



Publications



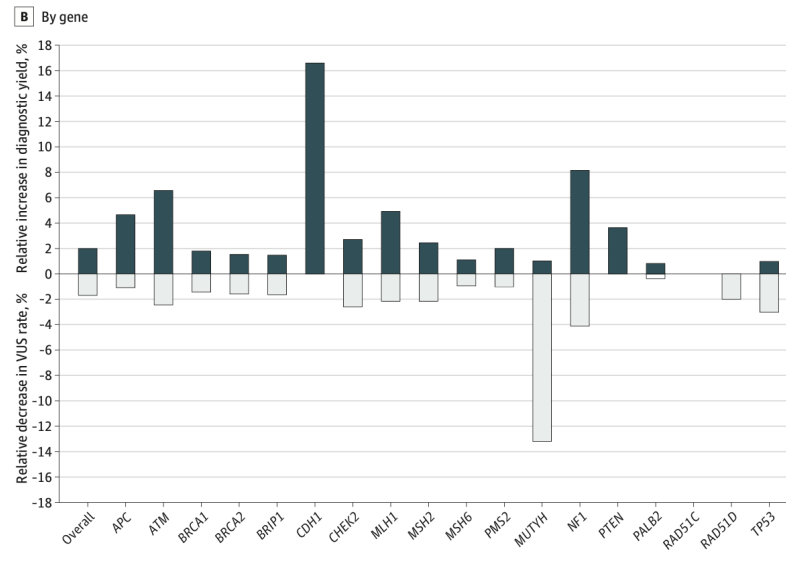
Diagnostic Outcomes of Concurrent DNA and RNA Sequencing in Individuals Undergoing Hereditary Cancer Testing

Carolyn Horton, MS; Lily Hoang, BS; Heather Zimmermann, PhD; Colin Young, PhD; Jessica Grzybowski, MS; Kate Durda, MS; Huy Vuong, PhD; David Burks, PhD; Ashley Cass, PhD; Holly LaDuca, MS; Marcy E. Richardson, PhD; Steven Harrison, PhD; Elizabeth C. Chao, MD; Rachid Karam, MD, PhD

IMPORTANCE Personalized surveillance, prophylaxis, and detection of disease-causing germline genetic variants and of uncertain significance (VUS) in individuals with hereditary cancer predisposition are important for clinical management. Improvements to genomic technology, such as the use of concurrent DNA and RNA sequencing, may increase identification of individuals eligible for personalized surveillance and improve the accuracy and yield of germline testing.

OBJECTIVE To assess the cumulative association of paired DNA and RNA sequencing for the detection of disease-causing germline genetic variants and of uncertain significance (VUS).

DESIGN, SETTING, AND PARTICIPANTS Paired DNA and RNA sequencing was performed on individuals undergoing germline testing for hereditary cancer at a clinical laboratory from March 2019 through April 2020. Demographic



A, Relative increase in positive rate and decrease in VUS rate by race and ethnicity. B, Relative increase in positive rate and decrease in VUS rate by gene.

MAPS: pathologist-level cell type annotation from tissue images through machine learning

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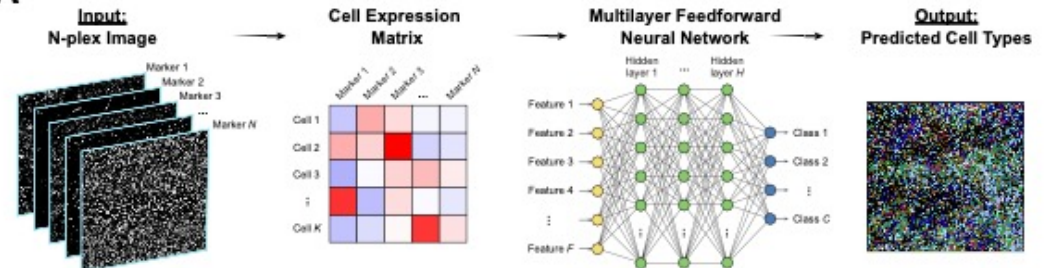
Muhammad Shaban^{1,2,3,4,10}, Yunhao Bai^{5,10}, Jason Yeung⁶, Yao Yu Yeo⁶, Vignesh Shanmugam⁶, Jason L. Weirather^{3,7}, Garry P. Nolan⁸, M. Sizun Jiang^{4,6,9,11} ✉ & Faisal Mahmood⁴ ✉

Highly multiplexed protein imaging is enabling the analysis of protein distribution within cells. However, existing cell annotation methods

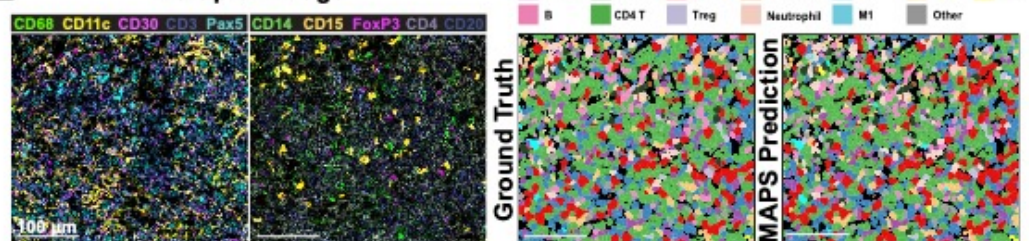
Article

<https://doi.org/10.1038/s41467-023-44188-w>

A Overview of MAPS:



B Multiplex Image



C

D

Article

Genomic data in the All of Us Research Program

<https://doi.org/10.1038/s41586-023-06957-x>

The All of Us Research Program Genomics Investigators*

Received: 22 July 2022

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Comprehensively mapping the genetic basis of human disease across diverse individuals is a long-standing goal for the field of human genetics¹⁻⁴. The All of Us

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Article

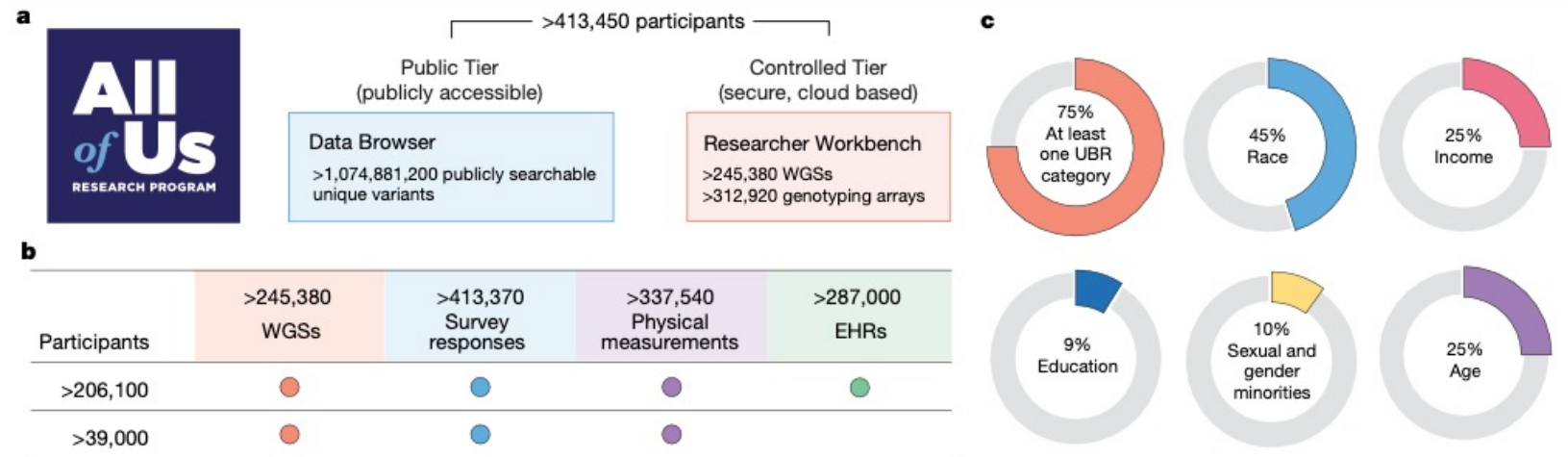


Fig. 1 | Summary of All of Us data resources. a, The All of Us Research Hub contains a publicly accessible Data Browser for exploration of summary wearables and genomic data. Dots indicate the presence of the specific data type for the given number of participants. **c**, Overall summary of participants

A Morphology Focused Diffusion Probabilistic Model for Synthesis of Histopathology Images

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Abstract

Visual microscopic study of diseased tissue by pathologists has been the cornerstone for cancer diagnosis and prognostication for more than a century. Recently, deep learning methods have made significant advances in the analysis and classification of tissue images. However, there has been limited work on the utility of such models in generating histopathology images. These synthetic images have several applications in pathology including utilities in education, proficiency testing, privacy, and data sharing. Recently, diffusion probabilistic models were introduced to generate high quality images. Here, for the first time, we investigate the potential use of such models along with prioritized morphology weighting and color normalization to synthesize high quality histopathology images of brain cancer. Our detailed results show that diffusion probabilistic models are capable of synthesizing a wide range of histopathology images and have superior performance compared to generative adversarial networks.

various stains (e.g., hematoxylin and eosin, silver nitrate, carmine, hematin, etc.) is used to emphasise the properties of the tissues and improve their contrast for examination [1]. Figure 1 shows a sample of digital pathology images.

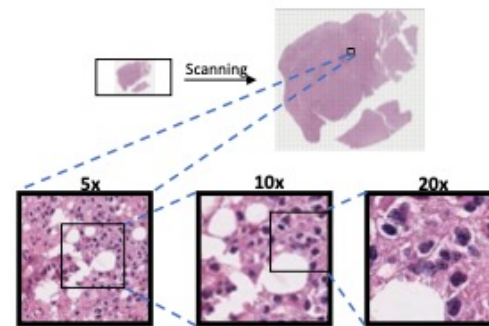


Figure 1: 3 sampled patches at different magnifications from a whole slide image

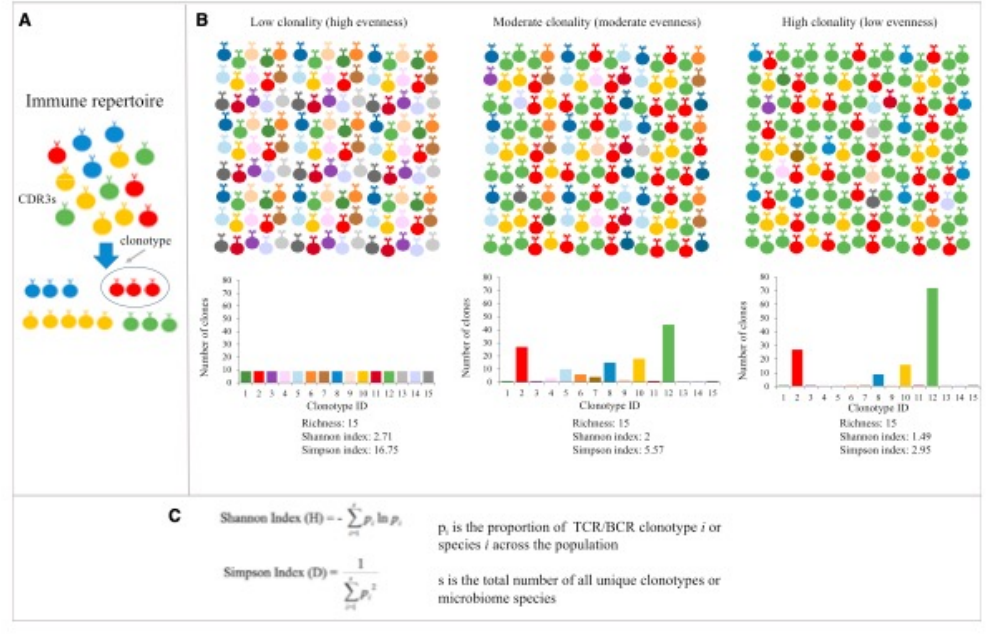
Review

Predicting patient outcomes after treatment with immune checkpoint blockade: A review of biomarkers derived from diverse data modalities

Yang Liu,¹ Jennifer Altreuter,¹ Sudheshna Bodapati,¹ Simona Cristea,^{1,2} Cheryl J. Wong,^{1,3} Catherine J. Wu,^{4,5,6,7} and Franziska Michor^{1,2,3,5,8,9,10,*}

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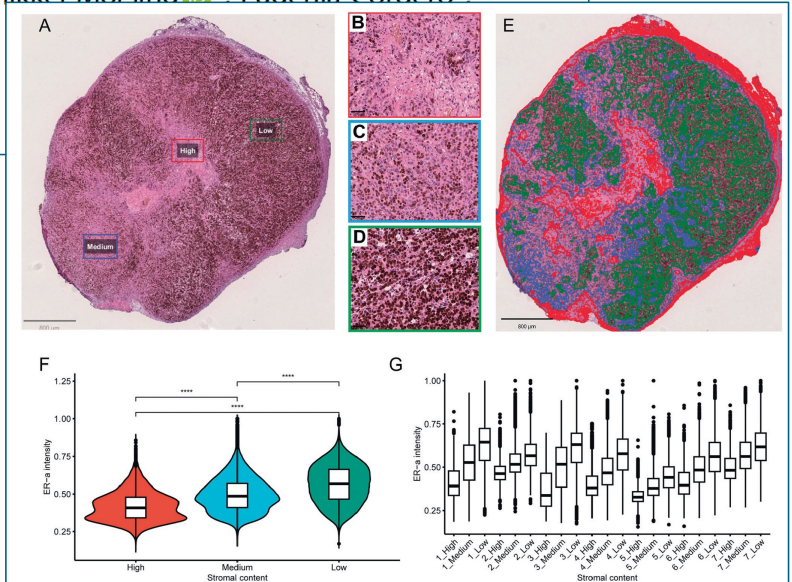
ARTICLE OPEN



Cancer-associated fibroblasts rewire the estrogen receptor response in luminal breast cancer, enabling estrogen independence

Steven E. Reid¹, Jessica Pantaleo¹, Paulina Bolivar¹, Matteo Bocci¹, Jonas Sjölund¹, Mikkel Morsing¹, Eugenia Cordero¹, Sara Larsson¹, Maria Malmberg¹, Brinton Seashore-Ludlow^{2,3} and Kristian Pietras¹✉

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Patients' ideas, concerns, and expectations (ICE) in general practice: impact on prescribing

Jan Matthys, Glyn Elwyn, Marc Van Nuland, Georges Van Maele, An De Sutter, Marc De Meyere and Myriam Deveugele

ABSTRACT

Background

INTRODUCTION

Good communication in medical care

Box 1. Registration form that GP trainees used to record possible ideas, concerns, and expectations of patients.

- ▶ Reason for contact, orally expressed by the patient:
For example, 'I have requested a consultation because of ...'
- ▶ Ideas
Are the ideas of the patient about a possible diagnosis, treatment, or prognosis expressed in the consultation? (Yes/No)
If yes, what ideas are expressed?
- ▶ Concerns
Is concern (fear/worry) of the patient about a possible diagnosis or therapy present in the consultation? (Yes/No)
If yes, what are the concerns about?
- ▶ Expectations
Is the expectation (what the patient wants) for a treatment, a diagnosis, or a therapy present in the consultation? (Yes/No)
If yes, what are the expectations of the patient?



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H&E image analysis pipeline for quantifying morphological features

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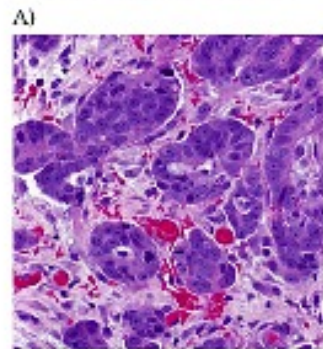
ABSTRACT

Detecting cell types from histopathological images is essential for various digital pathology applications. However, large number of cells in whole-slide images (WSIs) necessitates automated analysis pipelines for efficient cell type de-

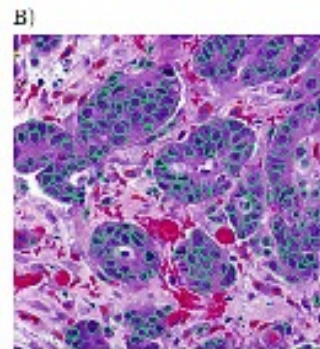
V. Ariotta et al.

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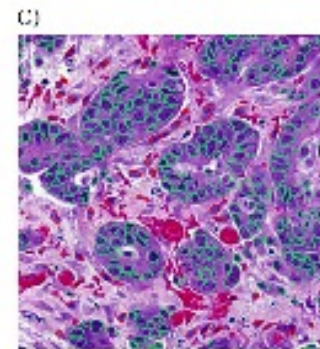
Original Tile



Predicted



Ground Truth



neoplastic
inflammatory
connective
dead
epithelial

SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for *KRAS* and *NRAS* Demonstrate Excellent Laboratory Performance

Ahmet Zehir, PhD; Valentina Nardi, MD; Eric Q. Konnick, MD, MS; Christina M. Lockwood, PhD; Thomas A. Long, MPH; Nikoletta Sidiropoulos, MD; Rhona J. Souers, MS; Patricia Vasalos, BS; Neal I. Lindeman, MD; Joel T. Moncur, MD, PhD, MS

• **Context.**—The Sustainable Predictive Oncology Therapeutics and Diagnostics quality assurance pilot study (SPOT/Dx pilot) on molecular oncology next-generation sequencing (NGS) reportedly demonstrated performance limitations of NGS laboratory-developed tests, including discrepancies with a US Food and Drug Administration–approved companion diagnostic. The SPOT/Dx pilot methods differ from those used in proficiency testing (PT) programs.

Objective.—To reanalyze SPOT/Dx pilot data using PT program methods and compare to PT program data.

Design.—The College of American Pathologists (CAP

Results.—Overall detection rates of *KRAS* and *NRAS* single-nucleotide variants (SNVs) and multinucleotide variants (MNVs) by SPOT/Dx pilot laboratories were 96.8% (716 of 740) and 81.1% (129 of 159), respectively. In CAP PT programs, the overall detection rates for the same SNVs and MNVs were 97.2% (2671 of 2748) and 91.8% (1853 of 2019), respectively. In 2022, the overall detection rate for

CONCLUSIONS

Reanalysis of the SPOT/Dx study data with methods modeled after established PT programs revealed an overall detection rate of 96.8% for SNVs and 81.1% for MNVs. The comparison with CAP PT program data, obtained from hundreds of laboratories at multiple time points, is a much more substantial representation of laboratory practice, and it demonstrated overall SNV and MNV detection rates of 97.2%

ISSUES

IN SCIENCE AND TECHNOLOGY

NATIONAL ACADEMIES OF SCIENCES,
ENGINEERING, AND MEDICINE
ARIZONA STATE UNIVERSITY

THE LATEST

How Health Data Integrity Can Earn Trust and Advance Health

JOCHEN LENNERZ, NICK SCHNEIDER, KARL LAUTERBACH

Health care providers and researchers now have an unprecedented wealth of



TRAVIS WHITFILL AND MARIANA MAZZUCATO

Offer Taxpayers a Fairer Shake

US drug companies turn taxpayer-funded innovation into astronomical profits.
A new agency focused on health innovation could shift the rewards
of medical advances to benefit public health.



Synergies and Challenges in the Preclinical and Clinical Implementation of Pathology Artificial Intelligence Applications

Hammad A. Qureshi, PhD;
Runjan Chetty, MBBCh, FRCPC, FRCPA, FRCPath, DPhil (Oxon);
Jogile Kuklyte, PhD; Karl Ratcliff; Maria Morrissey, PhD; Cairiona Lyons, PhD;
and Mairin Rafferty, PhD

Abstract

Recent introduction of digitalization in pathology has disrupted the field greatly with the potential to change the area immensely. Digital pathology has created the potential of applying advanced AI

CHALLENGES IN AI IMPLEMENTATION

TABLE 1. Scanners and Image Formats Supported*

Scanners	WSI Viewer	Format
Philips	Philips IntelliSite Pathology Solutions (PIPS)	iSyntax
3D Histech	SlideViewer/CaseViewer	MRXS, JPG, JPEG2000
Digipath Pathscope	PathSuite	Joint Photographic Experts Group (JPEG)
Hamamatsu	NDP.view2	JPEG, NDPI, VMS, VMU, SVS, SCN, MRXS, CZI, VSI
Huron	HuronViewer	BigTIFF (DICOM Compliant)
Leica	Aperio ImageScope/ WebScope	TIFF (SVS), SCN
Olympus	VS200	VSI, TIFF
Sakura Finetek	VisionTek Viewer	BigTIFF, TIFF, JPEG2000, SVSLIDE
Ventana	uPath	BIF, TIFF, JPEG2000
Optriscan	Optriscan Image Viewer	TIFF, JPEG2000

*BioImagene Image File (BIF), Big Tag Image File Format (BigTIFF), Carl Zeiss Image (CZI), Joint Photographic Experts Group (JPG/JPEG), MIRAX format (MRXS), NanoZoomer Digital Pathology Image (NDPI), ScanScope Virtual Slide (SVS), Leica Scan files (SCN), Virtual Microscope Image Standards (VMS, VMU) by Hamamatsu, Olympus VSI format (VSI)

application areas in pathology that are likely to be made possible only by the modern digital

TABLE 2. WSI Viewer Features and Comparison^a

Viewer	Type	Regulatory Status	Platform	Features
PaigeAI FullFocus Viewer	Proprietary	FDA cleared, CE-marked IVD	Cloud	LIS/LIMS integration and AI support
QuPath	Opensource	None	Windows, MacOS X, and Linux	Stain estimation, reporting, color transformation, AI support, and annotation
Deciphex Patholytix	Proprietary	Nondinical GLP compliant	Windows and Linux	GLP compliant workflow, AI support, image QC, WSI synced data capture, annotation, advanced visualization and multi-image display, and advanced quantification and measurements
Cytomine	Opensource	None	Web-based	Machine learning, object classification, scripting, annotation, user-behavior analytics, and multi-image display
Dynamyx	Proprietary	Research use only (US); CE-marked IVD	Web-based	LIS/LIMS integration, case management, collaboration, measure/quantify, annotate, coregister and multiple slides and view
Orbit	Opensource	None	Windows, Linux, and MacOS	Omero connectivity, spark integration, DL/ML ready, scripting support, object segmentation/classification, and annotations
ASAP	Opensource	None	Windows and Linux	Annotation, overlay-based visualization, ML support, and plugins
Sectra Digital Pathology Solution	Proprietary	FDA-cleared, CE-marked IVD	Web-based	LIMS/EMR integration, AI integration (any vendor), radiology PACs integration
Philips Intelisite Pathology Suite	Proprietary	FDA cleared	Web-based	Work-flow management, real-time collaboration, and measurement/annotation support
NDP.view2	Proprietary	None	Window and MacOS	Annotation, multiview of slides, case view, histogram, and LUT control

^aAI, Artificial Intelligence; CE, Conformité Européenne; DL, Deep Learning; EMR, Electronic Medical Records; FDA, Food and Drug Administration; GLP, Good Laboratory Practice; LIS/LIMS, Laboratory Information System and Laboratory Information Management System; LUT, Look-Up Table; ML, Machine Learning; PACS, Picture Archiving and Communication System; US, United States.

Digital and Computational Pathology: What a Time to Be Alive!

There is no doubt that the field of pathology is undergoing radical transformation, thanks to its digitalization and the emergence of artificial intelligence (AI). What was once a discipline that was heavily reliant on manual examination and interpretation under the microscope is rapidly entering an era where vast amounts of data will increasingly be managed in entirely digital workflows and analyzed with unprecedented precision and efficiency. The incorporation of AI and other digital tools is reshaping the specialty in a way that is not merely an in-

The timely article by Qureshi et al² published in this issue of *Mayo Clinic Proceedings: Digital Health* offers a valuable compass for navigating this journey. It combs through the literature, casting light on areas that are primed for an early adoption of Digital and Computational Pathology (DCP), while also highlighting the most pressing challenges on the horizon.

After reviewing the current landscape of digital slide scanners and WSI viewers and formats, the authors delve into the recent literature and identify the hottest areas of

RESEARCH ARTICLE

Open Access



The value of structured data elements from electronic health records for identifying subjects for primary care clinical trials

Mohammad B. Ateya^{1*}, Brendan C. Delaney² and Stuart M. Speedie³

Abstract

Background: An increasing number of clinical trials are conducted in primary care settings. Making better use of existing data in the electronic health records to identify eligible subjects can improve efficiency of such studies. Our study aims to quantify the proportion of eligibility criteria that can be addressed with data in electronic health records and to compare the content of eligibility criteria in primary care with previous work.

A comprehensive characterization of the cell-free transcriptome reveals tissue- and subtype-specific biomarkers for cancer detection

Matthew H. Larson^{1,2}✉, Wenying Pan^{1,2}, Hyunsung John Kim¹, Ruth E. Mauntz¹, Sarah M. Stuart¹,
Monica Pimentel¹, Yiqi Zhou¹, Per Knudsgaard¹, Vasiliki Demas¹, Alexander M. Aravanis¹ & Arash Jamshidi¹

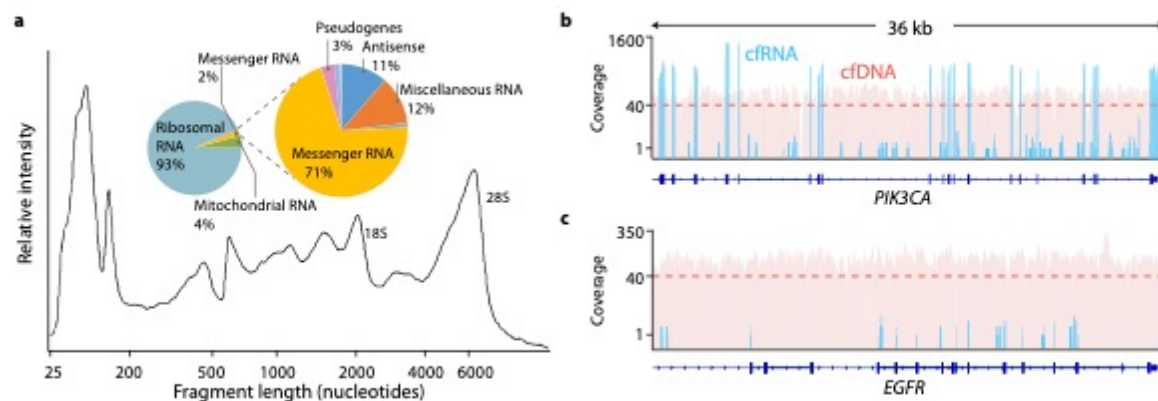


Fig. 1 Analytical characterization of cell-free RNA. **a** Fragment Analyzer (Agilent) trace of cRNA fragment lengths in a non-cancer sample following deoxyribonuclease (DNase) digestion. Inset: Relative proportion of different RNA types found by whole-transcriptome sequencing in a representative non-cancer sample prior to abundant transcript depletion. Sequencing coverage across a 36 kb region of **b** *PIK3CA*, a high abundance cell-free RNA gene, and



Multi-omic and functional analysis for classification and treatment of sarcomas with FUS-TFCP2 or EWSR1-TFCP2 fusions

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Julia Schöpf^{1,2,3,27}, Sebastian Uhrig^{4,5,27}, Christoph E. Heilig^{2,5,27}, Kwang-Seok Lee^{2,27}, Tatjana Walther², Alexander Carazzato², Anna Maria Dobberkau⁶, Dieter Weichenhan⁷, Christoph Plass⁷, Mark Hartmann⁶, Gaurav D. Diwan^{8,9}, Zunamys I. Carrero^{10,11}, Claudia R. Ball^{10,11,12,13}, Tobias Hohl^{1,3}, Thomas Kindler^{14,15,16}, Patricia Rudolph-Hähnel^{14,15,16}, Dominic Helm¹⁷, Martin Schneider¹⁷, Anna Nilsson¹⁸, Ingrid Øra¹⁹, Roland Imle^{20,21,22}, Ana Banito^{20,21}, Robert B. Russell^{8,9}, Barbara C. Jones^{5,21,22}, Daniel B. Lipka⁶, Hanno Glimm^{10,11,12,23}, Daniel Hübschmann^{4,5,24}, Wolfgang Hartmann²⁵, Stefan Fröhling^{2,5,26,28} ✉ & Claudia Scholl^{1,28} ✉

Linking clinical multi-omics with mechanistic studies may improve the understanding of rare cancers. We leverage two precision oncology programs

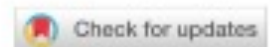
Comparison of Commercial AI Software Performance for Radiograph Lung Nodule Detection and Bone Age Prediction

Kicky G. van Leeuwen, MSc • Steven Schalekamp, MD, PhD • Matthieu J. C. M. Rutten, MD, PhDs • Merel Huisman, MD, PhD • Cornelia M. Schaefer-Prokop, MD, PhD • Maarten de Rooij, MD, PhD • Bram van Ginneken, PhD • Bas Maresch, MD • Bram H. J. Geurts, MD • Cornelius F. van Dijke, MD, PhD • Emmeline Laupman-Koedam, MD • Enzo V. Hulleman, MD • Eric L. Verboeff, MD • Evelyne M. J. Meys, MD, PhD • Firdaus A. A. Mohamed Hoessein, MD, PhD • Floor M. ter Brugge, MD • Francois van Hoorn, MD • Frank van der Wel, Ad • Inge A. H. van den Berk, MD • Jacqueline M. Lucyendijk, MD • James Meakin, PhD • Jesse Habets, MD, PhD • Jonathan I. M. L. Verbeke, MD • Joost Nederend, MD, PhD • Karlijn M. E. Meys, MD • Laura N. Deden, MSc • Lucianne C. M. Langezaal, MD • Mahtab Nasrollah, MD • Marleen Meij, MD • Martijn F. Boomsma, MD, PhD • Matthijs Vermeulen, MD • Myrthe M. Vesterling, MD • Onno Vijlbrief, MD • Paul Algra, MD • Selma Algra, MD, PhD • Stijn M. Bollen, MD • Tijs Samson, PDEng • Yntor H. G. von Brucken Fock, MD • for the Project AIR Working Group¹

From the Department of Medical Imaging, Radboud University Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, the Netherlands (K.G.v.L., S.S., M.J.C.M.R., M.H., C.M.S.P., M.d.R., B.v.G., B.H.J.G., J.M.); Department of Radiology (M.J.C.M.R.) and Department of MICT and Imaging Techniques (T.S.), Jeroen

Conclusion: Compared with human readers, four AI algorithms for detecting lung nodules on chest radiographs showed improved performance, whereas the remaining algorithms tested showed no evidence of a difference in performance.

BRIEF COMMUNICATION OPEN



Diagnostic reasoning prompts reveal the potential for large language model interpretability in medicine

Thomas Savage ^{1,2}✉, Ashwin Nayak ^{1,2}, Robert Gallo^{3,4}, Ekanath Rangan ¹ and Jonathan H. Chen ^{1,2,5,6}

One of the major barriers to using large language models (LLMs) in medicine is the perception they use uninterpretable methods to make clinical decisions that are inherently different from the cognitive processes of clinicians. In this manuscript we develop diagnostic reasoning prompts to study whether LLMs can imitate clinical reasoning while accurately forming a diagnosis. We find that GPT-4 can be prompted to mimic the common clinical reasoning processes of clinicians without sacrificing diagnostic accuracy. This is significant because an LLM that can imitate clinical reasoning to provide an interpretable rationale offers physicians a means to evaluate whether an LLMs response is likely correct and can be trusted for patient care. Prompting methods that use diagnostic reasoning have the potential to mitigate the “black box” limitations of LLMs, bringing them one step closer to safe and effective use in medicine.

npj Digital Medicine (2024)7:20; <https://doi.org/10.1038/s41746-024-01010-1>

<p>Question : A 30-year-old African American woman comes to the physician for the evaluation of a dry cough and chest discomfort for the past 3 days. During this period, the patient has had headaches, muscle aches, joint pain, fever, and chills. Ten days ago, she was hiking with her family in Mississippi. The patient has asthma that is treated with an albuterol inhaler. Her mother has a lung disease treated with methotrexate. The patient has smoked one pack of cigarettes daily for the past 10 years. Her temperature is 38.4°C (100.4°F). Physical examination shows slight wheezes throughout both lung fields. Laboratory studies and urinalysis are positive for polysaccharide antigen. Bronchoalveolar lavage using silver/PAS-staining shows macrophages filled with a dimorphic fungus with septate hyphae. What is the most likely cause of this patient's symptoms?</p> <p>Answer: Histoplasmosis</p>
<p>Traditional Chain-of-Thought (GPT-3.5) <i>'The patient has a dry cough, chest discomfort, and other symptoms such as fever, chills, headaches, and muscle aches. She has a positive polysaccharide antigen and bronchoalveolar lavage shows a dimorphic fungus with septate hyphae. This patient likely has Valley Fever.'</i></p>
<p>GPT-3.5 Differential Diagnosis CoT (GPT-3.5) <i>'The differential diagnosis for this patient includes: pneumonia, tuberculosis, eosinophilic pneumonia, hypersensitivity pneumonitis, and coccidioidomycosis. The patient's recent history of hiking in Mississippi and the presence of a dimorphic fungus with septate hyphae on bronchoalveolar lavage make coccidioidomycosis the most likely cause of her symptoms.'</i></p>
<p>GPT-3.5 Intuitive Reasoning CoT (GPT-3.5) <i>'The patient has a history of asthma, which increases the likelihood of asthma exacerbation. The positive result for polysaccharide antigen suggests atypical pneumonia. The presence of a dimorphic fungus with septate hyphae suggests the presence of fungal pneumonia. This patient most likely has fungal pneumonia.'</i></p>
<p>Analytic Reasoning CoT (GPT-3.5) <i>'The patient's recent history of hiking in Mississippi and the positive polysaccharide antigen and silver/PAS-staining results strongly suggest fungal pneumonia as the cause of her symptoms.'</i></p>
<p>Bayesian Inference CoT (GPT-3.5) <i>'The prior probability of blastomycosis is 1%, however the patient's recent travel increases the probability to 5%. The laboratory and urinalysis results increase the posterior probability to 30%. The presence of a dimorphic fungus on bronchoalveolar lavage increases the probability to 60%. This patient is likely suffering from blastomycosis.'</i></p>

Fig. 1 GPT 3.5 CoT and diagnostic reasoning rationale examples. Example GPT-3.5 rationales responding to a traditional CoT prompt as well as diagnostic reasoning prompts. LLM response and rationale results for the entire test set can be found in Supplementary Information 1.

Review

> [Nat Rev Clin Oncol](#). 2022 Apr;19(4):254-267. doi: 10.1038/s41571-022-00600-w.

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Immune-checkpoint inhibitors: long-term implications of toxicity

[Douglas B Johnson](#)¹, [Caroline A Nebhan](#)², [Javid J Moslehi](#)^{2 3}, [Justin M Balko](#)²

Affiliations + expand

PMID: 35082367 PMID: [PMC8790946](#) DOI: [10.1038/s41571-022-00600-w](#)

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ACTIONS

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Display Characteristics and Their Impact on Digital Pathology: A Current Review of Pathologists' Future "Microscope"

Jacob T. Abel¹, Peter Ouillette¹, Christopher L. Williams², John Blau³, Jerome Cheng¹, Keluo Yao⁴, Winston Y. Lee¹, Toby C. Cornish⁵, Ulysses G.J. Balis¹,
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Published: 11-Aug-2020

Abstract

Digital displays (monitors) are an indispensable component of a pathologists' daily workflow, from writing reports, viewing whole-slide images, or browsing the Internet. Due to a paucity of literature and experience surrounding display use and standardization in pathology, the Food and Drug Administration's (FDA) has currently restricted FDA-cleared whole-slide imaging systems to a specific model of display for each system, which at this time consists of only medical-grade (MG) displays. Further, given that a pathologists' display will essentially become their new surrogate "microscope," it becomes exceedingly important that all pathologists have a basic understanding of fundamental display properties and their functional consequences. This review seeks to: (a) define and summarize the current and emerging display technology, terminology,

Immunotherapy combination approaches: mechanisms, biomarkers and clinical observations

Lisa H. Butterfield¹✉ & Yana G. Najjar²✉

Abstract

The approval of the first immune checkpoint inhibitors provided a paradigm shift for the treatment of malignancies across a broad range

Sections

Introduction

Next testaments



Perspective

Opportunities for basic, clinical, and bioethics research at the intersection of machine learning and genomics

Shurjo K. Sen,^{1,*} Eric D. Green,¹ Carolyn M. Hutter,¹ Mark Craven,^{2,3} Trey Ideker,⁴ and Valentina Di Francesco^{1,*}

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<https://doi.org/10.1016/j.xgen.2023.100466>

SUMMARY

The data-intensive fields of genomics and machine learning researchers increasingly seek to harness the power of data; conversely, ML scientists recognize that genomic data are richly annotated datasets that can be used as a substrate for developing machine learning models.

Challenges facing the convergence of machine learning and genomics research:

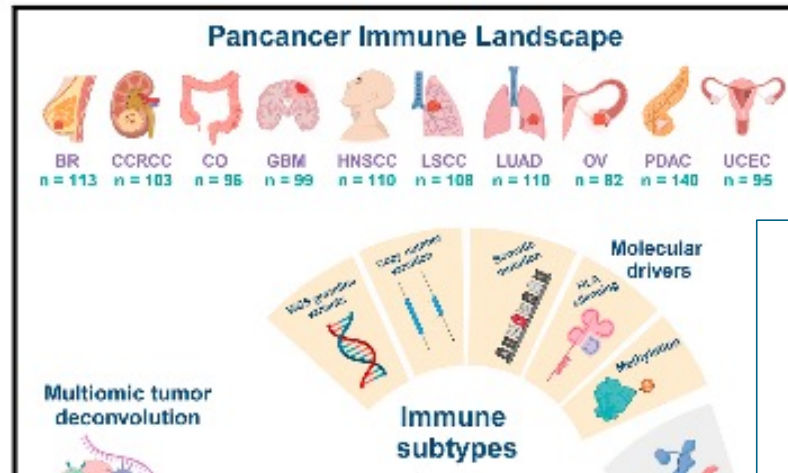
1. Limited availability of training datasets for machine learning models in genomics
2. Facilitating early and easy access to datasets coming out of consortium-based studies
3. Need for context-specific data (e.g., from different cell types and longitudinal experiments)
4. Difficulty in interpretation of outputs from machine learning models and causality inference
5. Limited ability of current machine learning models to include longitudinal data from clinical genomics studies
6. Lack of diversity in populations currently represented

Recommendations:

1. Increase data generation across matched omics datasets with extensive, standardized metadata
2. Promote the creation of machine learning models that can integrate genomics and other omics data from multiple cell types, individuals, and time points
3. Support functional testing of insights derived from machine learning applications
4. Develop machine learning methods for genomics that are less data-hungry but can yield rich biological, mechanistic, and causal insights
5. Consider and address social, environmental and health disparities of training datasets
6. Promote collaboration between researchers in bioethics, machine learning and genomics
7. Encourage machine learning algorithm development teams working in clinical settings to develop models that are interpretable and actionable.

Pan-cancer proteogenomics characterization of tumor immunity

Graphical abstract

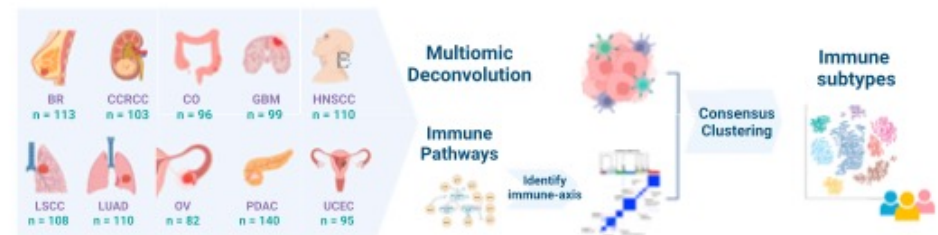


Authors

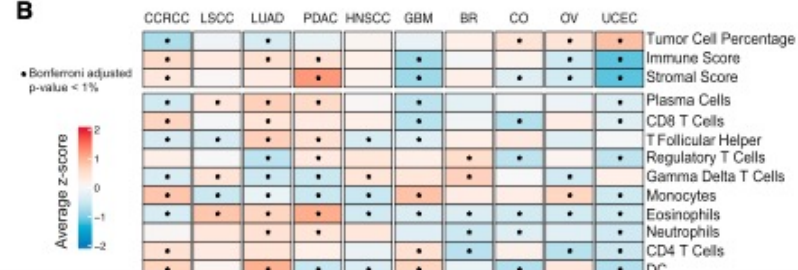
Francesca Petralia, Weiping Ma, Tomer M. Yaron, ..., Michele Ceccarelli, Pei Wang, Clinical Proteomic Tumor Analysis Consortium

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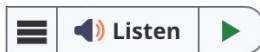
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Articles

Rethinking value in health innovation: *from mystifications towards prescriptions*

Mariana Mazzucato & Victor Roy

Pages 101-119 | Published online: 13 Dec 2018

Cite this article <https://doi.org/10.1080/17487870.2018.1509712>



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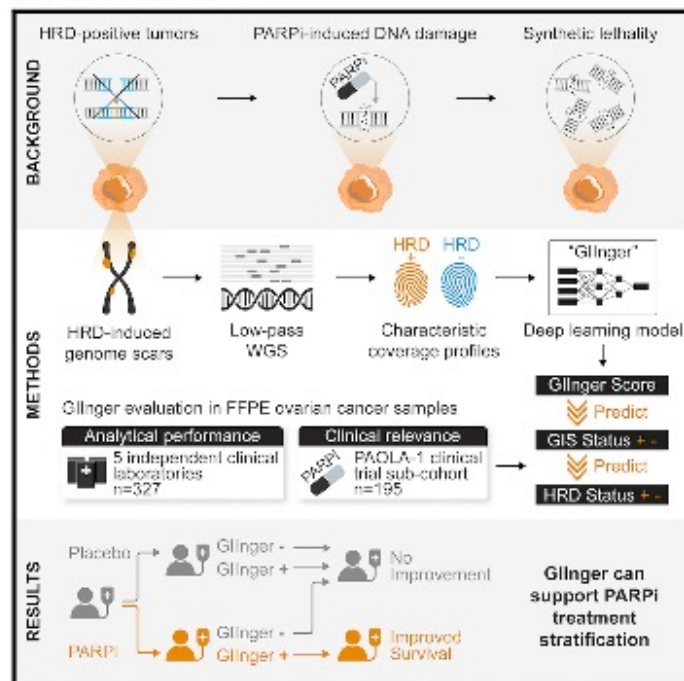
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In this article

Related re

GInger predicts homologous recombination deficiency and patient response to PARPi treatment from shallow genomic profiles

Graphical abstract



Authors

Christian Pozzorini, Gregoire Andre, Tommaso Coletta, ..., Pierre-Alexandre Just, Isabelle Ray-Coquard, Zhenyu Xu

Correspondence

z xu@sophiagenetics.com

In brief

Pozzorini et al. describe GInger, a deep learning method leveraging low-coverage sequencing data to identify HRD-induced scarring. Their multicenter study demonstrates reproducibly high concordance with the reference method. GInger is a cost-effective method to identify patients with PARPi-responsive ovarian cancer.

Special Issue: Celebrating 5 Years

Review

Clinical Development of BRAF plus MEK Inhibitor Combinations

Vivek Subbiah^{1,*}, Christina Baik² and John M. Kirkwood³

Genomic profiling shows that many solid tumors are characterized by specific driver aberrations, and this has expanded the therapeutic options for many patients. The mitogen-activating protein (MAPK) signaling pathway is a central driver pathway in many solid tumors. Driver mutations in this pathway are described in multiple solid tumor types. BRAF is a well-established target for inhibition in many solid tumors; however, most patients with BRAF-mutant tumors, combination therapy targeting BRAF and MEK

Highlights
Mutations in BRAF types and contribution to

Cell Reports Medicine

Review

Clinical development and management of adverse events associated with FGFR inhibitors

Vivek Subbiah^{1,3,*} and Srdan Verstovsek²

¹Sarah Cannon Research Institute, Nashville, TN, USA

²Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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*Correspondence: vivek.subbiah@scri.com

<https://doi.org/10.1016/j.xcrm.2023.101204>

SUMMARY

Approved fibroblast growth factor receptor (FGFR) inhibitors include erdafitinib, pemigatinib, and futibatinib. We review the most common toxicities associated with FGFR inhibitors and provide practical advice regarding their management. Hyperphosphatemia can be managed with careful monitoring, dose reduction or interruption, a prophylactic low-phosphate diet, and phosphate-lowering therapy. Ocular adverse events (AEs) are managed by withholding or adjusting the dose of the FGFR inhibitor. Dermatologic AEs include

Cell Reports Medicine

Review

Strategies for mitigating adverse events related to selective RET inhibitors in lung and thyroid cancer

Nelson,¹ Carmelia M.N. Barreto,¹ J. Hoyt Slade,^{1,4} Anna Poullard,¹ and Vivek Subbiah^{1,5,6,*}

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(FDA) approval of the selective RET inhibitors selpercatinib and pracinostat in the treatment of RET-altered lung and thyroid cancers has demonstrated a more tolerable safety and toxicity profile than multi-kinase inhibitors. This has led to a tissue-agnostic FDA approval for all RET-fusion-positive cancer types. Given the anticipated increase in the use of

Statistics did not prove that the Huanan Seafood Wholesale Market was the early epicentre of the COVID-19 pandemic

Dietrich Stoyan¹ and Sung Nok Chiu² 

¹Institut für Stochastik, TU Bergakademie Freiberg, Freiberg, Germany

²Department of Mathematics, Hong Kong Baptist University, Kowloon Tong, Hong Kong

Address for correspondence: Sung Nok Chiu, Department of Mathematics, Hong Kong Baptist University, Fong Shu Chuen Building, Ho Sin Hang Campus, Waterloo Road, Kowloon Tong, Hong Kong. Email: snchiu@hkbu.edu.hk

Abstract

In a recent prominent study, Worobey et al. (2022. The Huanan Seafood Wholesale Market in Wuhan was the early epicenter of the COVID-19 pandemic. *Science*, 377(6609), 951–959) purported to demonstrate statistically that the Huanan Seafood Wholesale Market was the epicentre of the early COVID-19 epidemic. We show that this statistical conclusion is invalid on two grounds: (a) The assumption that a centroid of early case locations or another simply constructed point is the origin of an epidemic is unproved. (b) A Monte Carlo test used to conclude that no other location than the seafood market can be the origin is flawed. Hence, the question of the origin of the pandemic has not been answered by their statistical analysis.

Keywords: centre of point cloud, COVID-19, critique of statistical methods, Monte Carlo test

Remote Pathology Practice

The Time for Remote Diagnostic Pathology in This Digital Era is Now

Casey P. Schukow, DO; Timothy Craig Allen, MD, JD

The coronavirus disease 2019 (COVID-19) pandemic exacerbated pathologists' retirement and increased pathologists' burnout, worsening the pathologist shortage. Medicine suffers from an unprecedented and growing pathologist shortage impacting hospital systems and their patients within the United States and worldwide. This shortage continues to erode pathologists' ability to serve all our patients' diagnostic needs; however, few immediate solutions are apparent. Digital pathology and remote pathology diagnosis have a growing capacity to improve pathologists' ability to serve our patients. On May 11, 2023, the Centers for Medicare & Medicaid Services (CMS), which "regulates all laboratory testing (except research) performed on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA),"¹ in cooperation with the Department of Health and Human Services over-

equipment. Therefore, the remote review of these materials does not require equipment that is essential to being a separate laboratory, while maintaining the accuracy, reliability, and timeliness of laboratory results.³

As such, pathologists' freedom to practice remotely remains intact postpandemic.

On May 16, 2023, the College of American Pathologists (CAP) released an advocacy update summarizing this new CLIA post-public health emergency guidance (see Table 1),⁴ which supersedes prior CMS directions regarding digital pathology and remote practice.^{3,4} The COVID-19 pandemic spotlighted the importance of laboratory medicine in diagnostic testing for societies and health care systems, but the pandemic's demands simultaneously accelerated an already critical patholo-

This Issue

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Viewpoint

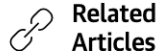
December 14, 2023

Increasing Telehealth Access Through Licensure Exceptions

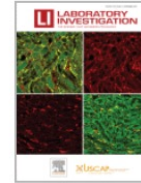
Carmel Shachar, JD, MPH¹; Kaylee Wilson²; Ateev Mehrotra, MD³

» [Author Affiliations](#)

JAMA. 2024;331(1):19-20. doi:10.1001/jama.2023.24960





At the start of the COVID-19 pandemic, temporary regulatory changes were implemented by almost all states to allow physicians to provide telehealth across state lines. Unfortunately, few of these flexibilities survived the end of the public health emergency.¹ Physicians and patients are frustrated because these changes have cut off many patients from their physicians,² which is particularly difficult for patients with rare illnesses, such as cancer, who may lack local physicians who can treat their condition.³



Review Article

Revolutionizing Digital Pathology With the Power of Generative Artificial Intelligence and Foundation Models

Asim Waqas^{a b}  , Marilyn M. Bui^{a c d}, Eric F. Glassy^e, Issam El Naqa^a,
Piotr Borkowski^{f g}, Andrew A. Borkowski^{d h i}, Ghulam Rasool^{a b d j}

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RESEARCH

Open Access



Coding undiagnosed rare disease patients in health information systems: recommendations from the RD-CODE project

Céline Angin^{1*}, Monica Mazzucato², Stefanie Weber³, Kurt Kirch³, Waed Abdel Khalek⁴, Houda Ali⁴, Sylvie Maiella⁴, Annie Oly⁴, Anne-Sophie Jannot^{1,5} and Ana Rath⁴

Abstract

Background In European Union countries, any disease affecting less than 5 people is rare. As expertise is scarce and rare diseases (RD) are complex, RD patients can remain undiagnosed for years. The period of searching for a diagnosis, called diagnostic delay, sometimes leads to a diagnostic dead end when the patient's disease is impossible to diagnose after undergoing all available in-depth tests. Extensive efforts have been made to support the implementation of ORPHA nomenclature for coding undiagnosed rare diseases in health information systems.

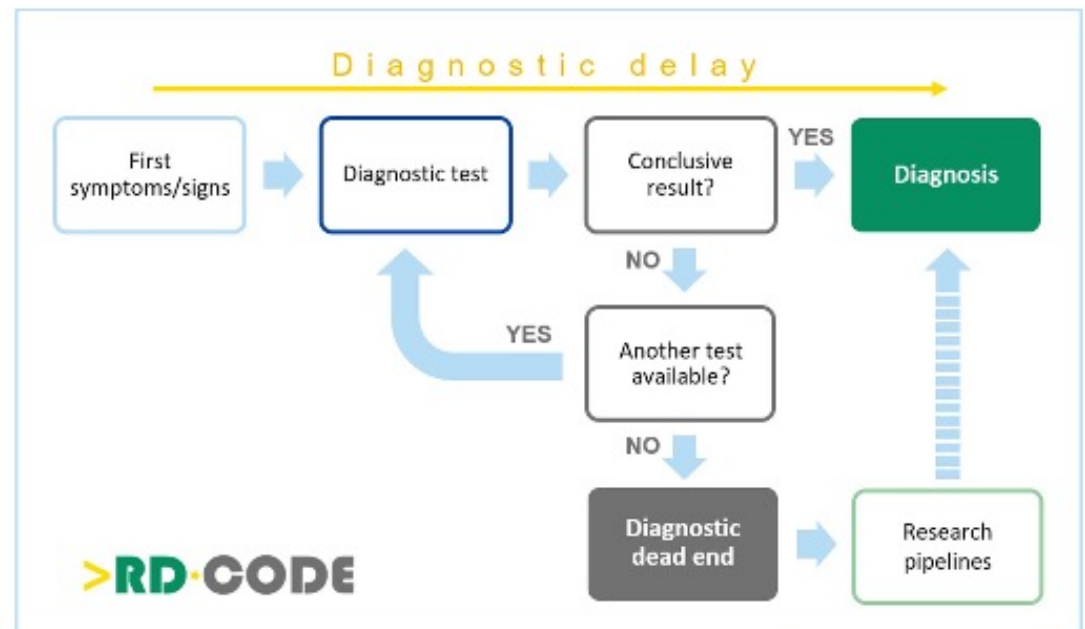


Fig. 2 A graphic representation of the workflow toward diagnosis

REVIEW

Open

Oncogenic alterations in advanced NSCLC: a molecular super-highway

Alex Friedlaender^{1,6}, Maurice Perol², Giuseppe Luigi Banna^{3,4}, Kaushal Parikh⁵ and Alfredo Addeo^{6*}

Abstract

Lung cancer ranks among the most common cancers world-wide and is the first cancer-related cause of death. Classification of lung cancer has evolved tremendously over the past two decades. Today, non-small cell lung cancer (NSCLC), particularly lung adenocarcinoma, comprises a multitude of molecular oncogenic subsets that impact both the prognosis and management of disease.

Since the first targeted oncogenic alteration identified in 2004 with the epidermal growth factor receptor (EGFR) mutation, the landscape of NSCLC treatment has been transformed. Today, both kinase inhibitors and antibody–drug conjugates are approved



Fig. 2 FDA timeline of drug approvals. Since 2003, there has been a rapid acceleration of drug development and approvals for molecular targeted therapies in NSCLC. Today, both kinase inhibitors and antibody–drug conjugates are approved



Fig. 3 EMA timeline of drug approvals. Since 2003, there has been a rapid acceleration of drug development and approvals for molecular targeted therapies in NSCLC. Today, both kinase inhibitors and antibody–drug conjugates are approved



Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial

Received: 25 July 2023

Accepted: 11 December 2023

Published online: 09 January 2024

Check for updates

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

Pancreatic and colorectal cancers are often KRAS mutated and are incurable when tumor DNA or protein persists or recurs after curative intent therapy. Cancer vaccine ELI-002 2P enhances lymph node delivery and immune response using amphiphile (Amph) modification of C12D and C12P.

scientific reports

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Magnitude of effect and sample size justification in trials supporting anti-cancer drug approval by the US Food and Drug Administration

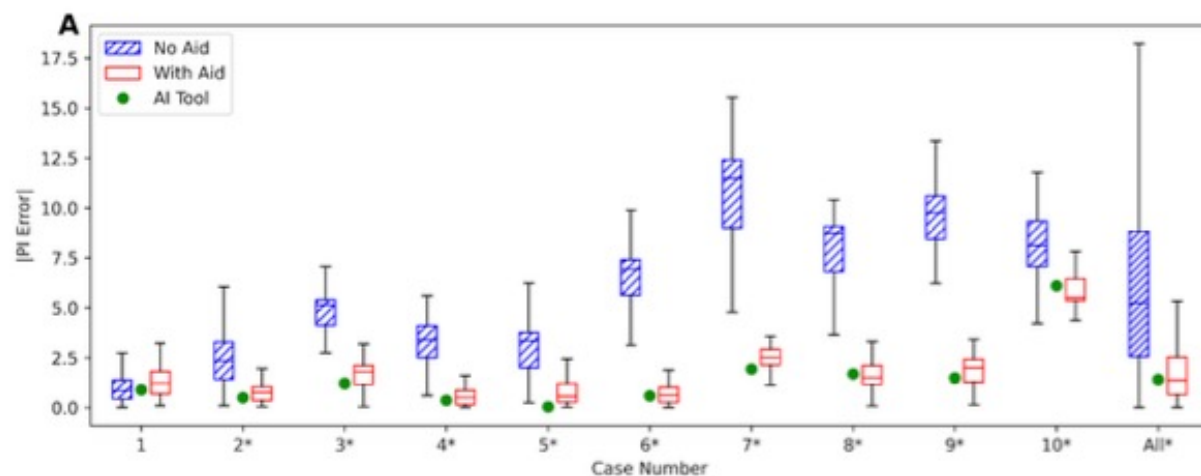
Michelle B. Nadler¹✉, Brooke E. Wilson^{1,2}, Alexandra Desnoyers^{1,3}, Consolacion Molto Valiente¹, Ramy R. Saleh⁴ & Eitan Amir¹

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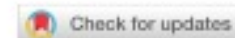
OPEN **AI improves accuracy, agreement and efficiency of pathologists for Ki67 assessments in breast cancer**

Amanda Dy^{1,3}, Ngoc-Nhu Jennifer Nguyen², Julien Meyer³, Melanie Dawe⁴, Wei Shi⁴, Dimitri Androutsos¹, Anthony Fyles⁴, Fei-Fei Liu⁴, Susan Done⁴ & April Khademi^{1,5,6,7,8}

The Ki-67 proliferation index (PI) guides treatment decisions in breast cancer. However, low inter-rater reproducibility. Although AI tools help, their impact on pathologists' work remains understudied. 9



PERSPECTIVE OPEN



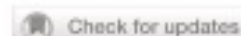
An intriguing vision for transatlantic collaborative health data use and artificial intelligence development

Daniel C. Baumgart¹

Our traditional approach to diagnosis, prognosis, and treatment, can no longer process and transform the enormous volume of information into therapeutic success, innovative discovery, and health economic performance. Precision health, i.e., the right treatment, for the right person, at the right time in the right place, is enabled through a learning health system, in which medicine and multidisciplinary science, economic viability, diverse culture, and empowered patient's preferences are digitally integrated and conceptually aligned for continuous improvement and maintenance of health, wellbeing, and equity. Artificial intelligence (AI) has been successfully evaluated in risk stratification, accurate diagnosis, and treatment allocation, and to prevent health disparities. There is one caveat though: dependable AI models need to be trained on population-representative, large and deep data sets by multidisciplinary and multinational teams to avoid developer, statistical and social bias. Such applications and models can neither be created nor validated with data at the country, let alone institutional level and require a new dimension of collaboration, a cultural change with the establishment of trust in a precompetitive space. The Data for Health (#DFH23) conference in Berlin and the Follow-Up Workshop at Harvard University in Boston hosted a representative group of stakeholders in society, academia, industry, and government. With the momentum #DFH23 created, the European Health Data Space (EHDS) as a solid and safe foundation for consented collaborative health data use and the G7 Hiroshima AI process in place, we call on citizens and their governments to fully support digital transformation of medicine, research and innovation including AI.

npj Digital Medicine (2024)7:19; <https://doi.org/10.1038/s41746-024-01005-y>

CORRESPONDENCE OPEN



Integrity matters in oncology: AORTIC takes a stand against research misconduct

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Oncology is a rapidly evolving field globally, with a growing need to maintain research integrity. The African Organization for Research and Training in Cancer (AORTIC) has initiated a comprehensive training program to enhance research quality and integrity in African oncology. This program covers topics such as predatory publishing, data manipulation, plagiarism, "paper mills," gender equity, and the critical appraisal of clinical trials and meta-analyses beyond statistical significance. This emphasizes the importance of ethical conduct and responsible research in enhancing cancer care through research. The commitment of the AORTIC serves as a model for other oncology societies in low- and middle-income countries, highlighting the importance of education and training to reduce disparities in cancer research and empower African researchers.

BJC Reports; <https://doi.org/10.1038/s44276-023-00032-8>

characteristics of predatory and hijacked journals as well as their deceptive tactics used to attract researchers and bypass the peer-review system, which is a vital component of research. The



Molecular Testing in Non–Small-Cell Lung Cancer: A Call to Action

Arani Sathiyapalan, MD, MSc^{1,2} and Peter Michael Ellis, MBBS, MMed, PhD^{1,2} 

DOI <https://doi.org/10.1200/JCO.2023.00669>

It has been nearly 15 years since the IPASS trial first demonstrated the importance of molecular testing to identify the population of patients with non–small-cell lung cancer (NSCLC) that benefit from molecularly targeted therapy.¹ Molecular genomic testing has become more widespread since then, with an increasing number of molecular targets and molecularly targeted therapies. As many as 50% of patients with advanced NSCLC are found to have an actionable oncogenic driver (including *KRAS* mutations).² In these patients, targeted treatments with tyrosine kinase inhibitors (TKIs) have been shown to improve overall response rates and progression-free survival (PFS) and are generally more tolerable than chemo(immuno)therapy.

Current clinical guidelines (European Society for Medical Oncology, ASCO) recommend broad-

ACCOMPANYING CONTENT

 [Article, p. 145](#)

Accepted October 25, 2023

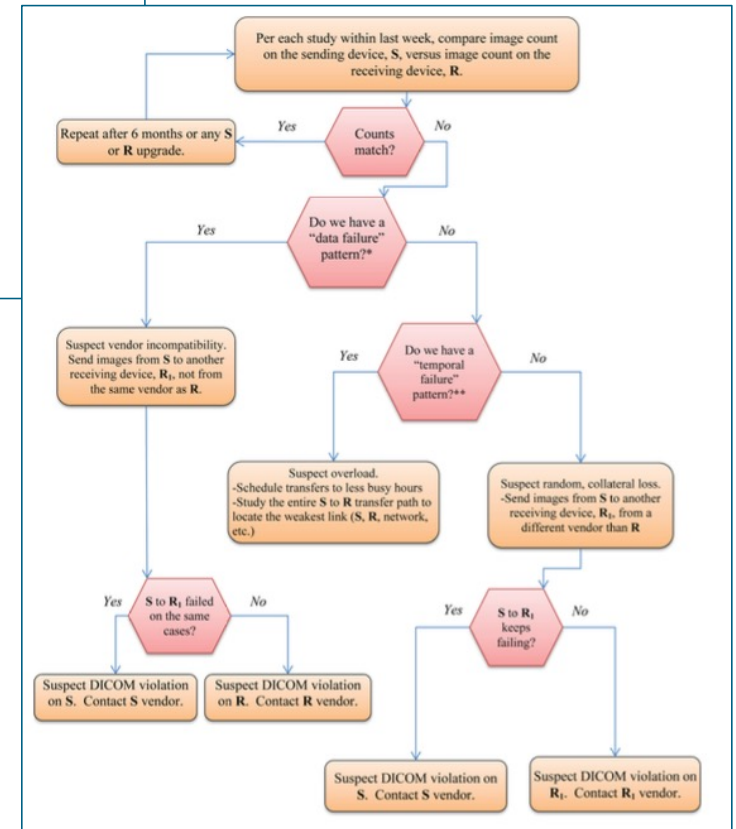
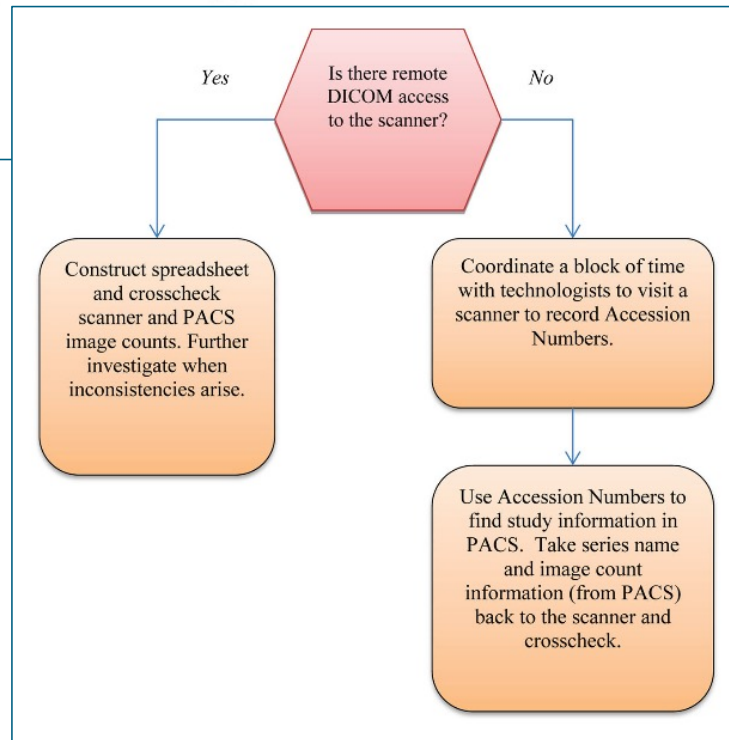
Published November 30, 2023

JCO Oncol Pract 20:7-9

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Losing Images in Digital Radiology: More than You Think

Catherine Oglevee · Oleg Pianykh



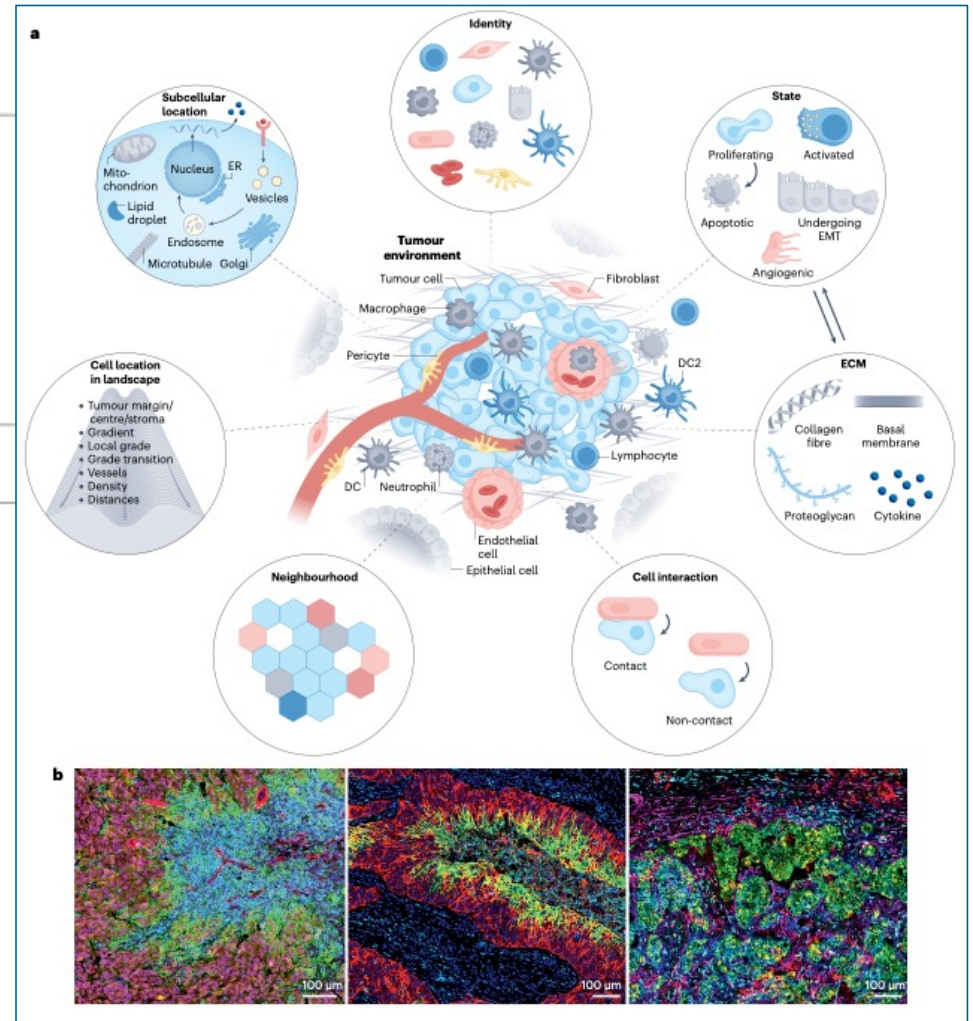
Review article

Multiplex protein imaging in tumour biology

Natalie de Souza^{1,2,3}, Shan Zhao^{1,3} & Bernd Bodenmiller^{1,3} ✉

Abstract

Tissue imaging has become much more colourful in the past decade. Advances in both experimental and analytical methods now make it possible to image protein markers in tissue samples in high multiplex. The ability to simultaneously image 40–50 markers simultaneously at



A Nationwide Network of Health AI Assurance Laboratories

Nigam H. Shah, MBBS, PhD; John D. Halamka, MD, MS; Suchi Saria, PhD; Michael Pencina, PhD; Troy Tazbaz, BS; Micky Tripathi, PhD, MPP; Alison Callahan, PhD; Hailey Hildahl, BS; Brian Anderson, MD

IMPORTANCE Given the importance of rigorous development and evaluation standards needed of artificial intelligence (AI) models used in health care, nationwide accepted procedures to provide assurance that the use of AI is fair, appropriate, valid, effective, and safe are urgently needed.

OBSERVATIONS While there are several efforts to develop standards and best practices to evaluate AI, there is a gap between having such guidance and the application of such guidance to both existing and new AI models being developed. As of now, there is no publicly available, nationwide mechanism that enables objective evaluation and ongoing assessment of the consequences of using health AI models in clinical care settings.

CONCLUSION AND RELEVANCE The need to create a public-private partnership to support a nationwide health AI assurance labs network is outlined here. In this network, community best practices could be applied for testing health AI models to produce reports on their performance that can be widely shared for managing the lifecycle of AI models over time and across populations and sites where these models are deployed.

JAMA. doi:10.1001/jama.2023.26930
Published online December 20, 2023.

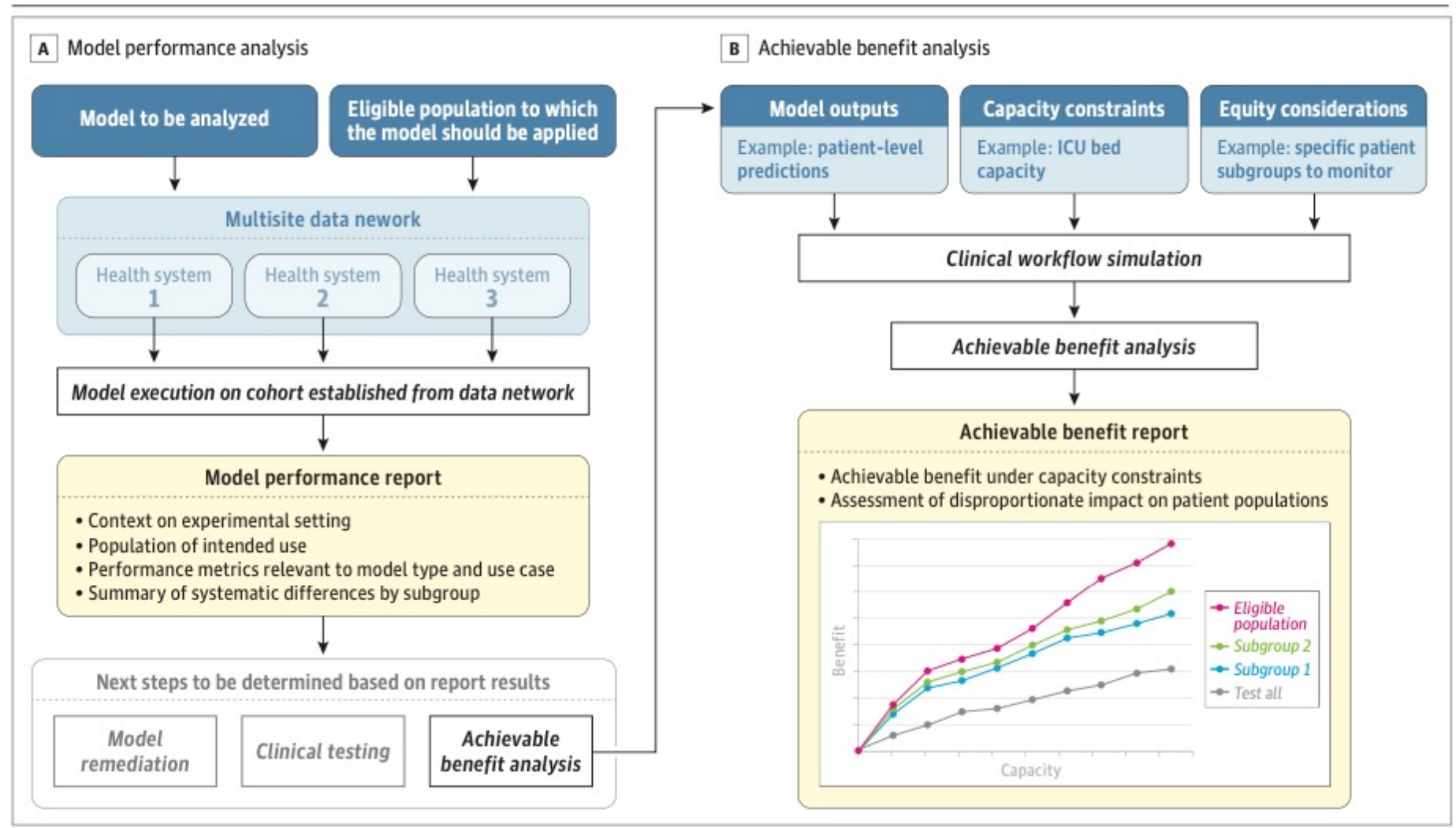
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Author Affiliations: Author affiliations are listed at the end of this article.

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Figure. Example Reports That Can Be Generated by an Assurance Laboratory



REVIEW

Open Access



Challenges and barriers of using large language models (LLM) such as ChatGPT for diagnostic medicine with a focus on digital pathology – a recent scoping review

Ehsan Ullah¹, Anil Parwani², Mirza Mansoor Baig³ and Rajendra Singh^{4*}

Table 2 Key differences between Image-based and Laboratory-based Diagnostics with a focus on LLM applications

Feature	Image-based diagnostics	Laboratory-based diagnostics
Data source	Medical images	Blood, tissue, other bodily fluids
Analysis method	Visual analysis, image processing, AI	Biochemical analysis, genetic testing, pathogen detection
Strengths	Non-invasive, rapid, can visualize anatomical structures	More specific, quantitative, can detect biochemical changes
Limitations	Subjective, requires trained specialists, prone to artifacts	Invasive, time-consuming, may not be specific to a single disease
LLM applications	Image analysis, classification, possibly segmentation and lesion characterisation	Analysing test results, predicting disease risk, identifying new biomarkers



Events

Next steering
committee
meeting

3/27/2024
3PM EST