# Pathology Innovation Collaborative Community
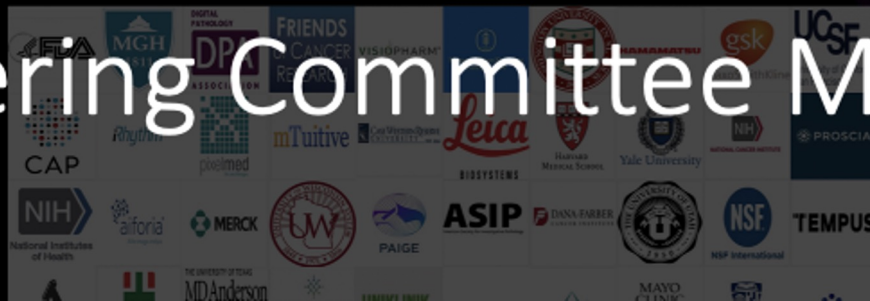
## PIcc

**The Alliance for Digital Pathology**

A collaborative community with FDA participation

# Steering Committee Meeting | March 2023

FDA

# Center for Drug Evaluation and Research | CDER

- Office of Compliance Annual Report Fiscal Year 2022

- Artificial Intelligence in Drug Manufacturing Discussion Paper 2023

- Q13 Continuous Manufacturing of Drug Substances and Drug Products



**BY THE NUMBERS**
Fiscal Year 2022: October 1, 2021, to September 30, 2022

**Promote Compliance**

**2** proposed rules issued by the Office of Compliance

**10** guidance documents, draft or final, published by, or in collaboration with, the Office of Compliance

**80+** conference presentations

**32** immediate public notifications issued regarding fraudulent health products

**13** presentations shared on FDA's YouTube channel, developed in collaboration with Center for Drug Evaluation and Research (CDER's) Small Business and Industry Assistance Program

**2,732** courses completed by stakeholders through the Compounding Quality Center of Excellence's training program in FY22, totaling 4,675 courses completed since training programs began

**Regulatory and Enforcement Actions**

**101** warning letters issued by the Office of Compliance

**50+** additional warning letters issued by the Office of Regulatory Affairs in collaboration with CDER

**343** drug recall events classified, totaling 1,500+ recalled products

**2** consent decrees of permanent injunction obtained for quality violations

**50+** facilities added to FDA import alerts that aim to prevent potentially unsafe products from entering the U.S.

**99+** percent of clinical inspection summaries issued by agreed-upon goal dates for new drug applications and biologics license applications under the Prescription Drug User Fee Amendments (PDUFA) and Biosimilar User Fee Amendments (BSUFA)

**Operational Excellence**

**183** drug manufacturing inspection classification letters issued

**10,220+** Electronic Certificates of Pharmaceutical Product issued to provide documentation of facilities' compliance with FDA standards

**21,440+** drug listings inactivated from FDA's Drug Listing and Registration System

**212** deficiency letters issued to firms for inaccurate or incomplete drug registration and listing data

5 Center for Drug Evaluation and Research, Office of Compliance Annual Report FY 2022

**FDA** U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

**Artificial Intelligence in Drug Manufacturing**

Discussion Paper | 2023

# Learn



Attendees participate in this annual training course where they learn best practices for ensuring data quality and integrity in BSL-4 facilities.

- Continuing Medial Education (CME): Assessment of Stromal Tumor-Infiltrating Lymphocytes



Continuous Medical Education Course
Assessment of Stromal Tumor-Infiltrating Lymphocytes

TILS | BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP

FDA U.S. FOOD & DRUG ADMINISTRATION

- Training Course: Achieving Data Quality and Integrity in Maximum Containment Laboratories
  - April 24-28
- Webinar on Guidances on COVID-19 Transition Plans for Medical Devices
  - April 18 at 1-2:30 PM ET

# Assessment of Stromal Tumor-Infiltrating Lymphocytes

3.00 CME Credits

4 Part Course:

1. Clinical context of stromal tumor-infiltrating lymphocytes (sTILs)

1. Video on steps of the sTILs Assessment

1. Pitfalls in the sTILs Assessment

1. Manuscript on sTILs evaluation (Salgado et al., Ann Oncol. 2015)



Create an account: https://ceportal.fda.gov/
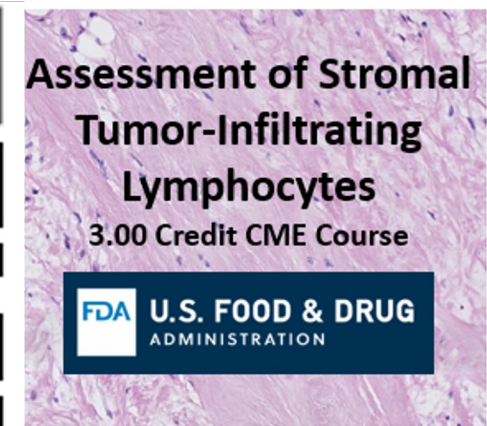
Click on "Online Learning" tab

Scroll to "Assessment of Stromal Tumor-Infiltrating Lymphocytes"

# Updates

- FDA approves dabrafenib with trametinib for pediatric patients with low-grade glioma with a BRAF V600E mutation

- End of the PHE: updated overview fact sheet from CMS

- Hillebrenner says FDA no longer waiting on Congress for LDT regulation

additional LDT updates:

- Article: Congress Holds Off on Enabling FDA Regulation of Clinical Laboratory-Developed Tests

- Article: FDA Resumes Move to Regulate LDTs, Likely Setting up Legal Battle With Lab Industry

GOVERNMENT UPDATES

# The White House: Bold Goals for U.S. Biotechnology and Biomanufacturing

## HARNESSING RESEARCH AND DEVELOPMENT TO FURTHER SOCIETAL GOALS

# Arkansas

# New York

- **STATE LEGISLATURE HB1121 - CONCERNING COVERAGE FOR BIOMARKER TESTING FOR EARLY DETECTION AND MANAGEMENT FOR CANCER DIAGNOSES.**

- **NEW YORK STATE APPROVED AI-BASED DIAGNOSTIC TEST FOR BREAST CANCER**


PreciseDx

Stricken language would be deleted from and underlined language would be added to present law.

| | |
|---|---|
| 1 | State of Arkansas    As Engrossed:  H2/15/23 H2/28/23 |
| 2 | 94th General Assembly    A Bill |
| 3 | Regular Session, 2023    HOUSE BILL 1121 |
| 4 | |
| 5 | By: Representatives F. Allen, *K. Brown, Dalby, Evans, K. Ferguson, L. Johnson, Nicks, Pilkington, J.* |
| 6 | *Richardson, Warren* |
| 7 | By: Senators D. Wallace, J. Boyd, Irvin, M. Johnson, R. Murdock |
| 8 | |
| 9 | **For An Act To Be Entitled** |
| 10 | AN ACT CONCERNING COVERAGE FOR BIOMARKER TESTING FOR |
| 11 | EARLY DETECTION AND MANAGEMENT FOR CANCER DIAGNOSES; |
| 12 | AND FOR OTHER PURPOSES. |
| 13 | |
| 14 | |
| 15 | **Subtitle** |
| 16 | CONCERNING COVERAGE FOR BIOMARKER TESTING |
| 17 | FOR EARLY DETECTION AND MANAGEMENT FOR |
| 18 | CANCER DIAGNOSES. |

# CMS

- CMS to work closely with FDA on accelerated approval payment reforms

- In February, CMS held a two day workshop on "coverage with evidence development"

- End of the PHE: updated overview fact sheet from CMS

# VALID act update

Plcc meeting 3/29/2023 – J. Lennerz

# Update

- **The VALID Act** is set to be reintroduced today (3/29/2023) — but its future is murky*

- VALID was cut twice from legislative packages
- VALID's main Senate champion retired

- **Rep. Larry Bucshon** plans to reintroduce the bill Wednesday afternoon with **Rep. Diana DeGette**

# FACTS (summary)

- This year's bill will resemble the version that came from Senate HELP last year, **with some changes based on omnibus discussions**, according to a source close to the matter

- The bill will **not include a carve-out** for academic medical centers.

# VALID: An oversight framework

- The bill would allow approval of one representative test.

- The LDT overhaul is needed to help developers react more quickly

- After VALID was cut from the FDA user fee reauthorization bill, advocates pushed to include it in the December omnibus.

- The provision didn't make the final version, in part because academic medical centers said it would hamper their ability to deliver and develop new tests.

# AMC (AAMC)

- Academic medical centers are still willing to **work on a policy agreement** — and having more time to do that is a benefit, said Heather Pierce, senior director for science policy and regulatory counsel at the Association of American Medical Colleges.

# What if, what if not

- The agency is moving forward with **rulemaking** on diagnostic testing regulation

- The VALID Act is one of the **agency's top legislative priorities** for PAHPA reauthorization

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ACLA Annual Meeting

### Hillebrenner says FDA no longer waiting on Congress for LDT regulation

By Mark McCarty    March 1, 2023

The question of the U.S. FDA's authority to regulate lab-developed tests (LDTs) has been percolating for more than a decade, but the recent failure of Congress to pass legislation granting the agency explicit authority to do so is seen in some quarters as a missed opportunity. The FDA's Elizabeth Hillebrenner said that while the agency would prefer to regulate LDTs under new statutory authorities, the agency sees a public health problem with the current state of affairs, and thus, "we are moving forward with rulemaking."

# VALID . LDT regulation

- LDT remain controversial
- Regulation of high-complexity testing top priority
- VALID or not, rules will come
- We should be actively involved in monitoring and staying informed
- No matter where you stand (Pro vs. Con)… the consequences will affect medical practice
- Once, the new version is release, we plan to host another **"test driving session"** and **examine changes**.
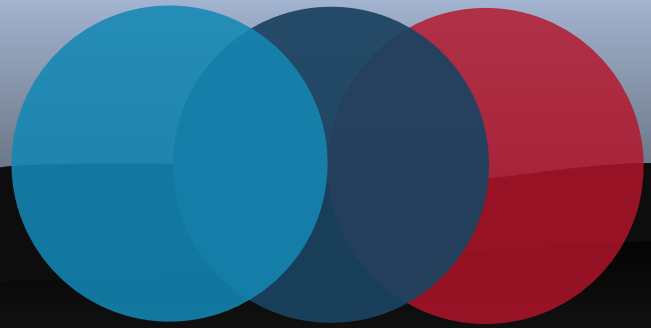
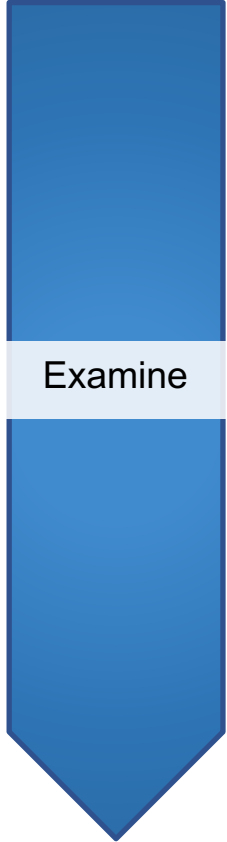# PIcc23

Meet. Synergize. Impact.

Annual Meeting

D.C. Area

June 27/28

# Purpose

- Several regulatory and legislative developments related to the end of the public health emergency will affect digital pathology and artificial intelligence tools in diagnostics.

- We are planning a **two-day in-person workshop** to
  - **Meet** to network and discuss specific regulatory and legislative changes
  - **Synergize** efforts on large-scale regulatory science projects
  - **Impact** regulatory science can help overcome some of the current regulatory challenges

# Scope

- We invite experts in regulatory affairs to speak about recent developments in regulations related to digital pathology and AI tools in diagnostics. This includes representatives from the FDA, NIH, and CMS

- We will host panel discussions with experts in the field to examine specific implementation challenges and opportunities.
  - Impulse update talks are 8-10 minutes each followed by a moderated panel discussion

- Aim to identify large-scale regulatory science projects that could help overcome implementation challenges.
  - These projects could focus on improving the accuracy and reliability of digital pathology and AI tools, developing standardized protocols for validation and verification, or creating regulatory frameworks for emerging technologies.

- Throughout the meeting we will use Mentimeter to capture audience preferences
  - For selection of topics and synergizing towards one main project we will include interactive polls and audience participation.

# Breakout sessions

- We will host breakout sessions where participants can work together on specific implementation challenges or regulatory science projects.
    - We ask all participants to bring and include case studies and practical examples. This will help to inspire participants and provide concrete examples of how to navigate the regulatory landscape.
- We select 4 topics
    - Remote work
    - Predetermined Change Control Plans
    - Statistics
    - Audience choice
- Interdisciplinary prioritization and move to synergy phase for realization

# Breakout Remote work

The proposed discontinuation of regulatory exemptions for digital pathology presents a significant challenge for the medical community.

To address this issue, a regulatory science project could propose several evidence creation approaches.

**(1)** one project could conduct a **systematic review of the existing literature** on digital pathology to identify any knowledge gaps or areas of uncertainty that require further investigation.

**(2)** a project could engage in a **comprehensive observational study** to collect data on the safety and efficacy of digital pathology in clinical settings.

**(3)** the project could design and conduct a randomized controlled trial to assess the impact of digital pathology on patient outcomes.

**(4)** a project could explore the **use of real-world data** and advanced analytical techniques to develop predictive models that can inform regulatory decision-making.

**(5)** a project could engage stakeholders from the medical device industry, regulatory agencies, and patient advocacy groups to develop **consensus-based recommendations** for change control plans for AI-based medical devices.

**By employing these regulatory evidence creation approaches, the project can provide a robust and evidence-based framework for evaluating the safety and efficacy of digital pathology, which can inform regulatory policy and practice.**

# Breakout

PIcc23
Meet. Synergize. Impact

The mandate for a predetermined change control plan for medical devices in Sec. 3308 of the Consolidated Appropriations Act 2023 presents a critical challenge for the regulatory science community.

To address this issue, a regulatory science project could propose several evidence creation approaches to establish appropriate regulatory guidance for artificial intelligence applications that learn and improve over time.

**(1)** a project could conduct a **comprehensive review of existing regulatory frameworks and guidelines** for AI-based medical devices to identify gaps and challenges that require further attention.

**(2)** a project could explore the use of **real-world data** and advanced analytical techniques to develop predictive models that can inform regulatory decision-making.

**(3)** a project could conduct a **randomized controlled trial to** assess the safety and efficacy of AI-based medical devices and their associated change control plans.

**(4)** a project could engage stakeholders from the medical device industry, regulatory agencies, and patient advocacy groups to develop **consensus-based recommendations** for change control plans for AI-based medical devices.

**By employing these regulatory evidence creation approaches, the project can provide a robust and evidence-based framework for establishing appropriate regulatory guidance for AI-based medical devices that learn and improve over time.**

# Breakout  Statistics

The FDA's Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests presents a significant challenge for the regulatory science community, particularly in the context of laboratory-developed tests, digital pathology, and AI-based diagnostic applications.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/statistical-guidance-reporting-results-studies-evaluating-diagnostic-tests-guidance-industry-and-fda

To address this issue, a regulatory science project could propose several evidence creation approaches to streamline the reporting of performance metrics for these tests.

**(1)** the project could conduct a **comprehensive review of existing regulatory frameworks and guidelines** for reporting performance metrics in laboratory-developed tests and AI-based diagnostic applications to identify gaps and challenges that require further attention.

**(2)** the project could engage in a **comprehensive observational study** to collect data on the safety and efficacy of digital pathology and AI-based diagnostic tests in clinical settings.

**(3)** the project could develop and **validate novel statistical methods** and predictive models to streamline the reporting of performance metrics for these tests.

**(4)** the project could engage with stakeholders from the medical device industry, regulatory agencies, and patient advocacy groups to develop **consensus-based recommendations** for reporting performance metrics in laboratory-developed tests and AI-based diagnostic applications.

**By employing these regulatory evidence creation approaches, the project can provide a robust and evidence-based framework for streamlining the reporting of performance metrics for laboratory-developed tests, digital pathology, and AI-based diagnostic applications, which can inform regulatory policy and practice.**

# Breakout

- The <state background>

- **State problem**

**(1) comprehensive review of existing regulatory frameworks and guidelines**

**(2) comprehensive observational study.**

**(3) methods**

**(4) consensus-based recommendations**

**By employing these regulatory evidence creation approaches, the project can provide a robust and evidence-based framework for streamlining the <<problem/context>>, which can inform regulatory policy and practice.**

# Summary

- Overall, the workshop aims to provide a forum for stakeholders in digital pathology and AI tools in diagnostics to discuss regulatory challenges and opportunities, and to identify concrete steps for moving the field forward.

# Location and details

- June 27/28

- Arlington?

- Hotel + Lunch/Dinner/Coffee etc...

- Registration?

- Survey
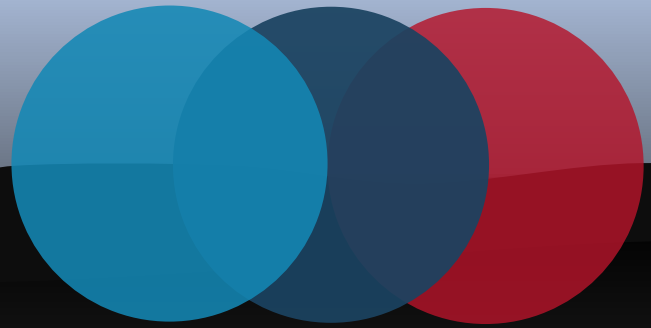
# PIcc23

Meet. Synergize. Impact.

Annual Meeting

D.C. Area

June 27/28

**MDIC Updates**

https://mdic.org/

# MDIC-PIcc 23

*PIcc23 Annual Meeting.*
*In-person collaborative community meeting*
## Meet. Synergize. Impact

- **Objectives:** PIcc is a regulatory science initiative that aims to facilitate innovations in pathology as well as advance safety and effectiveness evaluation, and to harmonize approaches to speed delivery to patients using collaborative, pre-competitive approaches. The collaborative community (PIcc) is open to all stakeholders, public or private, including, but not limited to, academia, industry, health care providers, patients and advocacy groups. The annual meeting will be a working meeting tackling four key challenges in the field: remote work, predetermined change control protocols, statistical performance metrics, and an audience-determined choice (e.g., RWE, LDT, etc.). We are open to all stakeholders and aim to identify large-scale, meaningful projects that cannot be tackled by individual stakeholders. The main aim of the meeting is to create resources and identify the most meaningful next step in overcoming some of the key hurdles in clinical adoption

- **Goals:**

  - **Examine** specific regulatory and legislative changes

  - **Focus** on a large-scale regulatory science project

  - **Synergize** efforts that can help overcome some of the current regulatory challenges

- **Suggested Dates:** June 27, 28 2023

- **Location:** Washington DC Metro Area

- **Mode:** In-person ONLY

- **Number of Seats: capped at** 100

- **Invited Speakers:** We need to identify ASAP. MDIC will officially submit and coordinate speaker requests

- **Funding/Cost:** Registration Fee (TBD) from non-government attendees OR Sponsorships

- **Sponsors:** If interested in being a sponsor for this meeting, please reach out to jveetil@mdic.org or nfalah@mdic.org

# MDIC Updates

- MDIC Live Fireside-Chat style conversation with MDIC Leadership

- LinkedIn Event

- https://www.linkedin.com/events/703893356719
9965184/

# MDIC Updates

- Join MDIC on March 30 for an informational webinar on the Medical Device Computational Modeling and Simulation Landscape Report

- https://mdic.org/event/webinarcmslandscape/

# MDIC Updates

- <u>Cybersecurity Benchmarking Webinar available On Demand</u>

  - Watch now and acquire key takeaways from the world's first-ever Cybersecurity Maturity Benchmarking Report and receive focused best practices on implementing the tool and report findings into your cybersecurity posture

  <u>Panelists:</u>
  - Jithesh Veetil, PhD, Senior Director of Digital Health and Technology (MDIC),
  - Chris Reed, Director of Digital Health and Product Security Policy at Medtronic,
  - Rob Suarez, Chief Information Security Officer at BD,
  - Greg Garcia, Executive Director, Cybersecurity Health Sector Coordinating Council

# MDIC Updates

### Call for Volunteers! MDIC Digital Health Software Vertical

- The MDIC Digital Health Software Vertical is looking for software experts with experience in deploying software in various formats like: embedded in medical device/diagnostics, mobile apps, and desktop apps, among others. We also seek more regulatory experts who have experience with Class III software submissions to participate in these activities. Selected volunteers work with abrader group to develop an MDIC framework

- For more information, please contact: Jithesh Veetil jveetil@mdic.org or Taylor Matheny TMetheny@mdic.org

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**MEDICAL DEVICE**
**INNOVATION CONSORTIUM**
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# MDIC Updates

## Seeking Subject Matter Expert volunteers to support Science of Patient Input Post-Market Patient Engagement Working Groups

- MDIC's Science of Patient Input (SPI) initiative invites experts to contribute to the scoping and initial landscaping in three focus areas within post-market patient engagement.
  - Focus areas include: Real World Evidence in Post-Market, Product Safety Communications, and/ or Patient Benefit/ Risk Assessments

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# MDIC Updates

## **<u>Leadership Engagement Culture Initiative</u>**

- The Leadership Engagement program implores leaders to focus on company performance with quality and safety as pillars. Presented as an essential toolbox with personalized messaging and training to organizational leaders, the program is looking for leaders to transform their organizational culture by applying this novel, practical approach.

- Interested? Contact cfqcc@mdic.org to get involved with Case for Quality initiatives.

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Diversity & Inclusion

# Women in Informatics

- Podcast - Women in Pathology Informatics: A Conversation with CAP Staffer Mary Kennedy

# Women in Informatics

- The Legacy of Mary Kenneth Keller, First U.S. Ph.D. in Computer Science



**FIGURE 3.** Sister Kenneth with Bi-Tran Six computer. Photo credit: Clarke University Archives.



**FIGURE 4.** Sister Kenneth in Clarke's Computer Center in September, 1980. Photo: Reprinted with permission of the *Dubuque Telegraph Herald.*
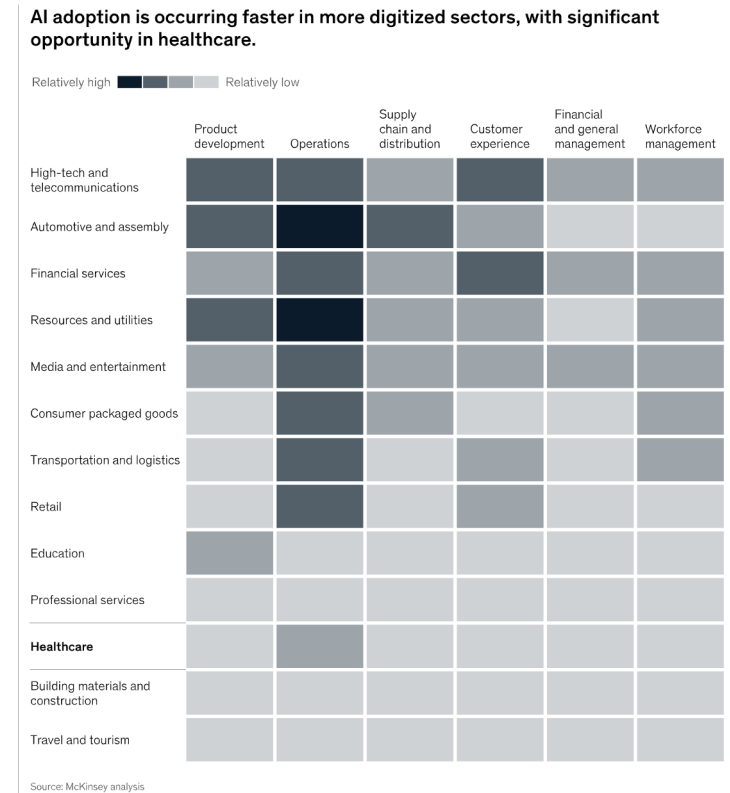
# Resources

# AI Prior Authorization



Language and image recognition capabilities of AI systems have improved rapidly
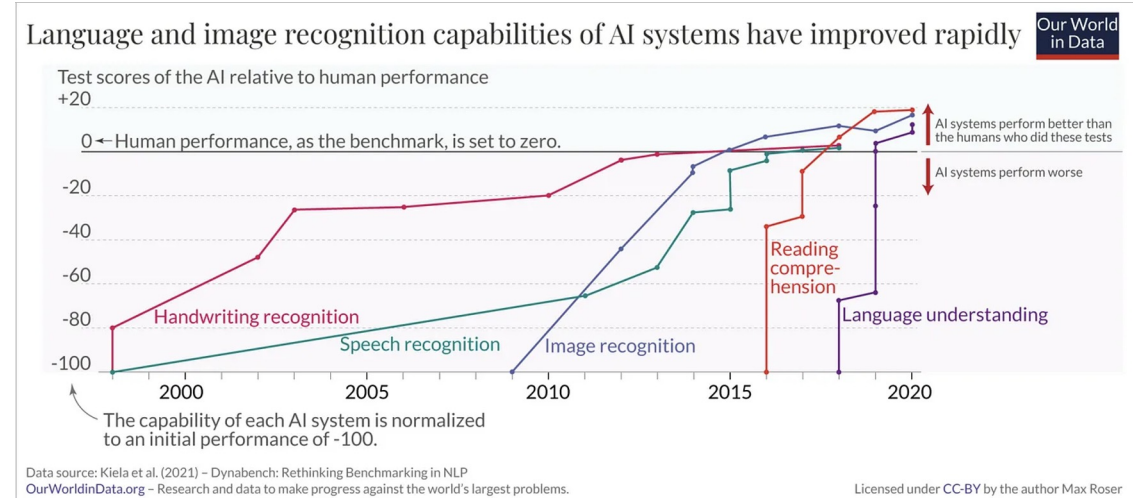
- McKinsey & Co: AI ushers in next-gen prior authorization in healthcare

- NEJM: Luo & Gellad. Electronic Prior Authorization for Prescription Drugs — Challenges and Opportunities for Reform

- Eric Topol: When M.D. is a Machine Doctor

# Additional news

- Pramana and PathPresenter announce collaboration to accelerate enterprise adoption of digital pathology workflows

# Coalition for Health AI (CHAI) Blueprint for Trustworthy AI Implementation Guidance and Assurance for Healthcare

# CADTH Horizon Scan 2023 Watch List: Top 10 Precision Medicine Technologies and Issues

# Global Pathology Workforce
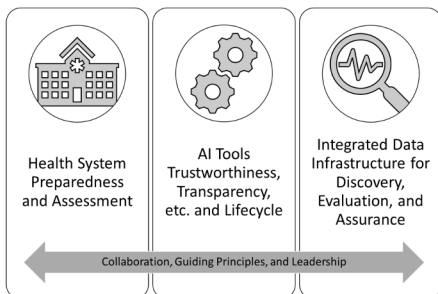
## CHAI
Coalition for Health AI

### NEXT STEPS

Every institution can have different flavors of AI tools. Yet, there is a need to use the same principles to build them and facilitate their use. Through an assurance accreditation lab, health systems as well as tool developers and vendors can submit processes and tools for evaluation to ensure readiness to employ AI tools in a way that benefits patients, is equitable, and promotes the ethical use of AI.

In large medical centers, there may be the resources to make this happen now. Other small and rural resource-constrained health systems may not have the resources to do it on their own. So, there may also be a need for an advisory body to move the field forward with these entities as well and ensure equity so that, for a given patient, ethical AI would not depend on where they live or with which health system they are interacting.

Below are the key pillars for how an AI assurance, evaluation, and discovery lab can help achieve results through health system preparation, AI tool use, and infrastructure for enabling trustworthy AI.

Health System Preparedness and Assessment | AI Tools Trustworthiness, Transparency, etc. and Lifecycle | Integrated Data Infrastructure for Discovery, Evaluation, and Assurance

Collaboration, Guiding Principles, and Leadership

## CADTH

### Table of Contents

Pathologists Per Million
- = >40
- = 30–39
- = 20–29
- = 10–19
- = 1–9
- = <1

# Publications of interest

CellPress

**Review**

# Deciphering breast cancer: from biology to the clinic

Emma Nolan,[1] Geoffrey J. Lindeman,[2,3,4,6] and Jane E. Visvader[2,5,6,*]
[1]Auckland Cancer Society Research Centre, University of Auckland, Auckland 1023, New Zealand
[2]ACRF Cancer Biology and Stem Cells Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC 3052, Australia
[3]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, VIC 3050, Australia
[4]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia
[5]Department of Medical Biology, University of Melbourne, Parkville, VIC 3010, Australia
[6]These authors contributed equally
*Correspondence: visvader@wehi.edu.au
https://doi.org/10.1016/j.cell.2023.01.040

## SUMMARY

Breast cancer remains a leading cause of cancer-related mortality in women, reflecting profound disease heterogeneity, metastasis, and therapeutic resistance. Over the last decade, genomic and transcriptomic data have been integrated on an unprecedented scale and revealed distinct cancer subtypes, critical molecular drivers, clonal evolutionary trajectories, and prognostic signatures. Furthermore, multi-dimensional integration of high-resolution single-cell and spatial technologies has highlighted the importance of the entire breast cancer ecosystem and the presence of distinct cellular "neighborhoods." Clinically, a plethora of new targeted therapies has emerged, now being rapidly incorporated into routine care. Resistance to therapy, however, remains a crucial challenge for the field.

## INTRODUCTION

Breast cancer is a global problem: it is the most commonly diagnosed cancer in women, with an estimated 2.3 million new cases and >685,000 deaths reported in 2020 (Sung et al., 2021). Although survival rates have markedly improved over the past two decades, the incidence of this disease continues to rise worldwide. Improved outcomes have been largely attributable to mammographic screening and adjuvant therapies (Hashim et al., 2016); however, highly effective systemic therapies for advanced disease are now making an important impact. A combination of genetic and non-genetic factors influences breast cancer incidence. The latter includes age, reproductive risk factors (e.g., early menarche and late menopause), exogenous female hormones, lifestyle factors (e.g., post-menopausal obesity and alcohol consumption), radiation exposure, high mammographic density, and the presence of histologic lesions such as atypical hyperplasia, although some of these factors can also be underpinned by genetic predisposition (Danaei et al., 2005; Hankinson et al., 2004).

Breast cancer comprises multiple biological entities characterized by heterogeneity in pathology, genomic alterations, gene expression, and the tumor microenvironment (TME), which collectively influence clinical behavior and treatment response. However, the classic parameters of histopathology, tumor size and grade, nodal involvement, and marker expression currently being used to guide treatment decisions are imperfect, particularly in the case of advanced cancers, which eventually develop resistance. Hence, there is a pressing need to better predict

response to therapy and a need to improve selection of optimized therapy. Over the past decade, the intrinsic molecular subtypes of breast cancer and predictive signatures have been further refined, while the genomics revolution has enabled the sequencing of vast numbers of breast tumors at unprecedented speed and resolution. Deep genomic analyses have also provided substantive insights into intratumoral heterogeneity and clonal evolution during disease progression and metastasis. Furthermore, it has become increasingly clear that the entire tumor ecosystem must be considered when dissecting the biology of breast cancer and improving therapeutic strategies. In this review, we focus on human disease and highlight recent developments in deciphering breast tumoral heterogeneity, genetic drivers, and cellular complexity within the whole tumor, much of which is being propelled through novel multi-modal platforms. Finally, we summarize the main players being incorporated into breast cancer therapy.

## TRADITIONAL BREAST CANCER CLASSIFICATION

Human breast carcinomas are stratified according to a multi-dimensional framework that incorporates histopathological classification, clinical characteristics, and advanced molecular analysis. At diagnosis, tumors are broadly classified by histology as *in situ* carcinoma or invasive carcinomas, depending on the spread of malignant cells from breast lobules or ducts into the surrounding stroma (Figure 1) (reviewed in WHO Classification of Tumours). The most common form of pre-invasive breast cancer is ductal carcinoma *in situ* (DCIS), for which only 10%–30%

# scientific reports
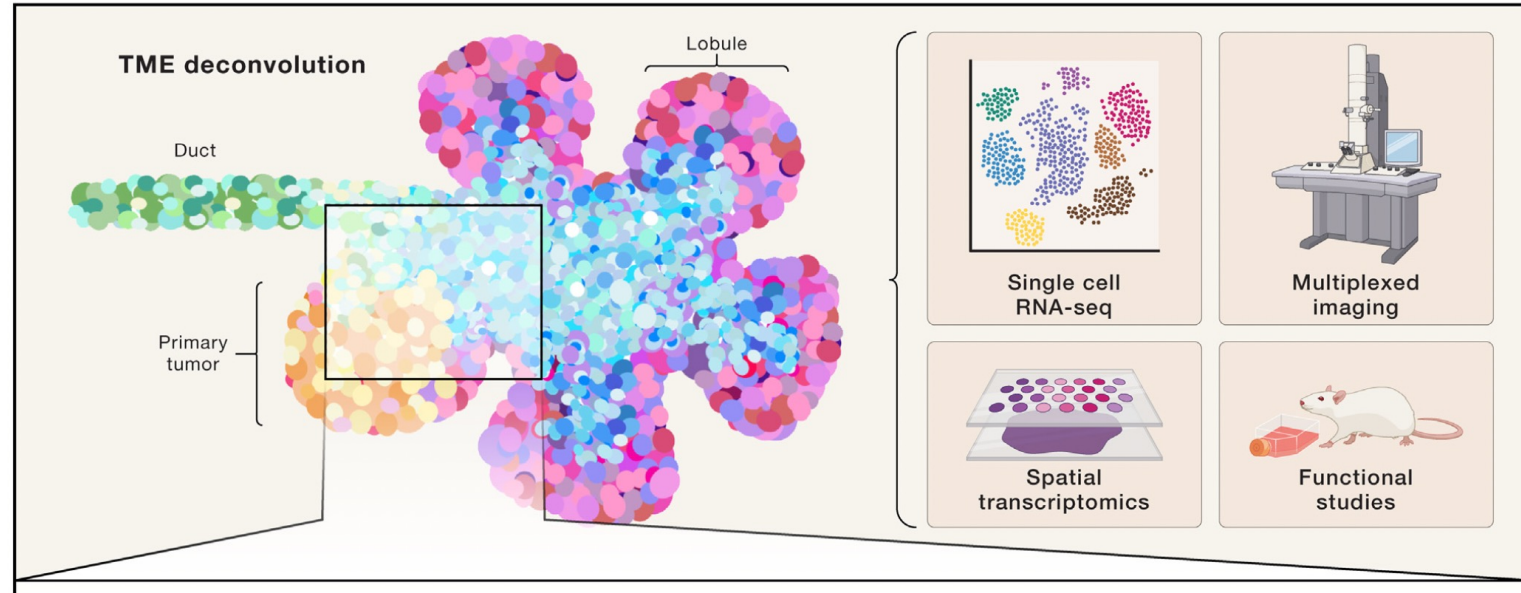
OPEN

# Predicting *EGFR* mutational status from pathology images using a real-world dataset

James J. Pao, Mikayla Biggs, Daniel Duncan, Douglas I. Lin, Richard Davis, Richard S. P. Huang, Donna Ferguson, Tyler Janovitz, Matthew C. Hiemenz, Nathanial R. Eddy, Erik Lehnert, Moran N. Cabili, Garrett M. Frampton, Priti S. Hegde & Lee A. Albacker[✉]

Treatment of non-small cell lung cancer is increasingly biomarker driven with multiple genomic alterations, including those in the epidermal growth factor receptor (*EGFR*) gene, that benefit from targeted therapies. We developed a set of algorithms to assess *EGFR* status and morphology using a real-world advanced lung adenocarcinoma cohort of 2099 patients with hematoxylin and eosin (H&E) images exhibiting high morphological diversity and low tumor content relative to public datasets. The best performing *EGFR* algorithm was attention-based and achieved an area under the curve (AUC) of 0.870, a negative predictive value (NPV) of 0.954 and a positive predictive value (PPV) of 0.410 in a validation cohort reflecting the 15% prevalence of *EGFR* mutations in lung adenocarcinoma. The attention model outperformed a heuristic-based model focused exclusively on tumor regions, and we show that although the attention model also extracts signal primarily from tumor morphology, it extracts additional signal from non-tumor tissue regions. Further analysis of high-attention regions by pathologists showed associations of predicted *EGFR* negativity with solid growth patterns and higher peritumoral immune presence. This algorithm highlights the potential of deep learning tools to provide instantaneous rule-out screening for biomarker alterations and may help prioritize the use of scarce tissue for biomarker testing.

Genomic-guided therapeutic choices are increasingly used in the management of advanced non-small cell lung cancer (NSCLC)[1]. Therapies requiring diagnostic testing include single-agent immunotherapy and kinase inhibitors targeting EGFR and ALK in the first-line and KRAS G12C, MET, and NTRK targeted therapies in the second-line[2]. Although multiplex diagnostic approaches such as next-generation sequencing are becoming more common, many labs perform testing for relevant biomarkers separately. As tissue acquired for testing is often limited and the number of diagnostics increases, care should be taken to prevent tissue exhaustion so that all appropriate clinical options may be determined[3]. One potential opportunity to mitigate this challenge is by leveraging machine learning with digital pathology.

Machine learning, and in particular deep learning, has recently gained broad traction across an expanse of medical domains, with its use showing promise in aiding diagnostics and biomarker discovery in applications relating to ophthalmology, heart disease, cancer care and more[4–11]. There is especially impactful opportunity within cancer care to leverage the immense data generated through clinical practice, including omics from sequencing technologies and gigapixel digital pathology scans. One such opportunity lays with the emerging sub-field of digital pathology, which investigates the rich trove of information present within high resolution scans of hematoxylin and eosin (H&E) stains alongside other stains such as immunohistochemistry stains. H&E stains are inexpensive and ubiquitous tissue specimen stains used during the pathology workflow that allow pathologists to better examine tumor morphologies and determine the diagnosis of the tumor[12]. Machine learning and deep learning models applied to digital scans of H&E-stained tissue slides have shown significant promise in enhancing a variety of aspects in cancer-care, including aiding in cancer diagnoses, improving operational efficiencies, and directly providing molecular insights.

In 2016, Wang et al. showed that deep learning could detect metastatic breast cancer in lymph node biopsies with high performance, and suggested value in computer-aided approaches augmenting the pathology workflow, with pathologist-computer combined methods achieving 0.995 AUC on the cancer detection task[13]. Following soon afterwards, Coudray et al. showed that deep learning could classify cancer subtypes effectively and, even

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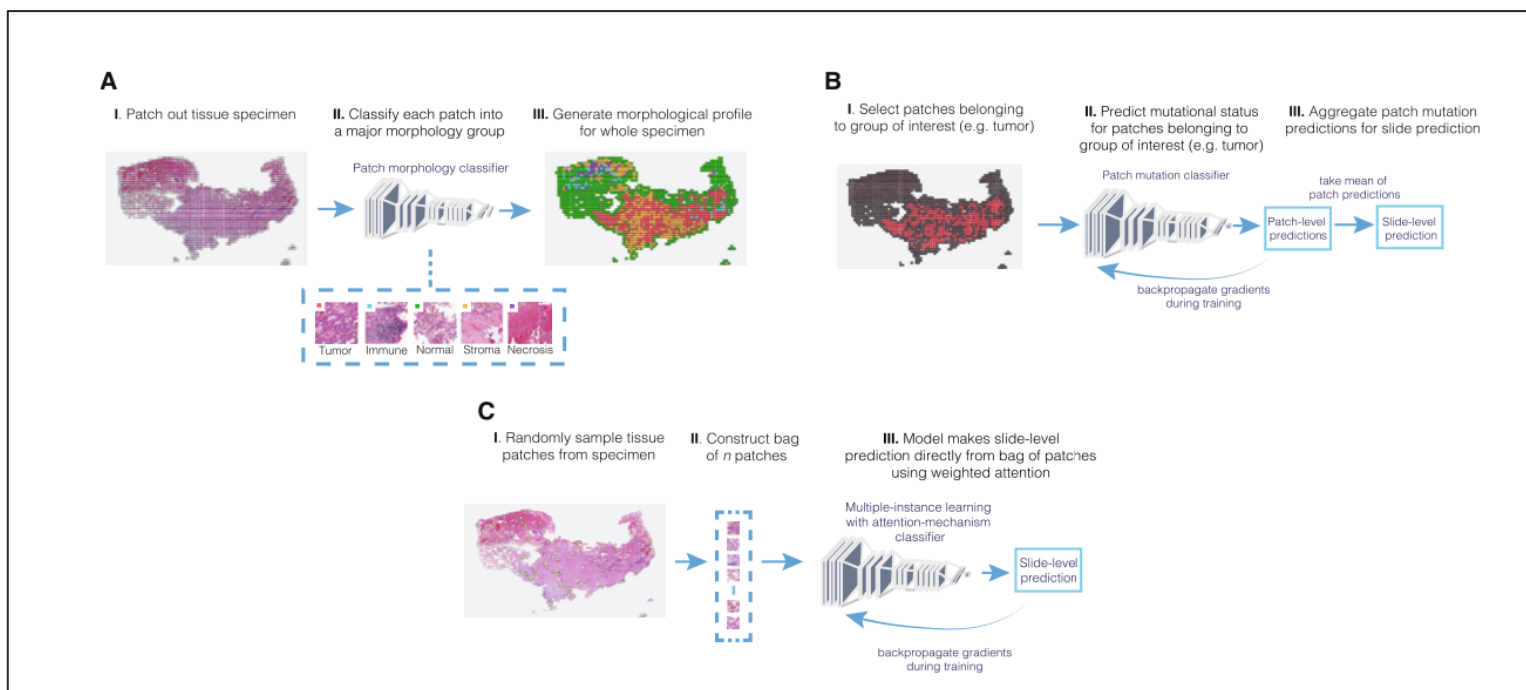
**Original Investigation | Health Policy**

# Perspectives of Patients About Immediate Access to Test Results Through an Online Patient Portal

Bryan D. Steitz, PhD; Robert W. Turer, MD; Chen-Tan Lin, MD; Scott MacDonald, MD; Liz Salmi, AS; Adam Wright, PhD; Christoph U. Lehmann, MD; Karen Langford, BBA; Samuel A. McDonald, MD; Thomas J. Reese, PhD; Paul Sternberg, MD; Qingxia Chen, PhD; S. Trent Rosenbloom, MD; Catherine M. DesRoches, DrPH

## Abstract

**IMPORTANCE** The 21st Century Cures Act Final Rule mandates the immediate electronic availability of test results to patients, likely empowering them to better manage their health. Concerns remain about unintended effects of releasing abnormal test results to patients.

**OBJECTIVE** To assess patient and caregiver attitudes and preferences related to receiving immediately released test results through an online patient portal.

**DESIGN, SETTING, AND PARTICIPANTS** This large, multisite survey study was conducted at 4 geographically distributed academic medical centers in the US using an instrument adapted from validated surveys. The survey was delivered in May 2022 to adult patients and care partners who had accessed test results via an online patient portal account between April 5, 2021, and April 4, 2022.

**EXPOSURES** Access to test results via a patient portal between April 5, 2021, and April 4, 2022.

**MAIN OUTCOMES AND MEASURES** Responses to questions related to demographics, test type and result, reaction to result, notification experience and future preferences, and effect on health and well-being were aggregated. To evaluate characteristics associated with patient worry, logistic regression and pooled random-effects models were used to assess level of worry as a function of whether test results were perceived by patients as normal or not normal and whether patients were precounseled.

**RESULTS** Of 43 380 surveys delivered, there were 8139 respondents (18.8%). Most respondents were female (5129 [63.0%]) and spoke English as their primary language (7690 [94.5%]). The median age was 64 years (IQR, 50-72 years). Most respondents (7520 of 7859 [95.7%]), including 2337 of 2453 individuals (95.3%) who received nonnormal results, preferred to immediately receive test results through the portal. Few respondents (411 of 5473 [7.5%]) reported that reviewing results before they were contacted by a health care practitioner increased worry, though increased worry was more common among respondents who received abnormal results (403 of 2442 [16.5%]) than those whose results were normal (294 of 5918 [5.0%]). The result of the pooled model for worry as a function of test result normality was statistically significant (odds ratio [OR], 2.71; 99% CI, 1.96-3.74), suggesting an association between worry and nonnormal results. The result of the pooled model evaluating the association between worry and precounseling was not significant (OR, 0.70; 99% CI, 0.31-1.59).

**CONCLUSIONS AND RELEVANCE** In this multisite survey study of patient attitudes and preferences toward receiving immediately released test results via a patient portal, most respondents preferred

_(continued)_

### Key Points

**Question** What are patient attitudes and perspectives related to viewing immediately released test results through an online patient portal?

**Findings** In this survey study of 8139 respondents at 4 US academic medical centers, 96% of patients preferred receiving immediately released test results online even if their health care practitioner had not yet reviewed the result. A subset of respondents experienced increased worry after receiving abnormal results.

**Meaning** In this study, most patients supported receiving immediately released test results via a patient portal, but some patients experienced increased worry, especially when test results were abnormal.

➕ **Supplemental content**

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

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Aug 26

# Information Blocking

21st Century Cures Act and Information Blocking

The information blocking provisions of the 21st Century Cures Act[1] will impact virtually every healthcare stakeholder with access to electronic health information.

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# Results

Of 43 380 surveys delivered, there were 8139 participants (18.8%), of whom 5129 (63.0%) identified as female, 2895 (35.6%) as male, and 115 (1.4%) as other or unknown gender. A total of 120 (1.5%) were American Indian or Pacific Native; 250 (3.1%), Asian; 428 (5.3%), Black or African American; 23 (0.2%), Native Hawaiian or Pacific Islander; 6900 (84.8%), White; and 245 (3.0%) other race; 420 (5.2%) were Spanish or Latino. Most patients spoke English as their primary language (7690 [94.5%]). The median age of participants was 64 years (IQR, 50-72 years). **Table 1** provides detailed respondent demographic characteristics. A total of 6306 of 7856 respondents (80.3%) reported reviewing at least 1 test result in the past month, and 5767 of 6245 (92.3%) reported receiving precounseling. Most tests were blood tests (4730 of 6276 [75.4%]). Imaging or biopsies accounted for 3044 of 6276 tests (48.5%). Most respondents reported normal findings (3582 of 6246 [57.3%]) (**Table 2**). Among 6200 respondents who reviewed results, 5418 (87.4%) reported being contacted

# Figure 1. Percentage of Patients at Each Level of Worry, Stratified by Normal vs Not Normal Test Results
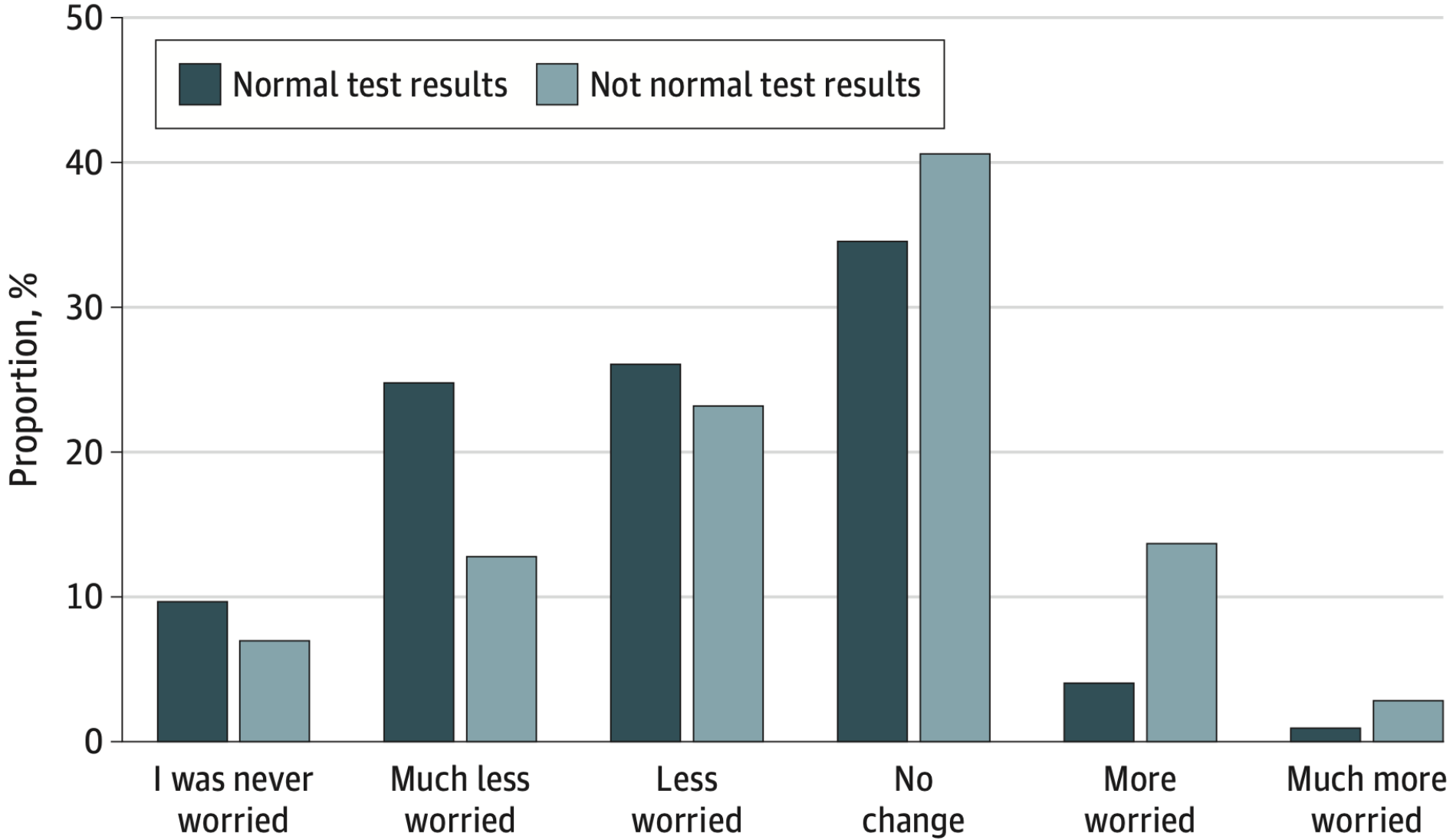
making.

A subset of respondents reported additional worry after viewing not normal results. Our modeling results support the findings reported by Giardina and colleagues[5] that patients receiving not normal results are at increased risk for negative emotions, potentially due to difficulty interpreting the results in the context of their own health. Prior literature[42,43] has highlighted a similar trend in worry when receiving news of abnormal results outside a patient portal, such as through a telephone call or during an in-person visit. We found that 95.3% of participants who received abnormal test results would like to continue to receive immediately released results through the portal. This finding suggests that there may be benefits to receiving abnormal results online, such as allowing patients to choose where and with whom to view such results. Additional research is necessary to better understand the nuance of worry from receiving abnormal test results, especially as it relates to release through the portal. A separate qualitative evaluation of the free-text questions in our survey is forthcoming and may provide insight into this phenomenon.

A large proportion of respondents (92.3%) reported receiving precounseling. Interestingly, we found no association between precounseling and lower levels of worry. Best practices for precounseling should be studied further. Additionally, the workflow and financial consequences of this added task for an already stressed clinical workforce warrants further consideration. Precounseling strategies might encompass both technical and social-technical approaches, including

# Cell

ⓒ CellPress

**Cell**
Review

## Review

# From patterns to patients: Advances in clinical machine learning for cancer diagnosis, prognosis, and treatment

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**SUMMARY**

Machine learning (ML) is increasingly used in clinical oncology to diagnose cancers, predict patient outcomes, and inform treatment planning. Here, we review recent applications of ML across the clinical oncology workflow. We review how these techniques are applied to medical imaging and to molecular data obtained from liquid and solid tumor biopsies for cancer diagnosis, prognosis, and treatment design. We discuss key considerations in developing ML for the distinct challenges posed by imaging and molecular data. Finally, we examine ML models approved for cancer-related patient usage by regulatory agencies and discuss approaches to improve the clinical usefulness of ML.
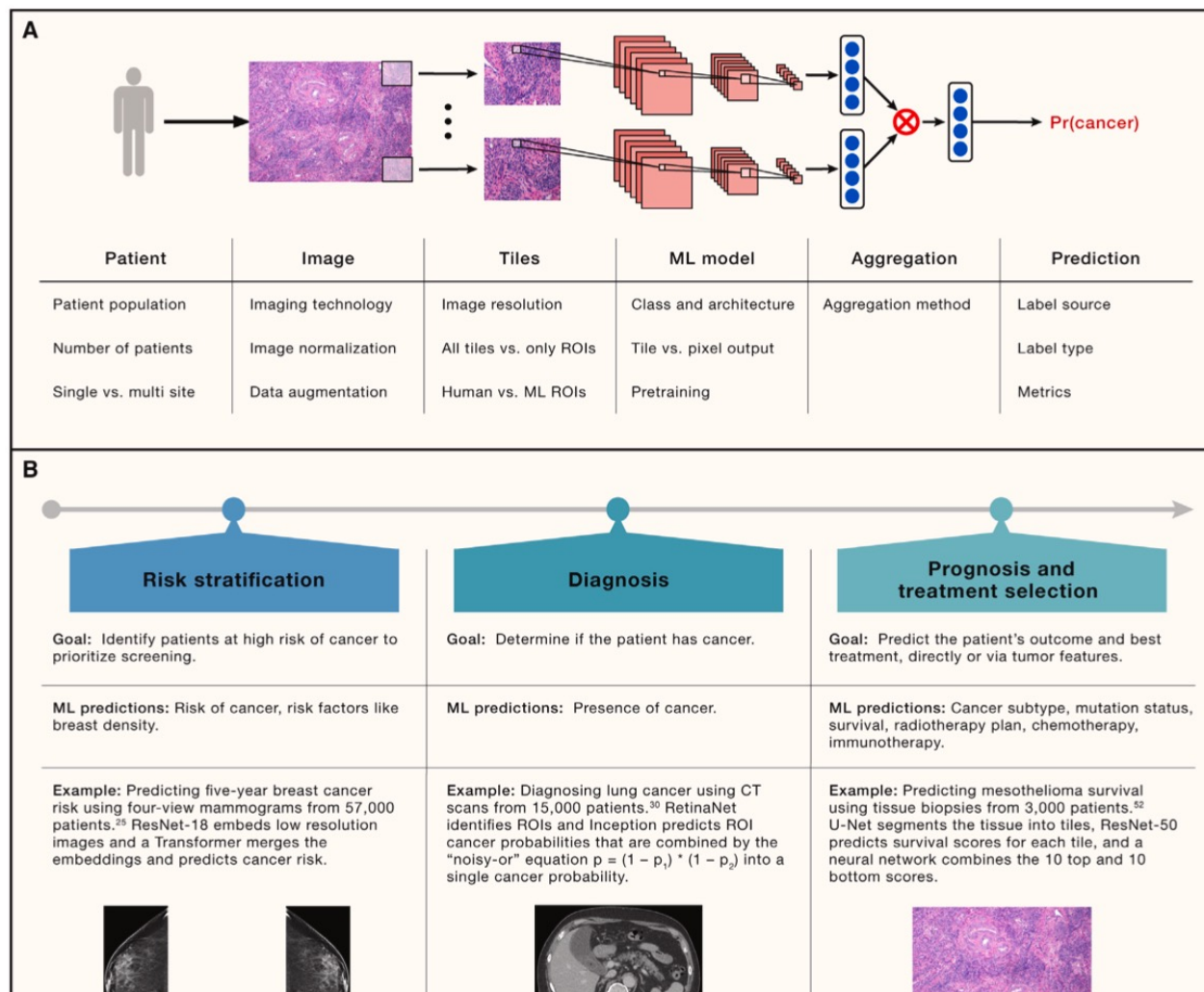
## INTRODUCTION

In the past decade, machine learning (ML) has seen an explosion of applications in medicine, particularly within oncology.[1] As a set of complex, heterogeneous, and prevalent diseases, cancers provide both a challenging set of diagnostic problems and copious data in multiple modalities.[2] This makes clinical oncology a promising field for ML, which utilizes data to learn patterns and the structure of a dataset (see machine learning primer section for a brief introduction to ML). In particular, rich imaging and molecular data have spurred the application of ML to correlate these data sources with early cancer detection, monitoring of cancer progression, and identification of optimized therapeutic treatment.

Medical imaging has been a powerful tool that has revolutionized cancer diagnostics. In particular, medical imaging enables non-invasive, cheap, and scalable detection, localization, and monitoring of cancer. Radiology images, as well as other image modalities like skin images or colonoscopy videos, are used for screening and diagnosis.[3] Pathology images of tissue samples are used to confirm a cancer diagnosis and determine prognostic factors such as cancer subtype.[4] Both radiology and pathology images can guide treatment by informing the selection of chemotherapy or immunotherapy and aiding radiotherapy planning.[5] As medical imaging is increasingly fundamental to the clinical oncology workflow, the quantity of imaging data is often growing faster than clinicians can handle.[3] This leads to a desire for automated methods of processing medical images to reduce clinician workload, accelerate the analysis of time-sensitive

images, and mitigate clinician errors. Advances in ML for computer vision have been adapted for medical imaging and are already showing great promise for rapidly and accurately analyzing a variety of imaging modalities in clinical oncology.[6,7]

Although imaging informs many aspects of cancer care, molecular characterization can provide a more fine-grained view of a patient's cancer status.[8] This is particularly important as cancer therapeutics become increasingly targeted and mechanistic.[9] Liquid biopsies, which measure molecular biomarkers present in non-invasive physiology samples such as blood or urine, have emerged as a promising approach to profiling tumor states for cancer diagnostics. Liquid and solid tumor biopsies also make it possible to serially profile tumor status and identify characteristics of tumor evolution and heterogeneity that are associated with resistance to therapies, recurrence, and poor survival outcomes.[10] Due to the wealth of information provided by liquid biopsies and solid tumor biopsies, ML has been instrumental in predicting clinical outcomes and cancer status from rich molecular features.

In this review, we explore recent advances in ML applied to clinical oncology. We focus on relatively mature ML technologies already deployed or close to deployment in clinical settings. There is a large body of exciting development of ML for more basic cancer research and drug discovery that we do not cover here. Because imaging and molecular data are two major data modalities in clinical oncology with distinct ML challenges, we structure the review to discuss imaging ML and molecular ML separately. For each modality, we discuss both the major applications of ML and the types of ML models and techniques that



**A**

| Patient | Image | Tiles | ML model | Aggregation | Prediction |
|---|---|---|---|---|---|
| Patient population | Imaging technology | Image resolution | Class and architecture | Aggregation method | Label source |
| Number of patients | Image normalization | All tiles vs. only ROIs | Tile vs. pixel output | | Label type |
| Single vs. multi site | Data augmentation | Human vs. ML ROIs | Pretraining | | Metrics |

**B**

**Risk stratification**

**Goal:** Identify patients at high risk of cancer to prioritize screening.

**ML predictions:** Risk of cancer, risk factors like breast density.

**Example:** Predicting five-year breast cancer risk using four-view mammograms from 57,000 patients.[25] ResNet-18 embeds low resolution images and a Transformer merges the embeddings and predicts cancer risk.

**Diagnosis**

**Goal:** Determine if the patient has cancer.

**ML predictions:** Presence of cancer.

**Example:** Diagnosing lung cancer using CT scans from 15,000 patients.[30] RetinaNet identifies ROIs and Inception predicts ROI cancer probabilities that are combined by the "noisy-or" equation $p = (1 - p_1) * (1 - p_2)$ into a single cancer probability.

**Prognosis and treatment selection**

**Goal:** Predict the patient's outcome and best treatment, directly or via tumor features.

**ML predictions:** Cancer subtype, mutation status, survival, radiotherapy plan, chemotherapy, immunotherapy.

**Example:** Predicting mesothelioma survival using tissue biopsies from 3,000 patients.[52] U-Net segments the tissue into tiles, ResNet-50 predicts survival scores for each tile, and a neural network combines the 10 top and 10 bottom scores.

**ORIGINAL RESEARCH**

# EMA-FDA Parallel Scientific Advice: Optimizing Development of Medicines in the Global Age

Shannon Thor[1] · Thorsten Vetter[2] · Anabela Marcal[3] · Sandra Kweder[4]

**Abstract**
As medicines development continues towards a globalized approach, both the pharmaceutical industry and regulatory agencies increasingly seek opportunities to proactively engage early in product development. The parallel scientific advice program shared by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) provides a mechanism for experts to concurrently engage in scientific discourse with sponsors on key issues during the development phase of new medicinal products (drugs, biologicals, vaccines, and advanced therapies).

**Keywords** Drug development · Regulatory · EMA · FDA · Innovation

## Introduction

Regulators at both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) support and foster increasingly globalized approaches to medicines development. Covering a broad range of relevant topics in medicines development, both Agencies participate in multilateral fora such as the International Council on Harmonization (ICH), International Coalition of Medicines Regulatory Authorities (ICMRA), and the World Health Organization (WHO) to address topics such as standards setting and policy convergence at the global level. On a smaller scale, the two Agencies lead more than 30 technical working groups or "clusters" where members exchange perspectives and experiences on regulatory science topics.[1] The cluster meetings are opportunities for regulatory experts to discuss amongst themselves challenges and difficult applications of regulatory science and policy based on the priorities of the Agencies and are not intended to serve as a forum for advising sponsors. There are situations, however, in which a developer can benefit from scientific advice on a product development program from both Agencies concurrently, and where convergent advice on the same or similar product-based scientific questions could benefit public health and facilitate patient access to needed therapies. To meet this need, EMA and FDA established a sponsor-initiated, product-specific exchange: the parallel scientific advice (PSA) program.[2]

PSA provides a mechanism for EMA and FDA experts, upon request by the applicant, to concurrently advise sponsors on scientific issues during the development of new medicinal products (drugs, biologicals, vaccines, and advanced therapies). Importantly, as part of the process the two agencies engage with each other to compare perspectives in advance of and during the actual interaction with the sponsor. This voluntary program was launched in 2005[3] with four goals: increase dialogue between the two agencies and sponsors from the beginning of the lifecycle of a new product; provide a deeper understanding of the bases

**Sandra Kweder's contributions were during the time of FDA employment.**

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[1] Tania Teixeira, Sandra L. Kweder, and Agnes Saint-Raymond. Are the European Medicines Agency, US Food and Drug Administration, and Other International Regulators Talking to Each Other?

[2] GENERAL PRINCIPLES EMA-FDA PARALLEL SCIENTIFIC ADVICE. July 2021.

[3] PSA Pilot Program Launch 2005.

🕊 Springer

**Table 2** PSA timeline

| Day | FDA | EMA |
|---|---|---|
| Anytime | Sponsor submits request for PSA to FDA and EMA<br>Agencies decline  no PSA<br>Agencies accept  Sponsor begins drafting meeting package according to SAWP procedures | |
| Varies | | Meeting Package Submission and Validation Phase; Option for preparatory meeting with EMA according to SAWP procedures |
| 0 | EMA validates meeting package; FDA receives validated meeting package; Procedure begins | |
| 15–25 | FDA internal meeting | EMA SAWP internal discussion |
| 30–34 | FDA sends Preliminary Comments to EMA | EMA sends List of Issues to FDA |
| 35 | Bilateral FDA/EMA meeting | |
| 65 | Trilateral Sponsor/FDA/EMA meeting | |
| 75 to 95 | FDA issues final meeting minutes (30 days after trilateral) | EMA issues final advice letter (10 days after trilateral) |

# Companion Diagnostics

## Lessons Learned and the Path Forward From the Programmed Death Ligand-1 Rollout

Joseph E. Willis, MD; Frederick Eyerer, MD; Eric E. Walk, MD; Patricia Vasalos, BS, MT; Georganne Bradshaw, MT(ASCP); Sophia Louise Yohe, MD; Jordan S. Laser, MD

● Context.—Programmed death ligand-1 (PD-L1) immunohistochemistry companion diagnostic assays play a crucial role as predictive markers in patients being considered for immune checkpoint inhibitor therapy. However, because of a convergence of several factors, including recognition of increased types of cancers susceptible to immunotherapy, increasing numbers of immune checkpoint inhibitors, and release of multiple PD-L1 immunohistochemistry antibodies with differing reporting systems, this complex testing environment has led to significant levels of confusion for pathologists and medical oncologists.

Objective.—To identify which processes and procedures have contributed to the current challenges surrounding programmed death receptor-1 (PD-1)/PD-L1 companion diagnostics and to propose potential remedies to this issue. This is based upon input from key industrial stakeholders in conjunction with the College of American Pathologists Personalized Health Care Committee.

Design.—A meeting of representatives of pharmaceutical and in vitro diagnostic companies along with the Personalized Health Care Committee reviewed the process of release of the PD-L1 companion diagnostic assays using a modified root cause analysis format. The modified root cause analysis envisioned an ideal circumstance of development and implementation of a companion diagnostic to identify shortcomings in the rollout of the PD-L1 assay and to suggest actions to improve future companion diagnostic assay releases.

Results.—The group recommended improvements to key principles in companion diagnostics implementation related to multi-stakeholder communication, increased regulatory flexibility to incorporate postapproval medical knowledge, improved cross-disciplinary information exchange between medical oncology and pathology societies, and enhanced postmarket training programs.

Conclusions.—The rapidly changing nature of and increasing complexity associated with companion diagnostics require a fundamental review of processes related to their design, implementation, and oversight.

(Arch Pathol Lab Med. 2023;147:62–70; doi: 10.5858/arpa.2021-0151-CP)

In 2011, the US Food and Drug Administration (FDA) approved ipilimumab for the treatment of metastatic

melanoma. This was followed by approval of several cancer immunotherapies directed against the programmed death receptor-1/ligand-1 (PD-1/PD-L1) pathways, starting with nivolumab and pembrolizumab in 2014 for treatment of metastatic melanoma. Following these earlier trials, an increasing number of cancers have been found to be susceptible to immune checkpoint inhibition,[1–4] and some studies have demonstrated synergy between CTLA-4 and PD-1/PD-L1 immune checkpoint inhibitors (ICIs) in a number of cancer systems.[4–7] Conventional cancer therapies leading to tumor cell death with T-cell activation by release of tumor antigens will likely have a pivotal role in cancer checkpoint inhibitor therapies.[8] Recent data have identified a promising role for neoadjuvant checkpoint inhibitor therapy in a variety of cancers, in addition to its role in treating advanced cancer patients who have failed first-line therapy.[7,9–18] There are currently 7 ICIs approved by the FDA: ipilimumab (an anti–CTLA-4); PD-1 inhibitors nivolumab, pembrolizumab, and cemiplimab; and PD-L1 inhibitors atezolizumab, avelumab, and durvalumab.[4] These drugs, as single agents or in combination with other standard therapies or ICIs, have been approved for an increasing number of solid and hematopoietic malignancies, with significant improvements in patient outcomes.[4] With further



Major drug development phases: The "typical life cycle" of a companion diagnostic. Note: This largely represents the timeline of how programmed death ligand-1 immunohistochemistry was developed and implemented. Other companion diagnostics, depending upon how they follow "the science," may have different critical paths.
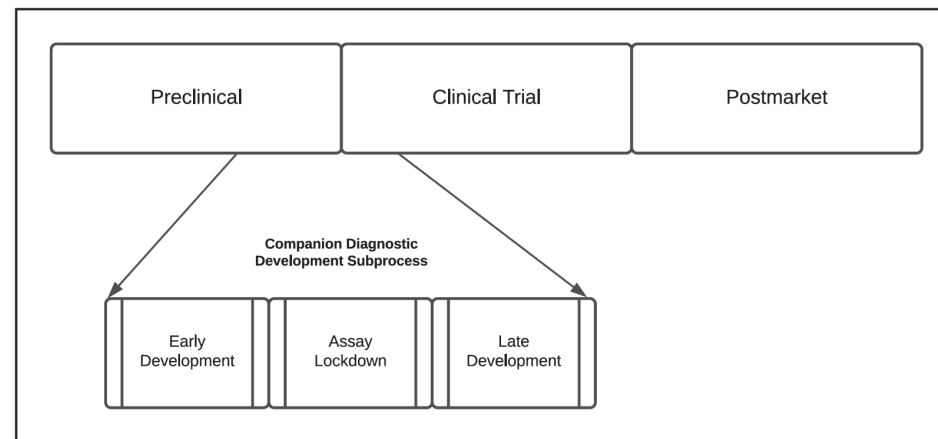
cetuximab therapy was very quickly negated by improved understanding of colorectal cancer molecular pathology.[17] In 2014, the FDA formally issued guidance that defined a companion diagnostic as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." The labeling requirements in 2014 noted that for each companion diagnostic, a list of specific therapeutic products should be provided for which the companion diagnostic could be used. Per this guidance, the corresponding label for the therapeutic product, however, should specify the use of an FDA-approved companion diagnostic device, rather than a specific companion diagnostic product.[18] A related term, complementary diagnostic, first appeared in the 1990s when used by GlaxoSmithKline and Alizyme in reference to predictive genetic diagnostics.[19] In 2016, the FDA provided a preliminary definition for complementary diagnostics, defining them as "tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre-requisites for receiving the drug."[20] The key difference between complementary diagnostics and companion diagnostics is that for complementary diagnostics, the therapy has been shown to provide benefit regardless of the result, whereas for companion diagnostics, the result predicts safe or effective use of the therapeutic product.[15] For example, ICIs may benefit patients and PD-L1 immunohis-

ARTIFICIAL INTELLIGENCE

# Predicting Response of Triple-Negative Breast Cancer to Neoadjuvant Chemotherapy Using a Deep Convolutional Neural Network–Based Artificial Intelligence Tool

Savitri Krishnamurthy, MD[1]; Parag Jain, MS[2]; Debu Tripathy, MD[1]; Roland Basset, MS[1]; Ramandeep Randhawa, PhD[2]; Hassan Muhammad, PhD[2]; Wei Huang, MD, PhD[2]; Hua Yang, PhD[2]; Shivaani Kummar, MD[3]; George Wilding, PhD[2]; and Rajat Roy, MS[2]

**PURPOSE** Achieving a pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) is associated with improved patient outcomes in triple-negative breast cancer (TNBC). Currently, there are no validated predictive biomarkers for the response to NAC in TNBC. We developed and validated a deep convolutional neural network–based artificial intelligence (AI) model to predict the response of TNBC to NAC.

**MATERIALS AND METHODS** Whole-slide images (WSIs) of hematoxylin and eosin–stained core biopsies from 165 (pCR in 60 and non-pCR in 105) and 78 (pCR in 31 and non-pCR in 47) patients with TNBC were used to train and validate the model. The model extracts morphometric features from WSIs in an [...] thereby generating clusters of morphologically similar patterns. Downstream ranking of cl[...] of interest and morphometric scores; a low score close to zero and a high score close to or[...] low probability of response to NAC.

**RESULTS** The predictive ability of AI score for the entire cohort of 78 patients with TNBC [...] operating characteristic analysis demonstrated an area under the curve (AUC) of 0.75. T[...] and III disease were 0.88, 0.73, and 0.74, respectively. Using a cutoff value of 0.35, the p[...] of the AI score for pCR was 73.7%, and the negative predictive value was 76.2% for [...]

**CONCLUSION** To our knowledge, this study is the first to demonstrate the use of an AI tool [...] and eosin–stained tissue images to predict the response to NAC in patients with TNBC[...] validated in subsequent studies, these results may serve as an ancillary aid for ind[...] decisions in patients with TNBC.
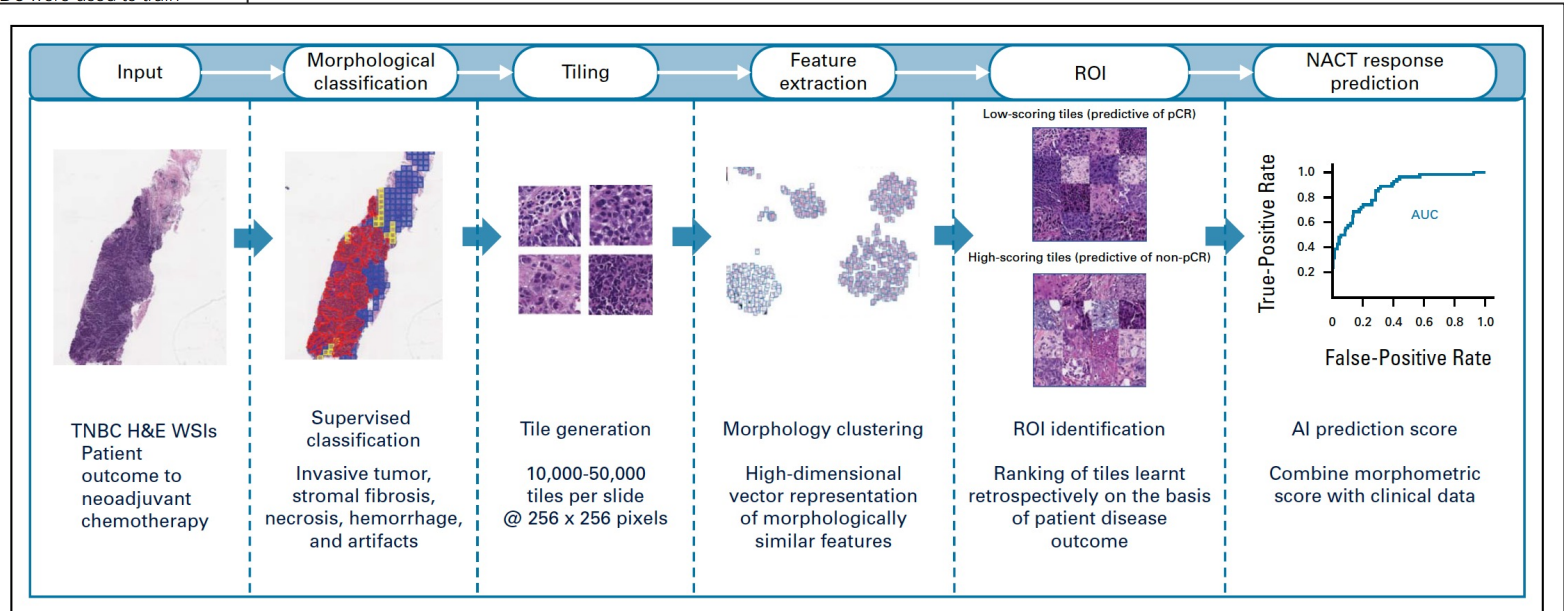
**FIG 1.** Study workflow for determination of AI prediction score. AI, artificial intelligence; AUC, area under the curve; H&E, hematoxylin and eosin; NACT, neoadjuvant chemotherapy; ROI, regions of interest; TNBC, triple-negative breast cancer; WSI, whole-slide image.

# A Road Map For Action:
## Recommendations Of The Health Affairs Council On Health Care Spending And Value

| EXECUTIVE SUMMARY

**EXHIBIT 4**

## The Alternative Payment Model Framework

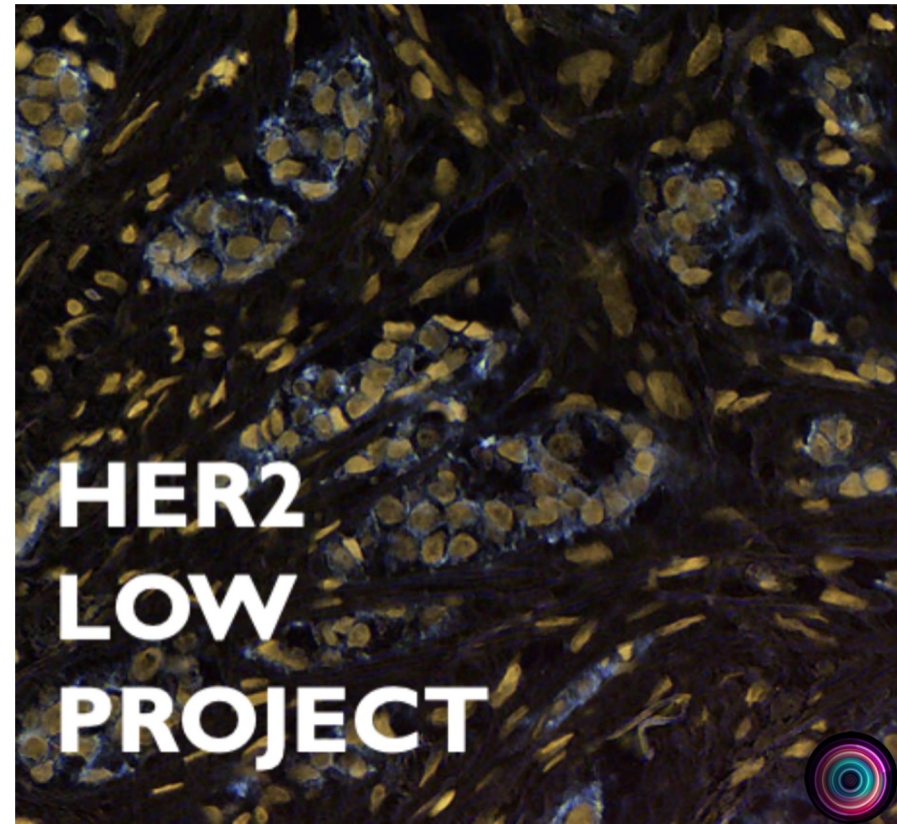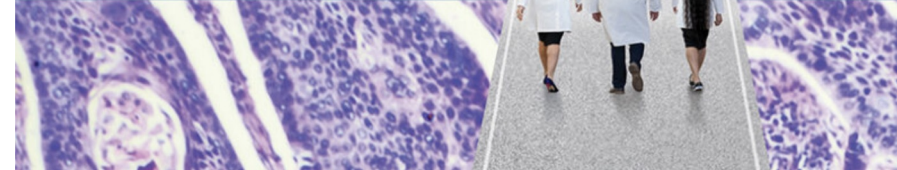| CATEGORY 1 | CATEGORY 2 | CATEGORY 3 | CATEGORY 4 |
|---|---|---|---|
| Fee-for-service: no link to quality and value | Fee-for-service: link to quality and value | APMs built on fee-for-service architecture | Population-based payment |
| | **2A** | **3A** | **4A** |
| | Foundational payments for infrastructure and operations<br>For example, care coordination fees and payments for health information technology investments | APMs with shared savings<br>For example, shared savings with upside risk only | Condition-specific population-based payment<br>For example, per member per month payments or payments for specialty services, such as oncology or mental health |
| | **2B** | **3B** | **4B** |
| | Pay-for-reporting<br>For example, bonuses for reporting data or penalties for not reporting data | APMs with shared savings and downside risk<br>For example, episode-based payments for procedures and comprehensive | Comprehensive population-based payment<br>For example, global budgets or the full or a percent of premium payments |

# Events of Interest
## *April 2023*

- April 4 11:00-12:00PM ET **DPA Webinar Series**: How to use Digital Pathology to accelerate the drug development pipeline: from target discovery to post market

- April 4-6 10th **World Digital Pathology & AI UCGCongress**

- April 7 at 1:00-2:00PM ET **HER2-Low Project**

- April 15-18 **CAP Pathologist Leadership Summit**

- April 26 3:00-4:00PM ET **PIcc April Meeting**