Plcc Alliance

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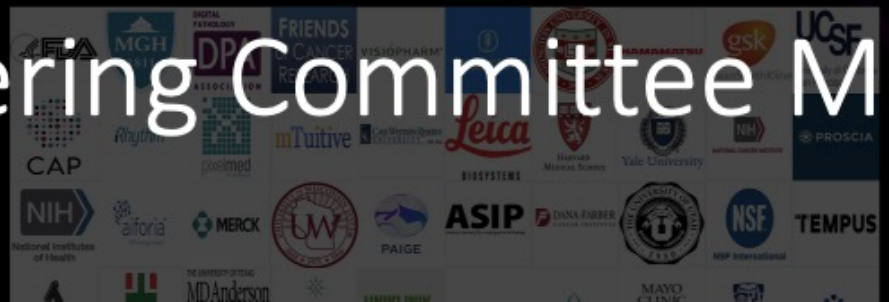
Join

Pathology Innovation Collaborative Community

Plcc

The Alliance for Digital Pathology

A collaborative community with FDA participation



Steering Committee Meeting

August 2023

FDA

Contains Nonbinding Recommendations

Off-The-Shelf Software Use in Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 11, 2023.

Document originally issued on September 9, 1999.

This document supersedes Off-The-Shelf Software Use in Medical Devices issued September 27, 2019.

For questions about this document, contact the Digital Health Center of Excellence by e-mail at digitalhealth@fda.hhs.gov.

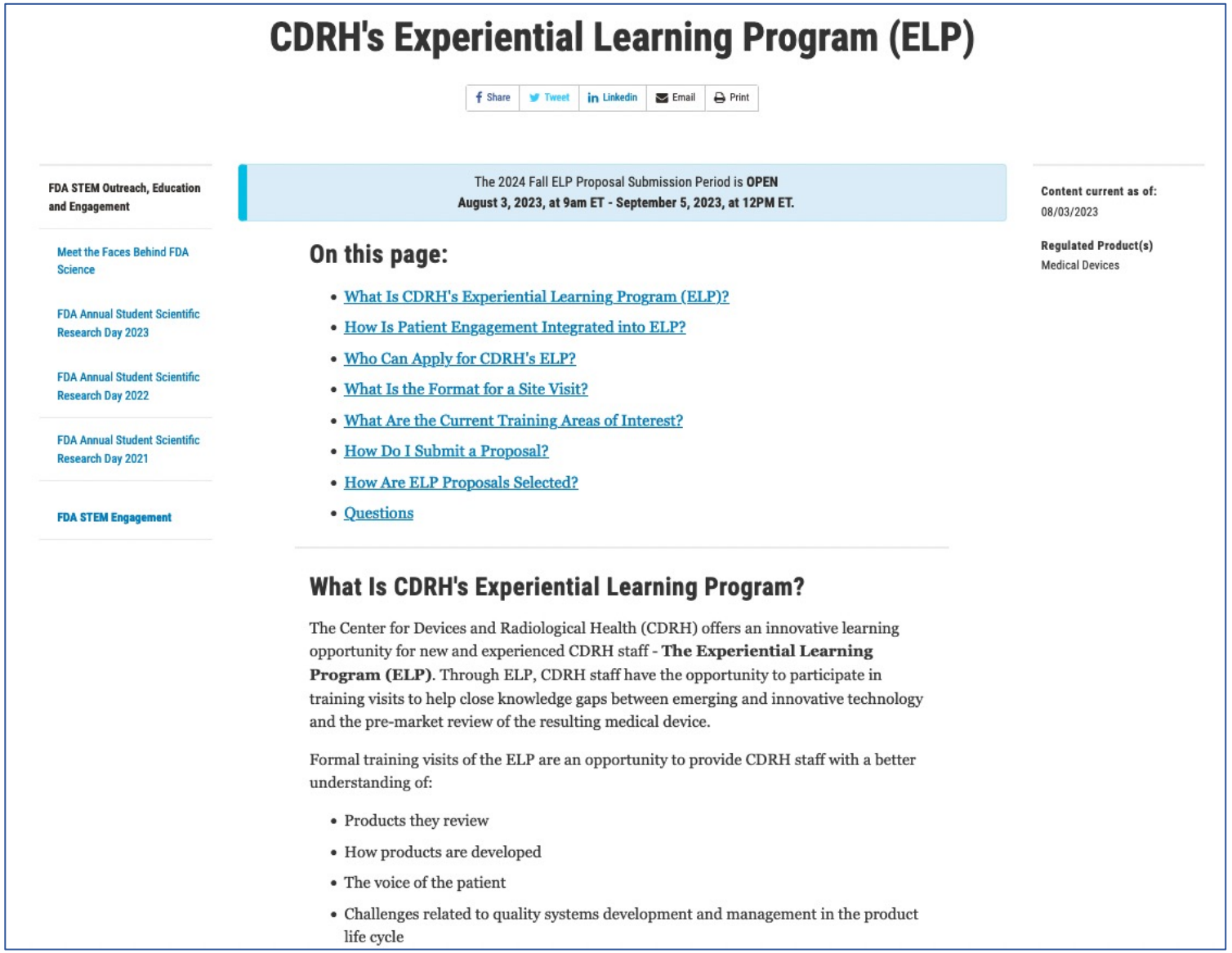
Advancing New Alternative Methods at FDA

Donna L. Mendrick, Ph.D.
Co-chair FDA's Alternative Methods Working Group
Associate Director of Regulatory Activities
NCTR/FDA

June 27, 2023

MPS World Summit 2023

Disclaimer: *This presentation reflects the views of the authors and does not necessarily reflect those of the U.S. Food and Drug Administration. Any mention of commercial products is for clarification only and is not intended as approval, endorsement, or recommendation.*



CDRH's Experiential Learning Program (ELP)

Share | Tweet | Linkedin | Email | Print

FDA STEM Outreach, Education and Engagement

- Meet the Faces Behind FDA Science
- FDA Annual Student Scientific Research Day 2023
- FDA Annual Student Scientific Research Day 2022
- FDA Annual Student Scientific Research Day 2021
- FDA STEM Engagement

The 2024 Fall ELP Proposal Submission Period is **OPEN**
August 3, 2023, at 9am ET - September 5, 2023, at 12PM ET.

Content current as of:
08/03/2023

Regulated Product(s)
Medical Devices

On this page:

- What Is CDRH's Experiential Learning Program (ELP)?
- How Is Patient Engagement Integrated into ELP?
- Who Can Apply for CDRH's ELP?
- What Is the Format for a Site Visit?
- What Are the Current Training Areas of Interest?
- How Do I Submit a Proposal?
- How Are ELP Proposals Selected?
- Questions

What Is CDRH's Experiential Learning Program?

The Center for Devices and Radiological Health (CDRH) offers an innovative learning opportunity for new and experienced CDRH staff - **The Experiential Learning Program (ELP)**. Through ELP, CDRH staff have the opportunity to participate in training visits to help close knowledge gaps between emerging and innovative technology and the pre-market review of the resulting medical device.

Formal training visits of the ELP are an opportunity to provide CDRH staff with a better understanding of:

- Products they review
- How products are developed
- The voice of the patient
- Challenges related to quality systems development and management in the product life cycle

FDA - ELP

The Center for Devices and Radiological Health (CDRH) offers an innovative learning opportunity for new and experienced CDRH staff - **The Experiential Learning Program (ELP)**. Through ELP, CDRH staff have the opportunity to participate in training visits to help close knowledge gaps between emerging and innovative technology and the pre-market review of the resulting medical device.

Tips for Submitting Comments on CDRH Guidance Documents

Guidance Documents (Medical Devices and Radiation-Emitting Products)

Cross-Center Final Guidance

Recent Final Medical Device Guidance Documents

Draft Medical Device Guidance

CDRH Proposed Guidance Development

Class II Special Controls Documents

Withdrawn or Expired Guidance

Public comments on the FDA's Center for Devices and Radiological Health (CDRH) guidance documents are critical to the guidance development process and help us ensure our recommendations meet stakeholder needs. In accordance with 21 CFR 10.115, the FDA considers comments received and revises guidances, as appropriate. Below are some tips and recommendations, as well as some instructions on how to submit comments for a guidance.

Tips

- Submit either electronic or written comments on the guidance by the comment close date listed on the CDRH guidance web page and associated Federal Register Notice announcing the draft guidance to ensure that FDA considers your comments on the draft guidance before it begins work on the final version of the guidance.
    - You can comment on any guidance document at any time (21 CFR 10.115(g)(5)), including final guidance documents. However, comments may not be acted upon by the Agency until the document is next revised or updated.
- Be concise and clear; proposing revised or additional language is also appreciated (if practical).

Content current as of:
08/16/2023

Regulated Product(s)
Medical Devices
Radiation-Emitting Products

Medical Device User Fee Amendments (MDUFA)

User Fees for FY 2023

Annual Establishment Registration Fee: $6,493

All establishments must pay the establishment registration fee. There are no waivers or reductions for small establishments, businesses, or groups in FY 2023.

Other fees for Fiscal Year 2023 (October 1, 2022 through September 30, 2023) are:

Application Type	Standard Fee	Small Business Fee†
510(k)‡	$19,870	$4,967
513(g)	$5,961	$2,980
PMA, PDP, PMR, BLA	$441,547	$110,387
De Novo Classification Request	$132,464	$33,116
Panel-track Supplement	$353,238	$88,309
180-Day Supplement	$66,232	$16,558
Real-Time Supplement	$30,908	$7,727
BLA Efficacy Supplement	$441,547	$110,387
30-Day Notice	$7,065	$3,532
Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs, and PMRs)	$15,454	$3,864

† ***Small Business Fee:*** *For businesses certified by the Center for Devices and Radiological Health (CDRH) as a small business.*

‡ ***510(k) Fees:*** *All types of 510(k)s (Traditional, Abbreviated, and Special) are subject to the user fee. However, there is no user fee for 510(k)s submitted to the FDA on behalf of an FDA-accredited third-party reviewer.*

Content current as of:
08/09/2023

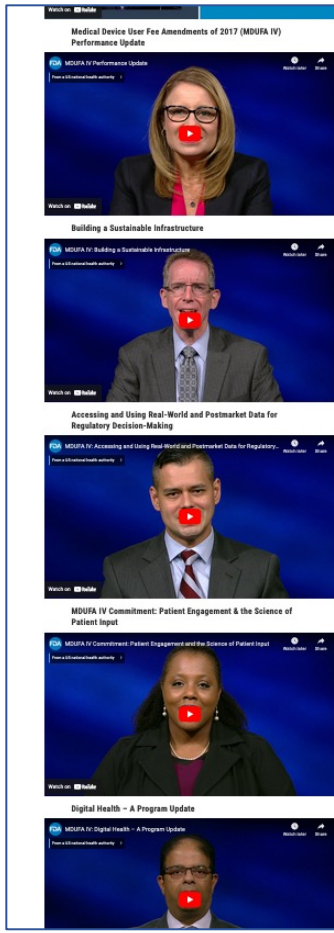
Regulated Product(s)
Medical Devices

MDUFA IV and Beyond – Video Reports

The Medical Device User Fee Amendments of 2017 (MDUFA IV), covers the period from October 1, 2017 through September 30, 2022. The FDA's Center for Devices and Radiological Health (CDRH) prepared a video series highlighting the significant progress the Center has made to date with implementing and going beyond the MDUFA IV commitments. These accomplishments help to advance the Center's mission to protect and promote the public health, and to assure that patients and providers have timely and

Content current as of:
10/15/2020

Regulated Product(s)
Medical Devices



List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

In Vitro Diagnostics

Companion Diagnostics

Biotin Interference with Troponin Lab Tests - Assays Subject to Biotin Interference

Direct-to-Consumer Tests

Nucleic Acid Based Tests

Blood Glucose Monitoring Devices

Drugs of Abuse Tests

Home Use Tests

Laboratory Developed Tests

Precision Medicine

Tests Used In Clinical Care

Warfarin INR Test Meters

Below, you would find a sortable and searchable table that lists all active indications.

A *companion diagnostic device* can be *in vitro* diagnostic (IVD) device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

The use of an IVD companion diagnostic device is stipulated in the instructions for use in the labeling of the diagnostic device, either including a specific therapeutic product(s) or, if approved for oncology products, a specific group of oncology therapeutic products (for information, see the guidance for industry Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products). In addition, the use of an IVD companion diagnostic device is stipulated in the labeling of the therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

Some devices have indication for a specific group of oncology therapeutic (group labeling). Their detailed information can be found in a second table below the main one.

For a list of all FDA cleared or approved nucleic acid based tests, see Nucleic Acid Based Tests.

Please submit any questions to DICE@fda.hhs.gov.

Download a Printable Version of this Table

Content current as of:
08/21/2023

Regulated Product(s)
Medical Devices

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

Search:

Export Excel | Show 10 entries

PMA / 510(k) / 513(f)(2) / HDE

Total Product Life Cycle Advisory Program (TAP)

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Total Product Life Cycle Advisory Program (TAP)

UPDATE – July 31, 2023: The FDA is announcing that beginning October 1, 2023, the Total Product Life Cycle (TPLC) Advisory Program (TAP) Pilot will expand to include the Office of Neurological and Physical Medicine Devices (OHT5).

As of July 31, 2023, the FDA has enrolled five (5) devices in the TAP Pilot. The FDA is still accepting requests for FY 2023 for devices in the Office of Health Technology 2 (OHT2): Office of Cardiovascular Devices.

Content current as of:
07/31/2023

Regulated Product(s)
Medical Devices
Radiation-Emitting Products

The FDA's Center for Devices and Radiological Health (CDRH) has launched the voluntary Total Product Life Cycle (TPLC) Advisory Program (TAP) Pilot. TAP is intended to help ensure that U.S. patients have access to high-quality, safe, effective, and innovative medical devices first in the world for years to come by promoting early, frequent, and strategic communications between the FDA and medical device sponsors.

The TAP Pilot is one of the commitments between the FDA and industry as part of the MDUFA V reauthorization. For more information, see the MDUFA V commitment letter, MDUFA Performance Goals And Procedures, Fiscal Years 2023 Through 2027.

On this page:

Goals of the TAP Pilot

The TAP Pilot is intended to demonstrate the feasibility and benefits of process improvements to the FDA's early interactions with participants and stakeholders that support the vision for TAP. Through the TAP Pilot, the FDA will provide the following types of strategic engagement for innovative devices of public health importance:

Goals of the TAP Pilot

The TAP Pilot is intended to demonstrate the feasibility and benefits of process improvements to the FDA's early interactions with participants and stakeholders that support the vision for TAP. Through the TAP Pilot, the FDA will provide the following types of strategic engagement for innovative devices of public health importance:

- Improving participants' experiences with the FDA by providing for more timely premarket interactions;
- Enhancing the experience of all participants throughout the device development and review process, including the FDA's staff;
- Facilitating improved strategic decision-making during device development, including earlier identification, assessment, and mitigation of device development risk;
- Facilitating regular, solutions-focused engagement between the FDA 's review teams, participants, and other stakeholders, such as patients, providers, and payers, beginning early in device development; and
- Collaborating to better align expectations regarding evidence generation, improve submission quality, and improve the efficiency of the premarket review process.

LEGISLATIVE & FEDERAL UPDATES

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, Mail Stop C2-21-16
Baltimore, Maryland 21244-1850

Center for Clinical Standards and Quality/Quality, Safety & Oversight Group

Ref: QSO-23-15-CLIA

DATE: May 11, 2023

TO: State Survey Agency Directors

FROM: Director, Quality, Safety & Oversight Group (QSOG)

SUBJECT: Clinical Laboratory Improvement Amendments of 1988 (CLIA) Post-Public Health Emergency (PHE) Guidance

Memorandum Summary

- **CMS only has authority to require reporting of SARS-CoV-2 test results until the end of the Federal PHE declaration. As a result, the CLIA requirement for laboratories to report SARS-CoV-2 test results will expire with the termination of the PHE.**
- **CMS is clarifying the post-PHE status of the temporary exercise of enforcement discretion and other flexibilities CMS utilized during the COVID-19 PHE.**

Background

However, when slides are reviewed remotely, a microscope and other laboratory equipment is necessary to perform the testing. The necessity of such equipment is a hallmark of a separate laboratory and, without heightened oversight, increases the potential for inaccurate laboratory results. In addition, physically transferring slides from one site to another constitutes a referral to another laboratory and involves increased risk of error. Therefore, after the PHE has terminated, CMS will not continue to exercise its enforcement discretion for the review of physical slides.

Laboratories that choose to allow staff to remotely review digital laboratory data, digital results and digital images may do so only if the following criteria are met:

- The primary, home site, laboratory has a current, unrevoked or unsuspended certificate of waiver, registration certificate, certificate of compliance, certificate for PPM procedures, or certificate of accreditation issued by HHS applicable to the category of examinations or procedures performed by the laboratory (42 C.F.R. § 493.3(a)(1))
- The primary laboratory complies with other applicable Federal laws, including HIPAA.
- The laboratory director of the primary site CLIA number is responsible for all testing performed under its CLIA certificate, including testing and reporting performed remotely.
- Survey findings will be cited under the primary laboratory's CLIA certificate. Enforcement actions, if taken, will affect the primary laboratory's CLIA certificate.
- The primary laboratory's test reports must indicate the remote site location where the testing is performed. The laboratory may use a coding system rather than the remote site address, e.g., personnel residence, on the final report. This coding system must be available upon request.
- The primary laboratory must be certified in the specialties and/or subspecialties of the work performed at the remote site.
- The primary laboratory must provide CMS a list of all staff working remotely, upon request.
- The primary location is responsible for retaining all documentation, including testing performed by staff working remotely.
- The individual performing remote review must be on the primary laboratory's Form CMS-209, Laboratory Personnel Report (CLIA).

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examine slides away from the primary location.

Pathologists that currently hold a CLIA certificate are exempt from this enforcement discretion. The pathology community has expressed their desire to make this enforcement discretion a permanent provision after the end of the PHE for COVID–19.

c. Clinical Cytogenetics

We require any testing facility that meets the CLIA regulatory definition of

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Remote work

Separate pptx presentation
Outlining background
Providing specifics
Comments (need input)

Federal register: includes specific set of questions

Comment?

HHS OIG Releases Adverse Events Toolkits

By **Thomas Sullivan** — Last Updated **Jul 23, 2023**

HHS-OIG

Share

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The United States Department of Health and Human Services Office of Inspector General (HHS OIG) recently released Adverse Events Toolkits: Medical Record Review Methodology and Clinical Guidance for Identifying Harm. HHS OIG released these two toolkits to help the health care community, government agencies, and researchers to identify and measure adverse events in hospitals or other inpatient settings. Adverse events are patient harm events that happen as a result of medical care (or lack of care), not by underlying disease. The toolkits were created based on OIG expertise that was acquired through seven medical record reviews over the course of 15 years.

U.S. Department of Health and Human Services
Office of Inspector General

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Copies can also be obtained by contacting the Office of Public Affairs.

Adverse Events Toolkits: Medical Record Review Methodology and Clinical Guidance for Identifying Patient Harm

Toolkit: Medical Record Review Methodology
07-06-2023 | OEI-06-21-00030 | Complete Toolkit

Toolkit: Clinical Guidance for Identifying Harm
07-06-2023 | OEI-06-21-00031 | Complete Toolkit

What are the Adverse Events (AE) Toolkits?

The AE toolkits are technical resources to assist the health care community, government agencies, and researchers in identifying and measuring adverse events in hospitals or other inpatient settings. They are based on the expertise the Office of Inspector General (OIG) acquired conducting seven medical record reviews over the past 15 years to identify and categorize adverse events. Adverse events are patient harm events that occur due to medical care or lack of care and are not caused by underlying disease.

Why did OIG create the AE Toolkits?

Protecting patients from harm is a goal shared by OIG and the health care community. We created the

EU-IVDR

European Parliament

Artificial intelligence in healthcare

Applications, risks, and ethical and societal impacts

STUDY

Panel for the Future of Science and Technology

EPRS | European Parliamentary Research Service

Scientific Foresight Unit (STOA)

PE 729.512 – June 2022

EN

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

Draft

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

List of EU MDR/IVDR Harmonized Standards & Common Specifications

February 7, 2023

Page Last Updated: 6 July 2023

Below are lists of the European MDR / IVDR Harmonised Standards and Common Specifications.

The source links are provided in each section. Further, Casus updates this page to include

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

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MDIC Updates

https://mdic.org/

Join us at MXR2023!

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

Click here for registration and poster submissions

Contact MXR@mdic.org for Exhibition/Sponsorship opportunities

Early Bird Registration ends: August 31, 2023

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MXR Highlighted Speakers

Join us at APF!

The APF theme is Insight. Innovation. Impact. This once-a-year event will bring together industry experts, patient advocates, regulators, and other community innovators to transform the future of medical technology and diagnostics. Topics to be discussed include health equity, cybersecurity, real-world evidence, and more.

Click here to register

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MEDICAL DEVICE INNOVATION CONSORTIUM
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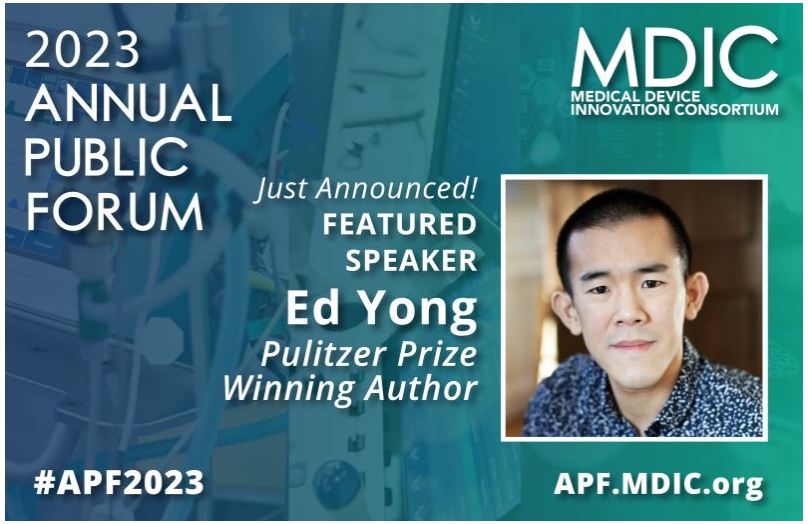
APF 2023 Highlighted Speakers



Learn How to Apply for $300,000 USD in Funding for Your Advanced Manufacturing Project!

MDIC recently demonstrated how to submit a successful application for the chance to earn $300,000 USD and project support to manufacture an innovative medical device through the Advanced Manufacturing Clearing House initiative.

Experts Steve Zera, Senior Program Manager, AMCH and Prakash Patwardhan, Program Director, CFQ Advanced Manufacturing, illustrated the application process including explaining the submission criteria and eligibility requirements.

Do you have an innovative idea and want to be eligible for funding? If so, view the video below for instructions and insight into completing the application. If you're ready, select the application button and get started. Good luck!

View Video

Start Application

Advanced Manufacturing Clearing House (AMCH)

MDIC's AMCH has funding for you to apply for!
To learn more, click here

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Professional Societies

CAP TODAY
Pathology • Laboratory Medicine • Laboratory Management

Lab leaders on moving markets and tipping points

in 2023 Issues, ARTICLES, July 2023

Create PDF

July 2023—*Digital pathology, the pathology workforce, and the clinical demand for subspecialty expertise were some of what Compass Group lab leaders took on in their June 6 conversation, with* CAP TODAY *publisher Bob McGonnagle leading the way. And Stan Schofield, VP and managing principal of the Compass Group, painted a picture of the precarious situation clinical labs are in: "Everyone I talk to says capital equipment is being cut, and staffing costs are increasing dramatically if you want to retain staff. Cost base is going up, reimbursement pressures will continue, and there is no margin left."*

The Compass Group is an organization of not-for-profit IDN system laboratory leaders who collaborate to identify and share best practices and strategies. Here is what they shared last month.

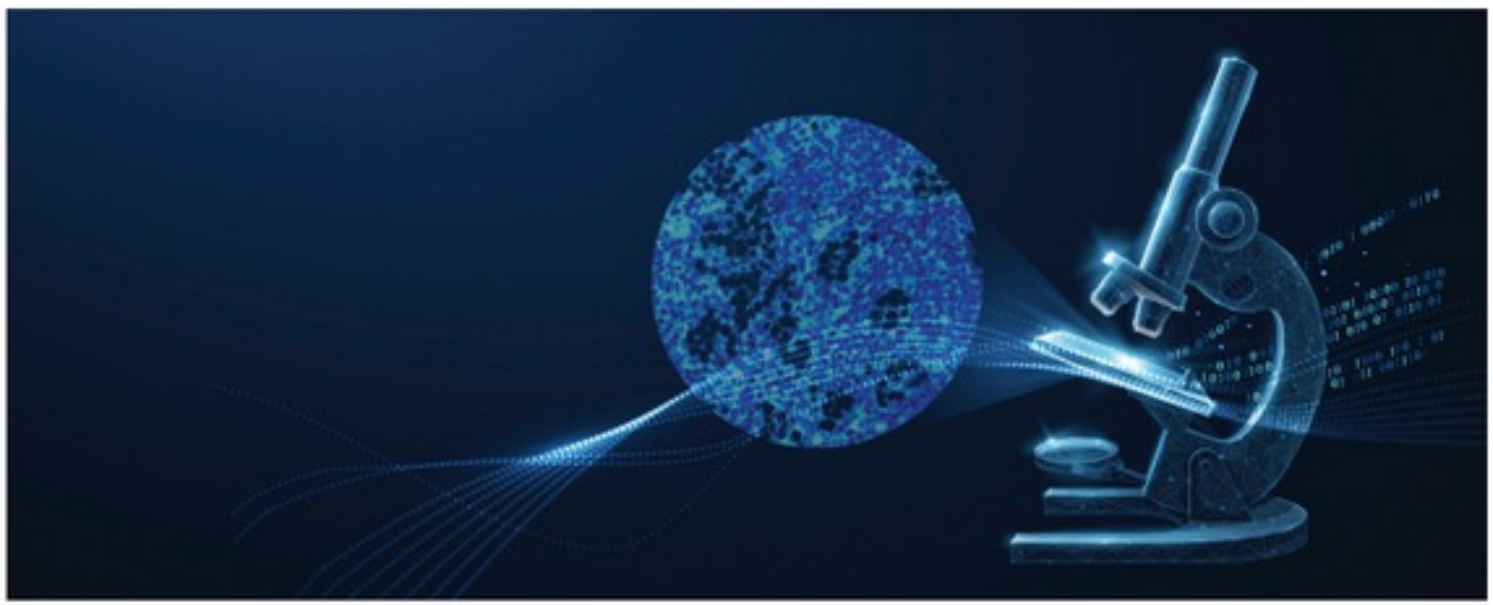
At the Pathology Informatics Summit in May, Alverno CEO Sam Terese gave an excellent presentation on Alverno Laboratories' decision to go completely digital. Wally Henricks, where is digital pathology today at the Cleveland Clinic?

Walter Henricks, MD, vice chair, Pathology and Laboratory Medicine Institute, and laboratory director, Cleveland Clinic: We use digital pathology for subspecialty case review conferences

COLLEGE of AMERICAN PATHOLOGISTS

Laboratory Quality Solutions

The Future of Cancer Data: Unlocking Insights With Pathology Reporting



We've just begun the journey to understanding the power of pathology data.

Explore and extend the use of pathology data generated from synoptic reporting to improve patient care.

This one-day summit, taking place before CAP23, will gather thought leaders in the field to share their experiences, best practices, and novel uses of pathology data for research, public health, population science, and quality improvement.

- Explore opportunities to shape the future of pathology data use.
- Identify new frontiers that will be shaped by the use of pathology data.
- Discover how quality improvement programs benefit from standardized use of synoptic reporting within and across laboratories.
- Discuss how public health initiatives benefit from the use of pathology reporting to add dimension to those efforts.

FRIDAY, OCTOBER 6 | 11:00 AM – 4:30 PM
HYATT REGENCY CHICAGO
$50 registration
CME/CE Available

Learn more.
#PathData

DIGITAL PATHOLOGY
DPA
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ABOUT MEMBERSHIP COLLABORATE PATHOLOGY VISIONS

PODCAST PUBLICATIONS EVENTS

WHY ATTEND PV?

CME & CE

TRAVEL AWARD RECIP

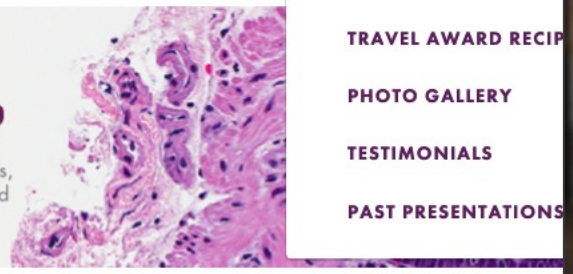
PHOTO GALLERY

TESTIMONIALS

PAST PRESENTATIONS

WHAT IS THE DIGITAL PATHOLOGY ASSOCIATION?

The DPA is a nonprofit organization comprised of pathologists, scientists, technologists and industry representatives dedicated to advancing the field of digital pathology.



PATHOLOGY VISIONS

SAVE THE DATE OCTOBER 29-31

HYATT REGENCY ORLANDO | ORLANDO, FL

#PathVisions23

NEWS

AMA Announces Codes

AMA Addition of Digital Pathology

Webinar: Can AI Regulatory Scien

Digital Pathology Association
6,506 followers
1w •

We're getting all checked in and kicking off #PathVisions22. It's so good to see everyone again!

PATHOLOGY VISIONS 23 | IGNITING DIGITAL PATHOLOGY TRANSFORMATION

OCT 29-31 | HYATT REGENCY | ORLANDO, FL

SCHEDULE OF EVENTS

Subject to change (all times Eastern)

Name badges required for entry to all conference programs, including the pre-conference workshops.

Sunday, October 29

8:00 AM–4:00 PM	Exhibitor Registration + Installation
10:30 AM–7:00 PM	Attendee Registration
11:00 AM–5:00 PM	Vendor Preconference Workshops
5:00–7:00 PM	Opening Reception
7:00–8:00 PM	Aiforia Dinner Workshop

Monday, October 30

7:00 AM–7:00 PM	Conference Registration
7:30–8:30 AM	Roche Breakfast Workshop
8:30–9:00 AM	Refreshment Break & Visit with Exhibitors
9:00–9:30 AM	**Welcome & Opening Remarks** Liron Pantanowitz, MD, PhD, UPMC; DPA President
9:30–9:45 AM	**DPA Foundation Remarks** Michael Rivers, Roche; DPAF President
9:45–10:45 AM	**KEYNOTE ADDRESS** Reflections of a Clinician-Data Scientist: Successes, Disappointments, and Future Directions of Artificial Intelligence in Healthcare | Anthony Chang, MD, MBA, MPH, MS, AIMed
10:45–11:15 AM	Large Language Models (LLM) | Rama Gullapalli, MD, PhD, University of New Mexico and Ehsan Ullah, MBBS, MPhil, PhD, Health New Zealand, Auckland
11:15–11:45 AM	The Cost of Digital Pathology: A Dynamic Customizable Cost Calculator for Informed Decision-making | Orly Ardon, PhD, MBA; Memorial Sloan Kettering Cancer Center
11:45 AM–12:45 PM	Lunch & Visit with Exhibitors

2023 DPA WEBINAR

Building Bridges Between Bytes and Biopsies: Resident Pathologists Discuss the Potential of Digital Pathology and AI

Tuesday, September 12, 2023
11 AM - 12 PM ET

REGISTER NOW

Member Rate: Complimentary!
Non-Member Rate: $100 (Individual membership is $100 & FREE for trainees!)

Join us and hear from pathology trainees from different institutions as they share their experiences and challenges with digital pathology and artificial intelligence along with their hopes for the future.

Panel:

Peter Louis
Rutgers New Jersey Medical School

Sean Niu, MD, PhD
Wake Forest University

Elisabet Pujadas, MD, PhD
Memorial Sloan Kettering Cancer Center

Mengxue Zhang, MD, PhD
University of Chicago

Moderator:

Kristina Doytcheva
Pathology Fellow
University of Chicago

Discussion topic (Esther Abels)

- DPA Pharma Taskforce
- Aims
- Vision
- Discussion

ctDNA - Genomics

HHS OIG Releases Adverse Events Toolkits

By **Thomas Sullivan** — Last Updated **Jul 23, 2023**

HHS-OIG

Share

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U.S. Department of Health and Human Services
Office of Inspector General

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Adverse Events Toolkits: Medical Record Review Methodology and Clinical Guidance for Identifying Patient Harm

Toolkit: Medical Record Review Methodology
07-06-2023 | OEI-06-21-00030 | Complete Toolkit

Toolkit: Clinical Guidance for Identifying Harm
07-06-2023 | OEI-06-21-00031 | Complete Toolkit

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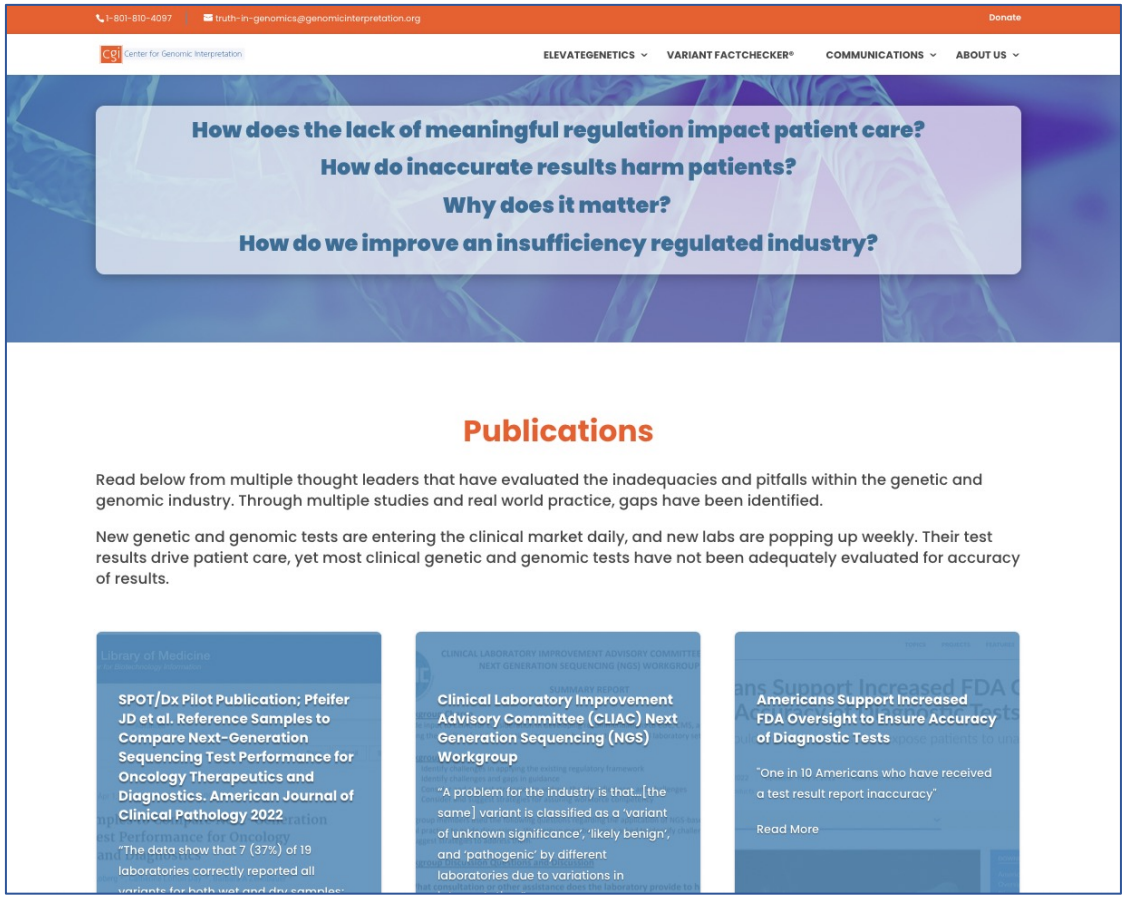
Why did OIG create the AE Toolkits?

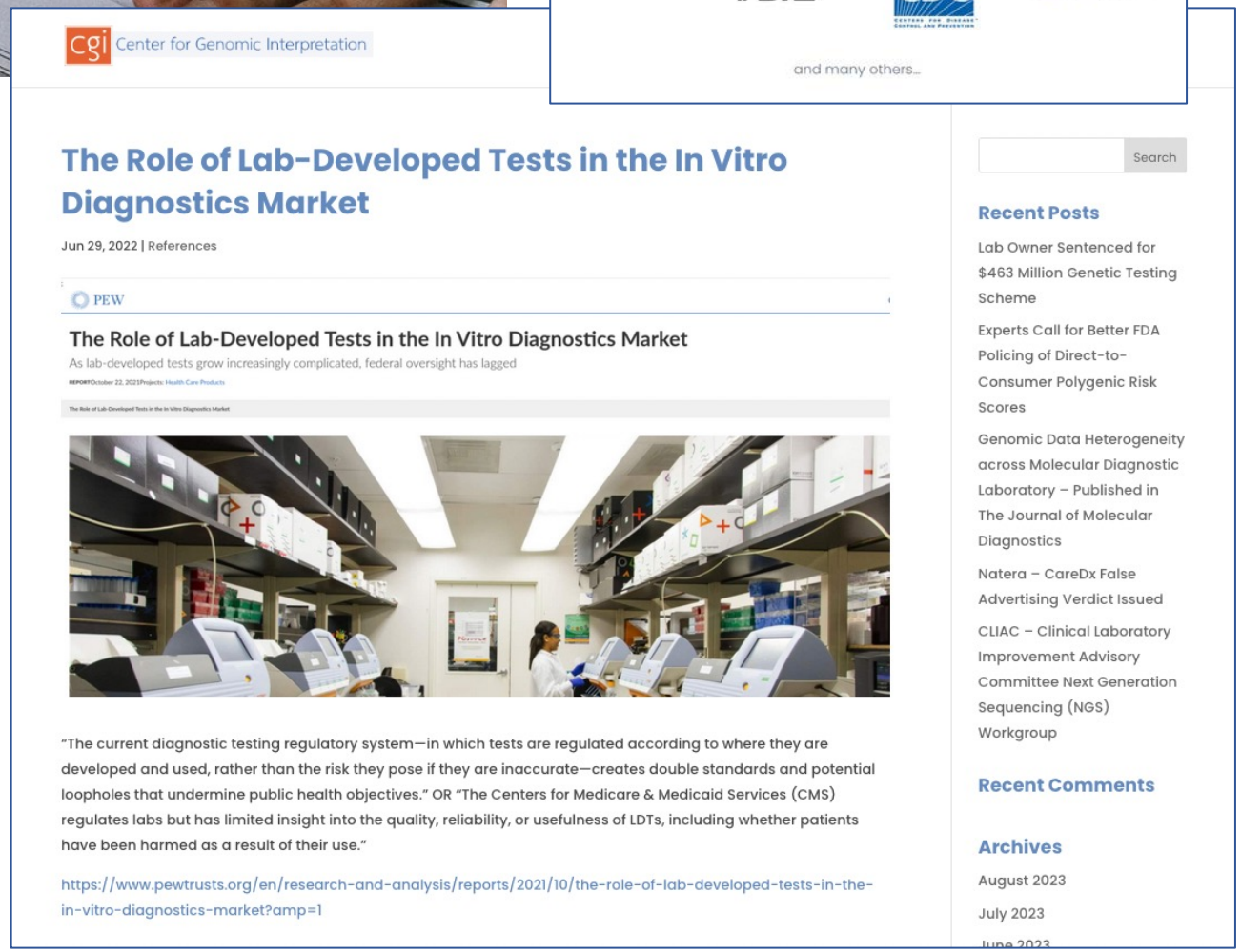
Protecting patients from harm is a goal shared by OIG and the health care community. We created the

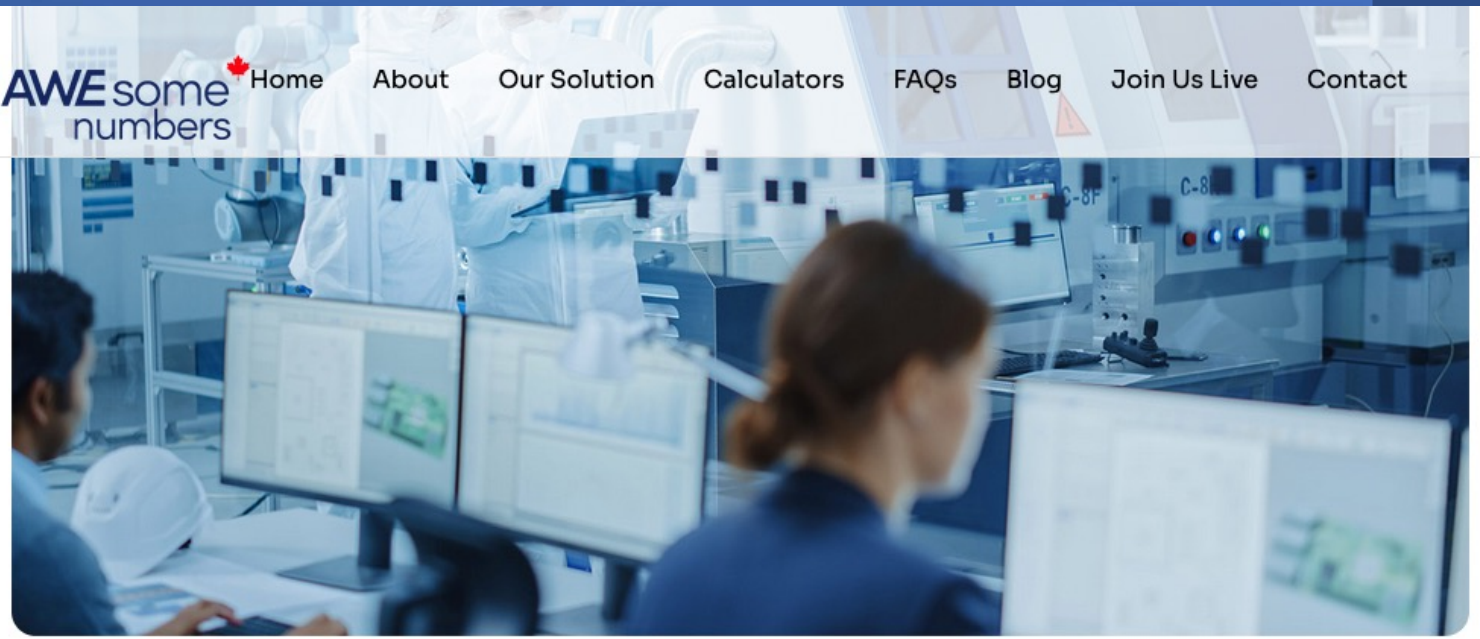
You're in good company

Bristol-Myers Squibb · US Oncology · NHCAA · World Economic Forum · Utah Department of Health Cancer Genomics Program · Optum · The American Society of Breast Surgeons · FAM 40th Anniversary · Ascension · FDA · CDC · CMS.gov

and many others...







AWESOME NUMBERS | DATA DRIVEN | PATIENT CARE | PERFORMANCE | QUALITATIVE - QUANTITATIVE

Labs Can't Eliminate Lab Error, But They Can Control It

Zoe Brooks • May 30, 2023

Some degree of error in the analytical phase of medical laboratory testing is unavoidable; this error will impact all samples tested on each specific instrument.

In the analytical phase of medical laboratory testing, patient samples in batches of one to 1,000+ are tested on each analytical instrument along with typically two quality control (QC) samples. Patient and QC samples are mixed with chemical **reagents** to produce a measurable result that is calculated by the instrument. **Calibrators**, on the other hand, are commercial samples with known amounts of a substance. Think of calibrators like a reference point or a ruler that

unknown genome

The Unknome | Ranked clusters | Cluster search | Settings | LMB Home

The Unknome project

The human genome encodes ~20,000 proteins, many still uncharacterised. Scientific and social factors have resulted in a focus on well-studied proteins, leading to a concern that poorly understood genes are unjustifiably neglected. To address this, we have developed an "Unknome database" that ranks proteins based on how little is known about them.

The database is intended to aid the selection poorly characterised proteins from humans or model organisms so that they can be targeted for investigation. We welcome feedback! Please email Tim Stevens tstevens@mrc-lmb.cam.ac.uk

Citation and Contributors

The Unknome database is described in this publication, along with our application of it to investigate in Drosophila a set of poorly understood proteins:

Functional unknomics: Systematic screening of conserved genes of unknown function
Joao Rocha, Satish Arcot Jayaram, Tim J Stevens, Nadine Muschalik, Rajen D Shah, Sahar Emran, Cristina Robles, Matthew Freeman, Sean Munro
PLoS Biol. 2023 Aug; 21(8): e3002222 PMID: 37552676

Technical details

The overall principle of the unknome database is to assign a knownness score to proteins. Each protein is placed in a cluster of orthologues based on the Panther database. The knowness score is defined as the largest number of Gene Ontology (GO) terms that has been assigned to a member of that cluster. Because GO annotations vary in confidence and relevance to function, different types of evidence can be assigned a different weight when calculating the score. The list of scored clusters can also be restricted to those containing proteins from humans and/or the main model organisms.

See the Ranked Clusters section for a list of protein clusters ranked by their knowness score with links to further information on the cluster and the proteins it contains.

See Cluster search for information about each cluster showing the GO terms assigned to its members, and how its knowness has changed over time.

Settings shows the weights applied to different types of GO annotation. Our default settings give most weight to manual curation and experimental evidence. We excluded 'Cellular component' as a Domain as it provides limited functional information. It is possible to alter these settings and calculate a custom unknome, but be patient!

The data that goes into the Unknome database and website is derived from:

XiFiN

THE POWER TO DO GOOD

Cracking the Code: Mastering Z-Codes for Molecular and Genetic Tests

JULY 28, 2023

Kyle Fetter
Chief Operating Officer

This blog is part of a series. Read Part 2 here.

I recently had the opportunity to collaborate with Dr. Gabriel Bien-Willner, the Medical Director of Molecular Diagnostic Services (MolDX) and Chief Medical Officer of **Palmetto GBA**, and Valerie Collier, Access

Diversity & Inclusion

Education…

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 3, 2023

AI and Medical Education — A 21st-Century Pandora's Box

Avraham Cooper, M.D., and Adam Rodman, M.D., M.P.H.

ChatGPT (Chat Generative Pre-trained Transformer), OpenAI's chatbot powered by artificial intelligence (AI), has become the fastest-growing Internet application in history.[1] Generative AI, which includes large language models such as GPT, has the ability to produce text resembling that generated by humans and seem-

ways in which this technology could affect the thought structures and practice patterns of medical trainees and physicians for gen-

with the malaise associated with it) were all profoundly influenced by this approach to record keeping.

In the months since its release in the fall of 2022, ChatGPT has shown the potential to be at least as disruptive as the problem-oriented medical record, having passed both licensing and clini-

Commitment Requests Do Not Affect Truth-Telling in Laboratory and Online Experiments

Tobias Cagala, Ulrich Glogowsky, Johannes Rincke, Simeon Schudy*

March 14, 2023

Abstract

Using a standard cheating game, we investigate whether the request to sign a no-cheating declaration affects truth-telling. Our design varies the content of a no-cheating declaration (reference to ethical behavior vs. reference to possible sanctions) and the type of experiment (online vs. offline). Irrespective of the declaration's content, commitment requests do not affect truth-telling, neither in the laboratory nor online. The inefficacy of commitment requests appears robust across different samples and does not depend on psychological measures of reactance.

Keywords: *cheating; lying; truth-telling; compliance; commitment; no-cheating rule; no-cheating declaration; commitment request*

Patient advocacy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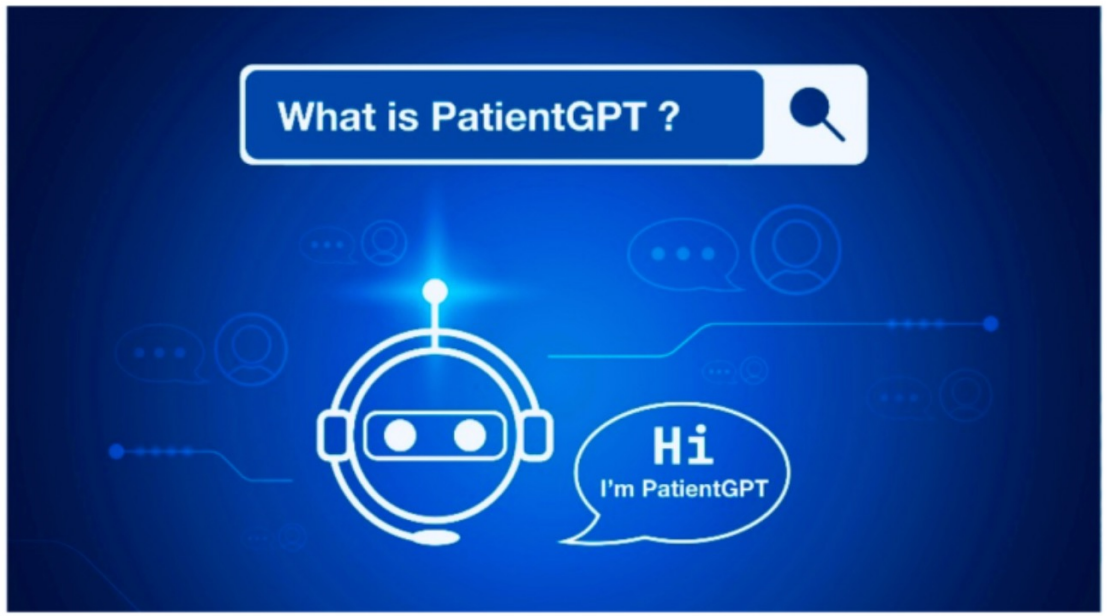

PatientGPT Reduces Months of Pharma Research To Seconds

Margaretta Colangelo

Leading AI Analyst tracking AI milestones in healthcare (80,000+ subscribers)

294 articles

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August 23, 2023

The Consequences and Future of Prior-Authorization Reform

Michael Anne Kyle, Ph.D., R.N., and Zirui Song, M.D., Ph.D.

Professional medical societies and state and federal policymakers have recently unveiled proposals to simplify and modernize prior authorization. Long used by insurers to restrain overuse of and unnecessary spending on drugs and services, prior authorization is frequently time-intensive, requiring phone calls and faxes by clinicians and other staff. Although it has been effective at reducing utilization, associated administrative burdens drive frustration and clinician burnout.

Among recent proposals from the Centers for Medicare and

CMS aims to transition to a fully electronic submission and initial-determination system for prior authorization, with separate user interfaces for patients and clinicians and a payer-to-payer exchange. Under the proposed rule, the patient interface would show application status and coverage determinations. Clinicians could see at the point of care whether a planned treatment requires prior authorization and transfer required details from electronic medical records into the application. The payer would electronically return a determination with

tus can be difficult to ascertain. The rule would allow clinicians to query prior-authorization criteria at the point of care and follow a submission's progress, oblige payers to reveal their reasons for approval or denial of prior-authorization requests, and permit payers to view each other's decisions. This increased transparency could support active legislation related to utilization management, such as step-therapy laws preventing patients on a stable treatment regimen from having to repeat a previous ineffective treatment course after a coverage change.

Review Article

Don't Fear the Artificial Intelligence

A Systematic Review of Machine Learning for Prostate Cancer I in Pathology

Aaryn Frewing; Alexander B. Gibson; Richard Robertson; Paul M. Urie, MD, PhD; Dennis Della Co

• *Context.*—Automated prostate cancer detection using machine learning technology has led to speculation that pathologists will soon be replaced by algorithms. This review covers the development of machine learning algorithms and their reported effectiveness specific to prostate cancer detection and Gleason grading.

Objective.—To examine current algorithms regarding their accuracy and classification abilities. We provide a general explanation of the technology and how it is being used in clinical practice. The challenges to the application of machine learning algorithms in clinical practice are also discussed.

Data Sources.—The literature for this review was identified and collected using a systematic search. Criteria were established prior to the sorting process to effectively direct the selection of studies. A 4-point system was implemented to rank the papers according to their relevancy. For papers accepted as relevant to our citing studies were also reviewed. categorized based on whether they im multi-class classification methods. Data papers that contained accuracy, area un or κ values in the context of prostate c results were visually summarized to pre between classification abilities.

Conclusions.—It is more difficul accuracy metrics for multiclassifica binary tasks. The clinical implementa that can assign a Gleason grade to images (WSIs) remains elusive. Machi ogy is currently not able to replace serve as an important safeguard again

(*Arch Pathol Lab Med.* doi: 10.5858/

The adoption of WSI scanners in clinical practice was of death in men. Pathologists diagnos

Editorial

Immunohistochemistry Should Be Regulated As an Assay

Barbarajean Magnani, PhD, MD; Clive R. Taylor, MD, Dphil

The time has come to regulate clinical immunohistochemistry (IHC) as an assay rather than a stain. Since IHC originally evolved as an extension of special stains in anatomic pathology,[1] regulating IHC as a stain made sense. A lot has changed since then.[1] In this article, we share our perspective explaining why IHC testing should be regulated similarly to immunoassays in clinical pathology. Similar checklist requirements should apply because the same quality assurance (QA) principles and methods are relevant to both. Right now, clinical IHC and clinical immunoassay checklist requirements bear little resemblance to each other. Contemplating such a change has far-reaching implications and will take several years to implement. It also requires the participation of the in vitro diagnostics industry. In the interest of patient care, it is time to start the discussion. The College of American Pathologists (CAP) could take a leading role.

Also see Miller DV. *The Chemistry in Immunohistochemistry.*

Context is important, and context has changed. IHC

Test (Dako, now Agilent) alongside the related drug, Herceptin (trastuzumab; Genenentech, now Roche), heralding the era of companion diagnostics. The need for more rigorous methods of analytic standardization became paramount; namely, the requirements of an assay, not a stain. Numerous additional biomarker-targeted drugs followed. FDA approval of HercepTest established a model for the development of a burgeoning series of IHC-based companion diagnostic tests, none of which meet the demands of a fit-for-purpose assay that is both accurate and quantitative. The necessity to accurately distinguish HER2 0 from HER2 1+ is only the most recent example of the need to achieve substantially higher levels of precision and accuracy than we are currently capable of. Without intervention, there will continue to be an ever-increasing gulf between IHC's current performance capabilities and what is required.

Despite exponential growth in IHC testing, the QA methods are still those of a histology stain. IHC QA has not sufficiently adapted over the decades to fit the many new purposes to which it is applied. To explain what is missing, compare the CAP checklist requirements of clinical IHC assays to clinical immunoassays relating to assay

Henderson et al.
Journal of Pharmaceutical Policy and Practice (2023) 16:84
https://doi.org/10.1186/s40545-023-00590-9

Journal of Pharmaceutical Policy and Practice

RESEARCH Open Access

Delivering the precision oncology paradigm: reduced R&D costs and greater return on investment through a companion diagnostic informed precision oncology medicines approach

Raymond H. Henderson[1,2,3,4*], Declan French[2], Elaine Stewart[2], Dave Smart[3], Adam Idica[5], Sandra Redmond[4], Markus Eckstein[6], Jordan Clark[3], Richard Sullivan[7], Peter Keeling[3] and Mark Lawler[1]

Conclusion

This study puts forward an evidence-informed estimation of the R&D spend associated with bringing an oncology medicine through R&D and clinical trials to market. The intelligence generated in this study indicates that the deployment of a CDx at the earliest stage substantially lowers the cost associated with oncology medicine development, potentially making it available to more patients, while staying within the cost constraints of cancer health systems. We have reached a crucial inflection point, which requires a flexible CDx development framework so that patients can truly benefit from a precision oncology approach, while at the same time ensuring that R&D spend in oncology medicine development overall is affordable to health systems.

Abbreviations

fast track, or priority review), and whether the medicine was first-in-class [11, 12]. Each medicine was assessed for the intention of requiring a CDx or not for clinical delivery. Those that were developed with the intention of deploying a CDx were considered precision oncology medicines, and those where there was no intention to deploy a CDx were considered non-precision oncology medicines. CAR T-cell therapies, radiopharmaceuticals, and hormonal blockers were excluded, to ensure our comparative dataset of med-

RESEARCH

Marie-Caroline Schulte

Evidence-Based Medicine – A Paradigm Ready To Be Challenged?

How Scientific Evidence Shapes Our Understanding And Use Of Medicine

OPEN

J.B. METZLER

Blueprint Labs

Discussion Paper #2023.10

Combining Human Expertise with Artificial Intelligence: Experimental Evidence from Radiology

Nikhil Agarwal
Alex Moehring
Pranav Rajpurkar
Tobias Salz

July 2023

MIT Department of Economics
77 Massachusetts Avenue, Bldg. E53-390
Cambridge, MA 02139

National Bureau of Economic Research
1050 Massachusetts Avenue, 3rd Floor
Cambridge, MA 02138

Are synthetic health data ‘personal data’?

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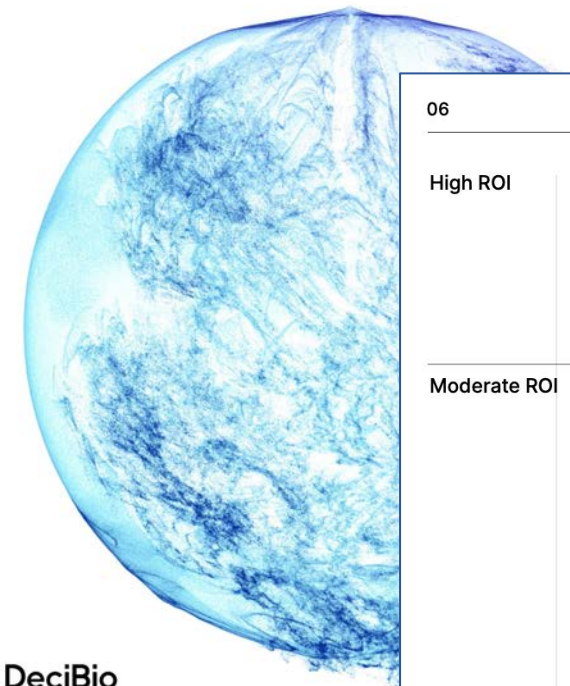
Pharma Investment Trends in Precision Oncology R&D

August 2023



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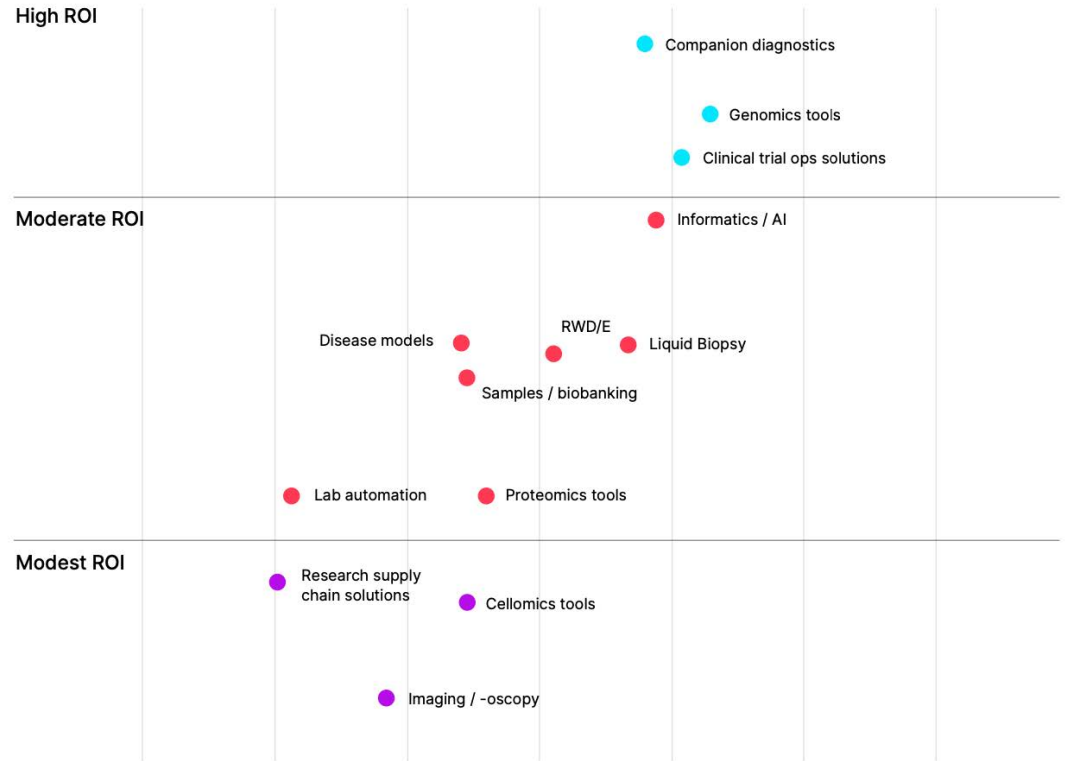

https://doi.org/10.1038/s42256-023-00699-1

Enabling collaborative governance of medical AI

W. Nicholson Price II, Mark Sendak, Suresh Balu & Karandeep Singh

Medical artificial intelligence needs governance to ensure safety and effectiveness, not just centrally (for example, by the US Food and Drug Administration) but also locally to account for differences in care, patients and system performance. Practical collaborative governance will enable health systems to carry out these challenging governance tasks, supported by central regulators.

Artificial intelligence (AI) is rapidly entering healthcare, from sepsis prediction to image analysis to patient management. Some AI systems are developed by venture-backed start-ups, others are homegrown, and many are embedded within electronic health records (EHR) systems. They demand governance: the task of ensuring safety and effectiveness at the time of integration into clinical care and throughout the product lifecycle. AI systems, including broadly deployed systems, have shown substantial quality problems and implementation challenges despite their overall promise[1]. Our team includes leaders at Michigan Medicine and Duke Health with substantial on-the-ground experience developing, implementing and maintaining AI systems used in clinical practice and extensive experience supporting government actors seeking to scale the potential benefits of AI. We argue the inadequacy of an exclusive focus on centralized governance — by, for example, the Food and Drug Administration (FDA), the Office of the National Coordinator for Health Information Technology (ONC), the Centers for Medicare and Medicaid Services (CMS) or even the Federal Trade Commission. Instead, centralized governors must also coordinate and support local governance within healthcare delivery settings with varying resources

clinicians are accountable, and potentially liable, for AI-related delivery of care, quality concerns and potential patient harm[5]. Accordingly, front-line clinicians must be made aware of medical AI's indications for use and understand how and how not to use it, using mechanisms such as the Duke-Health-developed and ACR-promoted 'model facts' label[6].

At the local health system level, governance helps ensure safe and effective use of AI in clinical care through oversight activities including screening, evaluating, integrating and maintaining AI models. At Michigan Medicine and Duke Health, these activities are tackled by teams combining technical, clinical and operational expertise. When health system leaders in either setting identify a priority clinical use case, there may be dozens of relevant, available models. Evaluation must consider many factors, including model performance, likelihood of generalizing to the local setting, transparency and bias, workflow burden and total product ownership cost. Rarely is there one best AI system. For example, within Duke Health, two different hospitals (a 1,000-bed quaternary academic hospital and a 300-bed community hospital) implemented the same medical AI system, Sepsis Watch, with two different workflows. Selected models then need to be tested on tightly controlled local EHR data. Models must be evaluated to determine how well their local performance matches reported performance and, more importantly, whether the model is good enough to be useful. Following this initial evaluation, the model may be ready for integration into a local clinical workflow. After integration, its performance and behaviour (for example, alerting pattern) require ongoing monitoring to detect changes that may negatively affect clinical care, including performance changes arising from differences in patient populations; local sociotechnical factors like workforce composition and care workflow, clinician training and credentialing; and resource availability. Rigorous maintenance requires close collaboration among technical and clinical experts, using skills that differ from those required for current healthcare delivery activities.

Retrospective Cohort Study on the Limitations of Direct-to-Consumer Genetic Screening in Hereditary Breast and Ovarian Cancer

Neelam V. Desai, MD[1]; Elizabeth D. Barrows, MD[2,3]; Sarah M. Nielsen, MS[4]; Kathryn E. Hatchell, PhD[4]; Michael J. Anderson, PhD[4]; Eden V. Haverfield, DPhil[4]; Blanca Herrera, PhD[4]; Edward D. Esplin, MD, PhD[4]; Anneke Lucassen, MD, PhD[5,6]; Nadine M. Tung, MD[7,8]; and Claudine Isaacs, MD[2,3]

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Accepted June 29, 2023
Published August 3, 2023

JCO Precis Oncol 7:e2200695

ABSTRACT

PURPOSE Among cancer predisposition genes, most direct-to-consumer (DTC) genetic tests evaluate three Ashkenazi Jewish (AJ) founder mutations in *BRCA1/2*, which represent a small proportion of pathogenic or likely pathogenic variants (PLPV) in cancer predisposing genes. In this study, we investigate PLPV in *BRCA1/2* and other cancer predisposition genes that are missed by testing only AJ founder *BRCA1/2* mutations.

METHODS Individuals were referred to genetic testing for personal diagnoses of breast and/or ovarian cancer (clinical cohort) or were self-referred (nonindication-based cohort). There were 348,692 participants in the clinical cohort and 7,636 participants in the nonindication-based cohort. Both cohorts were analyzed for *BRCA1/2* AJ founder mutations. Full sequence analysis was done for PLPV in *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, *STK11*, *TP53*, *ATM*, *BARD1*, *BRIP1*, *CHEK2* (truncating variants), *EPCAM*, *MLH1*, *MSH2/6*, *NF1*, *PMS2*, *RAD51C/D*, and 22 other genes.

RESULTS *BRCA1/2* AJ founder mutations accounted for 10.8% and 29.7% of *BRCA1/2* PLPV in the clinical and nonindication-based cohorts, respectively. AJ founder mutations accounted for 89.9% of *BRCA1/2* PLPV in those of full AJ descent, but

nature medicine

Article

https://doi.org/10.1038/s41591-023-02504-3

A visual–language foundation model for pathology image analysis using medical Twitter

Received: 26 March 2023

Accepted: 18 July 2023

Published online: 17 August 2023

Check for updates

Zhi Huang[1,2,4], Federico Bianchi[3,4], Mert Yuksekgonul[3], Thomas J. Montine[2] & James Zou[1,3]

The lack of annotated publicly available medical images is a major barrier for computational research and education innovations. At the same time, many de-identified images and much knowledge are shared by clinicians on public forums such as medical Twitter. Here we harness these crowd platforms to curate OpenPath, a large dataset of 208,414 pathology images paired with natural language descriptions. We demonstrate the value of this resource by developing pathology language–image pretraining (PLIP), a multimodal artificial intelligence with both image and text understanding, which is trained on OpenPath. PLIP achieves state-of-the-art performances for classifying new pathology images across four external datasets: for zero-shot classification, PLIP achieves F1 scores of 0.565–0.832 compared to F1 scores of 0.030–0.481 for previous contrastive language–image pretrained model. Training a simple supervised classifier on top of PLIP

nature medicine

Article

https://doi.org/10.1038/s41591-023-02482-6

Machine learning for genetics-based classification and treatment response prediction in cancer of unknown primary

Received: 6 January 2023

Accepted: 30 June 2023

Published online: 7 August 2023

Check for updates

Intae Moon[1,2], Jaclyn LoPiccolo[3], Sylvan C. Baca[3,4], Lynette M. Sholl[5], Kenneth L. Kehl[2], Michael J. Hassett[2], David Liu[2,3,6], Deborah Schrag[7] & Alexander Gusev[2,6,8]

Cancer of unknown primary (CUP) is a type of cancer that cannot be traced back to its primary site and accounts for 3–5% of all cancers. Established targeted therapies are lacking for CUP, leading to generally poor outcomes. We developed OncoNPC, a machine-learning classifier trained on targeted next-generation sequencing (NGS) data from 36,445 tumors across 22 cancer types from three institutions. Oncology NGS-based primary cancer-type classifier (OncoNPC) achieved a weighted F1 score of 0.942 for high confidence predictions ($\geq$ 0.9) on held-out tumor samples, which made up 65.2% of all the held-out samples. When applied to 971 CUP tumors collected at the Dana-Farber Cancer Institute, OncoNPC predicted primary cancer types with high confidence in 41.2% of the tumors. OncoNPC also identified CUP subgroups with significantly higher polygenic germline risk for the predicted cancer types and with significantly different survival

nature reviews cancer

https://doi.org/10.1038/s41568-023-00602-5

Review article

Check for updates

Cancers make their own luck: theories of cancer origins

Amir Jassim[1], Eric P. Rahrmann[1], Ben D. Simons[2,3] & Richard J. Gilbertson[1,4]

Abstract

Cancer has been a leading cause of death for decades. This dismal statistic has increased efforts to prevent the disease or to detect it early, when treatment is less invasive, relatively inexpensive and more likely to cure. But precisely how tissues are transformed continues to provoke controversy and debate, hindering cancer prevention and early intervention strategies. Various theories of cancer origins have emerged, including the suggestion that it is 'bad luck': the inevitable consequence of random mutations in proliferating stem cells. In this Review, we discuss the principal theories of cancer origins and the relative importance of the factors that underpin them. The body of available evidence suggests that developing and ageing tissues 'walk a tightrope', retaining adequate levels of cell plasticity to generate and maintain tissues while avoiding overstepping into transformation. Rather than viewing cancer as 'bad luck', understanding the complex choreography of cell intrinsic and extrinsic factors that characterize transformation holds promise to discover effective new ways to prevent, detect and stop cancer before it becomes incurable.

Sections

PAYERS

CMS Innovation Center, HHS release new dementia care model

By **Noah Tong** · Jul 31, 2023 10:31am

dementia | Medicare Part B | CMS Innovation Center | Department of Health and Human Services (HHS)

A new dementia care model, called GUIDE, was released jointly by Centers for Medicare & Medicaid Services and the U.S. Department of Health and Human Services July 31. (Khanchit Khirisutchalual/Getty Images)

JAMA Internal Medicine | Special Communication | HEALTH CARE POLICY AND LAW

Authority of Medicare to Limit Coverage of FDA-Approved Products
Legal and Policy Considerations

C. Joseph Ross Daval, JD; Aaron S. Kesselheim, MD, JD, MPH

IMPORTANCE When the US Food and Drug Administration (FDA) approves a drug or medical device on the basis of limited clinical evidence, the Centers for Medicare & Medicaid Services (CMS) must decide whether the therapy is "reasonable and necessary" for coverage among Medicare beneficiaries. However, the legal underpinnings of CMS's authority to shape coverage of FDA-regulated products under Medicare Part B are controversial. To clarify this area, we reviewed relevant legal precedents on CMS's approaches to limit coverage and recent decisions Medicare has issued affecting coverage for FDA-regulated products.

OBSERVATIONS The CMS continues to exercise considerable legal discretion to limit coverage of FDA-authorized products to only uses it determines are reasonable and necessary for patients with Medicare. Courts have upheld this discretion repeatedly, emphasizing the difference between Medicare's coverage criteria and the FDA's review standards. As more new drugs and devices come to market without solid evidence of efficacy on clinical outcomes, or have narrow benefit-risk considerations, CMS may increasingly rely on forms of limited or conditional coverage, including coverage with evidence development (CED), which provides reimbursement only in the context of a clinical trial or registry.

CONCLUSIONS AND RELEVANCE The ability of CMS to condition or limit coverage of FDA-approved products is a commonsense necessity for this crucial taxpayer-funded program. Although courts have thus far deferred to the authority of CMS to make such decisions on the basis of its clear statutory discretion and public health expertise, Congress may want to act to reaffirm statutory language giving CMS sufficient flexibility to craft coverage determinations that reflect the evidence for a product's use.

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Editorial

CME at jamacmelookup.com

Author Affiliations: Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Aaron S. Kesselheim, MD, JD, MPH, Brigham and Women's Hospital, 1620 Tremont St, Ste 3030, Boston, MA 02120 (akesselheim@bwh.harvard.edu).

Medicare, the largest health care payer in the US, covers about 65 million people, most of whom are older than 65 years, for about $829 billion, or 10% of total annual federal government spending.[1] Medicare Parts A and B, which pay for hospital costs and other medical services, are prohibited by law from paying for any medical products or procedures that are not "reasonable and necessary."[2] Historically, the determination of what is reasonable and necessary has been left up to the Centers for Medicare & Medicaid Services (CMS), the agency responsible for administering Medicare.[3]

For a limited number of major coverage decisions, CMS issues a National Coverage Determination (NCD), a statement of policy that supersedes local decision making and determines whether Medicare reimburses for a given product or service nationwide.[4] Depending on determinations by CMS of what coverage is appropriate under the statute, NCDs can require coverage, deny coverage, or place certain conditions on coverage. A fraction of NCDs limit coverage to only the context of approved clinical trials or registries, through a determination of "coverage with evidence development" (CED).[5] In 2022, CMS issued a CED for the class of drugs that includes aducanumab (Aduhelm), which was granted accelerated approval by the FDA based on unclear evidence of efficacy, requiring that covered patients be enrolled in a qualifying randomized trial.[6]

Recently, CMS announced a CED plan for another controversial Alzheimer drug of the same class, lecanemab (Leqembi), which in 1 trial slowed cognitive decline among patients with mild cognitive impairment or early-stage Alzheimer disease to a small degree that some experts consider not clinically meaningful, while presenting risks of brain swelling and bleeding.[7] Like aducanumab, lecanemab was initially granted accelerated approval from the FDA on the basis of a surrogate measure (changes in β-amyloid levels in the brain). Under the proposed plan, now that it has received full approval from the FDA in July 2023, CMS will cover lecanemab in the much broader context of clinicians' providing limited information to a clinical registry at the time of prescribing.

The ability of CMS to shape coverage of FDA-approved products carries substantial policy implications. As more new drugs and devices are approved by the FDA that lack solid evidence of efficacy on clinical outcomes, or have narrow benefit-risk considerations, CMS may increasingly rely on forms of limited or conditional coverage.[8] However, the legal underpinnings of CMS's authority to craft conditions on coverage of medical products under Medicare are controversial. The CED program has drawn scrutiny in the wake

Letters

RESEARCH LETTER

Utilization Management Trends in Medicare Part D Oncology Drugs, 2010-2020

Utilization management—such as prior authorization—is prevalent, and evidence from medical services indicates it disproportionately affects oncology treatments.[1] Orally administered cancer drugs are increasing in number and cost.[2] These products have mandatory coverage in Medicare Part D as a protected class; less is known about utilization management. Utilization management introduces administrative burdens on clinicians and patients to monitor or modify utilization, which can lead to delayed or forgone care.[3] We quantified Medicare Part D beneficiaries' exposure to utilization management for oral oncology drugs.

Supplemental content

Methods | We used 2010-2020 Medicare Part D formulary files to identify plans' use of prior authorization, quantity limits, and step therapy for each unique drug-dose-formulary combination of orally administered oncology drugs, the level at which a prescription would be written. We used the Master Beneficiary Summary Files to calculate midyear enrollment for each formulary and year. We identified oncology drugs using the 2021 Oncology Care Model drug list.[4] The Harvard Medical School Institutional Review Board waived review of this study.

We categorized drugs designated by Medicare as specialty (monthly cost above $600 in 2010-2016 and $670 in 2017-2020[5]) or nonspecialty and brand or generic. For each year, we estimated the enrollment-weighted proportion of drug-dose-formulary combinations subject to utilization management using Stata version 16 (StataCorp). Medicare beneficiaries' total potential exposure to utilization management includes the coverage policy for every drug-dose-formulary combination, weighted by number of enrollees in each plan.

Because noncoverage is a form of utilization management, we also examined coverage of brand specialty drugs when generic substitutes became available.

Results | In 2010, 28 030 290 beneficiaries were enrolled in 333 formularies covering 62 oral oncology drugs (26 specialty brand, 0 specialty generic, 28 nonspecialty brand, and 8 nonspecialty generic) (**Table**). In 2020, 47 337 020 beneficiaries were enrolled in 548 formularies covering 249 oral oncology

For specialty brand drugs, the proportion increased from 72.8% to 95.4% between 2010 and 2020. Specialty generic drugs entered the market in 2016; prior authorization use increased from 91.1% in 2016 to 95.0% in 2020. For nonspecialty brand drugs, the proportion of drug-dose-formulary combinations requiring prior authorization increased from 15.9% to 78.2% and for nonspecialty generic drugs from 1.0% to 8.0% between 2010 and 2020.

The proportion of drug-dose-formulary combinations for oral oncology drugs requiring quantity limits for specialty brand drugs increased from 31.4% to 62.5% between 2010 and 2020 (Figure, B). For specialty generic drugs, the proportion increased from 32.7% to 77.8% between 2016 and 2020. For nonspecialty brand drugs, the proportion with quantity limits increased from 11.8% to 47.3% and for nonspecialty generic drugs from 9.7% to 18.8% between 2010 and 2020.

Step therapy was rare in all oral oncology drug categories, and less than 1% of drug-dose-formulary combinations required step therapy for any of these drugs from 2013 onward (Figure, C). Coverage of specialty brand drugs declined once generic alternatives were available (Table).

Discussion | Utilization management for Medicare Part D oral oncology drugs increased between 2010 and 2020. Prior authorization was the most prevalent strategy for specialty brand and generic drugs, as well as nonspecialty brand drugs. Quantity limit use increased and was the most common strategy for nonspecialty generic drugs. Step therapy use was rare, perhaps because oral oncology drugs have few substitutes. Study limitations included a focus on Medicare and oral oncology drugs; future work could expand this scope.

Utilization management is entwined with spending[2]: it was most prevalent among specialty drugs—the most costly and least affordable to patients.[6] Utilization management may be appropriate for some oncology drugs, such as those approved with provisional evidence of efficacy. It is less clear why prior authorization is required for highly effective, first-line drugs such as generic imatinib. Policies aimed at reforming utilization management should prioritize reducing barriers to high-value treatment.

Michael Anne Kyle, PhD, RN
Stacie B. Dusetzina, PhD
Nancy L. Keating, MD, MPH

Commentary

Translational Research: Empowering the Role of Pathologists and Cytopathologists

Heba W. Z. Khella, MD, PhD[1,2]; and George M. Yousef, MD, PhD, FRCPC[1,3]

Research activity is in the core essence of pathology. Advancing our understanding of disease pathogenesis translates into better patient care. Because of their unique position, laboratorians are the best to accurately identify, annotate, and classify research specimens. They also are essential for the accurate interpretation of genomic testing. Currently, cytopathologists are moving to the center of patient care through active communication with clinicians and patients. There are certain research areas in which cytopathologists can be pioneers, such as image analysis, morphology research, and genotype-phenotype association studies integrating morphologic and molecular features. Health service utilization research is another domain in which cytopathologists can excel. Successful research is a journey that necessitates multiple steps. It also involves building expertise in how to overcome obstacles and handle challenges. ***Cancer Cytopathol* 2018;126:831-838.** *© 2018 American Cancer Society.*

KEY WORDS: cytopathology, funding, molecular diagnostics, pathology, precision medicine, research, translational research

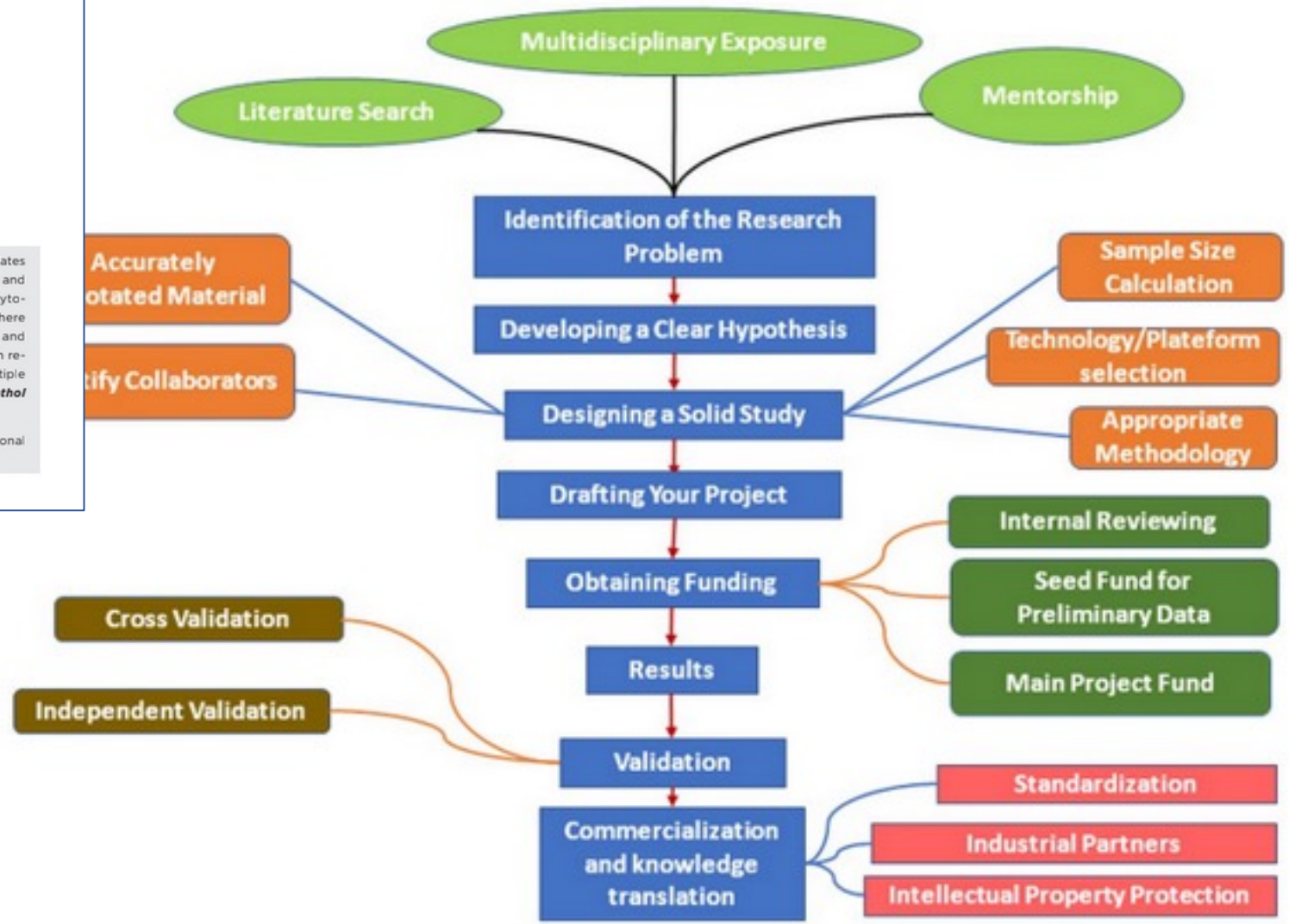

Figure 1. This schematic outlines the basic steps toward a successful research project. It starts with the identification of a clinically relevant research problem and the development of a clear hypothesis. The study design is also of prime importance. Obtaining funding is crucial for continuing successful research. Validation of the results is an essential step toward knowledge translation.

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BRIEF REPORT

RAD51 as a biomarker for homologous recombination deficiency in high-grade serous ovarian carcinoma: robustness and interobserver variability of the RAD51 test

Claire JH Kramer[1], Alba Llop-Guevara[2], Elisa Yaniz-Galende[3], Benedetta Pellegrino[4,5], Natalja T ter Haar[1], Andrea Herencia-Ropero[2], Nicoletta Campanini[4,5], Antonino Musolino[4,5], Tjalling Bosse[1], Alexandra Leary[3], Violeta Serra[2] and Maaike PG Vreeswijk[6*]

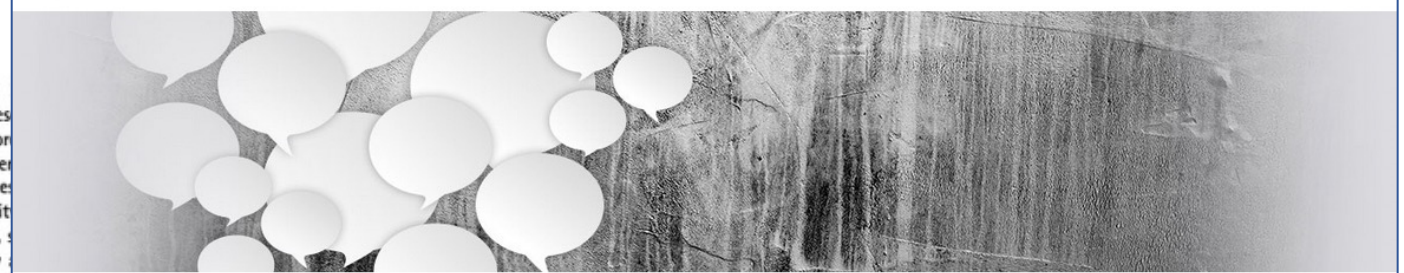
[1]*Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands*
[2]*Experimental Therapeutics Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[3]*Department of Oncology, Institute Gustave Roussy, Villejuif, France*
[4]*Department of Medicine and Surgery, University of Parma, Parma, Italy*
[5]*Medical Oncology and Breast Unit, University Hospital of Parma, Parma, Italy*
[6]*Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands*

**Correspondence to: Maaike PG Vreeswijk, Department of Human Genetics, Leiden University Medical Center, Leiden, Th*
E-mail: m.p.g.vreeswijk@lumc.nl

Abstract

The RAD51 test is emerging as a promising biomarker for the assessment of functional recombination deficiency (HRD). Yet, the robustness and reproducibility of the immunofluores RAD51 test, in different academic laboratories, have not been systematically investigated. Therefor the performance of the RAD51 assay in formalin-fixed paraffin-embedded (FFPE) high-grade se carcinoma (HGSOC) samples in four European laboratories. Here, we confirm that subtle differences procedures result in low variability of RAD51 and γH2AX scores. However, substantial variabilit scoring was observed in some samples, likely due to complicating technical and biological features, RAD51 signal-to-noise ratio and RAD51 heterogeneity. These results support the need to identify additional quality control steps and/or automating image analysis. Altogether, resolving technical i be a priority, as identifying tumours with functional HRD is urgently needed to guide the individual HGSOC patients. Follow-up studies are needed to define the key tissue quality requirements to as RAD51 in FFPE tumour samples, as this test could help in guiding the individual treatment of HGSOC

Keywords: analytical validation; biomarker; high-hrade serous ovarian carcinoma; homologous recombination d variability; RAD51 test



Novel 64-Protein Signature Predicts Treatment Response in High-Grade Serous Ovarian Cancer

Friday, August 4, 2023

In an effort recently published in *Cell*, CPTAC researchers aimed to identify patients with high-grade serous ovarian cancer (HGSOC) who may not respond to standard therapies. At present, there is no way to distinguish refractory from sensitive HGSOCs prior to therapy. As a result, patients with treatment-refractory disease at diagnosis (10-20%) often undergo standard-of-care platinum chemotherapy without benefit. Identifying these patients at diagnosis would limit toxicities and save critical time--study leader Amanda Paulovich, MD, PhD wrote, "If we can identify patients who are unlikely to respond

Data Portal
Antibody Portal
Assay Portal

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INVITED REVIEW

Pitfalls in machine learning-based assessment of tumor-infiltrating lymphocytes in breast cancer: a report of the international immuno-oncology biomarker working group

Jeppe Thagaard[1,2†], Glenn Broeckx[3,4†], David B Page[5], Chowdhury Arif Jahangir[6], Sara Verbandt[7], Zuzana Kos[8], Rajarsi Gupta[9], Reena Khiroya[10], Khalid Abduljabbar[11], Gabriela Acosta Haab[12], Balazs Acs[13,14], Guray Akturk[15], Jonas S Almeida[16], Isabel Alvarado-Cabrero[17], Mohamed Amgad[18], Farid Azmoudeh-Ardalan[19], Sunil Badve[20], Nurkhairul Bariyah Baharun[21], Eva Balslev[22], Enrique R Bellolio[23], Vydehi Bheemaraju[24], Kim RM Blenman[25,26], Luciana Botinelly Mendonça Fujimoto[27], Najat Bouchmaa[28], Octavio Burgues[29], Alexandros Chardas[30], Maggie Chon U Cheang[31], Francesco Ciompi[32], Lee AD Cooper[33], An Coosemans[34], Germán Corredor[35], Anders B Dahl[1], Flavio Luis Dantas Portela[36], Frederik Deman[3], Sandra Demaria[37,38], Johan Doré Hansen[2], Sarah N Dudgeon[39], Thomas Ebstrup[2], Mahmoud Elghazawy[40,41], Claudio Fernandez-Martín[42], Stephen B Fox[43], William M Gallagher[6], Jennifer M Giltnane[44], Sacha Gnjatic[45], Paula I Gonzalez-Ericsson[46], Anita Grigoriadis[47,48], Niels Halama[49], Matthew G Hanna[50], Aparna Harbhajanka[51], Steven N Hart[52], Johan Hartman[13,14], Søren Hauberg[1], Stephen Hewitt[53], Akira I Hida[54], Hugo M Horlings[55], Zaheed Husain[56], Evangelos Hytopoulos[57], Sheeba Irshad[58], Emiel AM Janssen[59,60], Mohamed Kahila[61], Tatsuki R Kataoka[62], Kosuke Kawaguchi[63], Durga Kharidehal[24], Andrey I Khramtsov[64], Umay Kiraz[59,60], Pawan Kirtani[65], Liudmila L Kodach[66], Konstanty Korski[67], Anikó Kovács[68,69], Anne-Vibeke Laenkholm[70,71], Corinna Lang-Schwarz[72], Denis Larsimont[73], Jochen K Lennerz[74], Marvin Lerousseau[75,76,77], Xiaoxian Li[78], Amy Ly[79], Anant Madabhushi[80], Sai K Maley[81], Vidya Manur Narasimhamurthy[82], Douglas K Marks[83], Elizabeth S McDonald[84], Ravi Mehrotra[85,86], Stefan Michiels[87], Fayyaz ul Amir Afsar Minhas[88], Shachi Mittal[89], David A Moore[90], Shamim Mushtaq[91], Hussain Nighat[92], Thomas Papathomas[93,94], Frederique Penault-Llorca[95], Rashindrie D Perera[96,97], Christopher J Pinard[98,99,100,101], Juan Carlos Pinto-Cardenas[102], Giancarlo Pruneri[103,104], Lajos Pusztai[105,106], Arman Rahman[6], Nasir Mahmood Rajpoot[107], Bernardo Leon Rapoport[108,109], Tilman T Rau[110], Jorge S Reis-Filho[111], Joana M Ribeiro[112], David Rimm[113,114], Anne Roslind[22], Anne Vincent-Salomon[115], Manuel Salto-Tellez[116,117], Joel Saltz[9], Shahin Sayed[118], Ely Scott[119], Kalliopi P Siziopikou[120], Christos Sotiriou[121,122], Albrecht Stenzinger[123,124], Maher A Sughayer[125], Daniel Sur[126], Susan Fineberg[127,128], Fraser Symmans[129], Sunao Tanaka[130], Timothy Taxter[131], Sabine Tejpar[7], Jonas Teuwen[132], E Aubrey Thompson[133], Trine Tramm[134,135], William T Tran[136], Jeroen van der Laak[137], Paul J van Diest[138,139], Gregory E Verghese[47,48], Giuseppe Viale[140,141], Michael Vieth[72], Noorul Wahab[142], Thomas Walter[75,76,77], Yannick Waumans[143], Hannah Y Wen[50], Wentao Yang[144], Yinyin Yuan[145], Reena Md Zin[146], Sylvia Adams[83,147], John Bartlett[148], Sibylle Loibl[149], Carsten Denkert[150], Peter Savas[97,151], Sherene Loi[97,151], Roberto Salgado[3,97] and Elisabeth Specht Stovgaard[22,152*]

[1] *Technical University of Denmark, Kongens Lyngby, Denmark*

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INVITED REVIEW

Spatial analyses of immune cell infiltration in cancer: current methods and future directions. A report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer

David B Page[1*], Glenn Broeckx[2,3], Chowdhury Arif Jahangir[4], Sara Verbandt[5], Rajarsi R Gupta[6], Jeppe Thagaard[7,8], Reena Khiroya[9], Zuzana Kos[10], Khalid Abduljabbar[11], Gabriela Acosta Haab[12], Balazs Acs[13,14], Jonas S Almeida[15], Isabel Alvarado-Cabrero[16], Farid Azmoudeh-Ardalan[17], Sunil Badve[18], Nurkhairul Bariyah Baharun[19], Enrique R Bellolio[20], Vydehi Bheemaraju[21], Kim RM Blenman[22,23], Luciana Botinelly Mendonça Fujimoto[24], Octavio Burgues[25], Maggie Chon U Cheang[26], Francesco Ciompi[27], Lee AD Cooper[28], An Coosemans[29], Germán Corredor[30], Flavio Luis Dantas Portela[31], Frederik Deman[2], Sandra Demaria[32,33], Sarah N Dudgeon[34], Mahmoud Elghazawy[35,36], Scott Ely[37], Claudio Fernandez-Martín[38], Susan Fineberg[39], Stephen B Fox[40], William M Gallagher[4], Jennifer M Giltnane[41], Sacha Gnjatic[42], Paula I Gonzalez-Ericsson[43], Anita Grigoriadis[44,45], Niels Halama[46], Matthew G Hanna[47], Aparna Harbhajanka[48], Alexandros Hardas[49], Steven N Hart[50], Johan Hartman[14,51], Stephen Hewitt[52], Akira I Hida[53], Hugo M Horlings[54], Zaheed Husain[55], Evangelos Hytopoulos[56], Sheeba Irshad[57], Emiel AM Janssen[58,59], Mohamed Kahila[60], Tatsuki R Kataoka[61], Kosuke Kawaguchi[62], Durga Kharidehal[21], Andrey I Khramtsov[63], Umay Kiraz[58,59], Pawan Kirtani[64], Liudmila L Kodach[65], Konstanty Korski[66], Anikó Kovács[67,68], Anne-Vibeke Laenkholm[69,70], Corinna Lang-Schwarz[71], Denis Larsimont[72], Jochen K Lennerz[73], Marvin Lerousseau[74,75,76], Xiaoxian Li[77], Amy Ly[78], Anant Madabhushi[79], Sai K Maley[80], Vidya Manur Narasimhamurthy[81], Douglas K Marks[82], Elizabeth S McDonald[83], Ravi Mehrotra[84,85], Stefan Michiels[86], Fayyaz ul Amir Afsar Minhas[87], Shachi Mittal[88], David A Moore[89], Shamim Mushtaq[90], Hussain Nighat[91], Thomas Papathomas[92,93], Frederique Penault-Llorca[94], Rashindrie D Perera[95,96], Christopher J Pinard[97,98,99,100], Juan Carlos Pinto-Cardenas[101], Giancarlo Pruneri[102,103], Lajos Pusztai[104,105], Arman Rahman[4], Nasir Mahmood Rajpoot[106], Bernardo Leon Rapoport[107,108], Tilman T Rau[109], Jorge S Reis-Filho[110], Joana M Ribeiro[111], David Rimm[60,112], Anne Vincent-Salomon[113], Manuel Salto-Tellez[114,115], Joel Saltz[116], Shahin Sayed[117], Kalliopi P Siziopikou[118], Christos Sotiriou[119,120], Albrecht Stenzinger[121], Maher A Sughayer[122], Daniel Sur[123], Fraser Symmans[124], Sunao Tanaka[125], Timothy Taxter[126], Sabine Tejpar[5], Jonas Teuwen[127], E Aubrey Thompson[128], Trine Tramm[129], William T Tran[130], Jeroen van der Laak[131], Paul J van Diest[132,133], Gregory E Verghese[44,45], Giuseppe Viale[134], Michael Vieth[135], Noorul Wahab[136], Thomas Walter[74,75,76], Yannick Waumans[137], Hannah Y Wen[47], Wentao Yang[138], Yinyin Yuan[139], Sylvia Adams[82,140], John Mark Seaverns Bartlett[141], Sibylle Loibl[142], Carsten Denkert[143], Peter Savas[96,144], Sherene Loi[96,145], Roberto Salgado[2,96], Elisabeth Specht Stovgaard[146,147], Guray Akturk[148] and Najat Bouchmaa[149]

[1] *Earle A Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA*
[2] *Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium*
[3] *Centre for Oncological Research (CORE), MIPPRO, Faculty of Medicine, Antwerp University, Antwerp, Belgium*
[4] *UCD School of Biomolecular and Biomedical Science, University College Dublin, Dublin, Ireland*
[5] *Digestive Oncology, Department of Oncology, KU Leuven, Leuven, Belgium*
[6] *Department of Biomedical Informatics, Stony Brook University, Stony Brook, NY, USA*
[7] *Technical University of Denmark, Kongens Lyngby, Denmark*
[8] *Visiopharm A/S, Hørsholm, Denmark*

nature machine intelligence

Article

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scBERT as a large-scale pretrained deep language model for cell type annotation of single-cell RNA-seq data

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Fan Yang[1,7], Wenchuan Wang[1,2,7], Fang Wang[1,7], Yuan Fang[1,3,4], Duyu Tang[1], Junzhou Huang[5], Hui Lu[2,6] ✉ and Jianhua Yao[1] ✉

Annotating cell types on the basis of single-cell RNA-seq data is a prerequisite for research on disease progress and tumour microenvironments. Here we show that existing annotation methods typically suffer from a lack of curated marker gene lists, improper handling of batch effects and difficulty in leveraging the latent gene–gene interaction information, impairing their generalization and robustness. We developed a pretrained deep neural network-based model, single-cell bidirectional encoder representations from transformers (scBERT), to overcome the challenges. Following BERT's approach to pretraining and fine-tuning, scBERT attains a general understanding of gene–gene interactions by being pretrained on huge amounts of unlabelled scRNA-seq data; it is then transferred to the cell type annotation task of unseen and user-specific scRNA-seq data for supervised fine-tuning. Extensive and rigorous benchmark studies validated the superior performance of scBERT on cell type annotation, novel cell type discovery, robustness to batch effects and model interpretability.

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REVIEW ARTICLE OPEN

Check for updates

The shaky foundations of large language models and foundation models for electronic health records

Michael Wornow[1✉], Yizhe Xu[2], Rahul Thapa[2], Birju Patel[2], Ethan Steinberg[1], Scott Fleming[2], Michael A. Pfeffer[2,3], Jason Fries[2] and Nigam H. Shah[2,3,4,5]

The success of foundation models such as ChatGPT and AlphaFold has spurred significant interest in building similar models for electronic medical records (EMRs) to improve patient care and hospital operations. However, recent hype has obscured critical gaps in our understanding of these models' capabilities. In this narrative review, we examine 84 foundation models trained on non-imaging EMR data (i.e., clinical text and/or structured data) and create a taxonomy delineating their architectures, training data, and potential use cases. We find that most models are trained on small, narrowly-scoped clinical datasets (e.g., MIMIC-III) or broad, public biomedical corpora (e.g., PubMed) and are evaluated on tasks that do not provide meaningful insights on their usefulness to health systems. Considering these findings, we propose an improved evaluation framework for measuring the benefits of clinical foundation models that is more closely grounded to metrics that matter in healthcare.

npj Digital Medicine (2023)6:135 ; https://doi.org/10.1038/s41746-023-00879-8

INTRODUCTION

Foundation models (FMs) are machine learning models capable of performing many different tasks after being trained on large, typically unlabeled datasets[1]. FMs represent a paradigm shift in how machine learning (ML) models are developed—rather than developing a bespoke model for each specific use case (as was other fields, such as natural language processing (NLP) and computer vision[21]. This makes it difficult to quantify and compare these models' capabilities.

If we believe that FMs can help both providers and patients[22], then rigorous evaluations must be conducted to test these beliefs. In this review, we uncover notable limitations in how clinical FMs

nature medicine

Brief Communication

https://doi.org/10.1038/s41591-023-02475-5

A reinforcement learning model for AI-based decision support in skin cancer

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Check for updates

Catarina Barata[1,16], Veronica Rotemberg[2,16], Noel C. F. Codella[3], Philipp Tschandl[4], Christoph Rinner[5], Bengu Nisa Akay[6], Zoe Apalla[7], Giuseppe Argenziano[8], Allan Halpern[2], Aimilios Lallas[7], Caterina Longo[9,10], Josep Malvehy[11,12], Susana Puig[11,12], Cliff Rosendahl[13], H. Peter Soyer[14], Iris Zalaudek[15] & Harald Kittler[4]

We investigated whether human preferences hold the potential to improve diagnostic artificial intelligence (AI)-based decision support using skin cancer diagnosis as a use case. We utilized nonuniform rewards and penalties based on expert-generated tables, balancing the benefits and harms of various diagnostic errors, which were applied using reinforcement learning. Compared with supervised learning, the reinforcement learning model improved the sensitivity for melanoma from 61.4% to 79.5% (95% confidence interval (CI): 73.5–85.6%) and for basal cell carcinoma from 79.4% to 87.1% (95% CI: 80.3–93.9%). AI overconfidence was also reduced while simultaneously maintaining accuracy. Reinforcement learning increased the rate of correct diagnoses made by dermatologists by 12.0% (95% CI: 8.8–15.1%) and improved the rate of optimal management decisions from 57.4% to 65.3% (95% CI: 61.7–68.9%). We further demonstrated that the reward-adjusted reinforcement learning model and a threshold-based model outperformed naïve supervised learning in various clinical scenarios. Our findings suggest the potential for incorporating human preferences into image-based diagnostic algorithms.

nature genetics

Letter

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Exome sequencing identifies breast cancer susceptibility genes and defines the contribution of coding variants to breast cancer risk

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Check for updates

A list of authors and their affiliations appears at the end of the paper

Linkage and candidate gene studies have identified several breast cancer susceptibility genes, but the overall contribution of coding variation to breast cancer is unclear. To evaluate the role of rare coding variants more comprehensively, we performed a meta-analysis across three large whole-exome sequencing datasets, containing 26,368 female cases and 217,673 female controls. Burden tests were performed for protein-truncating and rare missense variants in 15,616 and 18,601 genes, respectively. Associations between protein-truncating variants and breast cancer were identified for the following six genes at exome-wide significance ($P < 2.5 \times 10^{-6}$): the five known susceptibility genes *ATM*, *BRCA1*, *BRCA2*, *CHEK2* and *PALB2*, together with *MAP3K1*. Associations were also observed for *LZTR1*, *ATR* and *BARD1* with $P < 1 \times 10^{-4}$. Associations between predicted deleterious rare missense or protein-truncating variants and breast cancer

Article

Assembly of 43 human Y chromosomes reveals extensive complexity and variation

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Check for updates

Pille Hallast[1,18], Peter Ebert[2,3,4,18], Mark Loftus[5,6,18], Feyza Yilmaz[1], Peter A. Audano[1], Glennis A. Logsdon[7], Marc Jan Bonder[8,9], Weichen Zhou[10], W... Chong Li[12], Savannah J. Hoyt[13], Philip C. Dishuck[7], David Poru... Jee Young Kwon[1], Qihui Zhu[1], Katherine M. Munson[7], Patrick ... Alexandra P. Lewis[7], Jennifer Kordosky[7], Kendra Hoekzema[7], ... Variation Consortium (HGSVC)*,**, Rachel J. O'Neill[13,14,15], Jar... Evan E. Eichler[7,17], Xinghua Shi[12], Christine R. Beck[1,14,15], Tobia... Miriam K. Konkel[5,6,19] & Charles Lee[1,19]

The prevalence of highly repetitive sequences within the... prevented its complete assembly to date[1] and led to its sy... genomic analyses. Here we present de novo assemblies o... 182,900 years of human evolution and report considera... structure. Half of the male-specific euchromatic region i... with a greater than twofold higher recurrence rate com... chromosomes[2]. Ampliconic sequences associated with t... mutation rates that are sequence context dependent, an... exhibit evidence for concerted evolution with the acqu...

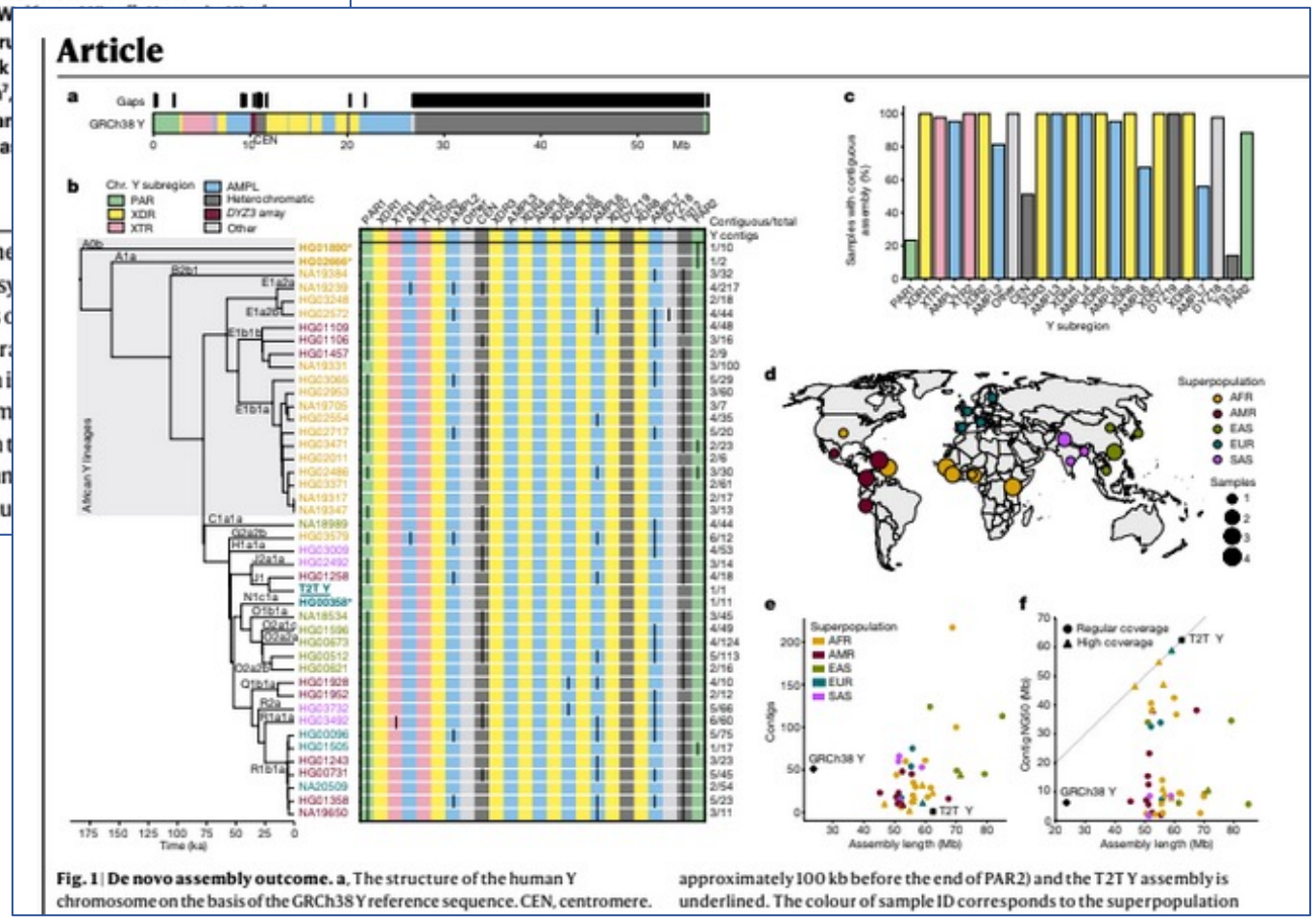

Fig. 1 | De novo assembly outcome. a, The structure of the human Y chromosome on the basis of the GRCh38 Y reference sequence. CEN, centromere. ... approximately 100 kb before the end of PAR2) and the T2T Y assembly is underlined. The colour of sample ID corresponds to the superpopulation

Article

A spatially resolved single-cell genomic atlas of the adult human breast

https://doi.org/10.1038/s41586-023-06252-9

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Check for updates

Tapsi Kumar[1,2,16], Kevin Nee[3,16], Runmin Wei[1,16], Siyuan He[1,2,16], Quy H. Nguyen[3,16], Shanshan Bai[1], Kerrigan Blake[4,5], Maren Pein[3,4], Yanwen Gong[3,5], Emi Sei[1], Min H Anna K. Casasent[1], Aatish Thennavan[1], Jianzhuo Li[1], Tuan Tran[1], Ken Chen[6], Ber Nachiket Kashikar[7], Oliver Braubach[8], Bassem Ben Cheikh[8], Nadya Nikulina[8], H Mediget Teshome[10], Brian Menegaz[11], Huma Javaid[11], Chandandeep Nagi[11], Jessica Montalvan[11], Tatyana Lev[4,5], Sharmila Mallya[4], Delia F. Tifrea[12], Robert E Erin Lin[12], Ritesh Parajuli[12], Summer Hanson[13], Sebastian Winocour[14], Alastair T Bora Lim[15,17], Devon A. Lawson[4,17] ✉, Kai Kessenbrock[3,17] ✉ & Nicholas Navin[1,2,6,17] ✉

The adult human breast is comprised of an intricate network of epithelial lobules that are embedded in connective and adipose tissue[1–3]. Although studies have focused on the breast epithelial system[4–6], many of the non-e types remain understudied. Here we constructed the comprehensive Hu Cell Atlas (HBCA) at single-cell and spatial resolution. Our single-cell trans study profiled 714,331 cells from 126 women, and 117,346 nuclei from 20 w identifying 12 major cell types and 58 biological cell states. These data rev perivascular, endothelial and immune cell populations, and highly divers epithelial cell states. Spatial mapping using four different technologies re unexpectedly rich ecosystem of tissue-resident immune cells, as well as d molecular differences between ductal and lobular regions. Collectively, t provide a reference of the adult normal breast tissue for studying mamma and diseases such as breast cancer.

Article

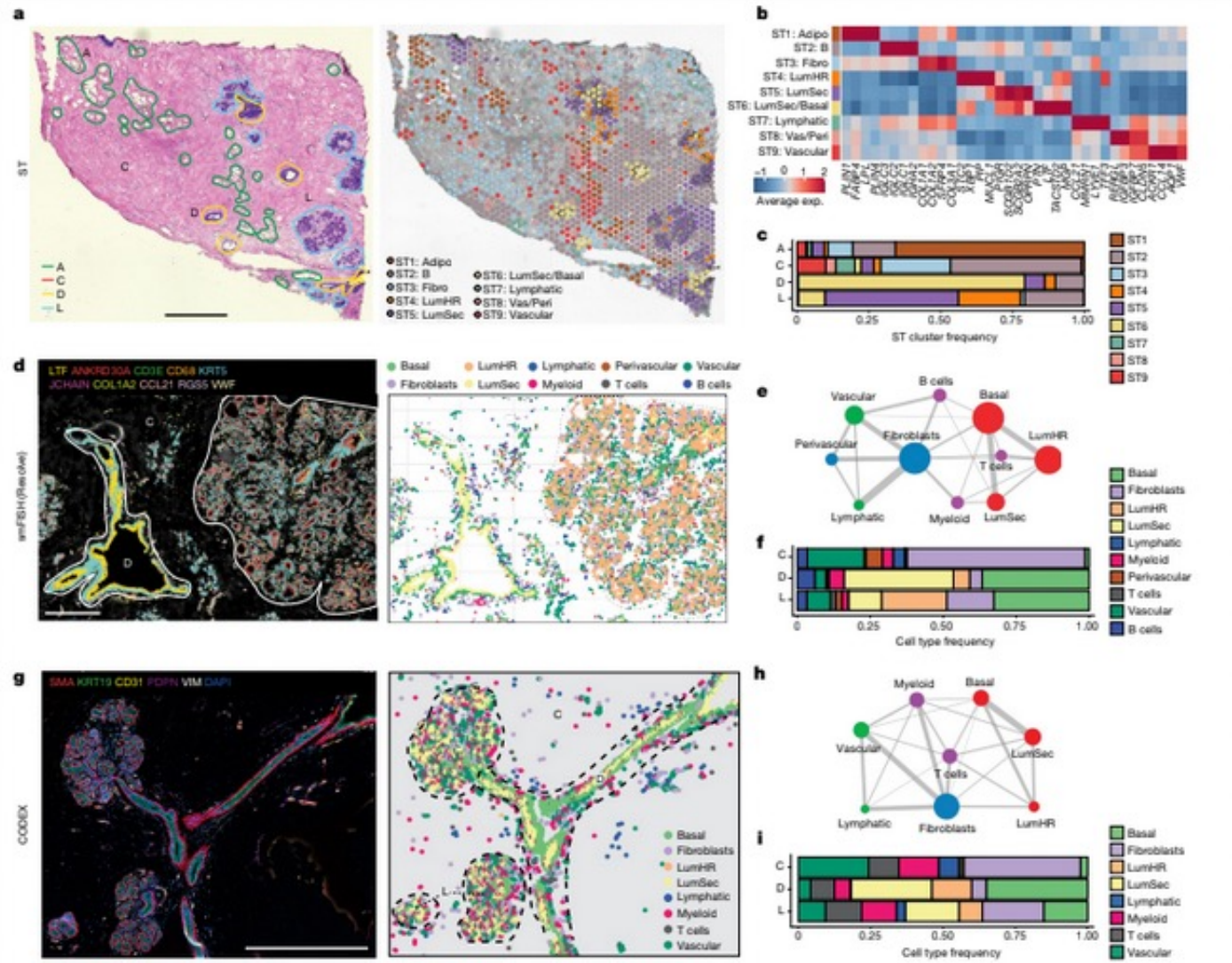

Fig. 2 | Spatial analysis of major breast cell types. a, ST experiment from patient P35 showing the H&E image with histopathological regions annotated (left) and clustering results (right). A, adipose tissue; C, connective tissue; 12 tissue samples. The node size represents the cell number and the edge width represents the probability of colocalization. **f**, Cell type frequencies across 3 topographic regions from 12 smFISH (Resolve) tissue samples. **g**, CODEX data

nature reviews immunology

https://doi.org/10.1038/s41577-023-00836-2

Perspective

Check for updates

Locally sourced: site-specific immune barriers to metastasis

Ana Luísa Correia

Abstract

Tumour cells migrate very early from primary sites to distant sites, and yet metastases often take years to manifest themselves clinically or never even surface within a patient's lifetime. This pause in cancer progression emphasizes the existence of barriers that constrain the growth of disseminated tumour cells (DTCs) at distant sites. Although the nature of these barriers to metastasis might include DTC-intrinsic traits, recent studies have established that the local microenvironment also controls the formation of metastases. In this Perspective, I discuss how site-specific differences of the immune system might be a major selective growth restraint on DTCs, and argue that harnessing tissue immunity will be essential for the next stage in immunotherapy development that reliably prevents the establishment of metastases.

Sections

Perspective

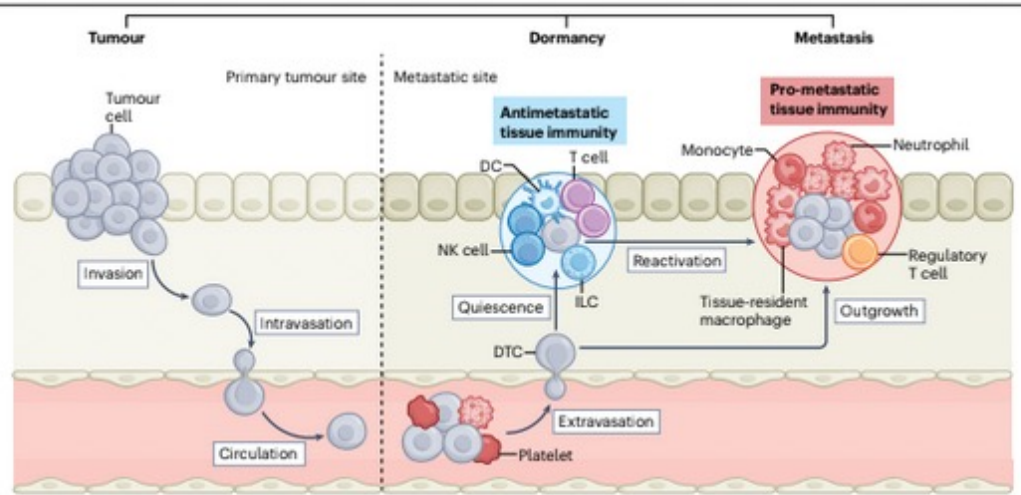

Fig. 1 | Tissue immunity determines metastatic progression. Before metastases manifest themselves clinically, tumour cells need to overcome multiple barriers throughout their journey from the primary site until they successfully colonize a distant site. First, they invade locally and intravasate the endothelium to enter the circulation, where they travel alone or in clusters with other cells, in search of a new site to extravasate and expand. The few disseminated tumour cells (DTCs) that survive the journey then face attrition from the specific immune environment within the distant site: where antimetastatic tissue-resident immune cell populations are dominant, DTCs blend into the physiological context and persist in a quiescent state for several years or even decades (dormancy stage of cancer); conversely, microenvironments depleted of antimetastatic immune cells or enriched in other immune cells conducive to DTC reactivation support metastatic outgrowth into clinically detectable metastases. Treating the specific immune microenvironment at distant sites may be a way to effectively control DTCs. DC, dendritic cell; ILC, innate lymphoid cell; NK, natural killer.

nature reviews drug discovery

https://doi.org/10.1038/s41573-023-00723-4

Review article

Check for updates

Trends in the approval of cancer therapies by the FDA in the twenty-first century

Emma C. Scott[1] ✉, Andrea C. Baines[1], Yutao Gong[1], Rodney Moore Jr[1], Gulsum E. Pamuk[1], Haleh Saber[1], Ashim Subedee[1,2], Matthew D. Thompson[1], Wenming Xiao[1], Richard Pazdur[3], V. Ashutosh Rao[4], Julie Schneider[3] & Julia A. Beaver[1,3]

Abstract

The cancer treatment landscape has changed dramatically since the turn of the century, resulting in substantial improvements in outcomes for patients. This Review summarizes trends in the approval of oncology therapeutic products by the United States Food and Drug Administration (FDA) from January 2000 to October 2022, based on a categorization of these products by their mechanism of action and primary target. Notably, the rate of oncology indication approvals has increased in this time, driven by approvals for targeted therapies, as has the rate of introduction of new therapeutic approaches. Kinase inhibitors are the dominant product class by number of approved products and indications, yet immune checkpoint inhibitors have the second most approvals despite not entering the market until 2011. Other trends

Sections

nature communications

Article

https://doi.org/10.1038/s41467-023-40324-8

EGFR-targeted fluorescence molecular imaging for intraoperative margin assessment in oral cancer patients: a phase II trial

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Check for updates

Jaron G. de Wit[1,11], Jasper Vonk[1,11], Floris J. Voskuil[1,2], Sebastiaan A. H. J. de Visscher[1], Kees-Pieter Schepman[1], Wouter T. R. Hooghiemstra[3,4], Matthijs D. Linssen[3,4], Sjoerd G. Elias[5], Gyorgy B. Halmos[6], Boudewijn E. C. Plaat[6], Jan J. Doff[2], Eben L. Rosenthal[7], Dominic Robinson[8], Bert van der Vegt[2], Wouter B. Nagengast[4], Gooitzen M. van Dam[9,10] & Max J. H. Witjes[1]

Inadequate surgical margins occur frequently in oral squamous cell carcinoma surgery. Fluorescence molecular imaging (FMI) has been explored for intraoperative margin assessment, but data are limited to phase-I studies. In this single-arm phase-II study (NCT03134846), our primary endpoints were to determine the sensitivity, specificity and positive predictive value of

Article

https://doi.org/10.1038/s41467-023-40324-8

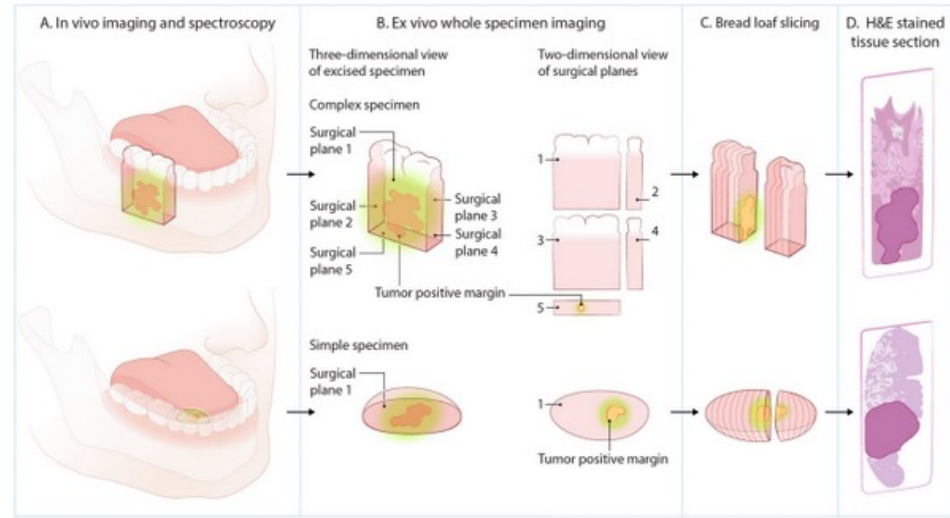

Fig. 1 | Overview of study workflow. A In vivo fluorescence imaging of the tumor. **B** Back table imaging of the excised specimen. Fluorescence imaging is performed from all surgical planes of the specimen. In the case of a complex specimen, multiple surgical planes can be identified and imaged, and in the case of a simple specimen, only one surgical plane per specimen is imaged. Fluorescent spots are observed in image 5 (top row) and image 1 (bottom row). **C** Bread loaf slicing of the specimen and fluorescence imaging of all bread loaf slices. **D** Correlation of the fluorescent spots relate to tumor-positive margins on histopathology.

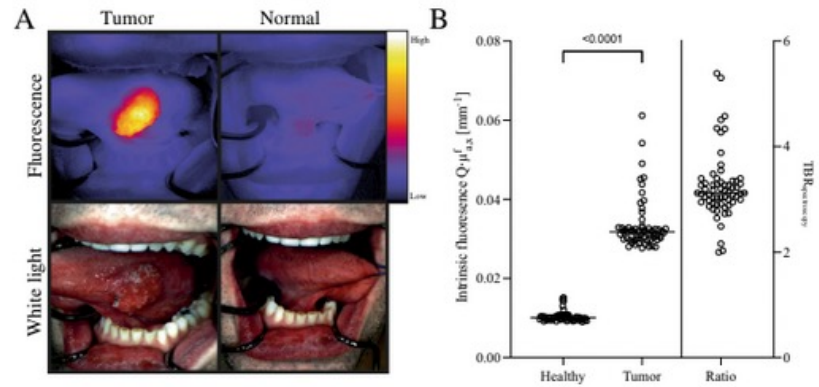

Fig. 2 | In vivo imaging and spectroscopy results. A In vivo fluorescence molecular imaging shows a sharp demarcation of a tumor on the lateral tongue. **B** In vivo multi-diameter single-fiber reflectance, single-fiber fluorescence contact measurefluorescence ($Q.\mu'_{a,x}$) [mm^{-1}]) in tumor (3.3 (2.7–6.1) × 10^{-2} mm^{-1}) compared to normal tissue (1.0 (0.9–1.5) × 10^{-2}), one-sided $p = 0.0001$ using Wilcoxon signed rank test. Source data are provided as a Source Data file.

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Advance access publication: June 20, 2023
Research Article

Health Affairs Scholar
EMERGING & GLOBAL HEALTH POLICY
OXFORD

The Better Care Plan: a blueprint for improving America's healthcare system

Stephen M. Shortell[1,*], John T. Toussaint[2], George C. Halvorson[3], Jon M. Kingsdale[4], Richard M. Scheffler[1], Allyson Y. Schwartz[5], Peter A. Wadsworth[6], Gail Wilensky[7]

[1]UC-Berkeley, 2121 Berkeley Way West, Berkeley, CA 94704, United States
[2]Catalysis, Inc. 3825 East Calumet Street, Suite 400-114, Appleton, WI 54915, United States
[3]The Institute for Intergroup Understanding, 1300 Bracketts Point Road, Wayzata, MN 55391, United States
[4]Brown University, Providence, RI, United States
[5]FTI Consulting, 555 12th Street, Washington, DC 20004, United States
[6]Amory Associates, 1310 Norwest Drive, Norwood, MA 02062, United States
[7]Project Hope, 1220 19th Street, Washington, DC 20036, United States

*Corresponding author: School of Public Health, UC-Berkeley, 2121 Berkeley Way West, Berkeley, CA 94704, United States. Email: Shortell@berkeley.edu

Abstract

The United States falls far short of its potential for delivering care that is effective, efficient, safe, timely, patient-centered, and equitable. We put forward the Better Care Plan, an overarching blueprint to address the flaws in our current system. The plan calls for continuously improving care, moving all payers to risk-adjusted prospective payment, and creating national entities for collecting, analyzing, and reporting patient safety and quality-of-care outcomes data. A number of recommendations are made to achieve these goals.

Key words: Healthcare reform; prospective payment; continuous quality improvement; patient safery and outcomes reporting.

Introduction

While there is much to be proud of in America's healthcare system, the flaws of the system are significant and stubbornly resistant to change. Care is expensive, fragmented, highly variable in quality, and too often unsafe. We need to change how we provide care, pay for it, and how we measure and report on the care provided.

Some progress has been made in improving risk-adjusted mortality, complication rates, and morbidity since publication

We also cannot improve our nation's health without developing credible, transparent, standardized, validated, timely, and understandable patient safety and quality outcomes reporting. We need to build on the process measures developed to date by focusing on measures of patient harm and other outcomes.[7] Consumers need this information for choosing health plans and plans and providers need it to continuously improve care, patient outcomes, and patient safety.

This paper puts forward principles and criteria of a Better

Short report

OPEN ACCESS

Artificial intelligence (AI) molecular analysis tool assists in rapid treatment decision in lung cancer: a case report

Barliz Waissengrin,[1,2] Alexandra Garasimov,[1] Or Bainhoren ,[1,2] Ofer Merimsky,[1,2] Sivan Shamai,[1,2] Ariel Erental,[2,3] Ido Wolf,[1,2] Dov Hershkovitz[2,3]

[1]Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[2]School of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Pathology, Tel Aviv Sourasky

ABSTRACT
Leptomeningeal invo
lung cancer (NSCLC)
disease that requires

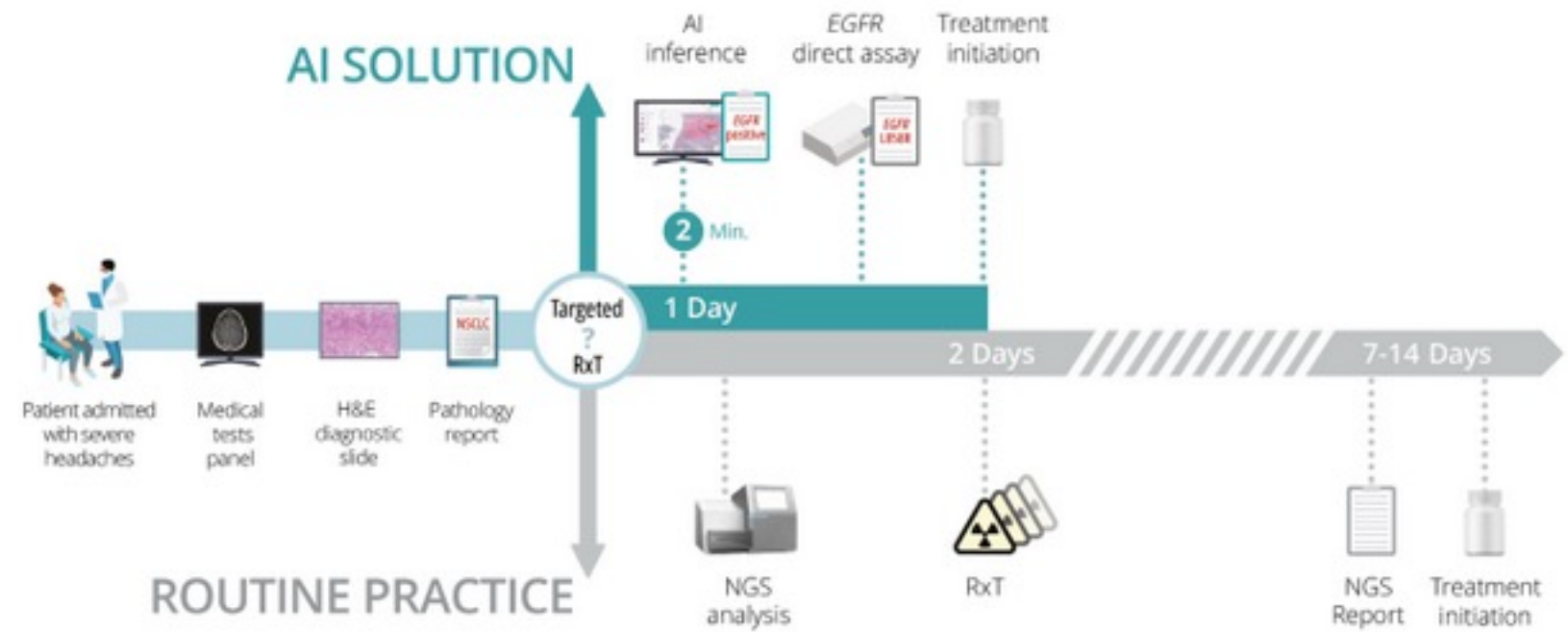

Figure 3 Schematic representation of the case. AI, artificial intelligence; RxT, artificial intelligence; NSG, next-generation sequencing.

Mortality Benefit of a Blood-Based Biomarker Panel for Lung Cancer on the Basis of the Prostate, Lung, Colorectal, and Ovarian Cohort

Ehsan Irajizad, PhD[1]; Johannes F. Fahrmann, PhD[2]; Tracey Marsh, PhD[3]; Jody Vykoukal, PhD[2]; Jennifer B. Dennison, PhD[2]; James P. Long, PhD[1]; Kim-Anh Do, PhD[1]; Ziding Feng, PhD[3]; Samir Hanash, MD, PhD[2]; and Edwin J. Ostrin, MD, PhD[4]

DOI https://doi.org/10.1200/JCO.22.02424

ABSTRACT

PURPOSE To investigate the utility of integrating a panel of circulating protein biomarkers in combination with a risk model on the basis of subject characteristics to identify individuals at high risk of harboring a lethal lung cancer.

METHODS Data from an established logistic regression model that combines four-marker protein panel (4MP) together with the Prostate, Lung, Colorectal, and Ovarian (PLCO) risk model ($PLCO_{m2012}$) assayed in prediagnostic sera from 552 lung cancer cases and 2,193 noncases from the PLCO cohort were used in this study. Of the 552 lung cancer cases, 387 (70%) died of lung cancer. Cumulative incidence of lung cancer death and subdistributional and cause-specific hazard ratios (HRs) were calculated on the basis of 4MP + $PLCO_{m2012}$ risk scores at a predefined 1.0% and 1.7% 6-year risk thresholds, which correspond to the current and former US Preventive Services Task Force screening criteria, respectively.

RESULTS When considering cases diagnosed within 1 year of blood draw and all noncases, the area under receiver operation characteristics curve estimate of the 4MP + $PLCO_{m2012}$ model for risk prediction of lung cancer death was 0.88 (95% CI, 0.86 to 0.90). The cumulative incidence of lung cancer death was statistically significantly higher in individuals with 4MP + $PLCO_{m2012}$ scores above the 1.0% 6-year risk threshold (modified χ^2, 166.27; $P < .0001$). Corresponding subdistributional and lung cancer death–specific HRs for test-positive cases were 9.88 (95% CI, 6.44 to 15.18) and 10.65 (95% CI, 6.93 to 16.37), respectively.

CONCLUSION The blood-based biomarker panel in combination with $PLCO_{m2012}$ identifies individuals at high risk of a lethal lung cancer.

ACCOMPANYING CONTENT

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EDITED BY
Patrizia Giannatempo,
Fondazione Istituto Nazionale dei Tumori, Italy

REVIEWED BY
Roubini Zakopoulou,
University General Hospital Attikon, Greece
Umang Swami,
The University of Utah, United States

*CORRESPONDENCE
Thomas Powles
thomas.powles1@nhs.net

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Molecular residual disease detection in resected, muscle-invasive urothelial cancer with a tissue-based comprehensive genomic profiling–informed personalized monitoring assay

Thomas Powles[1*], Amanda Young[2], Halla Nimeiri[2], Russell W. Madison[2], Alexander Fine[2], Daniel R. Zollinger[2], Yanmei Huang[2], Chang Xu[2], Ole V. Gjoerup[2], Vasily N. Aushev[3], Hsin-Ta Wu[3], Alexey Aleshin[3], Corey Carter[4], Nicole Davarpanah[4], Viraj Degaonkar[4], Pratyush Gupta[4], Sanjeev Mariathasan[4], Erica Schleifman[4], Zoe June Assaf[4], Geoffrey Oxnard[2] and Priti S. Hegde[2]

https://doi.org/10.1038/d41586-023-02546-0

News & views

Clinical neuroscience

Speech-enabling brain implants pass milestones

Nick F. Ramsey & Nathan E. Crone

Two brain–computer interfaces have been developed that bring unprecedented capabilities for translating brain signals into sentences – at speeds close to that of normal speech, and with vocabularies exceeding 1,000 words.

There is an urgent need to help people with neurological conditions that deprive them of the universal human need to communicate. Two articles published in *Nature* demonstrate that individuals who are unable to speak as a result of severe paralysis could potentially use implantable brain–computer interfaces (BCIs) to communicate at rates much greater than those typically achievable with alternative communication options. Willett *et al.*[1] report a device that records brain activity using electrodes that penetrate the brain's cortex, whereas Metzger and colleagues' device[2] uses electrodes placed on the cortical surface. These studies signal a turning point in the development of BCI technology that aims to restore communication for people with severe paralysis.

Various neurological disorders paralyse muscles crucial to speech and limb function while sparing cognitive functions, potentially resulting in locked-in syndrome – in which individuals can no longer initiate communication and can respond to queries only with eye blinks or minimal movements. A diverse range of systems, known as alternative and augmentative communication technologies, are available to help people with locked-in syndrome to communicate, but these require effort and are much slower (achieving, typically, just a few words per minute) than normal speech (about 150 words per minute). BCIs have the potential to solve these problems.

The first demonstration that a subject could be trained to increase the activity of single neurons, and thereby to exert a wilful action, was published in 1969, for a rhesus macaque (*Macaca mulatta*)[3]. Experiments in humans began[4] in the late 1990s, when an electrode was connected to neurons in a person with locked-in syndrome caused by motor neuron disease (amyotrophic lateral sclerosis, or ALS), a neurodegenerative disease. This was followed in 2006 by a study[5] in which arrays of millimetre-scale electrodes (known as microelectrodes) were implanted into the brain of a person with a spinal cord injury. This microelectrode array (MEA) recorded the activity of several hundred neurons in the motor cortex, the brain region responsible for the control of voluntary movements, and thereby controlled a robotic arm[5]. MEAs have since been used to enable communication, for instance by decoding handwriting attempts[6].

The complementary technique of electroencephalography (EEG) – in which electrodes are placed along the scalp to record electrical activity in the brain – has been used since 1999 (ref. 7) to help people with paralysis to communicate by controlling custom spelling software[8]. Around the same time, it was discovered that small disc-shaped electrodes (2–3 millimetres in diameter) placed on the surface of the brain could acquire much higher-quality signals than could be obtained using scalp electrodes[9]. This method for recording brain

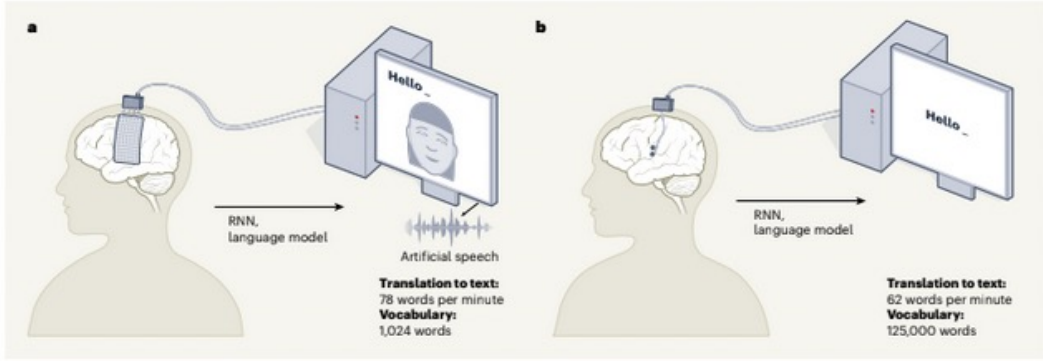

Figure 1 | Advanced techniques for translating thoughts into speech. Two brain activity into facial expressions, which are represented using an avatar. **b**,

Device

CellPress

Review

Theranostic gastrointestinal residence systems

Binbin Ying,[1,4] Hao Huang,[2,3,4] Yuyan Su,[2] Julia G. Howarth,[1] Zhen Gu,[2,*] and Kewang Nan[2,*]
[1]Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[2]College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China
[3]College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310058, China
[4]These authors contributed equally
*Correspondence: guzhen@zju.edu.cn (Z.G.), knan@zju.edu.cn (K.N.)
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THE BIGGER PICTURE Gastrointestinal (GI) residence systems have emerged as a promising area for the diagnosis and treatment of GI diseases. Compared with conventional drug pills and implantation systems, ingestible GI residence systems can be tailored to possess minimal invasiveness and multiple functionalities, therefore effectively addressing issues related to patient non-compliance, as well as monitoring and treating chronic diseases. A crucial aspect of GI residence systems is the *in vivo* retention time;

SUMMARY

Gastrointestinal (G
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CellPress

Device
Review

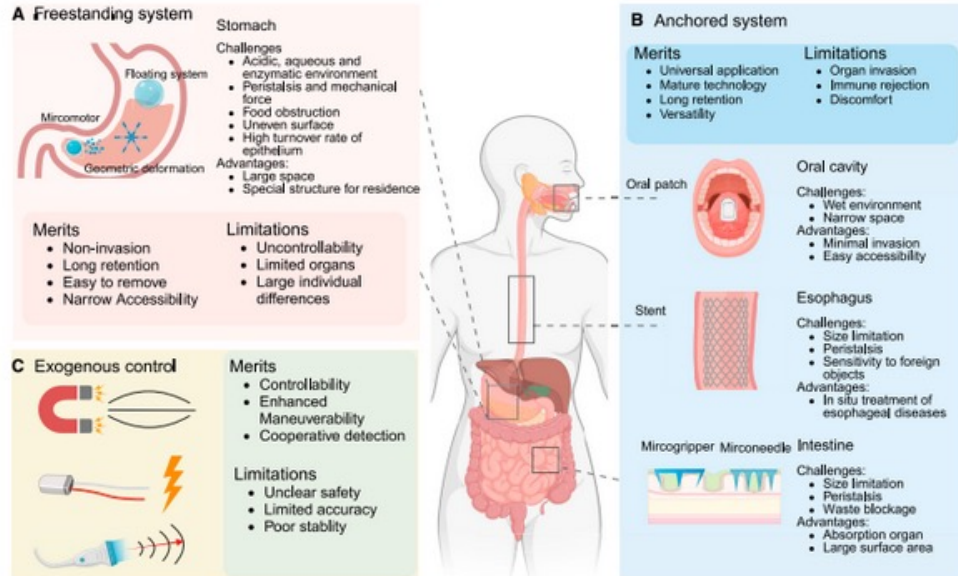

Figure 1. The mechanisms of GI residence systems and their merits and limitations
The corresponding GI regions with distinct challenges and advantages are also outlined.
(A) Freestanding system.
(B) Anchored system.
(C) Exogenous control.

JMI Journal of Medical Imaging

REVIEW

Artificial intelligence and digital pathology: clinical promise and deployment considerations

Mark D. Zarella,[a,*,†] David S. McClintock,[a,†] Harsh Batra,[b] Rama R. Gullapalli,[c,d] Michael Valante,[e] Vivian O. Tan,[f] Shubham Dayal,[g] Kei Shing Oh,[h] Haydee Lara,[i] Chris A. Garcia,[a] and Esther Abels[j]

[a]Mayo Clinic, Division of Computational Pathology and AI, Department of Laboratory Medicine and Pathology, Rochester, Minnesota, United States
[b]University of Texas MD Anderson Cancer Center, Department of Translational Molecular Pathology, Houston, Texas, United States
[c]University of New Mexico, Department of Pathology, Albuquerque, New Mexico, United States
[d]University of New Mexico, Chemical and Biological Engineering, Albuquerque, New Mexico, United States
[e]Dell Technologies, Unstructured Data Solutions, Hopkinton, Massachusetts, United States
[f]Leica Biosystems, Medical and Scientific Affairs, Vista, California, United States
[g]Leica Biosystems, Medical and Scientific Affairs, Danvers, Massachusetts, United States
[h]Mount Sinai Medical Center, Miami Beach, Florida, United States
[i]Biomarker Development, Alexion-AstraZeneca Rare Disease Unit, New Haven, Connecticut, United States
[j]SolarisRTC LLC, Boston, Massachusetts, United States

ABSTRACT. Artificial intelligence (AI) presents an opportunity in anatomic pathology to provide quantitative objective support to a traditionally subjective discipline, thereby enhancing clinical workflows and enriching diagnostic capabilities. AI requires access to digitized pathology materials, which, at present, are most commonly generated from the glass slide using whole-slide imaging. Models are developed collaboratively or sourced externally, and best practices suggest validation with internal datasets most closely resembling the data expected in practice. Although an array of AI models that provide operational support for pathology practices or improve diagnostic quality and capabilities has been described, most of them can be categorized into one or more discrete types. However, their function in the pathology workflow can vary, as a single algorithm may be appropriate for screening and triage, diagnostic assistance, virtual second opinion, or other uses depending on how it is implemented and validated. Despite the clinical promise of AI, the barriers to adoption have been numerous, to which inclusion of new stakeholders and expansion of reimbursement opportunities may be among the most impactful solutions.

 [DOI: 10.1117/1.JMI.10.5.051802]

Keywords: digital pathology; computational pathology; image analysis; whole-slide imaging; machine learning

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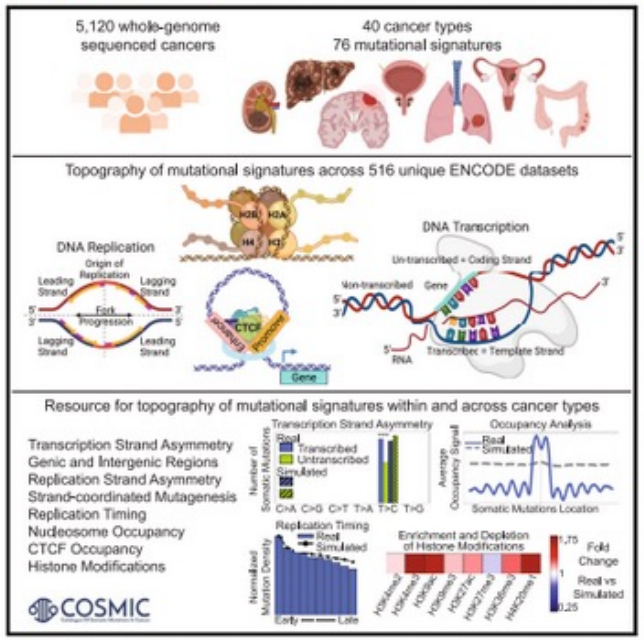
Cell Reports

Resource

Topography of mutational signatures in human cancer

Graphical abstract



Authors

Burçak Otlu, Marcos Díaz-Gay, Ian Vermes, Erik N. Bergstrom, Maria Zhivagui, Mark Barnes, Ludmil B. Alexandrov

Correspondence

L2alexandrov@health.ucsd.edu

In brief

Comprehensive topography analysis of mutational signatures encompassing 82,890,857 somatic mutations in 5,120 whole-genome-sequenced tumors across 40 cancer types. Otlu et al. provide an online resource, through the COSMIC signatures database, that allows researchers to explore the interactions between somatic mutational processes and genome architecture within and across cancer types.

Highlights

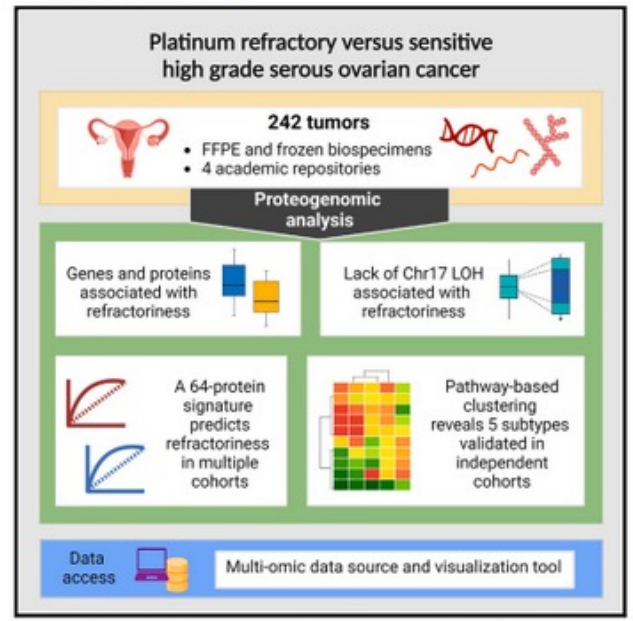
- Mutations imprinted by mutational signatures are affected by topographical genomic features
- Mutational signatures with related etiologies are similarly affected by genomic topography
- Periodicity and cancer-type-specific enrichments/depletions are observed for some signatures
- Updated COSMIC database links 76 signatures in 40 cancer types with 516 topography features

Cell

Resource

Proteogenomic analysis of chemo-refractory high-grade serous ovarian cancer

Graphical abstract



Authors

Shrabanti Chowdhury, Jacob J. Kennedy, Richard G. Ivey, ..., Pei Wang, Michael J. Birrer, Amanda G. Paulovich

Correspondence

mcieslik@med.umich.edu (M.C.), pei.wang@mssm.edu (P.W.), mjbirrer@uams.edu (M.J.B.), apaulovi@fredhutch.org (A.G.P.)

In brief

Patients with high-grade serous ovarian cancers (HGSOCs) have a poor outcome, with the standard of care not having changed over the decades. A detailed characterization of the proteogenomic landscape of HGSOCs across multiple cohorts and validation studies identifies a distinct signature that predicts with high specificity a subset of patients with chemotherapy-refractory cancers and implicates potential therapeutic vulnerabilities.

Highlights

- A comprehensive proteogenomic analysis of 242 HGSOC tumors was performed
- A lack of Chr17-LOH was observed to be associated with refractoriness
- A 64-protein signature predicts refractoriness in multiple tumor cohorts
- Pathway-based clustering reveals 5 subtypes validated in independent cohorts

Events

Next steering committee meeting

Sept. 27
3PM