], Ifeyinwa V. Asiodu[2], Linda S. Franck (ID)[1], Celestine Yayra Ofori-Parku[1], Daniel Felipe Martín Suárez-Baquero[1], Tracy Youngston[1] and Monica R. McLemore[1]✉

This commentary examines the impact of multi-level racism on reproductive health disparities in the United States. Multi-level racism and its impact on reproductive health over the lifespan are described on a societal, community, and individual level. To advance, we recommend using the Remove, Repair, Restructure, Remediate (R4P) approach combined with the Retrofit, Reform, and Reimagine (3R) model to address multiple forms of racism. Emergent policies and actions are identified to proceed towards health equity.

Representational ethical model calibration

Robert Carruthers[1]✉, Isabel Straw [2], James K. Ruffle [2], Daniel Herron[3], Amy Nelson [2], Danilo Bzdok [4], Delmiro Fernandez-Reyes [1], Geraint Rees [2] and Parashkev Nachev [2]✉

Equity is widely held to be fundamental to the ethics of healthcare. In the context of clinical decision-making, it rests on the comparative fidelity of the intelligence – evidence-based or intuitive – guiding the management of each individual patient. Though brought to recent attention by the individuating power of contemporary machine learning, such epistemic equity arises in the context of any decision guidance, whether traditional or innovative. Yet no general framework for its quantification, let alone assurance, currently exists. Here we formulate epistemic equity in terms of model fidelity evaluated over learnt multidimensional representations of identity crafted to maximise the captured diversity of the population, introducing a comprehensive framework for *Representational Ethical Model Calibration*. We demonstrate the use of the framework on large-scale multimodal data from UK Biobank to derive diverse representations of the population, quantify model performance, and institute responsive remediation. We offer our approach as a principled solution to quantifying and assuring epistemic equity in healthcare, with applications across the research, clinical, and regulatory domains.

The Development of Children's Gender-Science Stereotypes: A Meta-analysis of 5 Decades of U.S. Draw-A-Scientist Studies

David I. Miller iD, Kyle M. Nolla, Alice H. Eagly, and David H. Uttal
Northwestern University

This meta-analysis, spanning 5 decades of Draw-A-Scientist studies, examined U.S. children['s] stereotypes linking science with men. These stereotypes should have weakened over time [as women's] representation in science has risen substantially in the United States, and mass media i[ncreasingly depict] female scientists. Based on 78 studies (N = 20,860; grades K-12), children's drawings of s[cientists depicted] female scientists more often in later decades, but less often among older children. Children's [drawings of sci]entists therefore have become more gender diverse over time, but children still associate sci[ence with men as] they grow older. These results may reflect that children observe more male than female scien[tists in their envi]ronments, even though women's representation in science has increased over time.
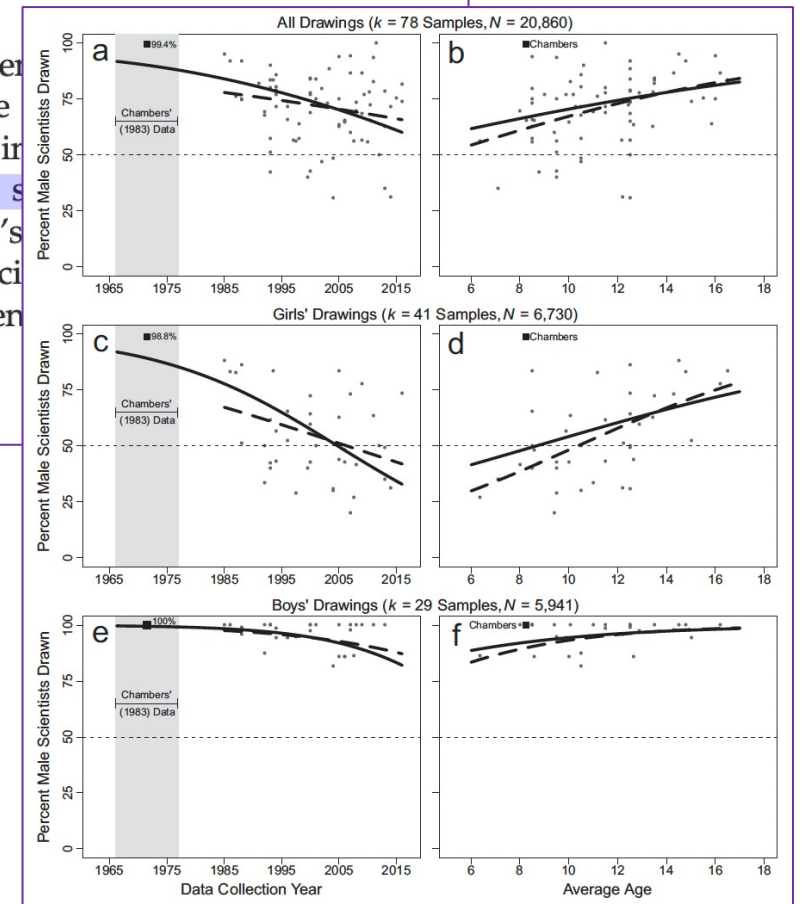
Patient advocacy

Thank you to all that attended the *Friends* Annual Meeting 2022!
Please find links below to watch each keynote and panel discussion, as well as the panel white papers.

Friends of Cancer Research Annual Meeting 2022

Thursday, November 17, 2022
10:00AM EST – 3:00PM EST
Washington Marriott Georgetown
1221 22nd St NW, Washington, DC

Click HERE to watch the full meeting.
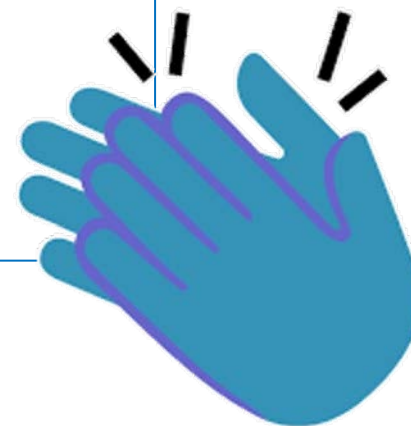
10:05 AM: Morning Keynote Conversation

Robert Califf, Commissioner, U.S. FDA

Richard Pazdur, Director, Oncology Center of Excellence, U.S. FDA

10:40 AM: Panel 1 — Applying Learnings from COVID-19 to Advance Clinical Trial Conduct

Panel White Paper

1:55 PM: Panel 3 — Accelerating Investigation of New Therapies in Earlier Metastatic Treatment Settings: Discussions about FDA OCE's Project FrontRunner

Panel White Paper

Assessing Variability Across HRD Assays: Findings from the *Friends'* HRD Harmonization Project

Hillary Stires,[1] Zhiwei Zhang,[2] Lisa McShane,[2] Jonathan Bieler,[3] Li Chen,[4] Mohit Gupta,[5] Alexander J. Lazar,[6] Brittany McKelvey,[1] Sarabjot Pabla,[7] Jerod Parsons,[8] Daniel Saul,[9] Omar Serang,[10] Ethan S. Sokol,[11] Elizabeth Starks,[12] Brad Thomas,[13] Shuang Yang,[14] Jennifer Yen,[15] Mark Stewart,[1] Jeff Allen[1]

1. Friends of Cancer Research, 2. National Cancer Institute, 3. Sophia Genetics, 4. Fredrick National Laboratory, 5. Thermo Fisher Scientific, 6. MD Anderson Cancer Center, 7. OmniSeq, 8. Tempus Labs, Inc., 9. Bionano Genomics, 10. DNAnexus, 11. Foundation Medicine, Inc., 12. Invitae, 13. Neogenomics, 14. AmoyDx, 15. Guardant Health, Inc.

Introduction

Homologous recombination deficiency (HRD) assays determine eligibility for treatment with PARP inhibitors and potentially other DNA repair targeting drugs. The assays measure several factors to define homologous recombination (HR) status including causes (i.e., inactivation in HR repair (HRR) pathway genes) and consequences (i.e., genomic scarring) of HRD. Methodological variability across HRD assays has not been investigated thoroughly, and an empirical assessment of assay variability may support broader adoption of HRD and strengthen clinical interpretation of test results.

CAUSES inactivation of genes in the HR pathway e.g., BRCA1, BRCA2, CHEK1, CHEK2, PALB2, RAD51B → **Homologous Recombination Deficiency** → **CONSEQUENCES** genomic instability e.g., loss of heterozygosity (gLOH) telomeric allelic imbalances (TAI) large-scale transitions (LST)

Materials & Methods

Assay Factors
We surveyed HRD assay developers (n=20) about factors their assays measure to determine HR status.

Surveyed Assay Factors

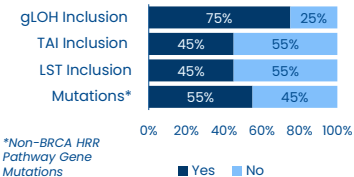| Surveyed Assay Factors |
|---|
| HRD Score |
| gLOH Inclusion |
| gLOH Cutoff |
| BRCA1/2 Inactivation |
| TAI Inclusion |
| LST Inclusion |
| Methylation in non-BRCA HRR Pathway Genes |
| Mutations in non-BRCA HRR Pathway Genes |
| Sig 3 Inclusion |

In Silico Analysis

A subset of assay developers (n=11) received de-identified segmented files,[i] MAF files,[ii] and BRCA germline mutation files for 348 TCGA ovarian cancer samples.[iii] Assay developers ran TCGA samples through their modified HRD pipeline to measure and report HR status and the contributing factor(s) for each sample. Statisticians from the NCI Biometric Research Program performed pairwise comparisons of assays' HR status calls to determine the level of agreement and considered specific factors measured by each assay to identify potential sources of variation. Additionally, they analyzed HR status agreement for BRCA1/2 mutated versus wild type BRCA1/2 samples. BRCA1/2 mutated samples were defined as samples included in the germline mutation file[iii] and samples in which any group identified a BRCA1 or BRCA2 alteration (n=83).

DNAnexus de-identified and shared 348 OvCa TCGA sample files with assay developers → 11 assay developers ran TCGA samples through their HRD pipeline → NCI Biometric Research Program compared HR status calls to determine the level of agreement → The HRD Harmonization Working Group reviewed and reported findings
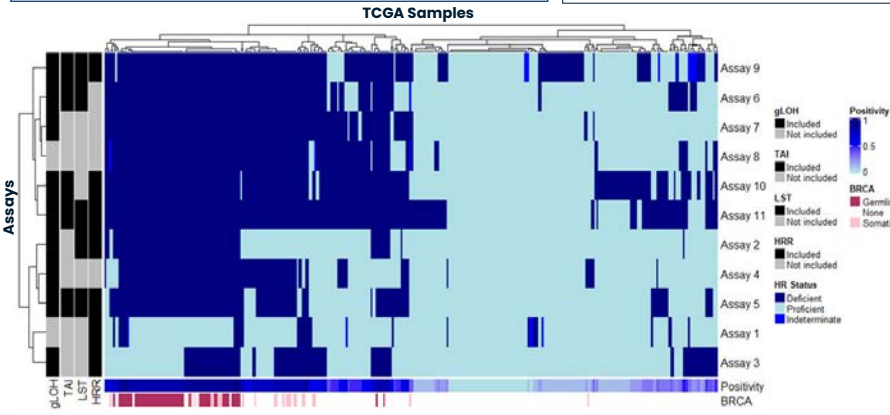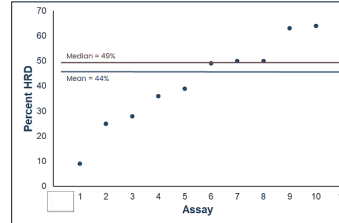
Results
Assay Factors

Assays vary in which factors are included in the HRD analysis pipeline. Assay developers (n=20) were surveyed to determine factors included in their algorithms to determine HRD. All groups measure *BRCA1* and *BRCA2* mutations (graph depicts those who measure genes other than *BRCA1* and *BRCA2*). None of the groups reported measuring methylation in HRR pathway genes. Assays included in the *in silico* analysis had a similar trend for assay factor inclusion.
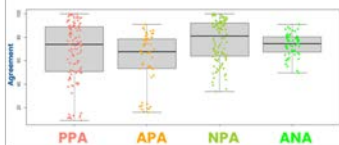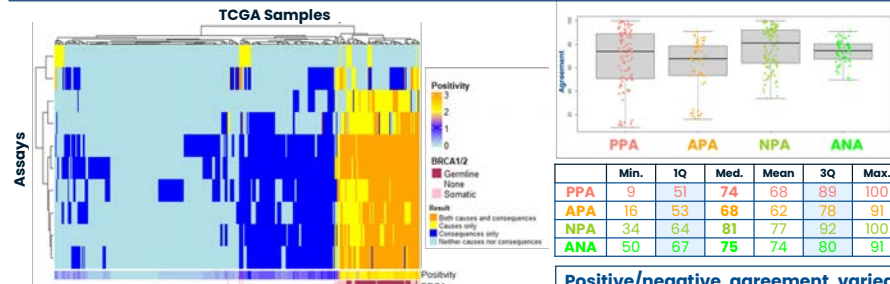
	Yes	No
gLOH Inclusion	75%	25%
TAI Inclusion	45%	55%
LST Inclusion	45%	55%
Mutations*	55%	45%

*Non-BRCA HRR Pathway Gene Mutations

Results
In Silico Analysis

The range of percent HRD positivity is 9-67% with a median of 49% and a mean of 44%. Assay developers (n=11) ran ovarian cancer TCGA samples (n=348) through their HRD pipelines and reported whether each sample was HRD or not. The percent of samples that were HRD out of all the samples was reported as the percent HRD for each assay. The assays are ordered by percent HRD here and throughout the analysis.

Median = 49%
Mean = 44%

TCGA Samples

Assay 9, Assay 6, Assay 7, Assay 8, Assay 10, Assay 11, Assay 2, Assay 5, Assay 1, Assay 3

gLOH: Included / Not included
TAI: Included / Not included
LST: Included / Not included
HRR: Included / Not included
HR Status: Deficient / Proficient / Indeterminate
Positivity: 1 / 0.5 / 0
BRCA: Germline / None / Somatic

There is variability in HR status calls across assays and samples, with BRCA1/2 mutated samples more uniformly called HRD. The tile plot depicts HRD calls by all assays (n=11) for all samples (n=348). Assays and samples are also clustered by relatedness using hierarchical clustering with complete linkage. Assay factors are depicted as yes/ no based on whether the factor to determine HR status was included in the assay algorithm.
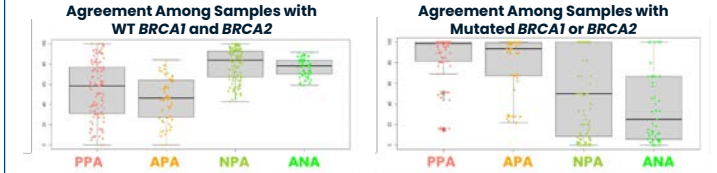
TCGA Samples

BRCA1/2: Germline / None / Somatic
Result: Both causes and consequences / Causes only / Consequences only / Neither causes nor consequences
Positivity: 3 / 2 / 1 / 0

There is moderate agreement between assays for both causes and consequences, but concordance is higher for causes than for consequences. For each sample (n=348), assays (n=9) provided whether causes or consequences determined the HR status call and results were combined into a tile plot. Assays and samples are both clustered by relatedness using hierarchical clustering with complete linkage.

Positive/negative agreement varied across assays, with modest to high levels of agreement. Percent positive agreement (PPA), negative positive agreement (NPA), average positive percent agreement (APA), and average negative percent agreement (ANA) were computed for all possible pairings of samples (n=348) and assays (n=11).

	Min.	1Q	Med.	Mean	3Q	Max.
PPA	9	51	74	68	89	100
APA	16	53	68	62	78	91
NPA	34	64	81	77	92	100
ANA	50	67	75	74	80	91

Results

Agreement Among Samples with WT *BRCA1* and *BRCA2*

PPA, APA, NPA, ANA

Agreement Among Samples with Mutated *BRCA1* or *BRCA2*

PPA, APA, NPA, ANA

PPA is higher when only samples with BRCA1/2 mutations are considered, NPA is lower. PPA, NPA, APA, and ANA were computed for all possible pairings of samples with WT *BRCA1* and *BRCA 2* (n=265) and for samples with altered *BRCA1* and/or *BRCA2* (n=83) across all assays (n=11).

CS Value	Assay Outcome	Result Options
0	Opposite	+/- or -/+
1	Same	+/+, -/-, or in/in

Y	CS	SE	95% CI	
HR Status	0.705	0.009	0.687	0.724
Causes	0.872	0.008	0.856	0.888
Consequences	0.680	0.010	0.661	0.700

Concordance for HR status is moderate with high concordance for causes and lower concordance for consequences. For each comparison, a concordance score (CS) was calculated using a CS Value = 0 if the assays have the opposite outcome and a CS Value = 1 if the assays have the same outcome. To determine the overall concordance, the score was averaged over samples and assays. (CS Value = undefined if "+/in" or "-/in" which was 1% for HR status, 18% for Causes, and 0% for Consequences.)

HRD Score Spearman Correlation summary statistics

%gLOH Spearman Correlation summary statistics

	Min.	Med.	Mean	Max.		Min.	Med.	Mean	Max.
ALL	0.20	0.66	0.62	0.93		0.52	0.70	0.74	1.00
Non-BRCA	0.17	0.64	0.60	0.91		0.50	0.66	0.73	1.00

Correlations among continuous HR scores varied substantially across assays. Spearman correlation coefficients were calculated between each pair of assays that provided continuous HRD scores (n=8) and for each pair of assays that provided continuous %gLOH scores (n=6). The Spearman correlation is based on ranks (assays have different scales). Since identical data inputs were used, low correlations are not explained by differences in copy number modeling or segmentation.

Conclusions

This unique partnership allowed us to further understand similarities and differences among HRD assays.

- While gLOH is presently the most used factor in HRD analysis pipelines (75%), most assays used multiple factors.
- The median HRD positivity rate of 49% is consistent with prior publications. The positivity rate varied widely across assays (9 to 67%).
- The inter-assay agreement on HR status calls was variable but does not appear to be strongly driven by which factors were included in the HRD scores, emphasizing the importance of developing best practices.
- There was more variability in approaches for measuring consequences versus causes and concordance for causes (0.87) was greater than concordance for consequences (0.68).

Understanding the agreement among assays will inform assay interpretation and improve alignment of HRD scores to help patients and providers make appropriate treatment decisions.

An analysis of freshly extracted formalin-fixed paraffin-embedded human archival ovarian tumor samples is planned for early 2023, which will provide additional context for interpreting the findings from the *in silico* dataset.

References: i. PanCan Atlas https://gdc.cancer.gov/about-data/publications/pancanatlas – ABSOLUTE-annotated seg file – TCGA_mastercalls.abs_segtabs.fixed.txt ii. Data Types Collected by TCGA https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga/using-tcga/types Whole Genome MAF Files iii. Maxwell, K. N., et al. (2017). BRCA locus-specific loss of heterozygosity in germline BRCA1 and BRCA2 carriers. Nature Communications 2017 8:1, 8(1), 1–11. Supplementary Data File 1

"*Friends is leading an initiative to assess the role of* *Digital Pathology* *in* **clinical oncology drug development** *that could help inform future research opportunities and regulatory frameworks*"

If you are interested, please e-mail PIcc

Pre-Analytics

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Anatomical Pathology Patient
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Tissue Optimization and
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General
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Guidelines

Best practices for handling specimens from tissue procurement through laboratory diagnostics

Tissue Optimization and Pre-analytic Standardization (TOPS)

Before laboratory:

1 **Tissue specimen labeling**
- Specimen label must contain two unique patient identifiers, and the source of specimen.
- Container should be labeled with the type of fixative used.
- Ensure label matches patient requisition identification.

2 **Tissue specimen handling**
- Use 10% aqueous Neutral Buffered Formalin (NBF) only.
- The fixative volume to tissue volume ratio should be 10:1 minimum.[3]
- If needed, bisect or open the specimen to ensure complete penetration of the fixative solution or as instructed by the Pathology laboratory.
- Ensure that the entire specimen is immersed in the fixative.

10:1 fixative to tissue ratio

Bisect or open specimen

3 **Time to fixation**
- Limit cold ischemia time to <5 minutes, but never exceed 1 hour.[1]
- Specimen should be immersed in fixative immediately at time of collection if possible, or immediately upon receipt at the laboratory if transported fresh.
- Document and record time of collection and start time of fixation (time 0).
- Proper fixation preserves specimen integrity and enables optimal tissue preservation and quality.
- Formalin penetrates tissues quickly (approx. 1mm per hour) but fixes slowly. If needed, specimens need to be opened, incised or sliced in the laboratory and left to fix for an adequate period of time prior to processing.

<1 hour

4 **Tissue specimen storage and transportation**
- Do not store specimens overnight at room temperature or at 4°C without fixative solution.[2]
- Fresh specimens should be transported to the lab immediately.
- Ensure that the specimen is transported via courier at ambient temperature (18°- 25°C).

LAB

(continued on next page)

1. Hammond M, Hayes D, Dowsett M, et al. American Society of Clinical Oncology/ College of American Pathologists guideline recommendations for immunohisto- chemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med 2010. 34 (7):e48–e72.
2. Khoury T, Sai S, Hwang H, et al. Delay to formalin fixation effect on breast biomarkers. Mod Pathol. 2009;22:1457-1467.
3. CLSI. Quality Assurance for Design Control and Implementation of Immunohisto- chemistry Assays; Approved Guideline – Second Edition. CLSI document I/LA28-A2. Wayne, PA: Clinical and Laboratory Standards Institute (CLSI). 2011.
4. Westra WH, Hruban RH, Phelps TH, Issacson D. eds. Surgical Pathology Dissection: An Illustrated Guide. 2nd ed. New York, NY: Springer-Verlag New York, Inc; 2003.
5. CLSI MM13 guidelines.

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New Results

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A personal, reference quality, fully annotated genome from a Saudi individual

ⓘ Maxat Kulmanov, ⓘ Rund Tawfiq, ⓘ Hatoon Al Ali, ⓘ Marwa Abdelhakim, ⓘ Mohammed Alarawi, ⓘ Hind Aldakhil, ⓘ Dana Alhattab, ⓘ Ebtehal A. Alsolme, ⓘ Azza Althagafi, ⓘ Angel Angelov, ⓘ Salim Bougouffa, ⓘ Patrick Driguez, ⓘ Yang Liu, ⓘ Changsook Park, ⓘ Alexander Putra, ⓘ Ana M. Reyes-Ramos, ⓘ Charlotte A. E. Hauser, ⓘ Ming Sin Cheung, ⓘ Malak S Abedalthagafi, ⓘ Robert Hoehndorf

Resources

ML Tools for Pathology Images
high-five to Heather from PixelScientia.com

ML Tools for Pathology Images ☆ △ ☁

File   Edit   View   Insert   Format   Data   Tools   Extensions   Help

This spreadsheet is an attempt to compile the many open source ML tools available for pathology images: code, Jupyter notebooks, pretrained models, and datasets (see the tabs across the bo

	A	B	C	D	E	F
1	This spreadsheet is an attempt to compile the many open source ML tools available for pathology images: code, Jupyter notebooks, pretrained models, and datasets (see the tabs across the bottom). Have you open sourced your own project? Have you used someone else's publicly accessible code or data that others might benefit from? I would greatly appreciate your help in expanding and updating this **Additions or corrections?** This spreadsheet is editable by all. Please add new resources or correct info in existing rows. **Questions or comments?** Email heather@pixelscientia.com					
2	**Category**	**Name & Link**	**Framework**	**License**	**Description**	**Comments**
3	annotation	QuickAnnotator	PyTorch	BSD 3-Clause C	Rapidly bootstrap annotation creation for digital pathology projects by helping identify images and small regions	
4	annotation	NuClick	PyTorch		CNN-based approach to speed up collecting annotations for microscopic objects requiring minimum interaction from the annotator	
5	anomaly detection	P-CEAD		Apache-2.0	Anomaly detection using a progressive autoencoder for inpainting	
6	augmentation	he-auto-augment	TensorFlow		H&E tailored Randaugment: automatic data augmentation policy selection for H&E-stained histopathology.	
7	augmentation	Stain Mix-up			Stain Mix-Up: Domanin Generalization for Histopathology Images as an image augmentation technique	
8	augmentation	style-transfer-for-digital-pathology	PyTorch		Learning domain-agnostic visual representation for computational pathology using medically-irrelevant style transfer augmentation	
9	augmentation stain normalization	stainlib		MIT	Augmentation & normalization of H&E images	
10	cell segmentation	FewShotCellSegmentation	PyTorch	MIT	Few-shot microscopy image cell segmentation	
11	cell segmentation	Cell-DETR	PyTorch	MIT	Attention-Based Transformers for Instance Segmentation of Cells in Microstructures	
12	co-registration	HistoReg			Framework for registration of sequential digitized histology slices	
13	co-registration	DeepHistReg	PyTorch	Apache-2.0		

The Free No-Code NLP Platform

- Annotate Text & Images
- AI Assisted Labeling
- Train & Tune NLP Models
- Test for Responsible AI
- Manage Projects & Teams
- Enterprise Security & Privacy

Install Software

Train & Publish

Define Project

Annotation Lab

Predict

Quality Tests

Reach Agreement

Annotate

Ridiculously good writing: How to write like a pro and publish like a boss

Susan C. Modesitt [a,*], Laura J. Havrilesky [b], Rebecca A. Previs [b], J. Alejandro Rauh-Hain [c], J. Michael Straughn [d], Jamie N. Bakkum-Gamez [e], Katherine C. Fuh [f], David E. Cohn [g]

[a] Gynecologic Oncology Division, Gynecology and Obstetrics Department and Winship Cancer Institute of Emory University, Atlanta, GA, United States
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Duke Cancer Institute, Duke University School of Medicine, Durham, NC, United States
[c] Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, the University of Texas, MD Anderson Cancer Center, Houston, TX, United States

Research paper

Writing a scientific article: A step-by-step guide for beginners

F. Ecarnot [*], M.-F. Seronde, R. Chopard, F. Schiele, N. Meneveau

EA3920, Department of Cardiology, University Hospital Jean-Minjoz, 3, Boulevard Fleming, 25000 Besançon, France

Co-author(s)?

Chapter (SJ Sirintrapun and …):

"Regulatory aspects of Digital Pathology"

Organizations and risk profiling are commonplace in decision making. Understanding the current regulatory aspects and influencing factors will protect institutions from liability.

Book Title: Digital Pathology: Implementation in Clinical Practice: AI applications within Digital Pathology Framework

Co-Editors: Meera Hameed and Matthew Hanna

Publisher: Elsevier

Deloitte.
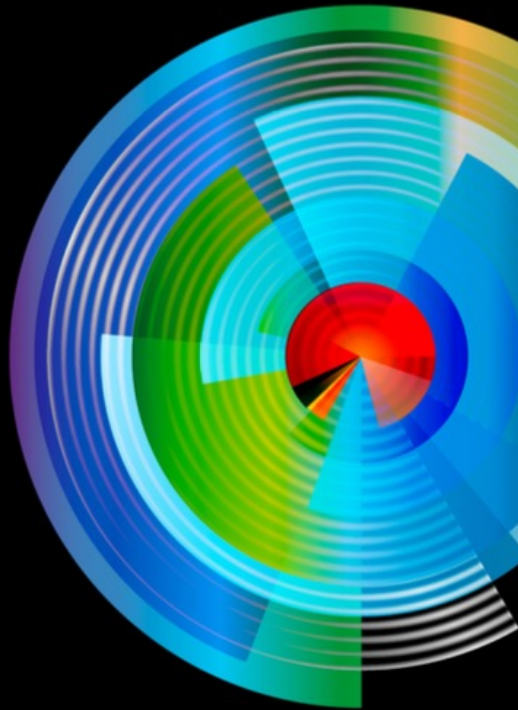
The future of diagnostics
Technology driven personalised and preventative healthcare in Europe

October 2022

Deloitte Centre for Health Solutions

Figure 6. Principles for funding and reimbursement of clinical diagnostics

Transparency of funding and reimbursement policies

Predictability and consistency in decision-making processes

Support and reward innovation

Stak
fund
pro

Enable patient access to care
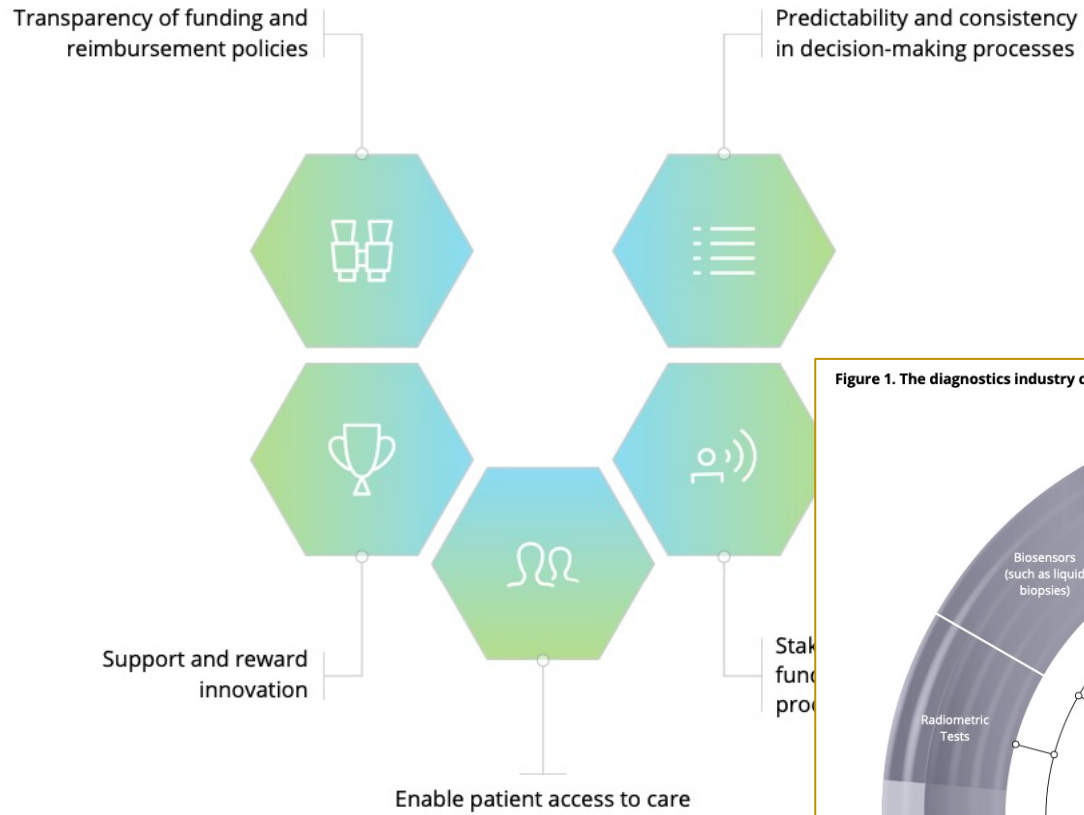
Figure 1. The diagnostics industry comprises a wide range of imaging, in vitro, and digital technologies

Medical Diagnostics

Epigenetics/ Genomics

Clinical Decision support

Biosensors (such as liquid biopsies)

Predictive algorithms

Radiometric Tests

IVDs*

Digital products, apps and software

Software as a medical device

Molecular diagnostics

Wearables and at home monitoring

Imaging

Other imaging**

CT & MRI scans

X-ray machines

PET scans
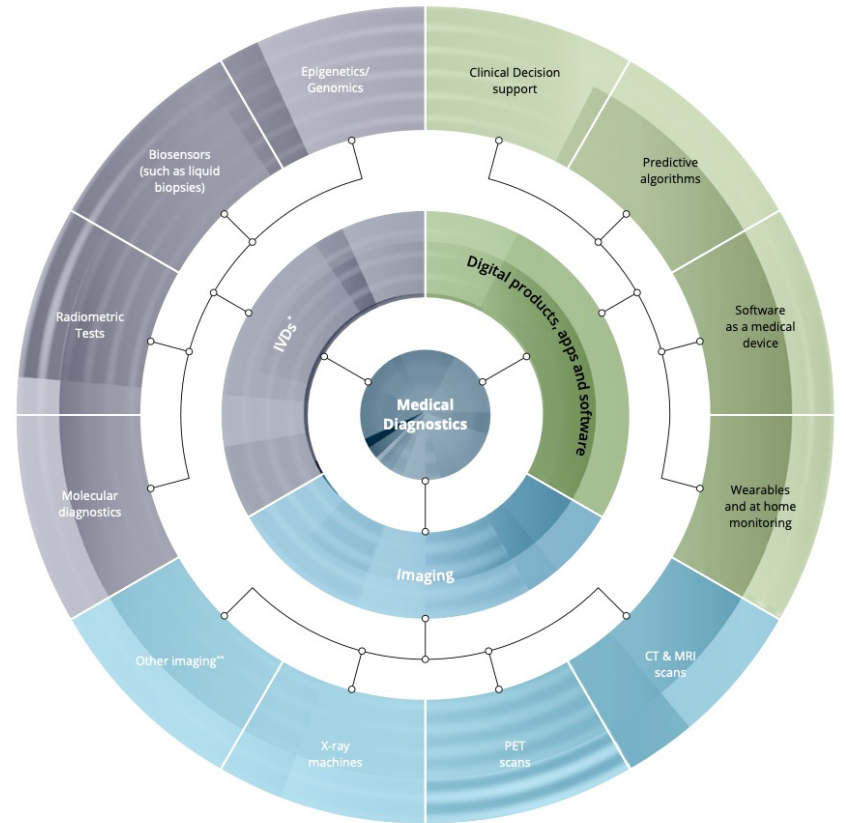
Non-genetic mechanisms of therapeutic resistance in cancer

Jean-Christophe Marine, Sarah-Jane Dawson and Mark A. Dawson
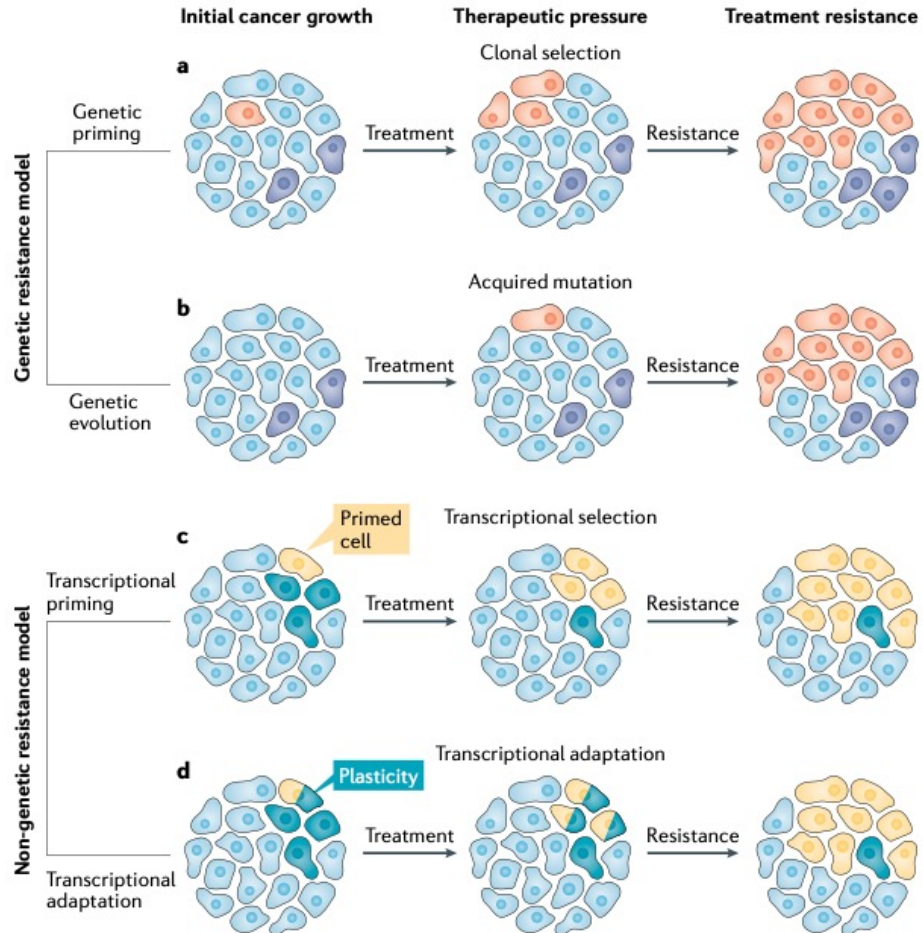
Artem Lomakin[1,2,3,15], Jessica Svedlund[4,15], Carina Strell[4,5], Milana Gataric[1,2], Artem Shmatko[3], Gleb Rukhovich[2,3], Jun Sung Park[1,2,3], Young Seok Ju[6], Stefan Dentro[1,2,3], Vitalii Kleshchevnikov[2], Vasyl Vaskivskyi[2], Tong Li[2], Omer Ali Bayraktar[2], Sarah Pinder[7,8], Andrea L. Richardson[9], Sandro Santagata[10,11,12], Peter J. Campbell[2], Hege Russnes[13,14], Moritz Gerstung[1,3✉], Mats Nilsson[4✉] & Lucy R. Yates[2✉]

Histological features
- Lobule contour (DCIS)
- Hyperplasia
- Normal duct
- Lymphocyte cluster
- Annotated microregions

COMMENT   **OPEN**

Check for updates
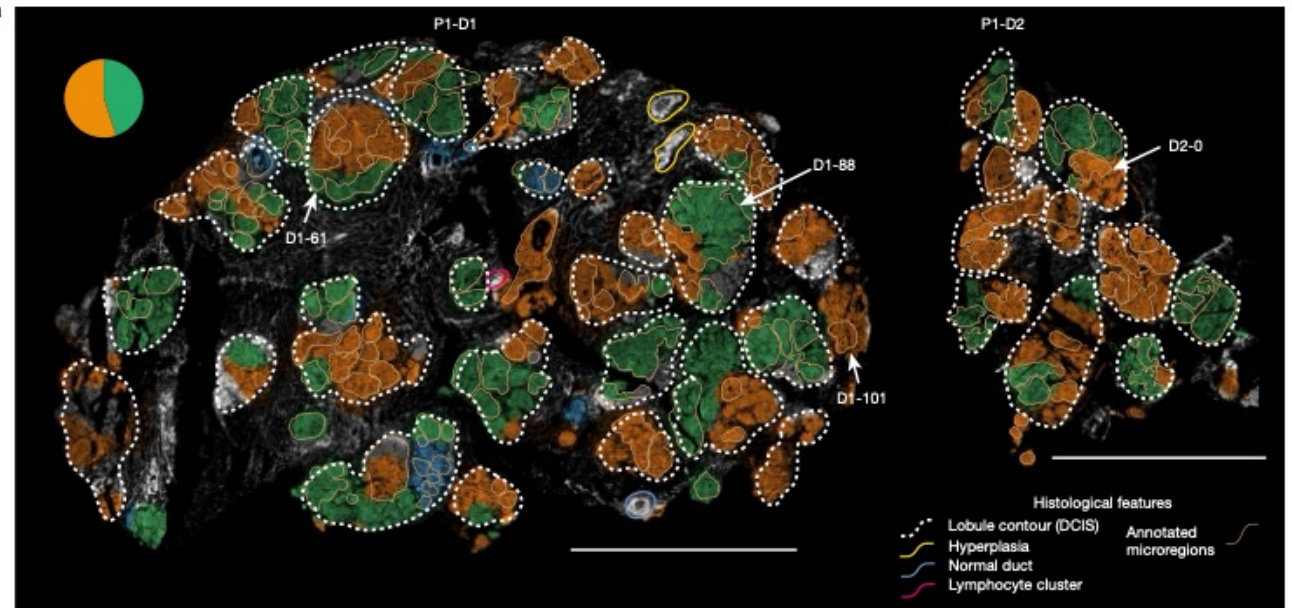
A unifying force for the realization of medical AI

Jochen K. Lennerz [ID][1][✉], Ursula Green [ID][1], Drew F. K. Williamson[2,3] and Faisal Mahmood [ID][1,2,3]

Artificial Intelligence (AI) in medicine has grown rapidly, yet few algorithms have been deployed. It is not the problem with the AI itself but with the way functions and results are communicated. Regulatory science provides the appropriate language and solutions to this problem for three reasons: First, there is value in the intentionally interdisciplinary regulatory language. Second, regulatory concepts are important for AI researchers because these concepts enable tackling of risk and safety concerns as well as understanding of recently proposed regulations in the US and Europe. Third, regulatory science is a scientific discipline that evaluates and challenges current regulation—aiming for evidence-based improvements. Knowledge of the regulatory language, concepts, and science should be regarded a core competency for communicating medical innovation. Regulatory grade communication will be the key to bringing medical AI from hype to standard of care. Foregoing the possible benefits of regulatory science as a unifying force for the realization of medical AI is a missed opportunity.

A unifying force for the realization of medical AI
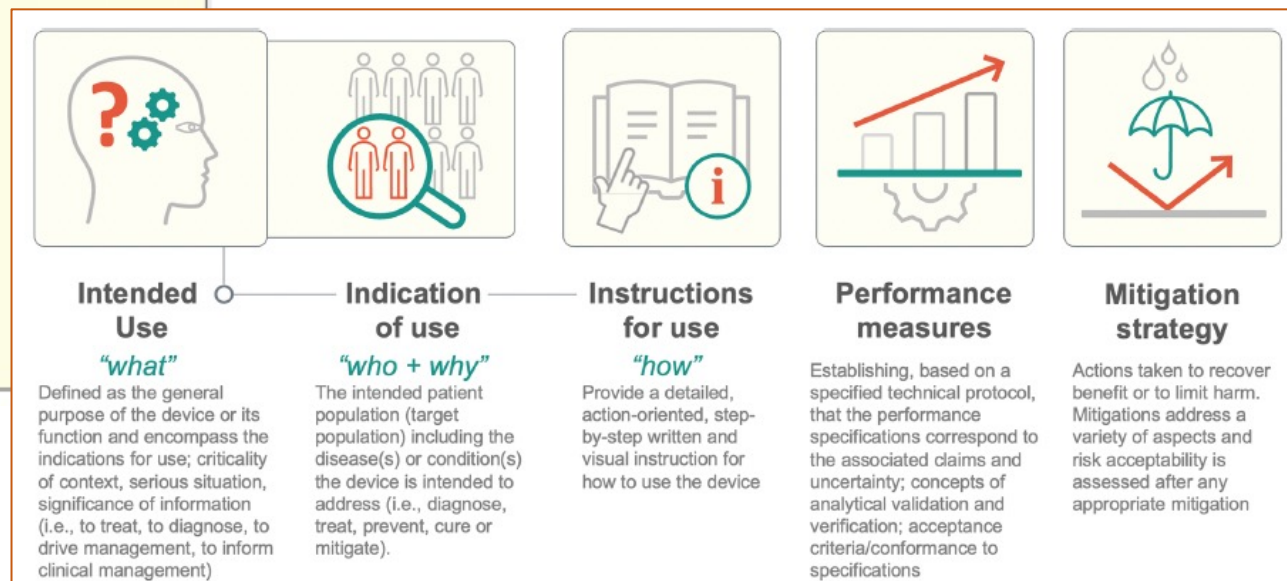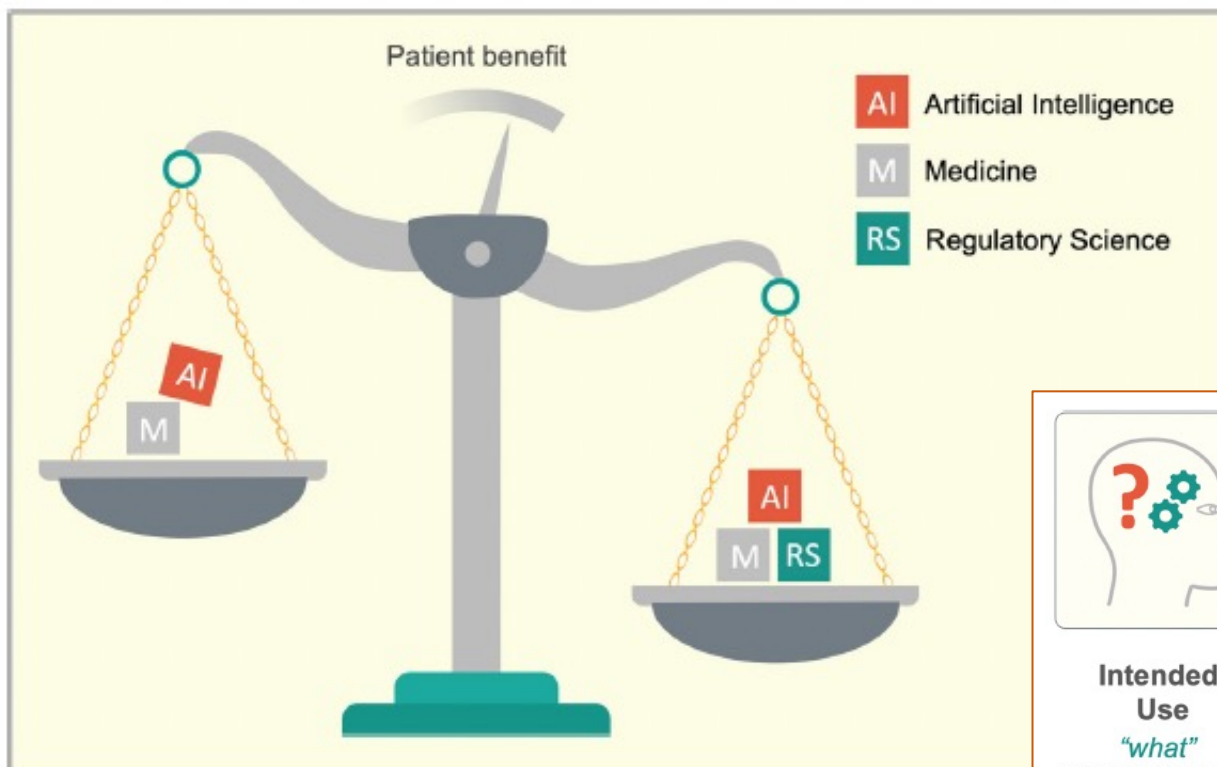
The landscape of mRNA nanomedicine

Xiangang Huang [1,7], Na Kong[1,2,7], Xingcai Zhang [3,7], Yihai Cao [4],
Robert Langer [5,6] & Wei Tao [1]

Table 2 | Selected completed and ongoing clinical trials of mRNA nanomedicine for protein replacement and gene editing

Product name	Sponsor	Target protein	mRNA payload	Disease	Trial number	Phase	Status	Comments and references
Protein replacement								
BNT211	BioNTech	CLDN6	Unknown	Solid tumors	NCT04503278	1/2	Recruiting	CAR-T cell therapy for solid tumors
BNT141	BioNTech	Cancer antibodies	Nucleoside modified	Solid tumors	NCT04683939	1/2	Recruiting	Target CLDN18.2
ARCT-810	Arcturus	OTC	Unknown	OTC deficiency	NCT04442347	1	Recruiting	Entering phase 2 (refs. [206,207])
mRNA-6231	Moderna	IL-2 mutein	Nucleoside modified	IL-2 autoimmune disorders	NCT04916431	1	Recruiting	
Gene editing								
NTLA-2001	Intellia	TTR	Cas9 and TTR sgRNA	hATTR	NCT04601051	1	Recruiting	87% protein reduction[181]

CLDN18.2, claudin 18.2; CLDN6, claudin 6; hATTR, hereditary transthyretin amyloidosis; IL-2, interleukin-2; OTC, ornithine transcarbamylase; TTR, transthyretin.

Check for updates

OPEN

Bias reduction in representation of histopathology images using deep feature selection

Azam Asilian Bidgoli[1,2], Shahryar Rahnamayan[2,3], Taher Dehkharghanian[4], Ali Grami[2] & H.R. Tizhoosh[5,6]
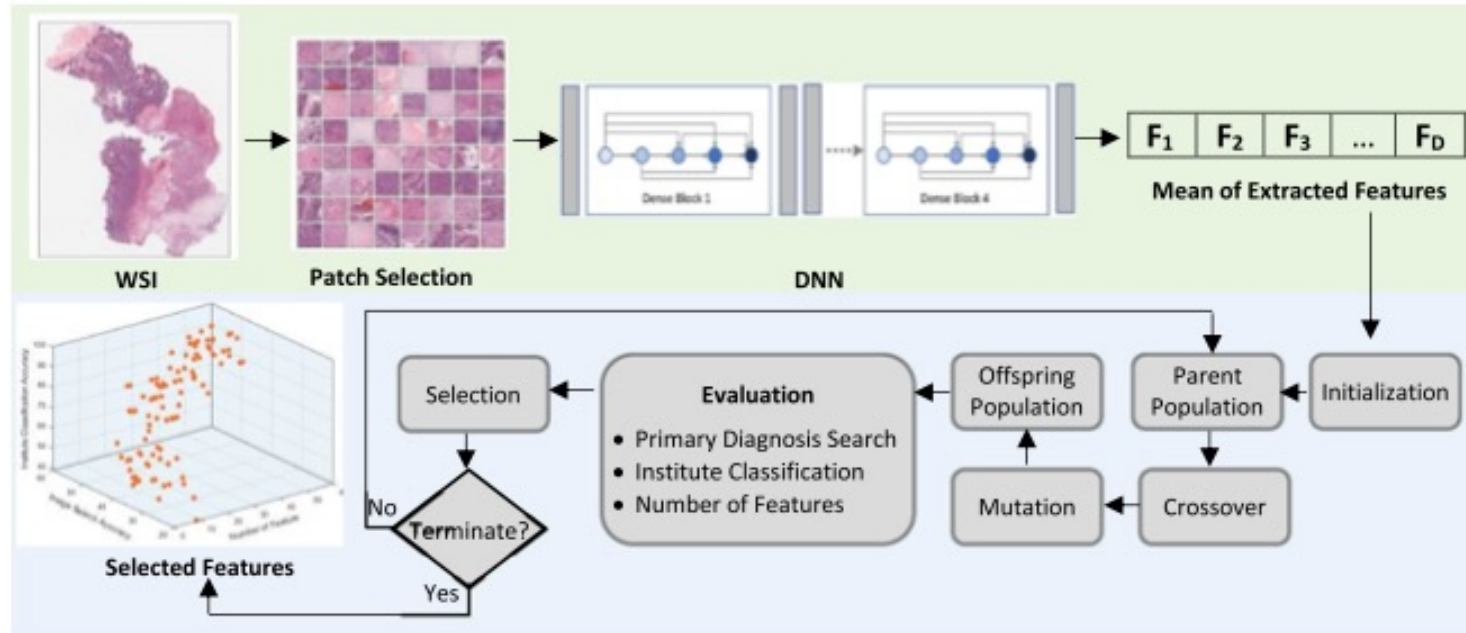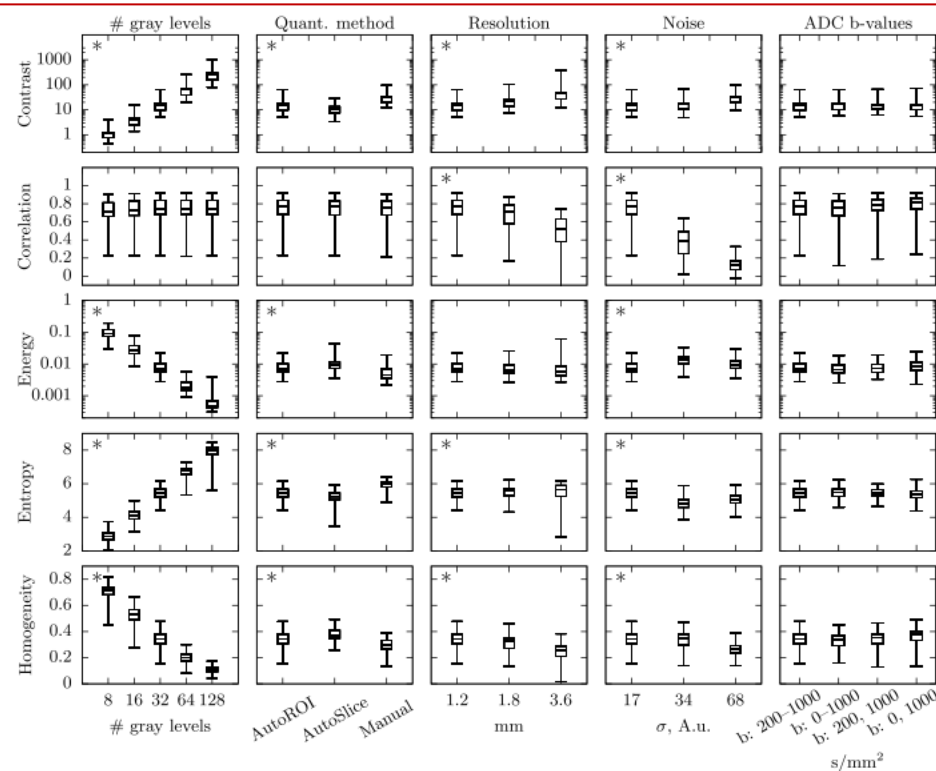
Image analysis

Haralick texture features from apparent diffusion coefficient (ADC) MRI images depend on imaging and pre-processing parameters

Patrik Brynolfsson[1], David Nilsson[2], Turid Torheim[3], Thomas Asklund[1], Camilla Thellenberg Karlsson[1], Johan Trygg[2], Tufve Nyholm[1] & Anders Garpebring[1]

Multi-Site Cross-Organ Calibrated Deep Learning (MuSClD): Automated Diagnosis of Non-Melanoma Skin Cancer

Yufei Zhou [1], Can Koyuncu [2,3], Cheng Lu [2], Rainer Grobholz [4], Ian Katz [5,b], Anant Madabhushi [3,6,#] 👤a ✉

, Andrew Janowczyk [2,7,c]

Multi-Site Cross-Organ Calibrated Deep Learning (MuSClD): Automated Diagnosis of Non-Melanoma Skin Cancer

Training Phase

Cross-organ calibration:
- Use lung tissue image from Site B to avoid data leakage

Skin (Site A) + Lung (Site B) → CycleGAN Calibrate → Calibrated Skin

Training of NMSC subtyping model with calibrated data:
- Mitigate pre-analytics variation across sites

Benign / Basal Cell Carcinoma / In situ Squamous cell carcinoma / Invasive squamous cell

Train the NMSC-subtyping model with calibrated site A data.

Evaluation Phase

Held-out test:
- Assess the generalizability of NMSC- subtyping model

Skin (Site B)

Evaluate the generalizability with site B data.

Subtyping Performance

Trastuzumab Deruxtecan in Anti–Human Epidermal Growth Factor Receptor 2 Treatment–Naive Patients With Human Epidermal Growth Factor Receptor 2–Low Gastric or Gastroesophageal Junction Adenocarcinoma: Exploratory Cohort Results in a Phase II Trial

Kensei Yamaguchi, MD[1]; Yung-Jue Bang, MD, PhD[2]; Satoru Iwasa, MD[3]; Naotoshi Sugimoto, MD[4]; Min-Hee Ryu, MD, PhD[5]; Daisuke Sakai, MD[6]; Hyun Cheol Chung, MD, PhD[7]; Hisato Kawakami, MD, PhD[8]; Hiroshi Yabusaki, MD[9]; Jeeyun Lee, MD[10]; Tatsu Shimoyama, MD[11]; Keun-Wook Lee, MD, PhD[12]; Kaku Saito, MSc, MBA[13]; Yoshinori Kawaguchi, MSc, MBA[13]; Takahiro Kamio, MD[13]; Akihito Kojima, MSc[14]; Masahiro Sugihara, PhD[14]; and Kohei Shitara, MD[15]

PURPOSE To investigate efficacy and safety of trastuzumab deruxtecan (T-DXd) in human epidermal growth factor receptor 2 (HER2)–low gastric or gastroesophageal junction (GEJ) adenocarcinoma.

METHODS Patients with locally advanced or metastatic HER2-low (cohort 1, immunohistochemistry 2+/in situ hybridization–negative; cohort 2, immunohistochemistry 1+) gastric/GEJ adenocarcinoma treated with at least two prior regimens, including fluoropyrimidine and platinum, but anti-HER2 therapy naive, received T-DXd 6.4 mg/kg intravenously once every 3 weeks. The primary end point was confirmed objective response rate by independent central review.

RESULTS Among 21 patients enrolled in cohort 1 and 24 enrolled in cohort 2, 19 and 21 patients, respectively, had central HER2 confirmation, received T-DXd, and had measurable tumors at baseline. The confirmed objective response rate was 26.3% (95% CI, 9.1 to 51.2) from five partial responses in cohort 1 and 9.5% (95% CI, 1.2 to 30.4) from two partial responses in cohort 2. Thirteen patients (68.4%) in cohort 1 and 12 (60.0%) in cohort 2 experienced reduced tumor size. The median overall survival was 7.8 months (95% CI, 4.7 to nonevaluable) in cohort 1 and 8.5 months (95% CI, 4.3 to 10.9) in cohort 2; the median progression-free survival was 4.4 months (95% CI, 2.7 to 7.1) and 2.8 months (95% CI, 1.5 to 4.3), respectively. The most common grade ≥ 3 treatment-emergent adverse events in cohorts 1 and 2 were anemia (30.0% and 29.2%), decreased neutrophil count (25.0% and 29.2%), and decreased appetite (20.0% and 20.8%). Drug-related interstitial lung disease/pneumonitis occurred in one patient in each cohort (grade 1 or 2). No drug-related deaths occurred.

CONCLUSION This study provides preliminary evidence that T-DXd has clinical activity in patients with heavily pretreated HER2-low gastric/GEJ adenocarcinoma.

Recurrence prediction

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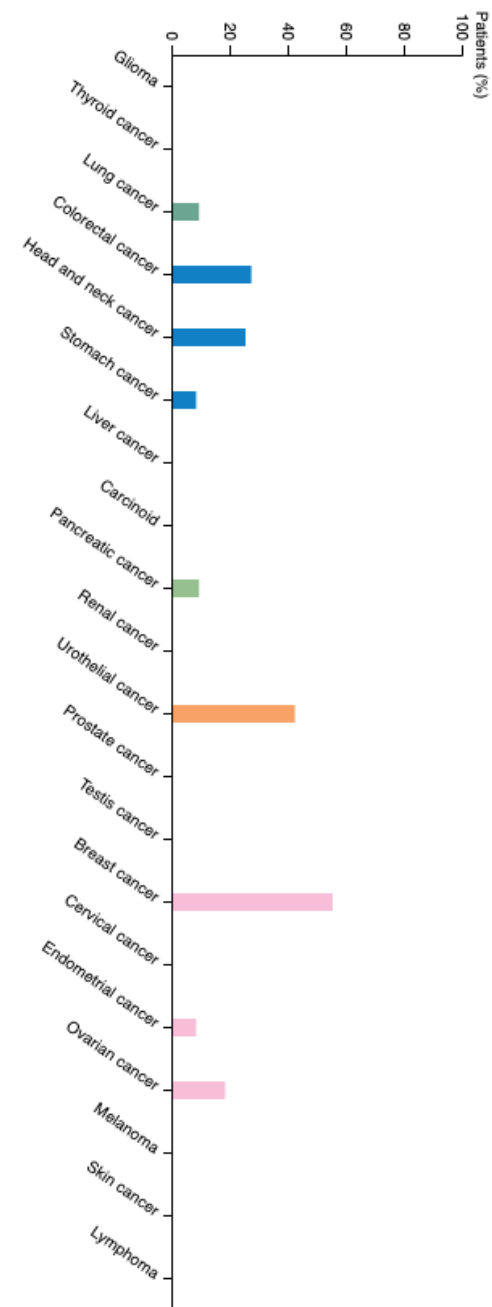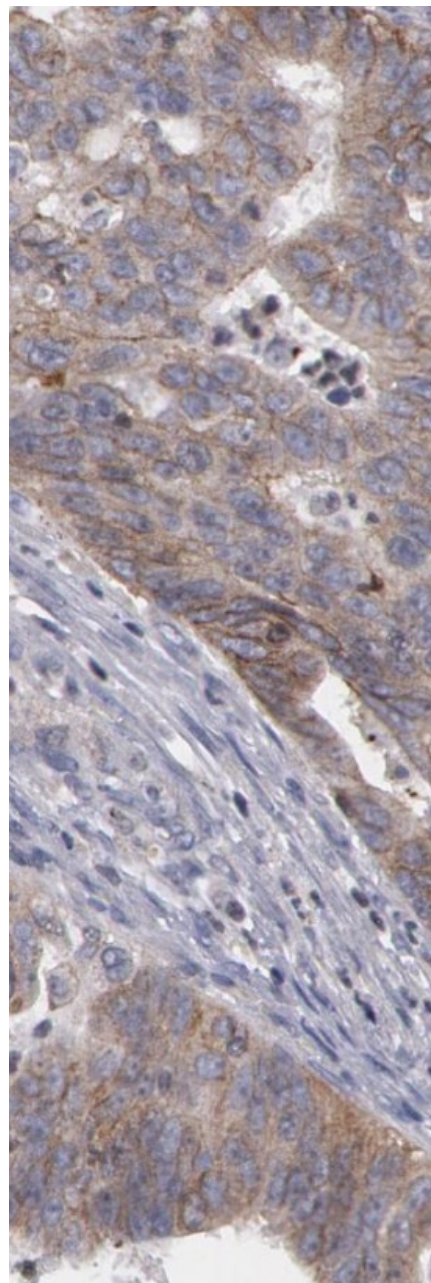
ARTICLE **OPEN**

Prediction of early-stage melanoma recurrence using clinical and histopathologic features

Guihong Wan [1,2,3,9], Nga Nguyen[1,9], Feng Liu [4,9], Mia S. DeSimone [5], Bonnie W. Leung [1], Ahmad Rajeh[1], Michael R. Collier[1], Min Seok Choi[1], Munachimso Amadife[1], Kimberly Tang[1], Shijia Zhang[1], Jordan S. Phillipps [1], Ruple Jairath[1], Nora A. Alexander [1], Yining Hua[1,2], Meng Jiao[4], Wenxin Chen[1,2], Diane Ho[1], Stacey Duey[1], István Balázs Németh[6], Gyorgy Marko-Varga[7], Jeovanis Gil Valdés [7], David Liu [8], Genevieve M. Boland [1], Alexander Gusev[8], Peter K. Sorger [3], Kun-Hsing Yu [2,5,10] and Yevgeniy R. Semenov [1,3,10 ✉]

Prognostic analysis for early-stage (stage I/II) melanomas is of paramount importance for customized surveillance and treatment plans. Since immune checkpoint inhibitors have recently been approved for stage IIB and IIC melanomas, prognostic tools to identify patients at high risk of recurrence have become even more critical. This study aims to assess the effectiveness of machine-learning algorithms in predicting melanoma recurrence using clinical and histopathologic features from Electronic Health Records (EHRs). We collected 1720 early-stage melanomas: 1172 from the Mass General Brigham healthcare system (MGB) and 548 from the Dana-Farber Cancer Institute (DFCI). We extracted 36 clinicopathologic features and used them to predict the recurrence risk with supervised machine-learning algorithms. Models were evaluated internally and externally. In the (1) five-fold cross-validation of the MGB cohort; (2) the MGB cohort for training and the DFCI cohort for testing independently. In the internal and external validations, respectively, we achieved a recurrence classification performance of AUC: 0.845 and 0.812, and a time-to-event prediction performance of time-dependent AUC: 0.853 and 0.820. Breslow tumor thickness and mitotic rate were identified as the most predictive features. Our results suggest that machine-learning algorithms can extract predictive signals from clinicopathologic features for early-stage melanoma recurrence prediction, which will enable the identification of patients that may benefit from adjuvant immunotherapy.

npj Precision Oncology (2022)6:79; https://doi.org/10.1038/s41698-022-00321-4
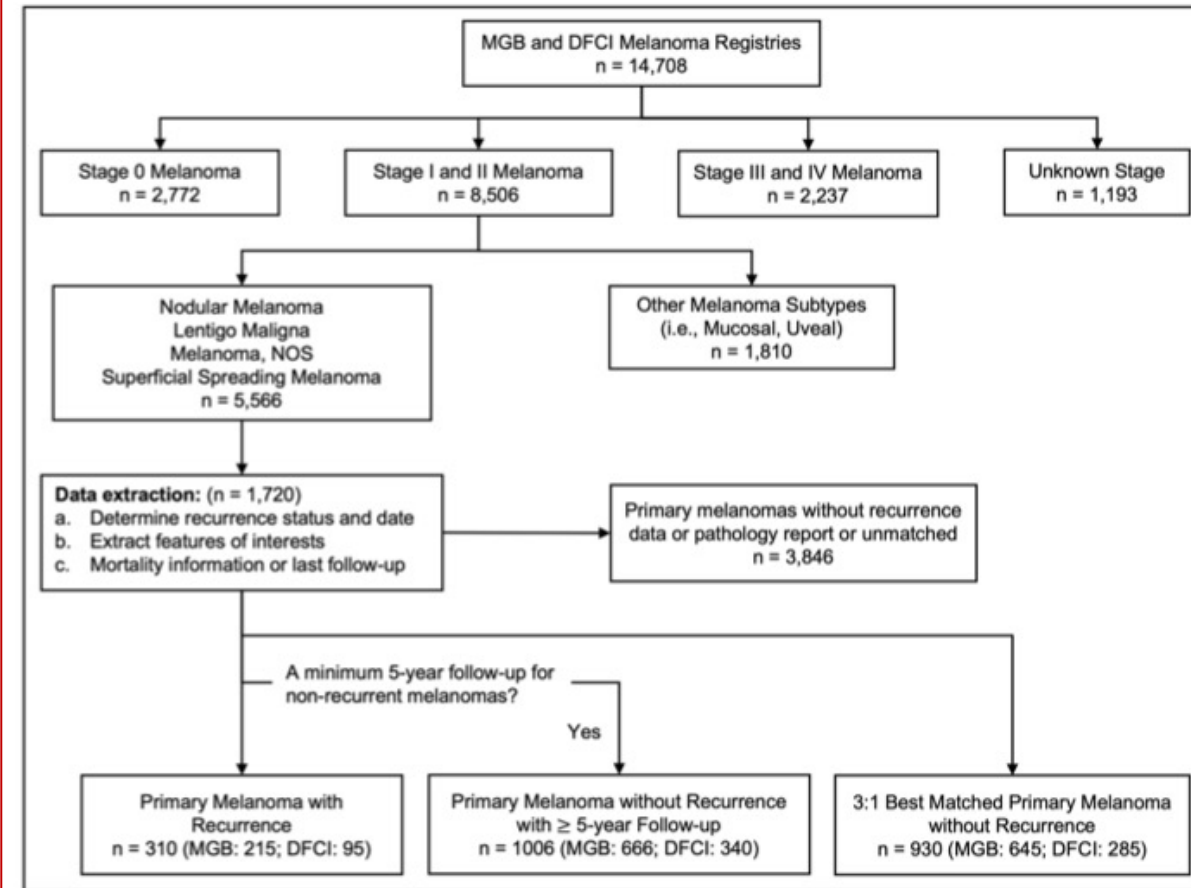
Opinion Paper

Anna Carobene*, Federico Cabitza, Sergio Bernardini, Raj Gopalan, Jochen K. Lennerz, Clare Weir and Janne Cadamuro

Where is laboratory medicine headed in the next decade? Partnership model for efficient integration and adoption of artificial intelligence into medical laboratories

Abstract

amenable to AI solutions; (3) Laboratory sub-specialization continues and from test selection to interpretation, tasks increase in complexity; (4) Expertise in AI implementation and partnerships with industry will emerge as a professional competency and require novel educational strategies for

AI Integration

The vendor-agnostic EMPAIA platform for integrating AI applications into digital pathology infrastructures

Christoph Jansen [a,*], Björn Lindequist [a], Klaus Strohmenger [a], Daniel Romberg [b], Tobias Küster [c], Nick Weiss [d], Michael Franz [a], Lars Ole Schwen [b], Theodore Evans [c], André Homeyer [b], Norman Zerbe [a]

[a] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Pathology, Charitéplatz 1, 10117 Berlin, Germany
[b] Fraunhofer Institute for Digital Medicine MEVIS, Max-von-Laue-Straße 2, 28359 Bremen, Germany
[c] Technische Universität Berlin, DAI-Labor, Ernst-Reuter-Platz 7, 10587 Berlin, Germany
[d] Fraunhofer Institute for Digital Medicine MEVIS, Maria-Goeppert-Straße 3, 23562 Lübeck, Germany

AI Integration

Fig. 2. Workbench Client: A browser-based web UI for pathologists, that enables the usage of EMPAIA compliant image processing apps. The screenshot shows annotations on a WSI that are the result of a successful job.
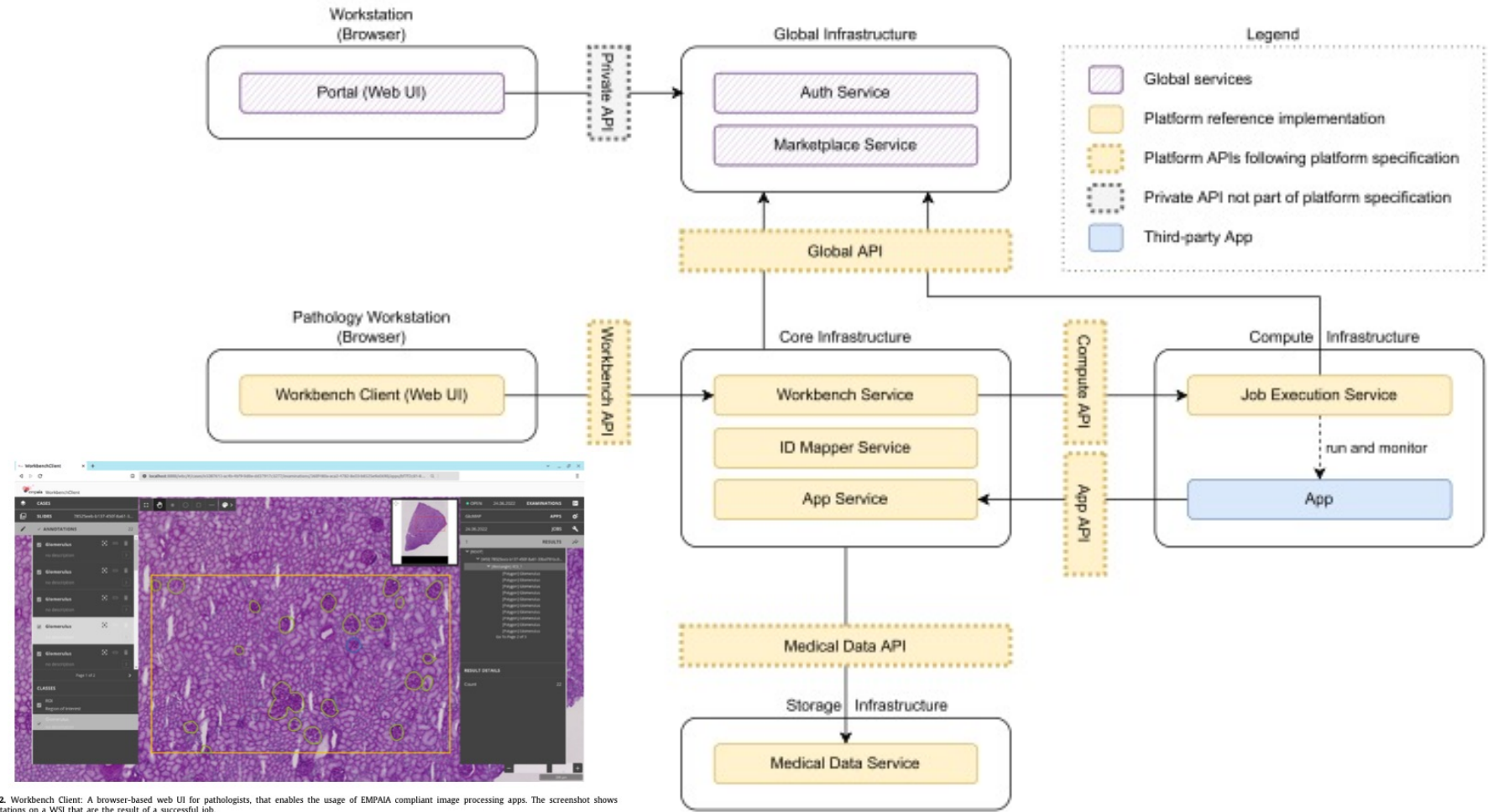
Fig. 1. Platform Architecture: Global Services for central user-/organization-management, authentication, and app distribution are rendered in purple. Decentralized Platform Services for pathology laboratories are rendered in yellow. Solid arrows denote the direction of HTTP API requests.

Opportunities and challenges in translational science

Christopher P. Austin

Original Investigation | Oncology

Characterization of Oncology Clinical Trials Using Germline Genetic Data

Ashwin V. Kammula, BS; Alejandro A. Schäffer, PhD; Padma Sheila Rajagopal, MD, MPH, MSc

Abstract

IMPORTANCE The recent successes of poly-ADP ribose polymerase (PARP) inhibitors and belzutifan support germline genetic data as an exciting, accessible source for biomarkers in cancer treatment. This study hypothesizes, however, that most oncology clinical trials using germline data largely prioritize *BRCA1/2* as biomarkers and PARP inhibitors as therapy.

OBJECTIVE To characterize past and ongoing oncology trials that use germline data.

DESIGN, SETTING, AND PA[...]
used the Informa Trialtrove [...]
(including the terms *germlin*[...]
points, objectives, results, o[...]
4, 2022 (data freeze date), [...]

MAIN OUTCOMES AND ME[...]
points, outcomes, and locati[...]
for studied therapeutic inter[...]
exclusion criteria are associated with end points, outcomes, and enrollment were also examined.

RESULTS A total of 887 of 84 297 (1.1%) oncology clinical trials in the Trialtrove database that use germline data were identified. Most trials were conducted in cancer types where PARP inhibitors are already approved. A total of 74.8% (672) of trials were performed in the phase 2 setting or above. Trials were primarily sponsored by industry (523 trials [59.0%]), academia (382 trials [43.1%]), and the government (274 trials [30.9%]), where trials may have multiple sponsor types. Among 343 trials using germline data with outcomes in Trialtrove, 180 (52.5%) reported meeting primary end points. Although *BRCA1/2* are the most frequent biomarkers seen (*BRCA1*, 224 trials [25.3%]; *BRCA2*, 228 trials [25.7%]), trials also examine pharmacogenomic variants and germline mediators of somatic biomarkers. PARP inhibitors or immunotherapy were tested in 69.9% of trials; PARP inhibition was the most frequently studied mechanism (367 trials [41.4%]). An overwhelming number of trials using germline data were conducted in the US, Canada, and Europe vs other countries, mirroring disparities in cancer genetics data. Germline data in inclusion and exclusion criteria are associated with altered end point, outcomes, and enrollment compared with oncology trials with no germline data use. Examples of inclusion and exclusion criteria regarding germline data that may unintentionally exclude patients were identified.

CONCLUSIONS AND RELEVANCE These findings suggest that for germline biomarkers to gain clinical relevance, trials must expand biomarkers, therapies, and populations under study.

Key Points

**Question** What are features of clinical trials in oncology that use germline data?

Findings In this cross-sectional study of 84 297 oncology clinical trials included in the Informa Trialtrove databse, 1.1% used germline data, with 52.5% of trials [...]

Meaning These findings suggest that for germline biomarkers to gain clinical relevance, trials must expand biomarkers, therapies, and populations under study.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

CONCLUSIONS AND RELEVANCE These findings suggest that for germline biomarkers to gain clinical relevance, trials must expand biomarkers, therapies, and populations under study.
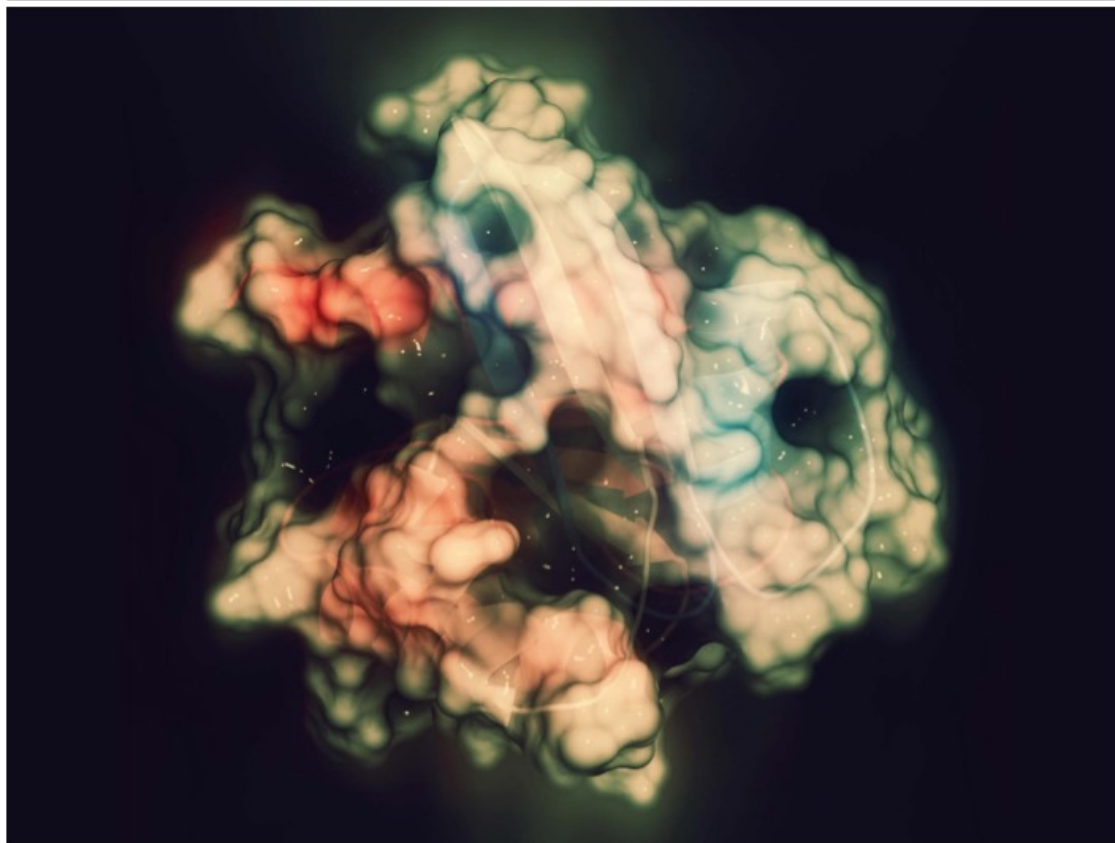
The relatively smooth surface of the KRAS protein has made it difficult to design drugs against it.

CLOSING IN ON CANCER'S DEADLIEST MUTATIONS

The protein KRAS, mutated in many cancers, was deemed 'undruggable'. Now scientists are hoping to save lives with a batch of new compounds that target it. **By Heidi Ledford**

KRAS INHIBITORS ON TRIAL

Dozens of trials for drugs that target the KRAS are for cancers that carry the G12C mutation,

Drug	Target
Sotorasib	G12C (targets 'off' state of the mutant protein)
Adagrasib	G12C
JAB-21822	G12C
D-1553	G12C
HRS-4642	G12D
ASP3082	G12D
RMC-6236	Multiple RAS mutations (targets protein 'on' state)
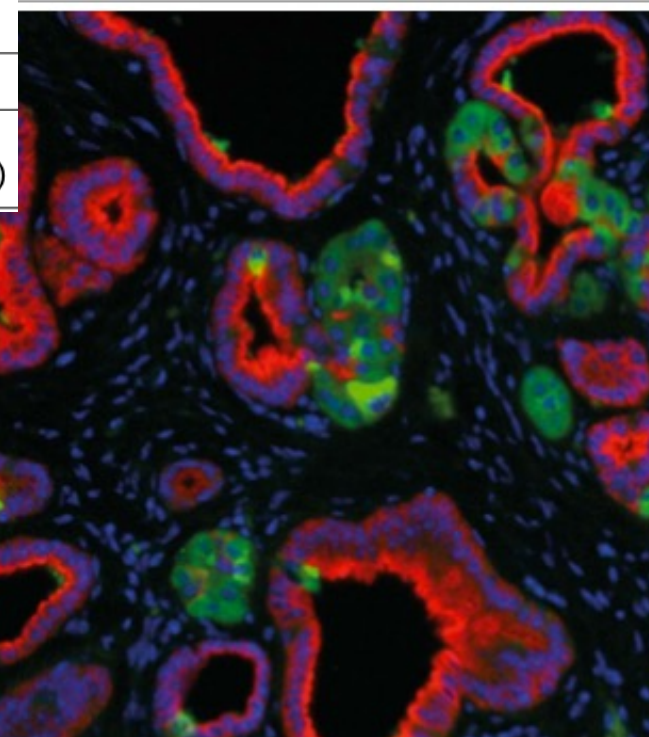
A *KRAS* mutation turns normal cells (green) precancerous (red) in a mouse pancreas.

Predictive biomarkers and personalized pharmacotherapy

Jan Trøst Jørgensen & Niels Westergaard

Table 1. List of the FDA-approved drugs and their CDx biomarkers.

CDx Biomarkers	Drugs
ALK/*ALK*	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
BCR-ABL1	Nilotinib
BRAF V600E or V600K	Binimetinib, cobimetinib, dabrafenib, encorafenib, trametinib, vemurafenib
BRCA1/BRCA2	Niraparib, olaparib, rucaparib, talazoparib
dMMR	Dostarlimab, pembrolizumab, nivolumab
EGFR	Amivantamab
EGFR	Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, mobocertinib
EZH2	Tazemetostat
FGFR2	Pemigatinib, infigratinib
FGFR3	Erdafitinib
FLT3	Midostaurin, gilteritinib
HER2/*HER2*	Trastuzumab, pertuzumab, trastuzumab emtansine, trastuzumab deruxtecan
HRR	Olaparib
IDH1	Ivosidenib
IDH2	Enasidenib
Ki-67	Abemaciclib
KIT/c-KIT, *PDGFRB*	Imatinib
KRAS G12C	Sotorasib
Software for MRI	Deferasirox
MET	Capmatinib
MSI-H	Pembrolizumab, nivolumab
NTRK1/2/3	Larotrectinib, entrectinib
PD-L1	Atezolizumab, cemiplimab, nivolumab, pembrolizumab
PIK3CA	Alpelisib, olaparib
POMC, PCSK1 and *LEPR*	Setmelanotide
RAS (KRAS/NRAS)/EGFR	Cetuximab, panitumumab
RET	Pralsetinib
ROS1	Crizotinib, entrectinib
TMB-H	Pembrolizumab
TP53	Venetoclax

Impact of Clinical Practice Gaps on the Implementation of Personalized Medicine in Advanced Non–Small-Cell Lung Cancer

Helen Sadik, PhD[1]; Daryl Pritchard, PhD[2]; Derry-Mae Keeling, BSc[1]; Frank Policht, PhD[1]; Peter Riccelli, PhD[1]; Gretta Stone, BS[3]; Kira Finkel, MSPH[3]; Jeff Schreier, MBA[1]; and Susanne Munksted, MS[1]
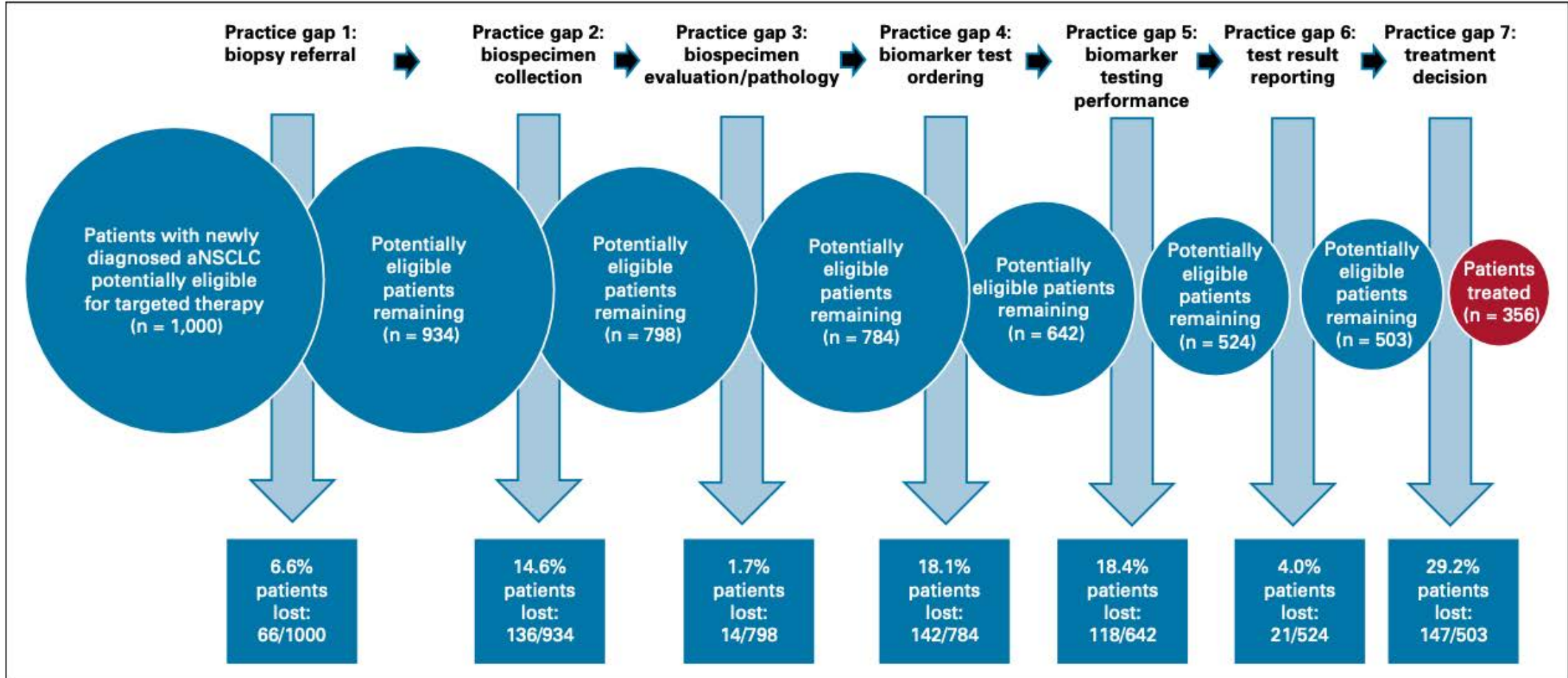
FIG 4. Impact of clinical practice gaps on the delivery of precision oncology for aNSCLC. aNSCLC, advanced non-small cell lung cancer.

Perspective

Check

The coming decade in precision oncology: six riddles

Adam Wahida [1,2,3,4,12] ✉, Lars Buschhorn [3,4,12] ✉, Stefan Fröhling[5,6], Philipp J. Jost[7], Andreas Schneeweiss[4],
Peter Lichter[3,8,9] & Razelle Kurzrock[10,11] ✉

Abstract

Sections

a

Chr. 9
Chr. 22

t(9;22) (q34;11)

BCR

ABL

Chr. 9
Chr. 22

BCR–ABL
fusion gene

Philadelphia
chromosome

b

Imatinib

c

d

Solid tumours

Clonal evolution

Chronic myeloid leukaemia

Molecular response

Newly diagnosed

Blast crisis

Box 1

Tapping the potential of the molecular tumour board

The success of targeting the BCR–ABL kinase in chronic myeloid

Box 2

Financial and equity hurdles of new technologies

Ever since the US National Human Genome Research Institute
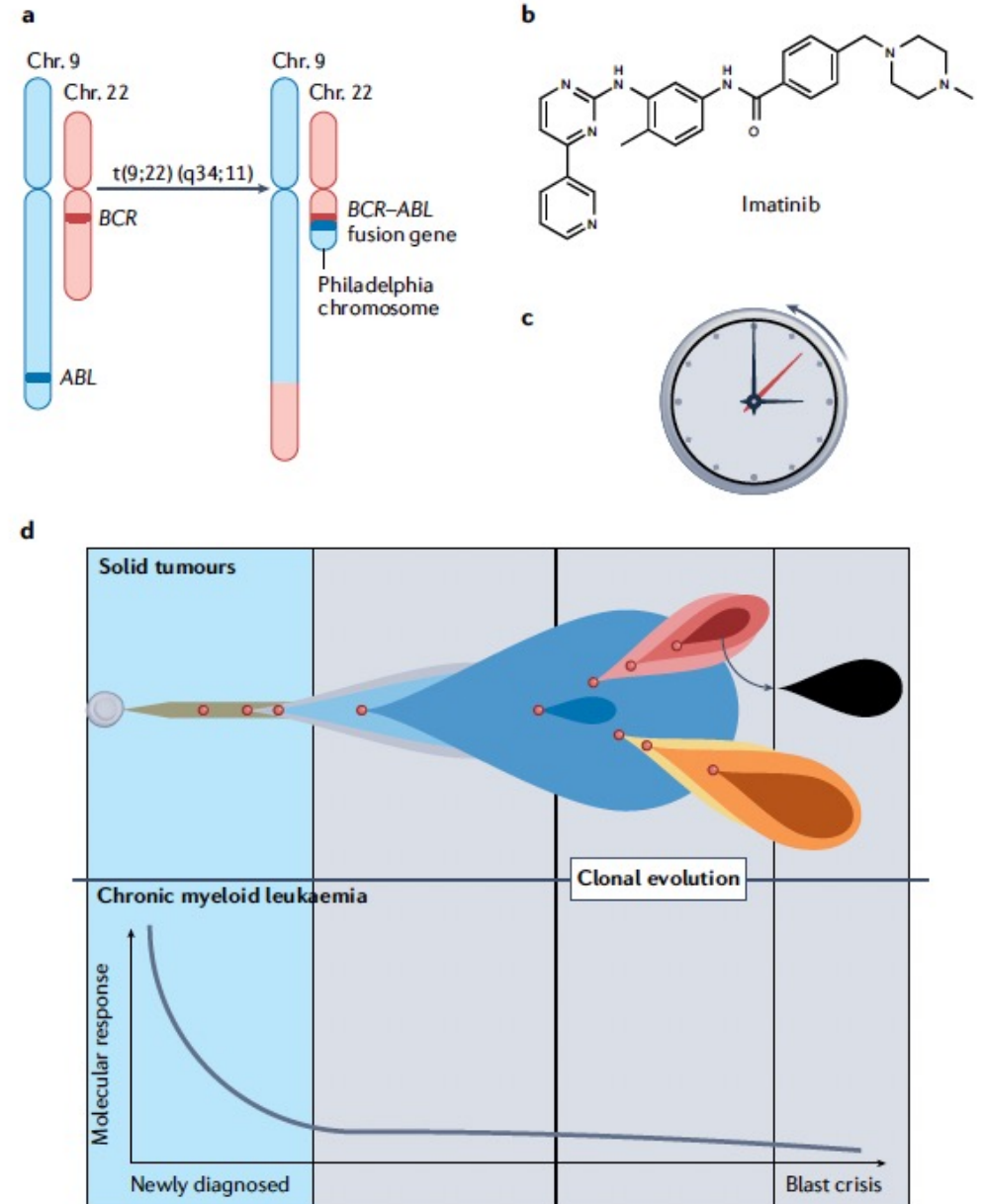
Overcoming the Interobserver Variability in Lung Adenocarcinoma Subtyping

A Clustering Approach to Establish a Ground Truth for Downstream Applications

Kris Lami, MD; Andrey Bychkov, MD, PhD, FRCPath; Keitaro Matsumoto, MD, PhD; Richard Attanoos, MBBS, FRCPath; Sabina Berezowska, MD, PhD; Luka Brcic, MD, PhD; Alberto Cavazza, MD; John C. English, FRCPC; Alexandre Todorovic Fabro, MD, PhD; Kaori Ishida, MD; Yukio Kashima, MD; Brandon T. Larsen, MD, PhD; Alberto M. Marchevsky, MD; Takuro Miyazaki, MD, PhD; Shimpei Morimoto, PhD; Anja C. Roden, MD; Frank Schneider, MD; Mano Soshi, MD; Maxwell L. Smith, MD; Kazuhiro Tabata, MD, PhD; Angela M. Takano, MD; Kei Tanaka, MMedSci; Tomonori Tanaka, MD; Tomoshi Tsuchiya, MD, PhD; Takeshi Nagayasu, MD, PhD; Junya Fukuoka, MD, PhD

● **Context.**—The accurate identification of different lung adenocarcinoma histologic subtypes is important for

determining prognosis but can be challenging because of overlaps in the diagnostic features, leading to considerable interobserver variability.

Objective.—To provide an overview of the diagnostic agreement for lung adenocarcinoma subtypes among pathologists and to create a ground truth using the clustering approach for downstream computational applications.

Design.—Three sets of lung adenocarcinoma histologic images with different evaluation levels (small patches, areas with relatively uniform histology, and whole slide images) were reviewed by 18 international expert lung pathologists. Each image was classified into one or several lung adenocarcinoma subtypes.

Results.—Among the 4702 patches of the first set, 1742 (37%) had an overall consensus among all pathologists. The overall Fleiss κ score for the agreement of all subtypes was 0.58. Using cluster analysis, pathologists were hierarchically grouped into 2 clusters, with κ scores of 0.588 and 0.563 in clusters 1 and 2, respectively. Similar results were obtained for the second and third sets, with fair-to-moderate agreements. Patches from the first 2 sets that obtained the consensus of the 18 pathologists were retrieved to form consensus patches and were regarded as the ground truth of lung adenocarcinoma subtypes.

Conclusions.—Our observations highlight discrepancies among experts when assessing lung adenocarcinoma subtypes. However, a subsequent number of consensus patches could be retrieved from each cluster, which can be used as ground truth for the downstream computational pathology applications, with minimal influence from interobserver variability.
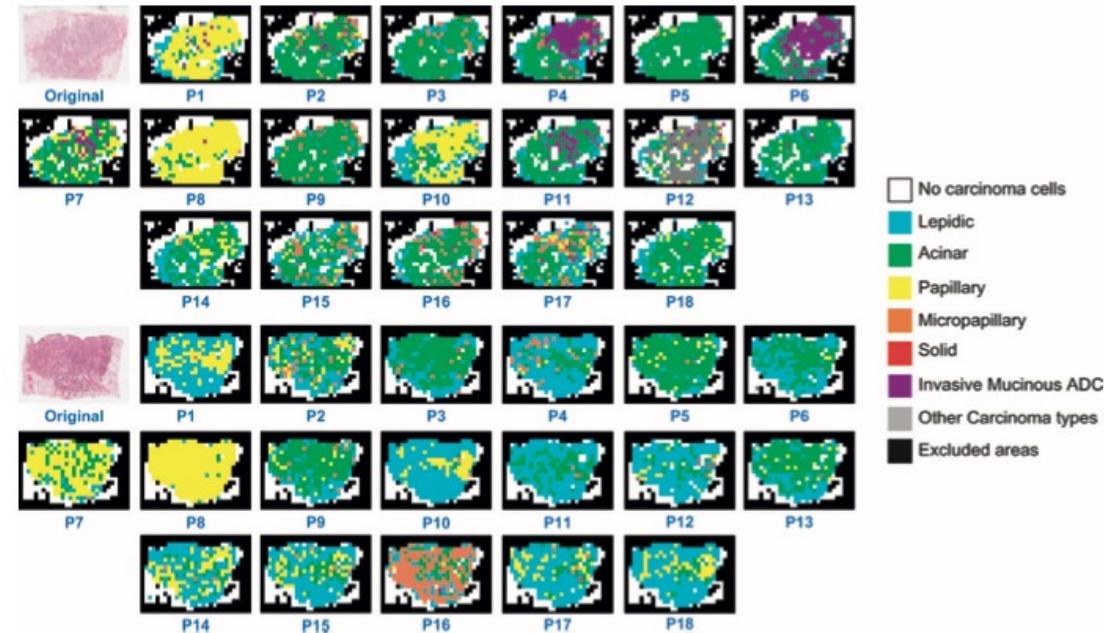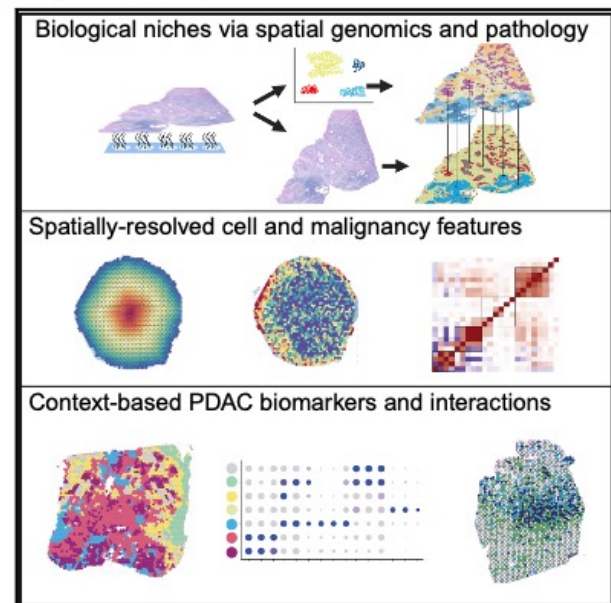
Figure 3. *Individual heat maps of whole slide images, with each color representing a specific pattern. The top image is predominantly acinar, papillary, or invasive mucinous adenocarcinoma debatable among pathologists. On the bottom, the case being predominantly noninvasive or invasive adenocarcinoma was debatable. Abbreviations: ADC, adenocarcinoma, P, pathologist.*

Check for updates

Multimodal machine learning in precision health: A scoping review

Adrienne Kline[1], Hanyin Wang[1], Yikuan Li[1], Saya Dennis[1], Meghan Hutch[1], Zhenxing Xu[2], Fei Wang[2], Feixiong Cheng[3] and Yuan Luo[1] ✉

Machine learning is frequently being leveraged to tackle problems in the health sector including utilization for clinical decision-support. Its use has historically been focused on single modal data. Attempts to improve prediction and mimic the multimodal nature of clinical expert decision-making has been met in the biomedical field of machine learning by fusing disparate data. This review was conducted to summarize the current studies in this field and identify topics ripe for future research. We conducted this review in accordance with the PRISMA extension for Scoping Reviews to characterize multi-modal data fusion in health. Search strings were established and used in databases: PubMed, Google Scholar, and IEEEXplore from 2011 to 2021. A final set of 128 articles were included in the analysis. The most common health areas utilizing multi-modal methods were neurology and oncology. Early fusion was the most common data merging strategy. Notably, there was an improvement in predictive performance when using data fusion. Lacking from the papers were clear clinical deployment strategies, FDA-approval, and analysis of how using multimodal approaches from diverse sub-populations may improve biases and healthcare disparities. These findings provide a summary on multimodal data fusion as applied to health diagnosis/prognosis problems. Few papers compared the outputs of a multimodal approach with a unimodal prediction. However, those that did achieved an average increase of 6.4% in predictive accuracy. Multi-modal machine learning, while more robust in its estimations over unimodal methods, has drawbacks in its scalability and the time-consuming nature of information concatenation.

Assessment of spatial transcriptomics for oncology discovery

Graphical abstract

Authors

Anna Lyubetskaya, Brian Rabe,
Andrew Fisher, ..., Kenzie MacIsaac,
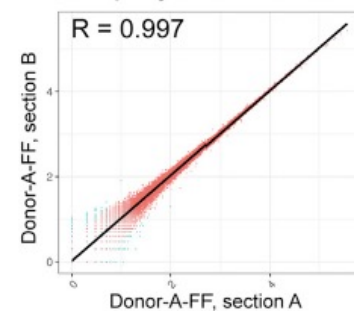Benjamin J. Chen, Eugene Drokhlyansky

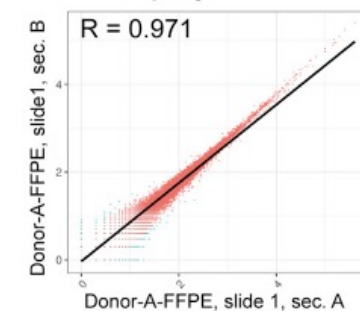### Correspondence

eugene.drokhlyansky@bms.com

In brief

Lyubetskaya et al. undertake an
assessment of spatial transcriptomics
methods across normal and tumor tissue
to help inform the selection of effective
approaches for profiling human tumors.
They demonstrate the potential of spatial
transcriptomics for probing the biology of
pancreatic cancer and future oncology
drug discovery.

COMMENT   **OPEN**

Check for updates

Emerging approaches to redressing multi-level racism and reproductive health disparities

Bethany Golden[1], Ifeyinwa V. Asiodu[2], Linda S. Franck (ID)[1], Celestine Yayra Ofori-Parku[1], Daniel Felipe Martín Suárez-Baquero[1], Tracy Youngston[1] and Monica R. McLemore[1]✉

This commentary examines the impact of multi-level racism on reproductive health disparities in the United States. Multi-level racism and its impact on reproductive health over the lifespan are described on a societal, community, and individual level. To advance, we recommend using the Remove, Repair, Restructure, Remediate (R4P) approach combined with the Retrofit, Reform, and Reimagine (3R) model to address multiple forms of racism. Emergent policies and actions are identified to proceed towards health equity.

npj Digital Medicine (2022)5:169; https://doi.org/10.1038/s41746-022-00718-2

Article

Collaborative study from the Bladder Cancer Advocacy Network for the genomic analysis of metastatic urothelial cancer

Jeffrey S. Damrauer [1,19], Wolfgang Beckabir[1,2,19], Jeff Klomp[1,3], Mi Zhou [1], Elizabeth R. Plimack [4], Matthew D. Galsky [5], Petros Grivas[6,7], Noah M. Hahn[8], Peter H. O'Donnell[9], Gopa Iyer [10], David I. Quinn [11], Benjamin G. Vincent [1,2,12,13,14], Diane Zipursky Quale[15], Sara E. Wobker[1,16], Katherine A. Hoadley [1,17], William Y. Kim [1,3,13,17,18,20] & Matthew I. Milowsky [1,13,18,20]

Urothelial Cancer - Genomic Analysis to Improve Patient Outcomes and Research (NCT02643043), UC-GENOME, is a genomic analysis and biospecimen repository study in 218 patients with metastatic urothelial carcinoma. Here we report on the primary outcome of the UC-GENOME—the proportion of subjects who received next generation sequencing (NGS) with treatment options—and present the initial genomic analyses and clinical correlates. 69.3% of subjects had potential treatment options, however only 5.0% received therapy based on NGS. We found an increased frequency of $TP53^{E28SK}$ mutations as compared to non-metastatic cohorts and identified features associated with benefit to chemotherapy and immune checkpoint inhibition, including: Ba/Sq and Stroma-rich subtypes, APOBEC mutational signature (SBS13), and inflamed tumor immune phenotype. Finally, we derive a computational model incorporating both genomic and clinical features predictive of immune checkpoint inhibitor response. Future work will utilize the biospecimens alongside these foundational analyses toward a better understanding of urothelial carcinoma biology.

COMMENT   **OPEN**

Medical domain knowledge in domain-agnostic generative AI

Jakob Nikolas Kather[1,2,3,4✉], Narmin Ghaffari Laleh[1], Sebastian Foersch[5] and Daniel Truhn[6]

The text-guided diffusion model GLIDE (Guided Language to Image Diffusion for Generation and Editing) is the state of the art in text-to-image generative artificial intelligence (AI). GLIDE has rich representations, but medical applications of this model have not been systematically explored. If GLIDE had useful medical knowledge, it could be used for medical image analysis tasks, a domain in which AI systems are still highly engineered towards a single use-case. Here we show that the publicly available GLIDE model has reasonably strong representations of key topics in cancer research and oncology, in particular the general style of histopathology images and multiple facets of diseases, pathological processes and laboratory assays. However, GLIDE seems to lack useful representations of the style and content of radiology data. Our findings demonstrate that domain-agnostic generative AI models can learn relevant medical concepts without explicit training. Thus, GLIDE and similar models might be useful for medical image processing tasks in the future - particularly with additional domain-specific fine-tuning.

Cell
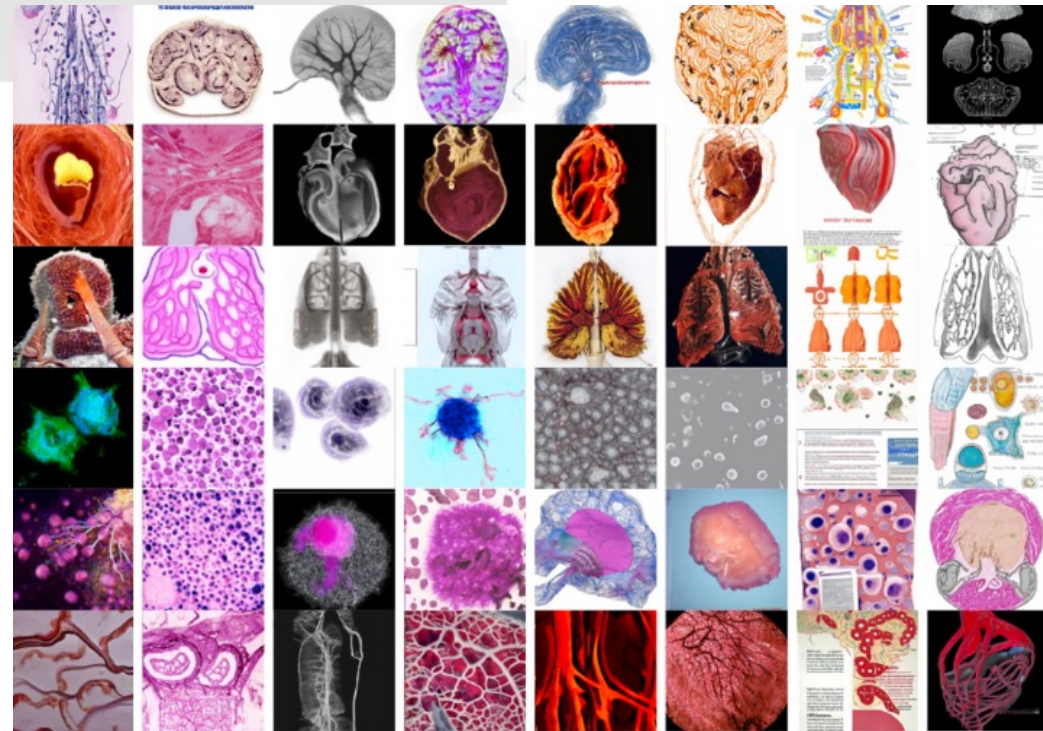
A Quantitative Proteome Map of the Human Body
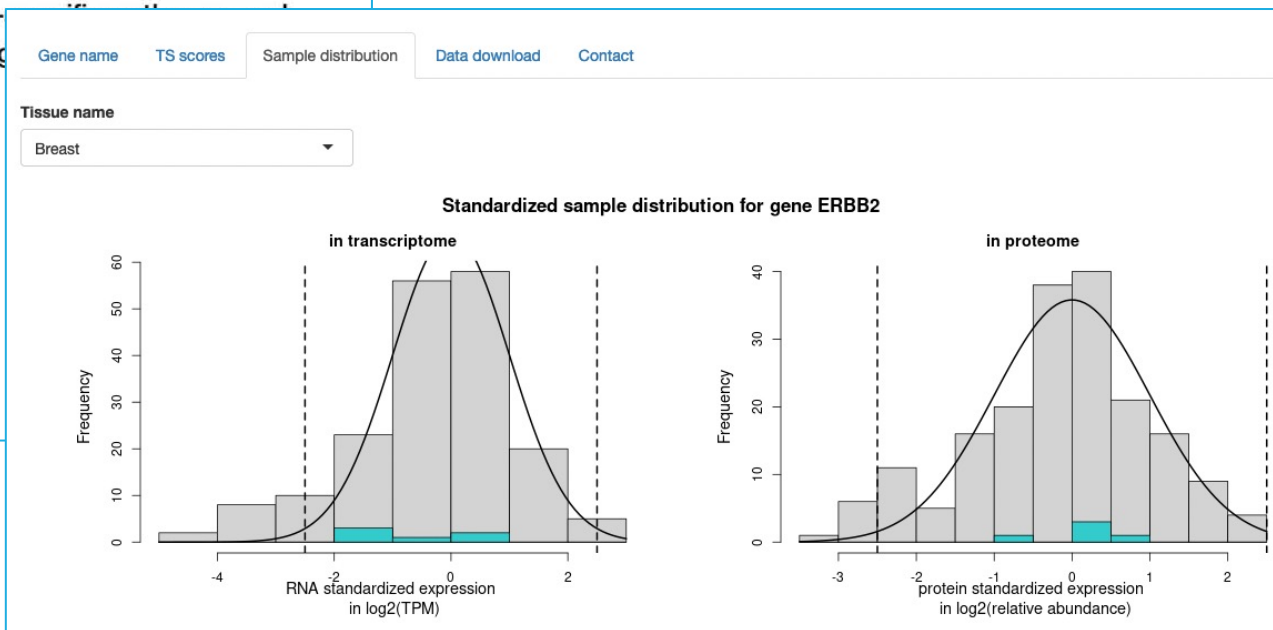
Graphical Abstract
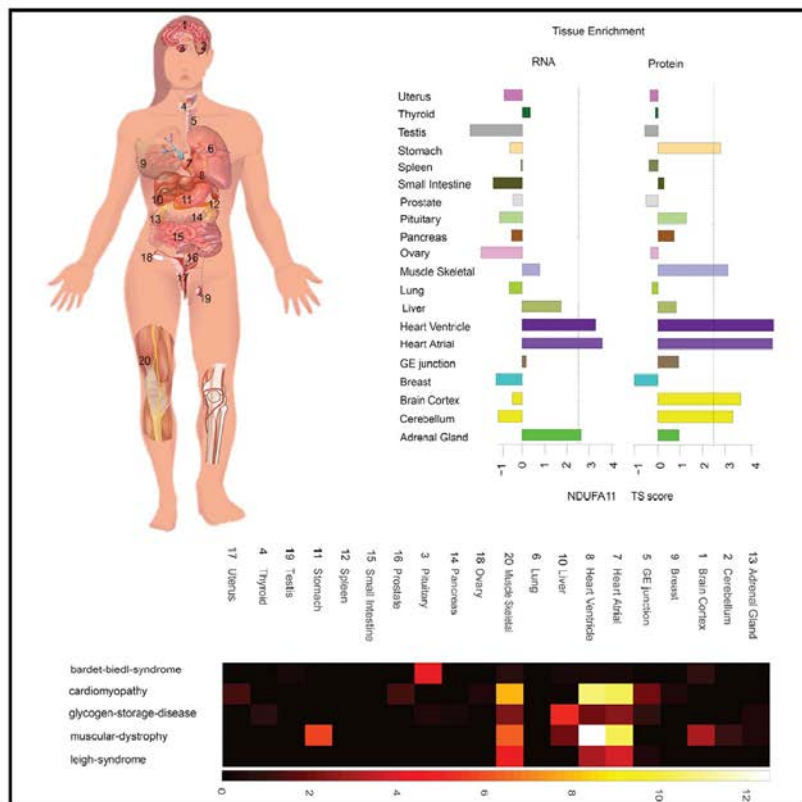
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Michael P. Snyder
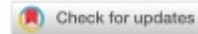
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mpsnyder@stanford.edu

In Brief

Proteomics analysis across human tissues from the GTEx resource reveals insight into tissue-specific pathways and phenotypes arising from diseases.

Payor

A reimbursement framework for artificial intelligence in healthcare

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

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 analytically determining value and cost of each unique AI service. The framework's 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 a real world, completed, an example of a specific autonomous AI service, to show how multiple "guardrails" for the AI system implementation enforce ethical principles. It can guide the development of sustainable reimbursement for future AI services, ensuring the 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, improve access, remove disparities, and reduce cost.

- Whether AI improves patient and population clinical outcomes (rather than worsening them); and
- AI bias and impact on health equity; and
- Potential lack of data privacy, meaningful consent, stewardship responsibilities, and ownership; and
- How liability is assigned.

COMMENT   OPEN

Paying for artificial intelligence in medicine

Ravi B. Parikh [1,2] ✉ and Lorens A. Helmchen [2,3]

Over the past 7 years, regulatory agencies have approved hundreds of artificial intelligence (AI) devices for clinical use. In late 2020, payers began reimbursing clinicians and health systems for each use of select image-based AI devices. The experience with traditional medical devices has shown that per-use reimbursement may result in the overuse use of AI. We review current models of paying for AI in medicine and describe five alternative and complementary reimbursement approaches, including incentivizing outcomes instead of volume, utilizing advance market commitments and time-limited reimbursements for new AI applications, and rewarding interoperability and bias mitigation. As AI rapidly integrates into routine healthcare, careful design of payment for AI is essential for improving patient outcomes while maximizing cost-effectiveness and equity.

Table 1. Selected AI devices that are reimbursed by US Medicare.

Manufacturer	Technology	Description	Payment mechanism	Year reimbursement granted
Digital diagnostics	IDX-DR	Deep learning algorithm to diagnose diabetic retinopathy from fundoscopic images in the outpatient setting	CPT	2020
viz.ai	Viz LVO	Radiological computer-assisted triage and notification software that analyzes CT images of the brain and notifies hospital staff when a suspected large-vessel occlusion (LVO) is identified	NTAP	2020
Rapid AI	Rapid LVO	AI-guided medical imaging acquisition system intended to assist medical professionals in the acquisition of cardiac ultrasound images.	NTAP	2020
Caption health	Caption guidance		NTAP	2021
viz.ai	Viz SDH	Radiological computer-assisted triage and notification software that analyzes CT images of the brain and notifies hospital staff when a suspected subdural hematoma is identified	NTAP	2022 (candidate)
Rapid AI	Rapid aspects	Computer-aided diagnostic device characterizing brain tissue abnormalities on brain CT images	NTAP	2022 (candidate)
AIDoc	Briefcase for PE	Radiological computer-assisted triage and notification software that analyzes CT images of the chest and notifies hospital staff when a suspected pulmonary embolism is identified	NTAP	2022 (candidate)
PROCEPT BioRobotics Corporation	The AQUABEAM system	Autonomous tissue removal robot for the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia (BPH).	NTAP	2020

EVENTS

Next steering committee meeting

12/21
or
12/28

Coming Reimbursement Opportunities for Digital Pathology

Dec 2, 2022 11:00 AM - 12:00 PM CT

Description

This webinar will be a moderated discussion of the new Digital Pathology CPT Codes available starting January 1st, 2023. Our moderators, Drs. Marilyn Bui, Savitri Krishnamurthy, and S. Joseph Sirintrapun, will lead an expert panel on how laboratories should use the codes and how these new codes may impact future reimbursement for digital pathology.

Panelists include Dr. W. Stephen Black-Schaffer, who as Chair of the Economic Affairs Committee was a leader in the CAP's effort to establish the new codes, and Drs. Anil Parwani and Juan Santa-Rosario, who both use digital pathology in their practices.

Objectives

- To help CAP Members understand the new Digital Pathology CPT Codes and why it is crucial that they are used starting January 1st.

Speakers

Moderators:
Marilyn Bui, MD, PhD, FCAP
Savitri Krishnamurthy, MD, FCAP
S. Joseph Sirintrapun, MD, FCAP

Presenters:
W. Stephen Black-Schaffer, MD, FCAP
Anil Parwani, MD, PhD, FCAP
Juan Santa-Rosario, MD, FCAP

RAPS WEBCASTS

FDA Forecast: What's Next for the FDA in 2023?

Presented by

POLITICO
AgencyIQ

Thursday, 8 December 2022
12:00-1:30PM Eastern Time (US & Canada)

REGISTER NOW

FDA Forecast: What's Next for the FDA in 2023?

Event by **Regulatory Affairs Professionals Society (RAPS)**

Thu, Dec 8, 2022, 12:00 PM - 1:30 PM (your local time)

Online

Event link · https://bit.ly/3F8cRe9

VIRTUAL

2022 FDA Digital Transformation Symposium

DECEMBER 5 - 7, 2022

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On This Page

- Meeting Information
- Event Materials

Date:	December 5 - 7, 2022
Day1:	Mon, Dec 5 9:00 AM - 3:00 PM ET
Day2:	Tue, Dec 6 9:00 AM - 4:30 PM ET
Day3:	Wed, Dec 7 9:00 AM - 3:30 PM ET

FDA | U.S. FOOD & DRUG ADMINISTRATION

DIGITAL TRANSFORMATION SYMPOSIUM 2022

Hosted by FDA's Office of Digital Transformation

Public Workshop – Appropriate Use of Consensus Standards

DECEMBER 7, 2022

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On This Page

- [Meeting Information](#)

Date: December 7, 2022

Time: 1:00 PM - 3:00 PM ET

SUMMARY

The Food and Drug Administration (FDA) is announcing a public workshop "Appropriate Use of Consensus Standards." The purpose of the workshop is to obtain public input on

CDER SMALL BUSINESS AND INDUSTRY ASSISTANCE (SBIA)

FDA

FDA CLINICAL INVESTIGATOR TRAINING COURSE (CITC) 2022

DECEMBER 7-8

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VIRTUAL

FDA Clinical Investigator Training Course (CITC) 2022

DECEMBER 7 - 8, 2022

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On This Page

- Meeting Information

Date:	December 7 - 8, 2022
Day1:	Wed, Dec 7 11:00 AM - 3:35 PM ET
Day2:	Thu, Dec 8 10:55 AM - 2:40 PM ET

Attend

Register for This Event

Agenda

Visit CDER Small Business and Industry Assistance Page

ABOUT THIS CONFERENCE

This course is designed to promote professionalism in the clinical trial industry for individuals involved with FDA submissions (Investigational New Drug (IND) Application, New Drug Application (NDA), Biologic License Application (BLA), and Investigational Device Exemption (IDE)) and to familiarize stakeholders with the regulatory and

Next "in-person" Plcc meeting - March 2023

March 4/5 or
March 18/19

March 11-16, 2023 USCAP,
New Orleans, Lousiana

D.C. Area
(coordination with FDA + MDIC pending)

March 2023

S	M	T	W	T	F	S
26	27	28	1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	1
2	3	4	5	6	7	8