Publications

From trial => RWE

- Preregistration of real-world evidence (RWE) study protocols provides transparency and sa result-driven post h doesn't ensure valic
- Unlike randomized with primary data c utilizing secondary unique challenges i and reliability.
- Thorough data expl before protocol registration are crucial for identifying and addressing potential issues with data sources and measurement algorithms, ultimately enhancing the validity of the study design and findings.

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Viewpoint

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April 8, 2024

Data Checks Before Registering Study Protocols for Health Care Database Analyses

Shirley V. Wang, PhD[1]; Sebastian Schneeweiss, MD, ScD[1]

» Author Affiliations | Article Information

JAMA. Published online April 8, 2024. doi:10.1001/jama.2024.2988

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma

Choueiri TK et al. DOI: 10.1056/NEJMoa2312695

CLINICAL PROBLEM

The anti–programmed death 1 antibody pembrolizumab was approved by the Food and Drug Administration as adjuvant therapy after surgery for renal-cell carcinoma on the basis of improvements in disease-free survival observed in the KEYNOTE-564 trial. Data on overall survival are needed.

CLINICAL TRIAL

Design: The phase 3, double-blind, randomized, placebo-controlled KEYNOTE-564 trial examined the efficacy and safety of pembrolizumab in patients who were disease-free according to investigator assessment after surgery for clear-cell renal-cell carcinoma.

Intervention: 994 participants who had undergone surgery in the previous 12 weeks and had an increased risk of recurrence were assigned to receive intravenous pembrolizumab (200 mg) or placebo every 3 weeks for up to 17 cycles. The key secondary end point was overall survival. (As noted, disease-free survival, the primary end point, was reported previously.)

RESULTS

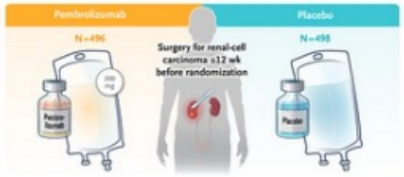
Efficacy: At the third interim analysis, after a median follow-up of 57.2 months, overall survival was significantly improved with pembrolizumab as compared with placebo.

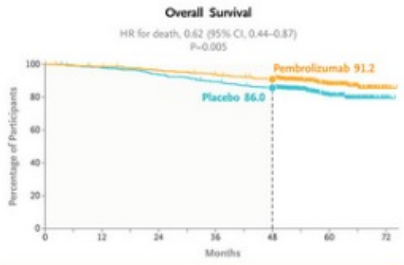
Safety: Serious adverse events, grade 3 or 4 adverse events related to pembrolizumab or placebo, and discontinuations of pembrolizumab or placebo due to adverse events occurred more often in the pembrolizumab group.

LIMITATIONS AND REMAINING QUESTIONS

- Some key subgroups (e.g., participants with high-risk stage M0 disease) had small sample sizes and numbers of deaths. In addition, subgroup analyses were hypothesis-generating, given that no formal statistical testing was planned.
- Additional data are needed to determine key considerations for the selection of subsequent systemic therapy in patients who have recurrence with distant metastasis after receiving adjuvant pembrolizumab.

Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

Among patients with clear-cell renal-cell carcinoma at increased risk for recurrence after surgery, adjuvant pembrolizumab significantly improved overall survival, as compared with placebo.

Data Sharing Statement

Choueiri TK, Tomczak P, Park SH, et al. Overall Survival with Adjuvant Pembrolizumab in Renal-Cell Carcinoma. N Engl J Med. DOI: 10.1056/NEJMoa2312695.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	Complete de-identified patient data set. Other (eg, partial data sets) — please describe
Additional information about data	—
How or where can the data be obtained?	Merck & Co., Inc.'s data sharing policy, including restrictions is available at : http://engagezone.merck.com/ds_documentation.php. Requests for access to the clinical study data can be submitted thru the Engage Zone site or via email to: dataaccess@merck.com
When will data availability begin?	Beginning Date: After product approval in US and EU or after product development is discontinued
When will data availability end?	End Date:
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—
When will supporting documents availability begin?	Beginning Date:
When will supporting documents availability end?	End Date:
To whom will data be available?	Qualified scientific researchers
For what type of analysis or purpose?	Scientific purpose outlined in a proposal
By what mechanism?	After researcher enters into a standard data sharing agreement and the proposal is approved.
Any other restrictions?	Researchers must commit to transparency in publication

Cell
Leading Edge

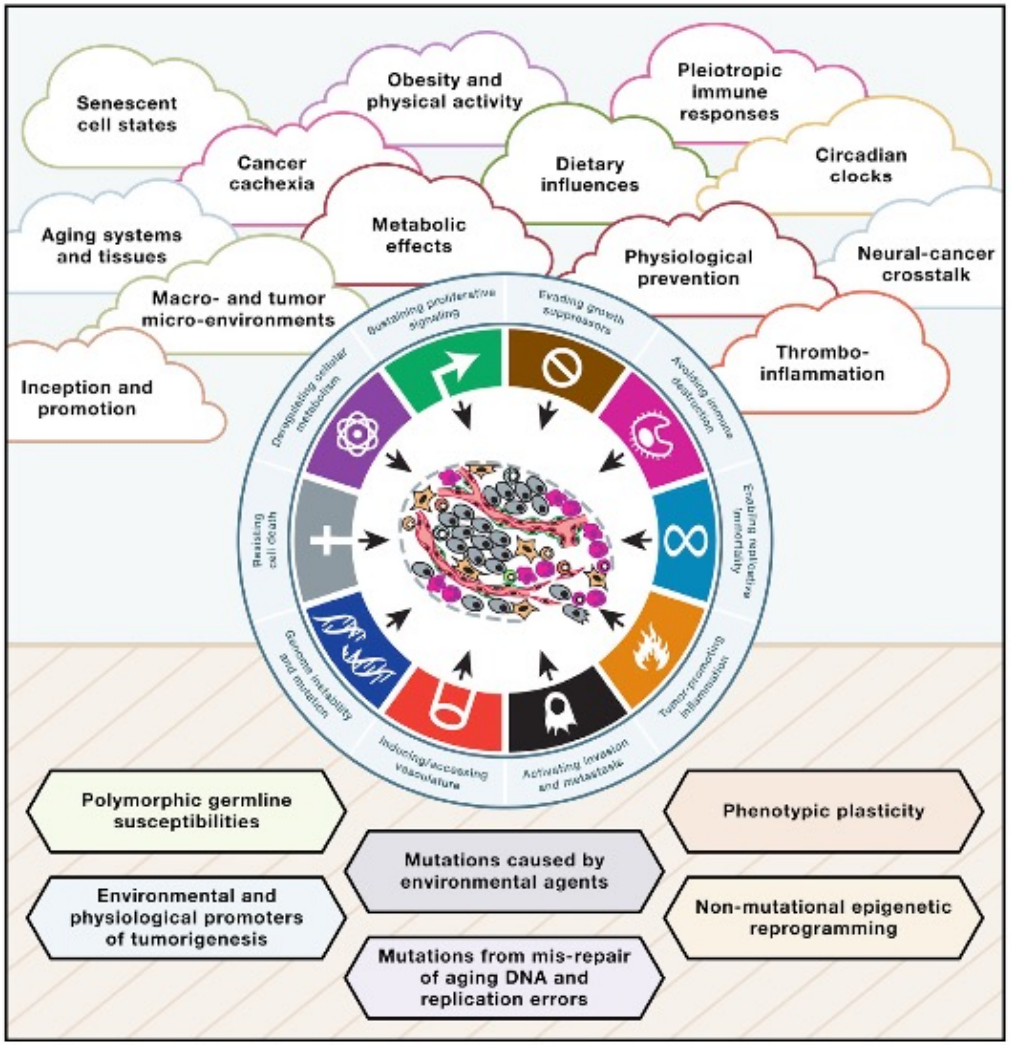
Perspective

Embracing cancer complexity: Hallmarks of systemic disease

Charles Swanton,[1,2,41,*] Elsa Bernard,[1,3,41] Chris Abbosh,[4,42] Fabrice André,[3,5,6] Johan Auwerx,[7] Allan Balmain,[8] Dafna Bar-Sagi,[9] René Bernards,[10] Susan Bullman,[11] James DeGregori,[12] Catherine Elliott,[13] Ayelet Erez,[14] Gerard Evan,[15,16] Mark A. Febbraio,[17] Andrés Hidalgo,[18,19] Mariam Jamal-Hanjani,[2]

(Author list continued on next page)

[1]The Francis Crick Institute, London, UK
[2]Cancer Research UK Lung Cancer Centre of Excellence, University College London Cancer Institute, London, UK
[3]INSERM U981, Gustave Roussy, Villejuif, France
[4]AstraZeneca, Cambridge, UK
[5]Department of Medical Oncology, Gustave Roussy, Villejuif, France
[6]Paris Saclay University, Kremlin-Bicetre, France
[7]Laboratory of Integrative Systems Physiology, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland
[8]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA
[9]NYU Langone Health, New York, NY, USA
[10]Division of Molecular Carcinogenesis, Oncode Institute, the Netherlands Cancer Institute, Amsterdam, the Netherlands



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ARTICLE OPEN

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Deep representation learning of tissue metabolome and computed tomography annotates NSCLC classification and prognosis

Marc Boubnovski Martell[1], Kristofer Linton-Reid[1], Sumeet Hindocha[2], Mitchell Chen[1], Paula Moreno[3,4], Marina Álvarez-Benito[3,5], Ángel Salvatierra[3,5], Richard Lee[2,6], Joram M. Posma[1], Marco A. Calzado[3,7]✉ and Eric O. Aboagye[1]✉

The rich chemical information from tissue metabolomics provides a powerful means to elaborate tissue physiology or tumor characteristics at cellular and tumor microenvironment levels. However, the process of obtaining such information requires invasive biopsies, is costly, and can delay clinical patient management. Conversely, computed tomography (CT) is a clinical standard of care but does not intuitively harbor histological or prognostic information. Furthermore, the ability to embed metabolome information into CT to subsequently use the learned representation for classification or prognosis has yet to be described. This study develops a deep learning-based framework -- tissue-metabolomic-radiomic-CT (TMR-CT) by combining 48 paired CT images and tumor/normal tissue metabolite intensities to generate ten image embeddings to infer metabolite-derived representation from CT alone. In clinical NSCLC settings, we ascertain whether TMR-CT results in an enhanced feature generation model solving histology classification/prognosis tasks in an unseen international CT dataset of 742 patients. TMR-CT non-invasively determines histological classes - adenocarcinoma/squamous cell carcinoma with an F1-score = 0.78 and further asserts patients' prognosis with a c-index = 0.72, surpassing the performance of radiomics models and deep learning on single modality CT feature extraction. Additionally, our work shows the potential to generate informative biology-inspired CT-led features to explore connections between hard-to-obtain tissue metabolic profiles and routine lesion-derived image data.

npj Precision Oncology (2024)8:28 ; https://doi.org/10.1038/s41698-024-00502-3

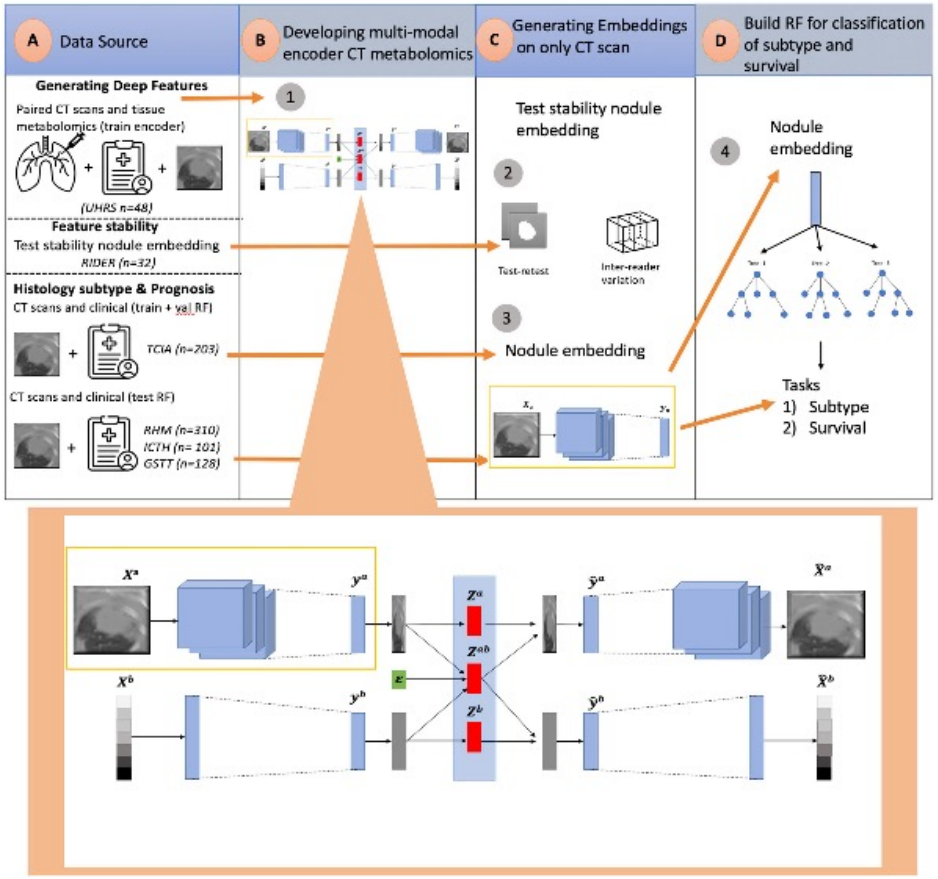

Fig. 1 Study workflow. a Dataset collection for generating deep features, evaluating feature stability, histology subtype classification and prognosis. **b** The DPCCA model is used to find a shared latent space between the CT scans and metabolomics. An enlarged version of this model is shown, with the purple box highlighting the section responsible for generating TMR-CT features. In this model, X^a, X^b is the original

Cancer Treatment Reviews 125 (2024) 102721

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Controversy

If it's a target, it's a pan-cancer target: Tissue is not the issue

Jacob J. Adashek [a,*], Shumei Kato [b], Jason K. Sicklick [b,c,d], Scott M. Lippman [b], Razelle Kurzrock [e,f,g,*]

[a] Department of Oncology, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins Hospital, Baltimore, MD, USA
[b] Center for Personalized Cancer Therapy and Division of Hematology and Oncology, Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA, USA
[c] Department of Surgery, Division of Surgical Oncology, University of California San Diego, UC San Diego Health, San Diego, CA, USA
[d] Department of Pharmacology, University of California San Diego, UC San Diego Health, San Diego, CA, USA
[e] Genomic Sciences and Precision Medicine Center, Medical College of Wisconsin, Milwaukee Wisconsin, USA
[f] WIN Consortium, Paris France
[g] University of Nebraska, United States

Fig. 1. Tissue-agnostic FDA approval. Figure Legend: This figure represents tissue-agnostic FDA-approvals. Colorectal cancer was excluded from the *BRAF V600E*-directed trametinib plus dabrafenib approval. Created with BioRender.com.

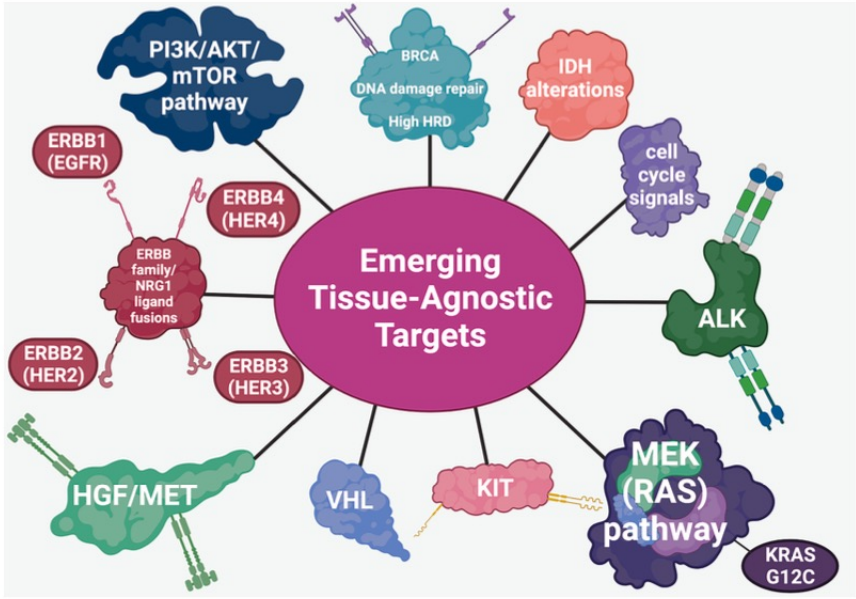

Fig. 2. Examples of emerging tissue-agnostic targets. Figure Legend: This figure represents multiple potential tissue-agnostic targets. Created with BioRender.com.

Article

CLINICAL TRIALS

Clinical Trials
1–11


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Risk–benefit trade-offs and precision utilities in phase I-II clinical trials

Pavlos Msaouel[1,2,3], **Juhee Lee**[4] **and Peter F Thall**[5]

Abstract

Background: Identifying optimal doses in early-phase clinical trials is critically important. Therapies administered at doses that are either unsafe or biologically ineffective are unlikely to be successful in subsequent clinical trials or to obtain regulatory approval. Identifying appropriate doses for new agents is a complex process that involves balancing the risks and benefits of outcomes such as biological efficacy, toxicity, and patient quality of life. **Purpose:** While conventional phase I trials rely solely on toxicity to determine doses, phase I-II trials explicitly account for both efficacy and toxicity, which enables them to identify doses that provide the most favorable risk–benefit trade-offs. It is also important to account for patient covariates, since one-size-fits-all treatment decisions are likely to be suboptimal within subgroups determined by prognostic variables or biomarkers. Notably, the selection of estimands can influence our conclusions based on the prognostic subgroup studied. For example, assuming monotonicity of the probability of response, higher treatment doses may yield more pronounced efficacy in favorable prognosis compared to poor prognosis subgroups when the estimand is mean or median survival. Conversely, when the estimand is the 3-month survival probability, higher treatment doses produce more pronounced efficacy in poor prognosis compared to favorable prognosis subgroups. **Methods and Conclusions:** Herein, we first describe why it is essential to consider clinical practice when designing a clinical trial and outline a stepwise process for doing this. We then review a precision phase I-II design based on utilities tailored to prognostic subgroups that characterize efficacy–toxicity risk–benefit trade-offs. The design chooses each patient's dose to optimize their expected utility and allows patients in different prognostic subgroups to have different optimal doses. We illustrate the design with a dose-finding trial of a new therapeutic agent for metastatic clear cell renal cell carcinoma.

Pan *et al. Genome Biology* (2024) 25:104
https://doi.org/10.1186/s13059-024-03246-2

Genome Biology

DATABASE **Open Access**

Single Cell Atlas: a single-cell multi-omics human cell encyclopedia

Lu Pan[1], Paolo Parini[2,3], Roman Tremmel[4,5], Joseph Loscalzo[6], Volker M. Lauschke[4,5,7], Bradley A. Maron[6], Paola Paci[8], Ingemar Ernberg[9], Nguan Soon Tan[10,11], Zehuan Liao[10,9], Weiyao Yin[1], Sundararaman Rengarajan[12] and Xuexin Li[13,14*] on behalf of The SCA Consortium

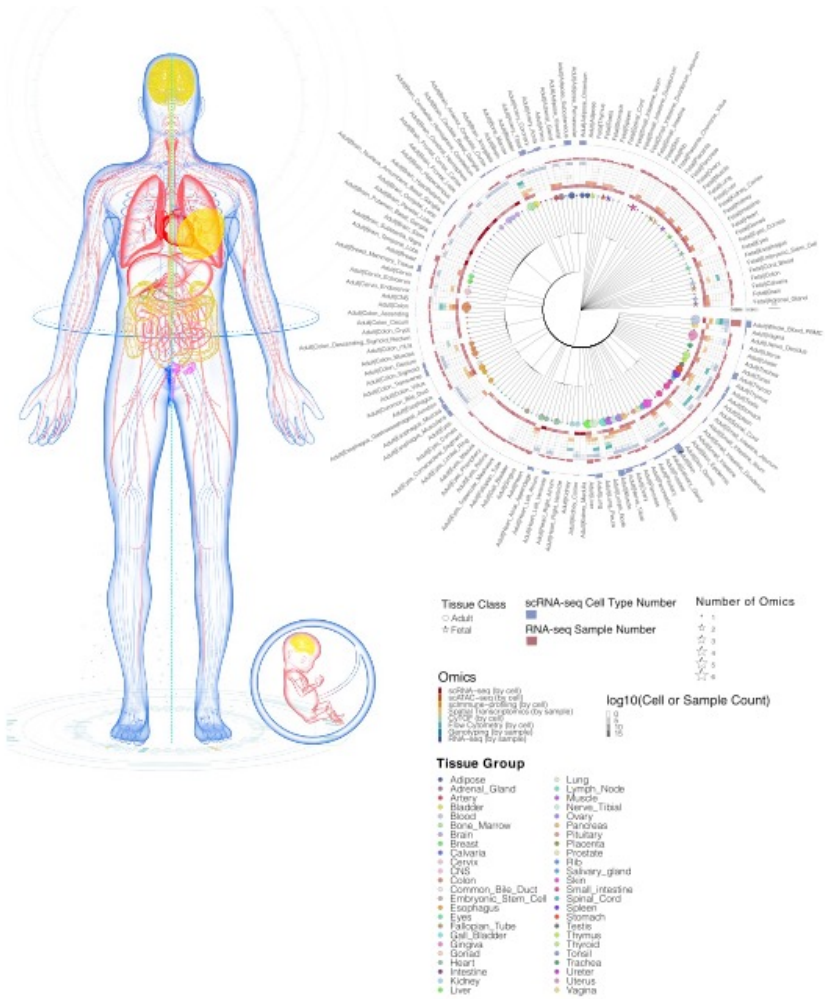
*Correspondence:
xuexin.li@ki.se

[13] Department of General Surgery, The Fourth Affiliated Hospital, China Medical University, Shenyang 110032, China
Full list of author information is available at the end of the article

Abstract

Single-cell sequencing datasets are key in biology and medicine for unraveling insights into heterogeneous cell populations with unprecedented resolution. Here, we construct a single-cell multi-omics map of human tissues through in-depth characterizations of datasets from five single-cell omics, spatial transcriptomics, and two bulk omics across 125 healthy adult and fetal tissues. We construct its complement web-based platform, the Single Cell Atlas (SCA, www.singlecellatlas.org), to enable vast interactive data exploration of deep multi-omics signatures across human fetal and adult tissues. The atlas resources and database queries aspire to serve as a one-stop, comprehensive, and time-effective resource for various omics studies.

Keywords: Single-cell omics, Multi-omics, Single Cell Atlas, Human database, Single-cell RNA-sequencing, Spatial transcriptomics, Single-cell ATAC-sequencing, Single-cell immune profiling, Mass cytometry, Flow cytometry



nature cancer

Analysis

https://doi.org/10.1038/s43018-024-00756-7

PERCEPTION predicts patient response and resistance to treatment using single-cell transcriptomics of their tumors

Received: 20 June 2023

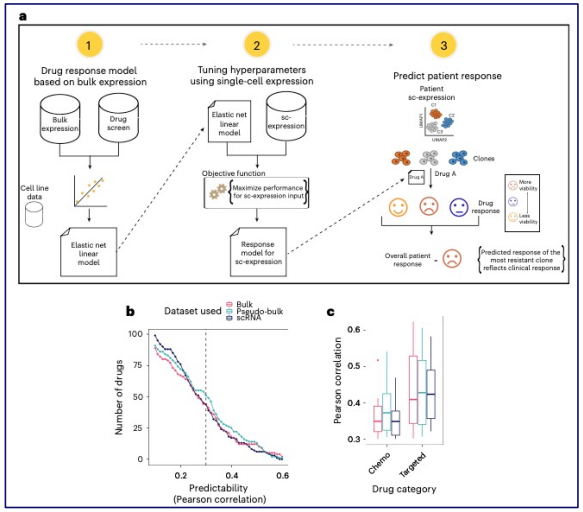
Accepted: 8 March 2024

Published online: 18 April 2024

Check for updates

Sanju Sinha[1,16,17], Rahulsimham Vegesna[1,17], Sumit Mukherjee[1], Ashwin V. Kammula[1,2], Saugato Rahman Dhruba[1], Wei Wu[3], D. Lucas Kerr[3], Nishanth Ulhas Nair[1], Matthew G. Jones[4,5,6,7], Nir Yosef[4,5], Oleg V. Stroganov[8], Ivan Grishagin[8,9], Kenneth D. Aldape[10], Collin M. Blakely[3,11], Peng Jiang[1], Craig J. Thomas[9,12], Cyril H. Benes[13], Trever G. Bivona[2,11,14,15], Alejandro A. Schäffer[1] & Eytan Ruppin[1]

Tailoring optimal treatment for individual cancer patients remains a significant challenge. To address this issue, we developed PERCEPTION (PERsonalized Single-Cell Expression-Based Planning for Treatments In ONcology), a precision oncology computational pipeline. Our approach uses publicly available matched bulk and single-cell (sc) expression profiles from large-scale cell-line drug screens. These profiles help build treatment response models based on patients' sc-tumor transcriptomics. PERCEPTION demonstrates success in predicting responses to targeted therapies in cultured and patient-tumor-derived primary cells, as well as in two clinical trials for multiple myeloma and breast cancer. It also captures the resistance development in patients with lung cancer treated with tyrosine kinase inhibitors. PERCEPTION outperforms published state-of-the-art sc-based and bulk-based predictors in all clinical cohorts. PERCEPTION is accessible at https://github.com/ruppinlab/PERCEPTION. Our work, showcasing patient stratification using sc-expression profiles of their tumors, will encourage the adoption of sc-omics profiling in clinical settings, enhancing precision oncology tools based on sc-omics.



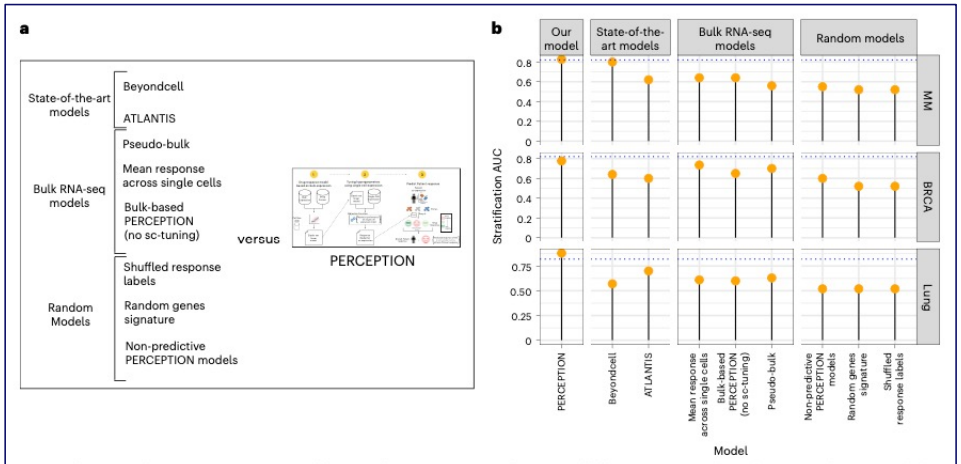


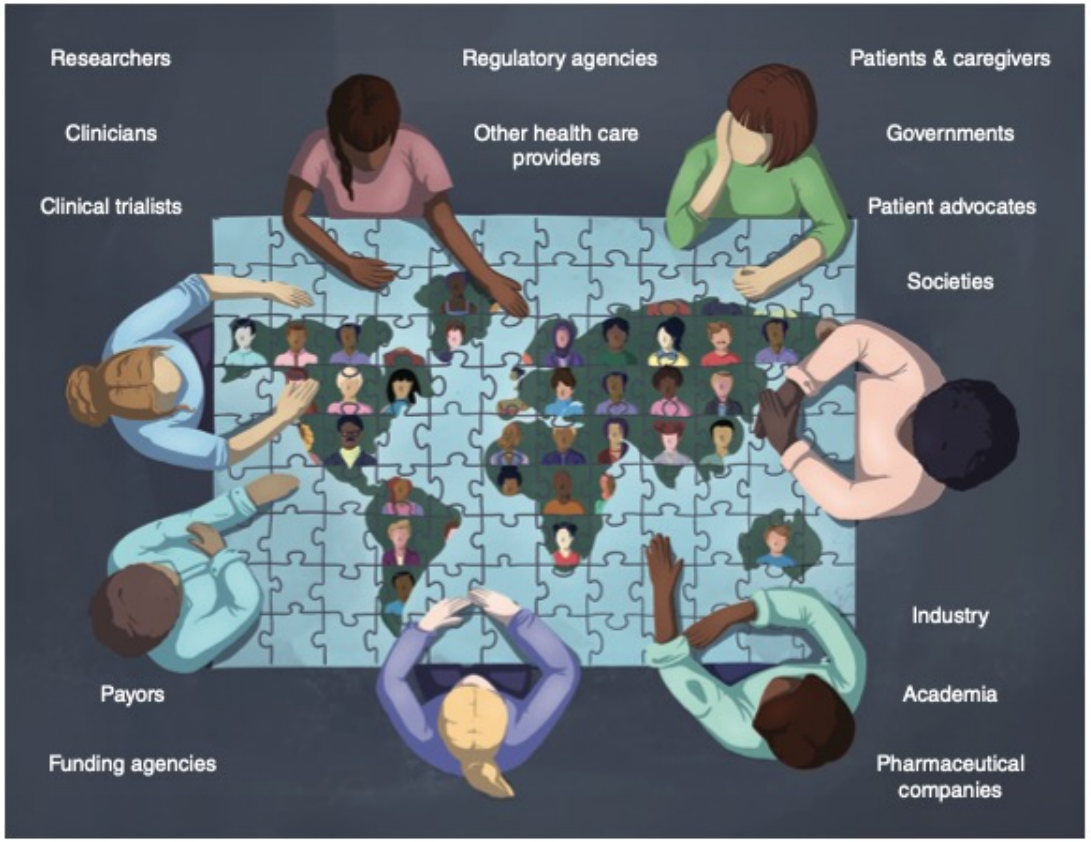
Fig. 5 | Performance of PERCEPTION versus state-of-the-art and RNA-seq models. a, Illustration of our overall comparison comparing the PERCEPTION model (on the right) versus eight other models, including two state-of-the-art sc models (Beyondcell and ATLANTIS), three bulk-RNA-seq-based models (pseudo-bulk, mean response across all single cells and PERCEPTION trained on only bulk-model without sc-training) and finally three random models. **b**, The stratification performances of differentiating responders and non-responders are provided on the *y* axis for each model versus the PERCEPTION in three clinical cohorts: MM (multiple myeloma, 21 responders, 7 non-responder), BRCA (breast cancer, $n = 7$ each of responders and non-responders) and lung cancer (17 progressive and 7 responding). The dotted blue line denotes the mean performance of PERCEPTION across the three cohorts.

IN FOCUS

A Vision for Democratizing Next-Generation Oncology Clinical Trials

Vivek Subbiah[1], Denis Horgan[2], and Ishwaria M. Subbiah[1,3]

Summary: Revolutionary advancements in oncology have transformed lives, but the clinical trials ecosystem encounters challenges, including restricted access to innovative therapies and a lack of diversity in participant representation. A vision emerges for democratized, globally accessible oncology trials, necessitating collaboration among researchers, clinicians, patients, and policymakers to shift from converting complex, exclusive trials into a dynamic, inclusive force against cancer.

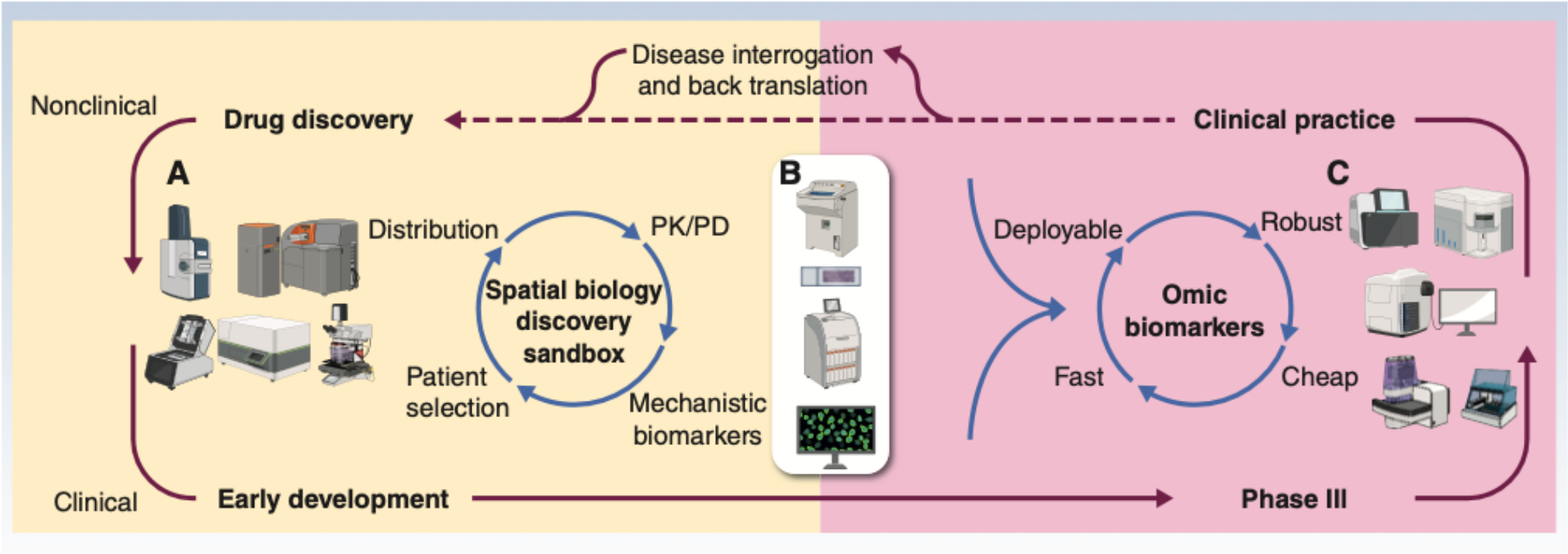


IN FOCUS

Accelerating Drug Development Using Spatial Multi-omics

Richard J.A. Goodwin[1], Stefan J. Platz[2], Jorge S. Reis-Filho[3], and Simon T. Barry[4]

Summary: Spatial biology approaches enabled by innovations in imaging biomarker platforms and artificial intelligence–enabled data integration and analysis provide an assessment of patient and disease heterogeneity at ever-increasing resolution. The utility of spatial biology data in accelerating drug programs, however, requires balancing exploratory discovery investigations against scalable and clinically applicable spatial biomarker analysis.



Radiology

ORIGINAL RESEARCH • COMPUTER APPLICATIONS

Data Extraction from Free-Text Reports on Mechanical Thrombectomy in Acute Ischemic Stroke Using ChatGPT: A Retrospective Analysis

Nils C. Lehmen, MD • Franziska Dorn, MD • Isabella C. Wiest, MD, MSc • Hanna Zimmermann, MD • Alexander Radbruch, MD, JD • Jakob Nikolas Kather, MD, MSc • Daniel Paech, MD, PhD

From the Department of Neuroradiology, University Hospital Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Venusberg-Campus 1, 53127 Bonn, Germany (N.C.L., F.D., A.R., D.P.); Research Group Clinical Neuroimaging, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany (N.C.L., A.R.); Department of Medicine II, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (I.C.W.); Else Kroener Fresenius Center for Digital Health, Medical Faculty Carl Gustav Carus, Technical University Dresden, Dresden, Germany (I.C.W., J.N.K.); Institute of Neuroradiology, University Hospital, LMU Munich, Munich, Germany (H.Z.); and Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass (D.P.). Received October 10, 2023; revision requested December 18; final revision received February 18, 2024; accepted March 12. **Address correspondence to** N.C.L. (email: *nils.lehmen@ukbonn.de*).

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

Radiology 2024; 311(1):e232741 • https://doi.org/10.1148/radiol.232741 • Content codes: NR AI

Background: Procedural details of mechanical thrombectomy in patients with ischemic stroke are important predictors of clinical outcome and are collected for prospective studies or national stroke registries. To date, these data are collected manually by human readers, a labor-intensive task that is prone to errors.

Purpose: To evaluate the use of the large language models (LLMs) GPT-4 and GPT-3.5 to extract data from neuroradiology reports on mechanical thrombectomy in patients with ischemic stroke.

Materials and Methods: This retrospective study included consecutive reports from patients with ischemic stroke who underwent mechanical thrombectomy between November 2022 and September 2023 at institution 1 and between September 2016 and December 2019 at institution 2. A set of 20 reports was used to optimize the prompt, and the ability of the LLMs to extract procedural data from the reports was compared using the McNemar test. Data manually extracted by an interventional neuroradiologist served as the reference standard.

Results: A total of 100 internal reports from 100 patients (mean age, 74.7 years ± 13.2 [SD]; 53 female) and 30 external reports from 30 patients (mean age, 72.7 years ± 13.5; 18 male) were included. All reports were successfully processed by GPT-4 and GPT-3.5. Of 2800 data entries, 2631 (94.0% [95% CI: 93.0, 94.8]; range per category, 61%–100%) data points were correctly extracted by GPT-4 without the need for further postprocessing. With 1788 of 2800 correct data entries, GPT-3.5 produced fewer correct data entries than did GPT-4 (63.9% [95% CI: 62.0, 65.6]; range per category, 14%–99%; $P < .001$). For the external reports, GPT-4 extracted 760 of 840 (90.5% [95% CI: 88.3, 92.4]) correct data entries, while GPT-3.5 extracted 539 of 840 (64.2% [95% CI: 60.8, 67.4]; $P < .001$).

Conclusion: Compared with GPT-3.5, GPT-4 more frequently extracted correct procedural data from free-text reports on mechanical thrombectomy performed in patients with ischemic stroke.

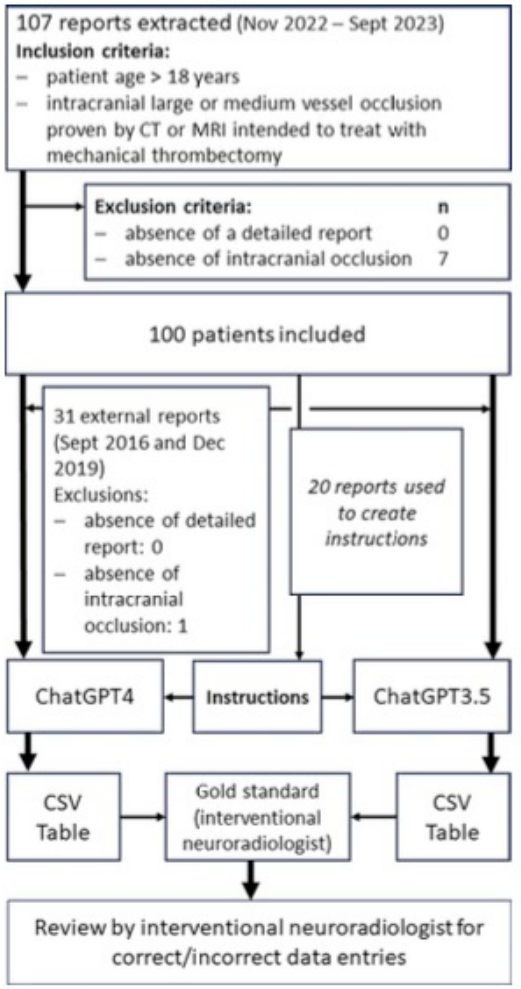


Figure 1: Flowchart of patient inclusion and exclusion criteria, data analysis, and generation of results. The same 30 external reports were used for GPT-4 and GPT-3.5. CSV = comma-separated value.

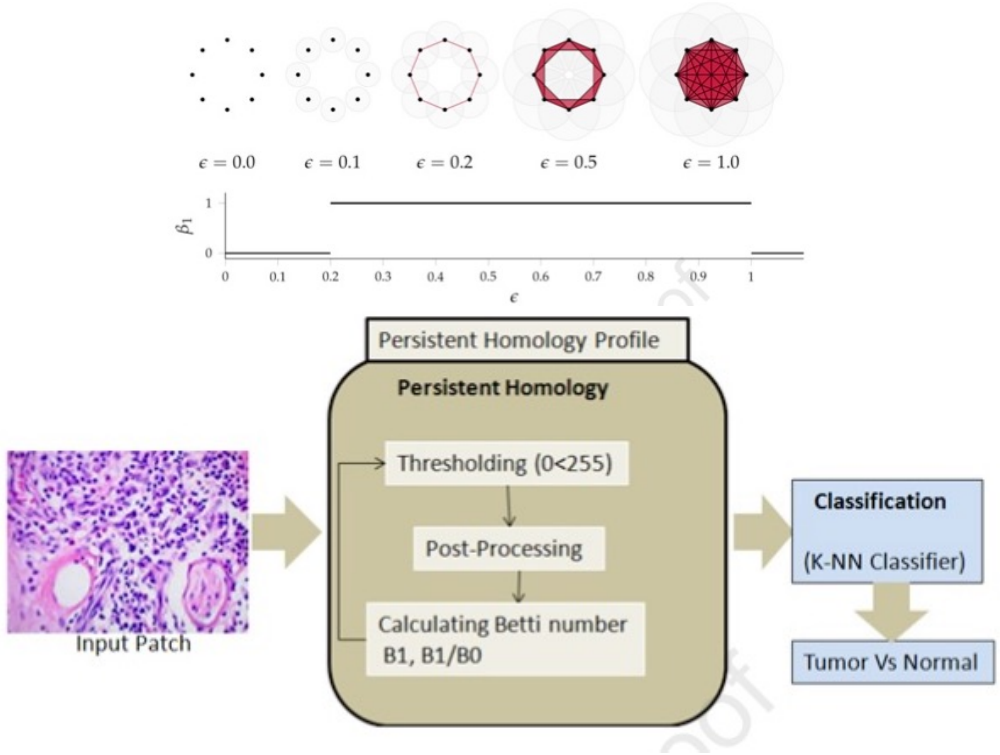
COMMENTARY

Radiologist Workforce Changes: Going Remote or Hybrid

Madison R. Kocher, MD, MBA, Christoph I. Lee, MD, MS, MBA

Advancing Precision Medicine: Algebraic Topology and Differential Geometry in Radiology and Computational Pathology

Richard M Levenson[1*], Yashbir Singh[2*], Bastian Rieck[3], Quincy A. Hathaway[4], Colleen Farrelly[5], Jennifer Rozenblit[6], Prateek Prasanna[7], Bradley Erickson[2], Ashok Choudhary[8], Gunnar Carlsson[9], Deepa Deepa[10]



Programmed Death Ligand-1 and Tumor Mutation Burden Testing of Patients With Lung Cancer for Selection of Immune Checkpoint Inhibitor Therapies

Guideline From the College of American Pathologists, Association for Molecular Pathology, International Association for the Study of Lung Cancer, Pulmonary Pathology Society, and LUNGevity Foundation

Lynette M. Sholl, MD; Mark Awad, MD, PhD; Upal Basu Roy, PhD, MS, MPH; Mary Beth Beasley, MD; Richard Walter Cartun, PhD, MS; David M. Hwang, MD, PhD; Gregory Kalemkerian, MD; Fernando Lopez-Rios, MD, PhD; Mari Mino-Kenudson, MD; Ajit Paintal, MD; Kearin Reid, MLS(ASCP), MLIS; Lauren Ritterhouse, MD, PhD; Lesley A. Souter, PhD; Paul E. Swanson, MD; Christina B. Ventura, MPH, MT(ASCP); Larissa V. Furtado, MD

Results.—Six recommendation statements were developed.

Conclusions.—This guideline summarizes the current understanding and hurdles associated with the use of PD-L1 expression and TMB testing for immune checkpoint inhibitor therapy selection in patients with advanced non–small cell lung cancer and presents evidence-based recommendations for PD-L1 and TMB testing in the clinical setting.

Table 2. Summary of Guideline Statements

Guideline Statement	Strength of Recommendation
1. In patients with advanced NSCLC, pathologists should use a validated PD-L1 IHC expression assay, in conjunction with other targetable genomic biomarker assays where appropriate, to optimize selection for treatment with ICIs.	Strong recommendation
2. Pathologists should ensure appropriate validation has been performed on all specimen types and fixatives. *Note:* Specific validation requirements are out of the scope of this guideline, and laboratories should refer to the Principles of Analytic Validation of Immunohistochemical Assays Guideline[57] for details on how to validate IHC specimens.	Conditional recommendation
3. When feasible, pathologists should use clinically validated PD-L1 IHC assays as intended.	Conditional recommendation
4. Pathologists who choose to use LDTs for PD-L1 expression should validate according to the requirements of their accrediting body.	Strong recommendation
5. Pathologists should report PD-L1 IHC results using a percentage expression score.	Conditional recommendation
6. Clinicians should not use tumor mutation burden alone to select patients with advanced NSCLC for ICIs, based on insufficient evidence in this population.	Conditional recommendation

Abbreviations: ICIs, immune checkpoint inhibitors; IHC, immunohistochemistry; LDTs, laboratory-developed tests; NSCLC, non–small cell lung cancer; PD-L1, programmed death ligand-1.

nature communications

Article

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Tumor histoculture captures the dynamic interactions between tumor and immune components in response to anti-PD1 in head and neck cancer

Received: 24 May 2023

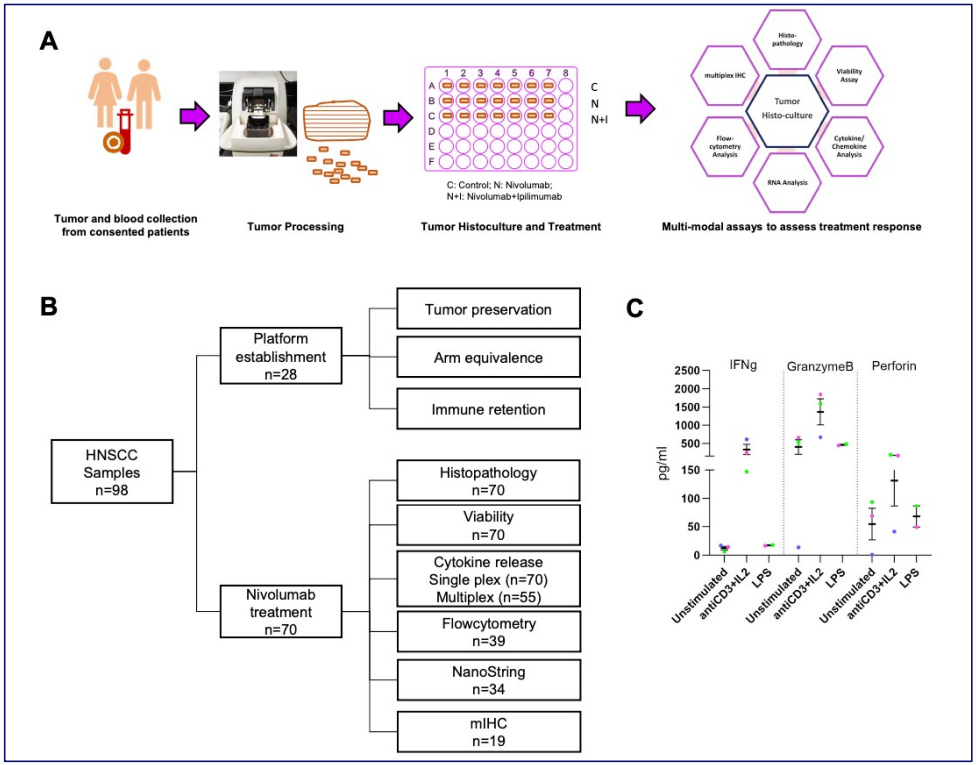
Accepted: 2 February 2024

Published online: 21 February 2024

Check for updates

Nandini Pal Basak[1,7], Kowshik Jaganathan[1,7], Biswajit Das[1], Oliyarasi Muthusamy[1], Rajashekar M[1], Ritu Malhotra[1], Amit Samal[1], Moumita Nath[1], Ganesh MS[2], Amritha Prabha Shankar[2], Prakash BV[3], Vijay Pillai[4], Manjula BV[5], Jayaprakash C[6], Vasanth K[1], Gowri Shankar K[1], Sindhu Govindan[1], Syamkumar V[1], Juby[1], Koushika R[1], Chandan Bhowal[1], Upendra Kumar[1], Govindaraj K[1], Mohit Malhotra[1] & Satish Sankaran[1]

Dynamic interactions within the tumor micro-environment drive patient response to immune checkpoint inhibitors. Existing preclinical models lack true representation of this complexity. Using a Head and Neck cancer patient derived TruTumor histoculture platform, the response spectrum of 70 patients to anti-PD1 treatment is investigated in this study. With a subset of 55 patient samples, multiple assays to characterize T-cell reinvigoration and tumor cytotoxicity are performed. Based on levels of these two response parameters, patients are stratified into five sub-cohorts, with the best responder and non-responder sub-cohorts falling at extreme ends of the spectrum. The responder sub-cohort exhibits high T-cell reinvigoration, high tumor cytotoxicity with T-cells homing into the tumor upon treatment whereas immune suppression and tumor progression pathways are predominant in the non-responders. Some moderate responders benefit from combination of anti-CTLA4 with anti-PD1, which is evident from better cytotoxic T-cell: T-regulatory cell ratio and enhancement of tumor cytotoxicity. Baseline and on-treatment gene expression signatures from this study stratify responders and non-responders in unrelated clinical datasets.



NEJM AI

NEJM AI 2024; 1 (4)
DOI: 10.1056/AIdbp2300110

DATASETS, BENCHMARKS, AND PROTOCOLS

CORAL: Expert-Curated Oncology Reports to Advance Language Model Inference

Madhumita Sushil, M.Sc., Ph.D.,[1] Vanessa E. Kennedy, M.D.,[2] Divneet Mandair, M.D.,[2] Brenda Y. Miao, B.A.,[1] Travis Zack, M.D., Ph.D.,[1,2] and Atul J. Butte, M.D., Ph.D.[1,2,3,4]

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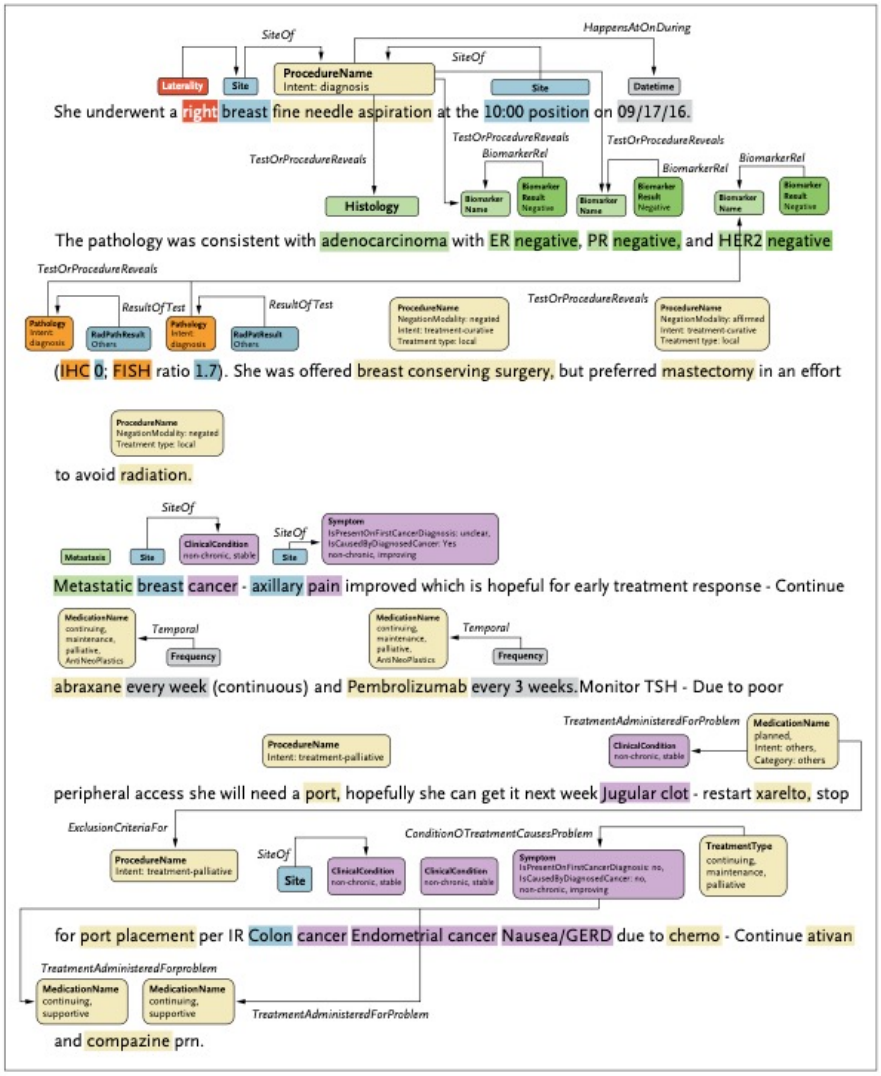
No current information representation schema fully encapsulates the diversity of oncology information within clinical notes, and no compre- hensively annotated oncology notes exist publicly, thereby limiting a thorough evaluation.

By developing a comprehensive schema and benchmark of oncology- specific information in oncology notes, we uncovered both the strengths and the limitations of LLMs. Our evaluation showed variable zero-shot extraction capability among the GPT-3.5-turbo, GPT-4, and FLAN-UL2 models and highlighted a need for further improvements, particularly in complex medical reasoning, before perform- ing reliable information extraction for clinical research and complex population management and documenting quality patient care



npj | digital medicine

Brief communication

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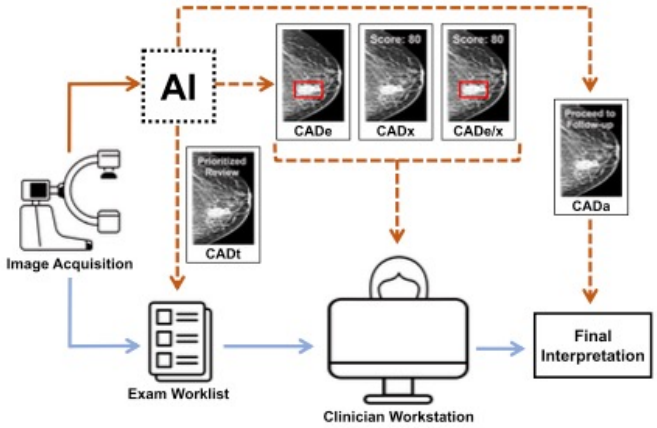
The clinician-AI interface: intended use and explainability in FDA-cleared AI devices for medical image interpretation

Check for updates

Stephanie L. McNamara[1], Paul H. Yi[2] & William Lotter[1,3,4]

As applications of AI in medicine continue to expand, there is an increasing focus on integration into clinical practice. An underappreciated aspect of this clinical translation is where the AI fits into the clinical workflow, and in turn, the outputs generated by the AI to facilitate clinician interaction in this workflow. For instance, in the canonical use case of AI for medical image interpretation, the AI could prioritize cases before clinician review or even autonomously interpret the images without clinician review. A related aspect is explainability – does the AI generate outputs to help explain its predictions to clinicians? While many clinical AI workflows and explainability techniques have been proposed, a summative assessment of the current scope in clinical practice is lacking. Here, we evaluate the current state of FDA-cleared AI devices for medical image interpretation assistance in terms of intended clinical use, outputs generated, and types of explainability offered. We create a curated database focused on these aspects of the clinician-AI interface, where we find a high frequency of "triage" devices, notable variability in output characteristics across products, and often limited explainability of AI predictions. Altogether, we aim to increase transparency of the current landscape of the clinician-AI interface and highlight the need to rigorously assess which strategies ultimately lead to the best clinical outcomes.

Fig. 1 | Overview of types of FDA-cleared CAD products and their integration into medical image interpretation workflows. CAD types vary according to their outputs and place within the clinical workflow. CADt (triage) devices are designed to flag cases for prioritized review and do not place marks on the image. CADe (detection) devices mark regions of interest to aid in the detection of lesions as a clinician is interpreting an exam. CADx (diagnosis) devices are designed to aid in diagnosis, such as by outputting a score or category, but do not explicitly detect lesions across the exam. CADe/x (detection & diagnosis) devices provide both detection and diagnosis support. Finally, an autonomous system, which we denote as CADa, aims to automatically interpret the exam without clinician input.



Type	Intended Use	Description
CADt	Triage	Flag suspicious cases for prioritized review
CADe	Detection	Mark suspicious regions to aid in detection
CADx	Diagnosis	Score or categorize to aid in diagnosis
CADe/x	Detection/Diagnosis	Mark and score/categorize to aid in detection and diagnosis
CADa	Autonomous	Automatically interpret image without clinician input

Comment

Guardrails for the use of generalist AI in cancer care

Stephen Gilbert & Jakob Nikolas Kather

Artificial narrow intelligence models, trained for specific intended purposes, have gained approval and recommendation for cancer treatment. Generalist medicial artificial intelligence (GMAI) models are now being developed for cancer treatment. Policy makers have a stark choice: radically adapt frameworks, block generalist approaches or force them onto narrower tracks.

and therapeutic option
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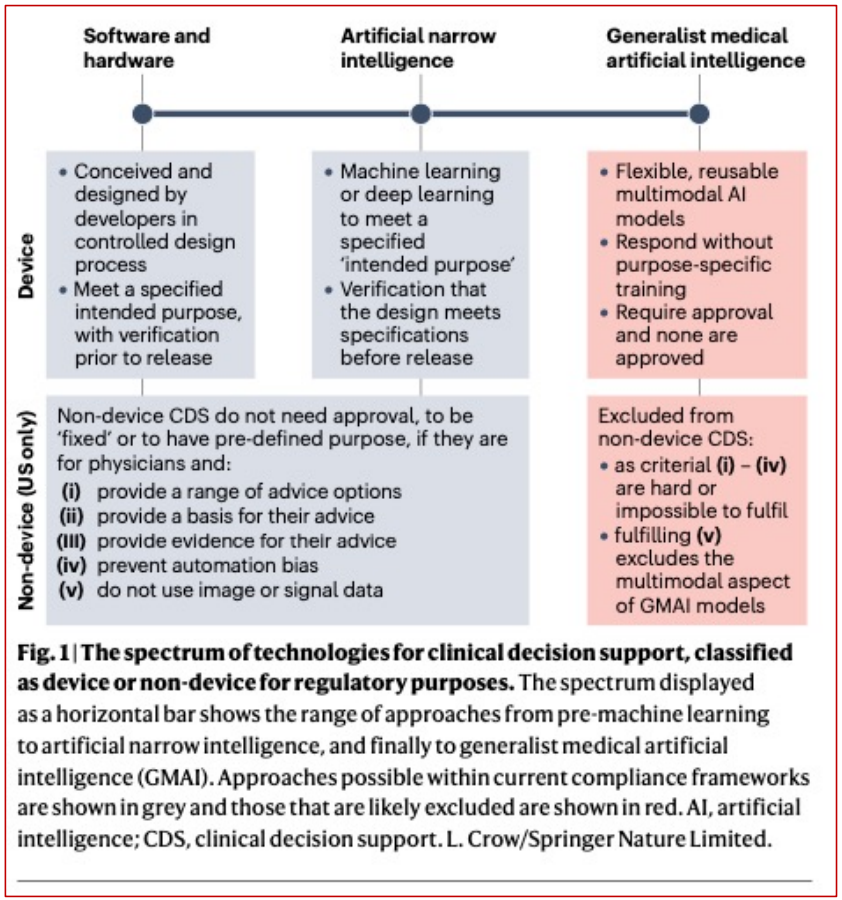

Fig. 1 | The spectrum of technologies for clinical decision support, classified as device or non-device for regulatory purposes. The spectrum displayed as a horizontal bar shows the range of approaches from pre-machine learning to artificial narrow intelligence, and finally to generalist medical artificial intelligence (GMAI). Approaches possible within current compliance frameworks are shown in grey and those that are likely excluded are shown in red. AI, artificial intelligence; CDS, clinical decision support. L. Crow/Springer Nature Limited.

nature reviews drug discovery

FROM THE ANALYST'S COUCH | 16 April 2024

The antibody–drug conjugate landscape

By Patrick Flynn, Smruthi Suryaprakash, Dan Grossman, Val Panier & John Wu

To explore the impact of next-generation ADC technology on these challenges, we investigated innovation in the ADC clinical pipeline across five design levers — target, payload MoA, antibody, linker and conjugation method — and assessed the likelihood for expanding the addressable indications or widening the therapeutic window of ADCs.

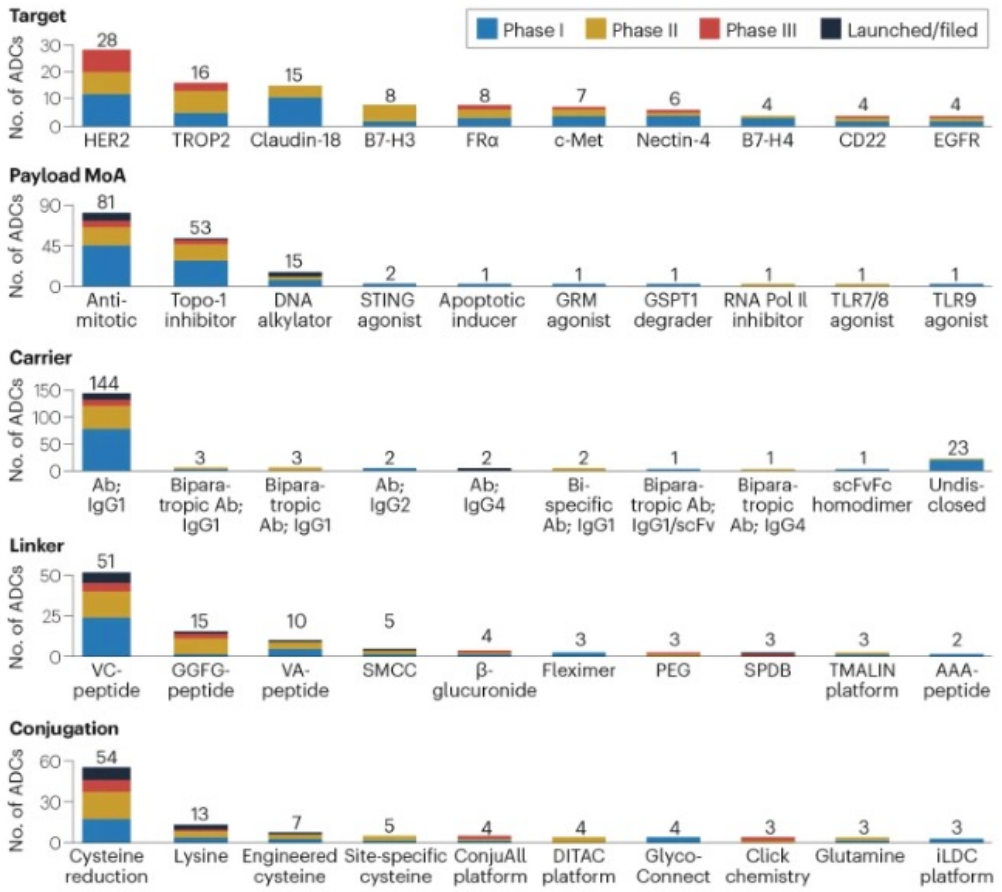

Fig. 1 | Assessment of ADCs in clinical development. Innovation across specific design levers used in clinical assets. The top 10 targets and technologies for each lever are shown. Ab, antibody; ADC, antibody–drug conjugate; IgG, immunoglobulin. See Supplementary information for details and an expanded version.

Precision needle-punch tumor enrichment from paraffin blocks improves the detection of clinically actionable genomic alterations and biomarkers

Douglas I. Lin[1]*, Richard S. P. Huang[1], Ioannis Ladas[1], Rachel B. Keller[1], Nimesh R. Patel[1], Sotirios Lakis[2], Brennan Decker[1], Tyler Janovitz[1], Douglas A. Mata[1], Jeffrey S. Ross[1], Jo-Anne Vergilio[1], Julia A. Elvin[1], Roy S. Herbst[3], Philip C. Mack[4] and Jonathan K. Killian[1]*

[1]Department of Pathology and Diagnostic Medicine, Foundation Medicine, Inc., Cambridge, MA, United States, [2]Foundation Medicine GmbH, Pathology Department, Penzberg, Germany, [3]Department of Medical Oncology, Yale School of Medicine, Yale Cancer Center, New Haven, CT, United States, [4]Division of Hematology and Oncology, Department of Medicine, Tisch Cancer Institute at Mount Sinai, New York, NY, United States

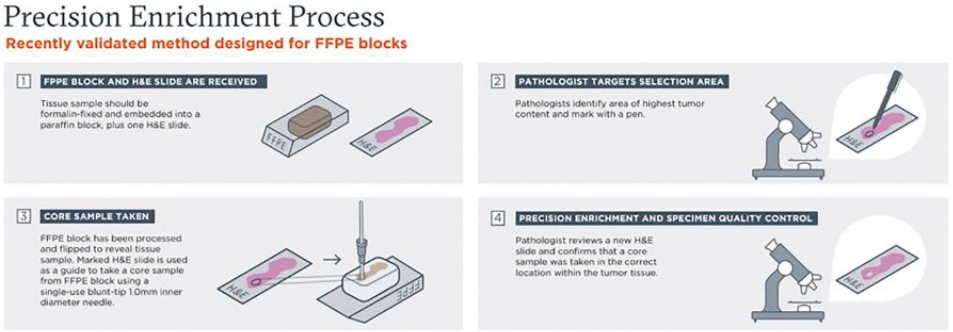

FIGURE 1
Overview of pathologist-directed, precision needle punch enrichment (NPE), a quality-controlled process.

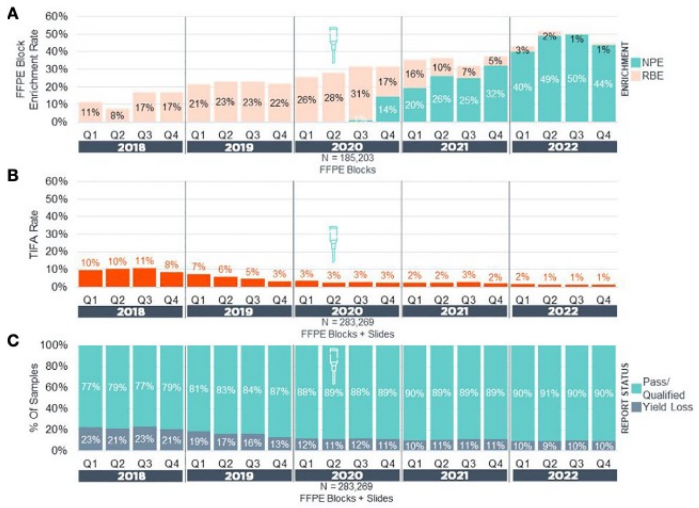

FIGURE 2
Precision Enrichment Real-World Experience Pan-F1CDx. **(A)** Overall enrichment rates in real-world samples (NPE + RBE) for FFPE blocks received from 2018-2022 (N = 185,203). **(B)** Tissue Insufficient For Analysis (TIFA) rates in real-world samples (FFPE Blocks + Slides) before and after implementation of NPE. **(C)** Reporting status rates in real-world samples (FFPE Blocks + Slides) before and after implementation of NPE. Yield Loss = Unsuccessful Samples + TIFA. Approximate date of NPE implementation is denoted by a needle icon. NPE, Needle Punch Enrichment; RBE, Razor-Blade Macro-Enrichment.

scientific reports

OPEN

Extracting interpretable features for pathologists using weakly supervised learning to predict p16 expression in oropharyngeal cancer

Masahiro Adachi[1,2], Tetsuro Taki[1], Naoya Sakamoto[1,3], Motohiro Kojima[1,3], Akihiko Hirao[3], Kazuto Matsuura[4], Ryuichi Hayashi[4], Keiji Tabuchi[2], Shumpei Ishikawa[3,5], Genichiro Ishii[1,6] & Shingo Sakashita[1,3]✉

One drawback of existing artificial intelligence (AI)-based histopathological prediction models is the lack of interpretability. The objective of this study is to extract p16-positive oropharyngeal squamous cell carcinoma (OPSCC) features in a form that can be interpreted by pathologists using AI model. We constructed a model for predicting p16 expression using a dataset of whole-slide images from 114 OPSCC biopsy cases. We used the clustering-constrained attention-based multiple-instance learning (CLAM) model, a weakly supervised learning approach. To improve performance, we incorporated tumor annotation into the model (Annot-CLAM) and achieved the mean area under the receiver operating characteristic curve of 0.905. Utilizing the image patches on which the model focused, we examined the features of model interest via histopathologic morphological analysis and cycle-consistent adversarial network (CycleGAN) image translation. The histopathologic morphological analysis evaluated the histopathological characteristics of image patches, revealing significant differences in the numbers of nuclei, the perimeters of the nuclei, and the intercellular bridges between p16-negative and p16-positive image patches. By using the CycleGAN-converted images, we confirmed that the sizes and densities of nuclei are significantly converted. This novel approach improves interpretability in histopathological morphology-based AI models and contributes to the advancement of clinically valuable histopathological morphological features.

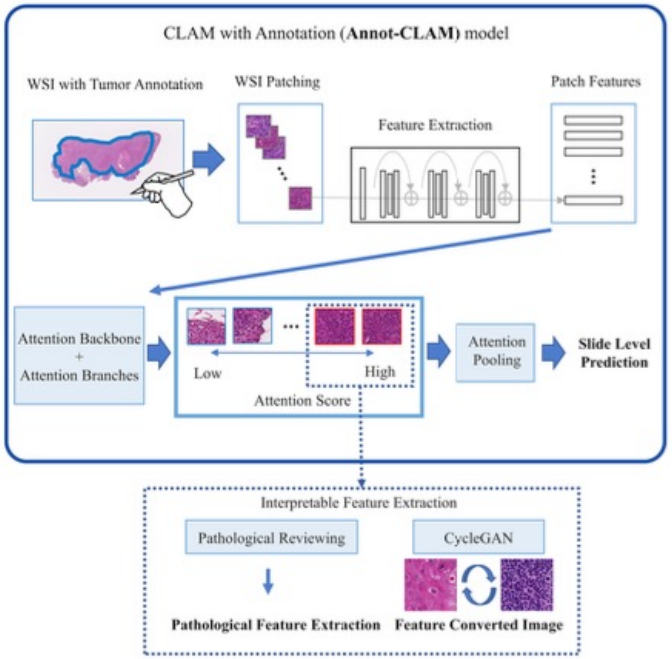

Figure 1. Overview of the study The Annot-CLAM model, a version of the CLAM model modified to use annotated ROIs, was applied. Two analysis approaches were used to interpret the features that the prediction model focused on.

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Review Article

Pathologic Assessment and Staging of Multiple Non–Small Cell Lung Carcinomas: A Paradigm Shift with the Emerging Role of Molecular Methods

Jason C. Chang, Natasha Rekhtman*

Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

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comparative molecular profiling
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next-generation sequencing
separate primary lung carcinoma

ABSTRACT

Non–small cell lung carcinomas (NSCLCs) commonly present as 2 or more separate tumors. Biologically, this encompasses 2 distinct processes: separate primary lung carcinomas (SPLCs), representing independently arising tumors, and intrapulmonary metastases (IPMs), representing intrapulmonary spread of a single tumor. The advent of computed tomography imaging has substantially increased the detection of multifocal NSCLCs. The strategies and approaches for distinguishing between SPLCs and IPMs have evolved significantly over the years. Recently, genomic sequencing of somatic mutations has been widely adopted to identify targetable alterations in NSCLC. These molecular techniques have enabled pathologists to reliably discern clonal relationships among multiple NSCLCs in clinical practice. However, a standardized approach to evaluating and staging multiple NSCLCs using molecular methods is still lacking. Here, we reviewed the historical context and provided an update on the growing applications of genomic testing as a clinically relevant benchmark for determining clonal relationships in multiple NSCLCs, a practice we have designated "comparative molecular profiling." We examined the strengths and limitations of the morphology-based distinction of SPLCs vs IPMs and highlighted pivotal clinical and pathologic insights that have emerged from studying multiple NSCLCs using genomic approaches as a gold standard. Lastly, we suggest a practical approach for evaluating multiple NSCLCs in the clinical setting, considering the varying availability of molecular techniques.

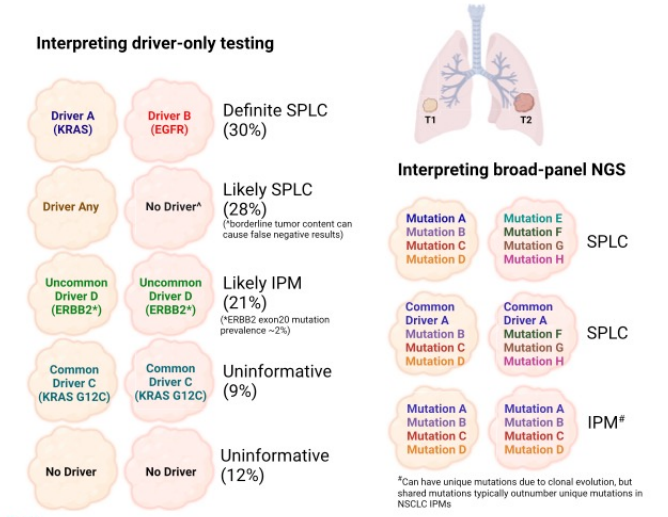
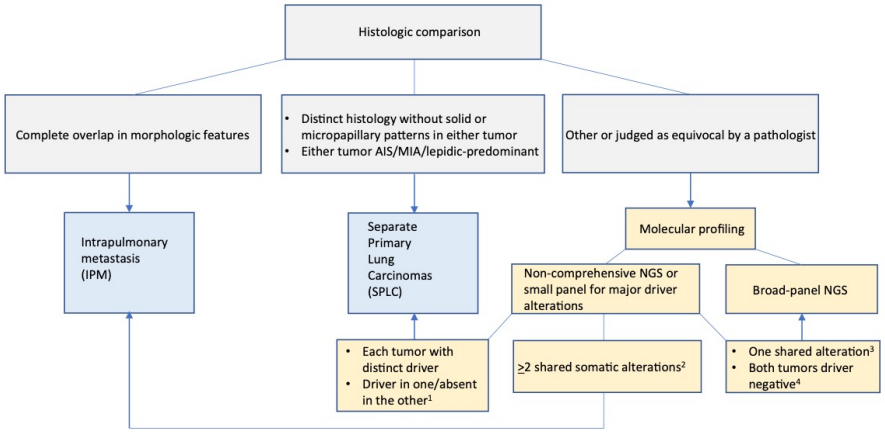


Figure 1.
Molecular profile interpretation in the evaluation of multiple non–small cell lung carcinomas using driver-only testing vs broad-panel NGS testing. Percentages are derived from Chang et al.[13] IPM, intrapulmonary metastasis; NGS, next-generation sequencing; NSCLC, non–small cell lung carcinomas; SPLC, separate primary lung cancer. Created with BioRender.com.



ARTICLE

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Quantitative measurement of HER2 expression to subclassify *ERBB2* unamplified breast cancer

Myrto Moutafi[1,2], Charles J. Robbins[1], Vesal Yaghoobi[1], Aileen I. Fernandez[1], Sandra Martinez-Morilla[1], Vasiliki Xirou[1], Yalai Bai[1], Yan Song[1], Patricia Gaule[1], Joseph Krueger[3], Kenneth Bloom[3], Salisha Hill[4], Daniel C. Liebler[4], Regan Fulton[5] and David L. Rimm[1,6]✉

The efficacy of the antibody drug conjugate (ADC) Trastuzumab deruxtecan (T-DXd) in HER2 low breast cancer patients suggests that the historical/conventional assays for HER2 may need revision for optimal patient care. Specifically, the conventional assay is designed to distinguish amplified HER2 from unamplified cases but is not sensitive enough to stratify the lower ranges of HER2 expression. Here we determine the optimal dynamic range for unamplified HER2 detection in breast cancer and then redesign an assay to increase the resolution of the assay to stratify HER2 expression in unamplified cases. We used the AQUA™ method of quantitative immunofluorescence to test a range of antibody concentrations to maximize the sensitivity within the lower range of HER2 expression. Then, using a cell line microarray with HER2 protein measured by mass spectrometry we determined the amount of HER2 protein in units of attomols/mm^2. Then by calculation of the limits of detection, quantification, and linearity of this assay we determined that low HER2 range expression in unamplified cell lines is between 2 and 20 attomol/mm^2. Finally, application of this assay to a serial collection of 364 breast cancer cases from Yale shows 67% of the population has HER2 expression above the limit of quantification and below the levels seen in HER2 amplified breast cancer. In the future, this assay could be used to determine the levels of HER2 required for response to T-DXd or similar HER2 conjugated ADCs.

Laboratory Investigation (2022) 102:1101–1108; https://doi.org/10.1038/s41374-022-00804-9

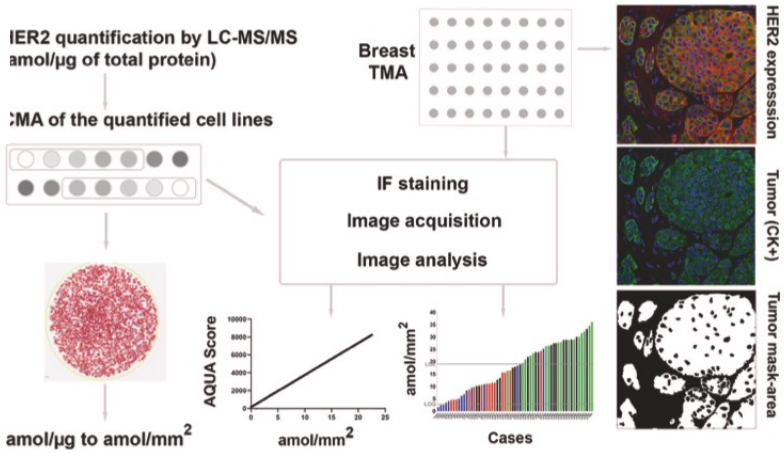

Fig. 1 Schematic overview of the low HER2 assay. Cell lines with a range of HER2 expression, as quantified by LC-MS/MS are used to generate a cell microarray (CMA) standard. Determination of the cell area in mm^2, allows the transformation of the HER2 expression from amol/ug of total protein to amol/mm^2. The CMA is stained using different primary anti-HER2 antibody concentrations and the Limit of Detection (LOD)/ Limit of quantification (LOQ) and Limit of Linearity (LOL) are identified. Linear regression analysis between AQUA Score and amol/mm^2 allows for the generation of a standard curve that can be used to calculate HER2 expression in amol/mm^2 on a tissue area basis. Breast cancer tissue is stained and analyzed by AQUA. After analysis, HER2 expression/case is quantified by amol/mm^2. Liquid Chromatography (LC) with tandem mass spectrometry, LC-MS/MS; Cell MicroArray, CMA; Tissue MicroArray, TMA; Immunofluorescence, IF; Automated Quantitative Analysis, AQUA; Cytokeratin, CK.

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ARTICLE OPEN

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Epigenetically upregulating TROP2 and SLFN11 enhances therapeutic efficacy of TROP2 antibody drug conjugate sacitizumab govitecan

Ming Zhao[1], Timothy P. DiPeri[2], Maria Gabriela Raso[3], Xiaofeng Zheng[4], Yasmeen Qamar Rizvi[1], Kurt W. Evans[1], Fei Yang[3], Argun Akcakanat[1], Marco Roberto Estecio[5], Debu Tripathy[6], Ecaterina E. Dumbrava[1], Senthil Damodaran[6] and Funda Meric-Bernstam[1,7]✉

TROP2 antibody drug conjugates (ADCs) are under active development. We seek to determine whether we can enhance activity of TROP2 ADCs by increasing TROP2 expression. In metaplastic breast cancers (MpBC), there is limited expression of TROP2, and downregulating transcription factor ZEB1 upregulates E-cad and TROP2, thus sensitizing cancers to TROP2 ADC sacituzumab govitecan (SG). Demethylating agent decitabine decreases DNA methyltransferase expression and TROP2 promoter methylation and subsequently increases TROP2 expression. Decitabine treatment as well as overexpression of TROP2 significantly enhance SG antitumor activity. Decitabine also increases SLFN11, a biomarker of topoisomerase 1 inhibitor (TOP1) sensitivity and is synergistic with SG which has a TOP1 payload, in TROP2-expressing SLFN11-low BC cells. In conclusion, TROP2 and SLFN11 expression can be epigenetically modulated and the combination of demethylating agent decitabine with TROP2 ADCs may represent a novel therapeutic approach for tumors with low TROP2 or SLFN11 expression.

npj Breast Cancer (2023)9:66 ; https://doi.org/10.1038/s41523-023-00573-8

Article

A distinct *Fusobacterium nucleatum* clade dominates the colorectal cancer niche

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Martha Zepeda-Rivera[1], Samuel S. Minot[2], Heather Bouzek[1], Hanrui Wu[3], Aitor Blanco-Míguez[4], Paolo Manghi[4], Dakota S. Jones[1], Kaitlyn D. LaCourse[3], Ying Wu[1], Elsa F. McMahon[1], Soon-Nang Park[5], Yun K. Lim[6], Andrew G. Kempchinsky[3], Amy D. Willis[6], Sean L. Cotton[7], Susan C. Yost[7], Ewa Sicinska[8], Joong-Ki Kook[5], Floyd E. Dewhirst[7,9], Nicola Segata[4], Susan Bullman[3,10] ✉ & Christopher D. Johnston[1,10] ✉

Fusobacterium nucleatum (*Fn*), a bacterium present in the human oral cavity and rarely found in the lower gastrointestinal tract of healthy individuals[1], is enriched in human colorectal cancer (CRC) tumours[2–5]. High intratumoural *Fn* loads are associated with recurrence, metastases and poorer patient prognosis[5–8]. Here, to delineate *Fn* genetic factors facilitating tumour colonization, we generated closed genomes for 135 *Fn* strains; 80 oral strains from individuals without cancer and 55 unique cancer strains cultured from tumours from 51 patients with CRC. Pangenomic analyses identified 483 CRC-enriched genetic factors. Tumour-isolated strains predominantly belong to *Fn* subspecies *animalis* (*Fna*). However, genomic analyses reveal that *Fna*, considered a single subspecies, is instead composed of two distinct clades (*Fna* C1 and *Fna* C2). Of these, only *Fna* C2 dominates the CRC tumour niche. Inter-*Fna* analyses identified 195 *Fna* C2-associated genetic factors consistent with increased metabolic potential and colonization of the gastrointestinal tract. In support of this, *Fna* C2-treated mice had an increased number of intestinal adenomas and altered metabolites. Microbiome analysis of human tumour tissue from 116 patients with CRC demonstrated *Fna* C2 enrichment. Comparison of 62 paired specimens showed that only *Fna* C2 is tumour enriched compared to normal adjacent tissue. This was further supported by metagenomic analysis of stool samples from 627 patients with CRC and 619 healthy individuals. Collectively, our results identify the *Fna* clade bifurcation, show that specifically *Fna* C2 drives the reported *Fn* enrichment in human CRC and reveal the genetic underpinnings of pathoadaptation of *Fna* C2 to the CRC niche.

SCIENCE ADVANCES | RESEARCH ARTICLE

EPIDEMIOLOGY

Tissue-specific genetic variation suggests distinct molecular pathways between body shape phenotypes and colorectal cancer

Laia Peruchet-Noray[1,2], Anja M. Sedlmeier[3,4,5], Niki Dimou[1], Hansjörg Baurecht[5], Béatrice Fervers[6], Emma Fontvieille[1], Julian Konzok[5], Kostas K. Tsilidis[7,8], Sofia Christakoudi[7,9], Anna Jansana[1], Reynalda Cordova[1,10], Patricia Bohmann[5], Michael J. Stein[5], Andrea Weber[5], Stéphane Bézieau[11], Hermann Brenner[12,13,14], Andrew T. Chan[15], Iona Cheng[16], Jane C. Figueiredo[17], Koldo Garcia-Etxebarria[18,19], Victor Moreno[2,20,21,22], Christina C. Newton[23], Stephanie L. Schmit[24,25], Mingyang Song[15,26], Cornelia M. Ulrich[27], Pietro Ferrari[1], Vivian Viallon[1], Robert Carreras-Torres[28]†*, Marc J. Gunter[1,7]†*, Heinz Freisling[1]†*

It remains unknown whether adiposity subtypes are differentially associated with colorectal cancer (CRC). To move beyond single-trait anthropometric indicators, we derived four multi-trait body shape phenotypes reflecting adiposity subtypes from principal components analysis on body mass index, height, weight, waist-to-hip ratio, and waist and hip circumference. A generally obese (PC1) and a tall, centrally obese (PC3) body shape were both positively associated with CRC risk in observational analyses in 329,828 UK Biobank participants (3728 cases). In genome-wide association studies in 460,198 UK Biobank participants, we identified 3414 genetic variants across four body shapes and Mendelian randomization analyses confirmed positive associations of PC1 and PC3 with CRC risk (52,775 cases/45,940 controls from GECCO/CORECT/CCFR). Brain tissue–specific genetic instruments, mapped to PC1 through enrichment analysis, were responsible for the relationship between PC1 and CRC, while the relationship between PC3 and CRC was predominantly driven by adipose tissue–specific genetic instruments. This study suggests distinct putative causal pathways between adiposity subtypes and CRC.

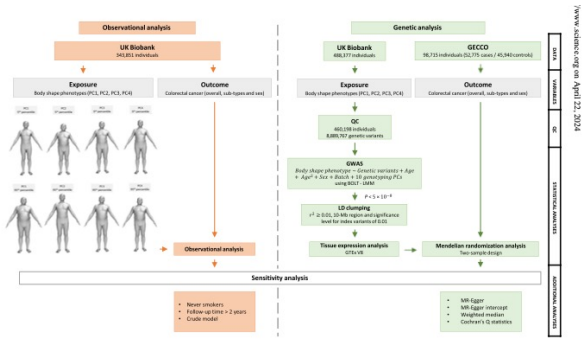

Fig. 1. Flowchart summarizing study methods. Body shape phenotypes have been derived by a PCA on six anthropometric traits (BMI, weight, height, WHR, WC, and HC). PC1 showed high and same sign loadings for all traits except height. PC2 showed high but opposite loadings for height and WHR. PC3 was characterized by high and same direction loadings for height and WHR. PC4 showed high loadings for weight and BMI and low loadings for HC and WC. QC, quality control.

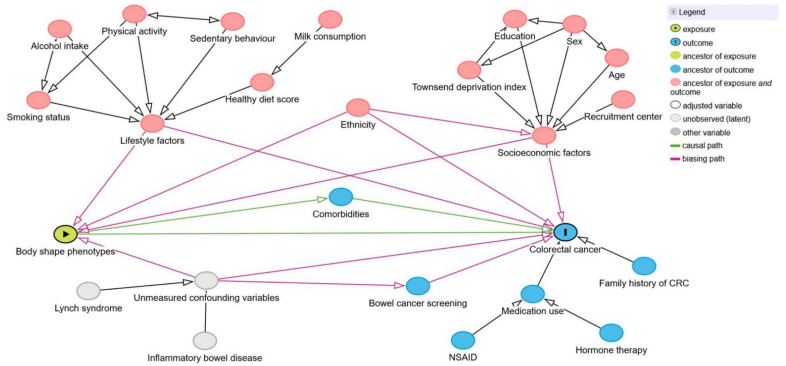

Figure S16. Extended directed acyclic graph (DAG) depicting the assumed causal relationship between body shape phenotypes and colorectal cancer risk with its confounding and mediating paths.
Socioeconomic factors: age, sex, recruitment center, the Townsend deprivation index, and education; ethnicity: White, Mixed, Asian/British Asian, Black/Black British, Chinese, other; lifestyle factors: tobacco smoking, physical activity, sedentary behavior, adherence to a healthy diet score, milk intake, alcohol intake frequency; medication use: nonsteroidal anti-inflammatory drugs (NSAID) and hormone therapy in postmenopausal women; bowel cancer screening, and family history of colorectal cancer (father and/or mother).

We did not adjust for comorbidities such as type 2 diabetes, because we assumed that in the pathway from body shapes to colorectal cancer this comorbidity would rather be a mediator than a confounder.

Unmeasured (known) confounders: inflammatory bowel syndrome and Lynch syndrome. Both phenotypes are difficult to diagnose clinically and data availability in the UK Biobank is therefore limited. However, as indicated in the DAG, we assumed that the confounding paths for both phenotypes are at least partly blocked by accounting for family history of colorectal cancer.

Understanding the Financial Aspects of Digital Pathology: A Dynamic Customizable Return on Investment Calculator for Informed Decision-Making

Orly Ardon*[1], PhD MBA; Sylvia L. Asa[2] MD, Mark C. Lloyd[3], Giovanni Lujan[4] MD, Anil Parwani[4] MD PhD MBA, Juan C. Santa-Rosario[5] MD, Jennifer Samboy[6] MHA, Danielle Pirain[7] BS, Scott Blakely[8] MBA, Matthew G. Hanna[1], MD

Table 4: Categories used for return-on-investment calculations.

Costs
Annual cost pathologists
Cost to generate stained glass slides per year
Cost for FS digital workflow
Cost for ROSE digital workflow
Cost Pathologist workstation
Cost for clinical digital workflow
Costs for information technology to support digital workflow
Costs for digital storage
Cost savings/avoidance
Cost avoidance by using digital workflow
Cost avoidance for FS digital workflow
Cost avoidance for ROSE digital workflow
Cost avoidance for Consult workflow
Cost avoidance for clinical digital workflow
Cost avoidance for glass slide storage
Cost avoidance glass slide retrieval
Cost avoidance educational recuts
Cost savings conferences (personnel time)
Cost savings Case Review & Collaboration
Cost avoidance Legal
Revenue
Additional consultation practice
Data commercialization
Computer assisted quantification reimbursement
Future CPT reimbursement

The customizable user input is used for predictions/calculations in rea

PLOS DIGITAL HEALTH

RESEARCH ARTICLE

Machine learning for healthcare that matters: Reorienting from technical novelty to equitable impact

Aparna Balagopalan[1☯], Ioana Baldini[2☯], Leo Anthony Celi[3,4,5☯], Judy Gichoya[6☯], Liam G. McCoy[7☯*], Tristan Naumann[8☯], Uri Shalit[9☯], Mihaela van der Schaar[10,11☯], Kiri L. Wagstaff[12☯]

1 Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology; Cambridge, Massachusetts, United States of America, **2** IBM Research; Yorktown Heights, New York, United States of America, **3** Laboratory for Computational Physiology, Massachusetts Institute of Technology; Cambridge, Massachusetts, United States of America, **4** Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center; Boston, Massachusetts, Unit
5 Department of Biostatistics, Harvard T.H. Chan School of Public Health; Bost
States of America, **6** Department of Radiology and Imaging Sciences, School o
Atlanta, Georgia, United States of America, **7** Division of Neurology, Departmer
Alberta; Edmonton, Alberta, Canada, **8** Microsoft Research; Redmond, Washin
America, **9** The Faculty of Data and Decision Sciences, Technion; Haifa, Israel,
Mathematics and Theoretical Physics, University of Cambridge; Cambridge, Un
Turing Institute; London, United Kingdom, **12** Independent Researcher; United

☯ These authors contributed equally to this work.

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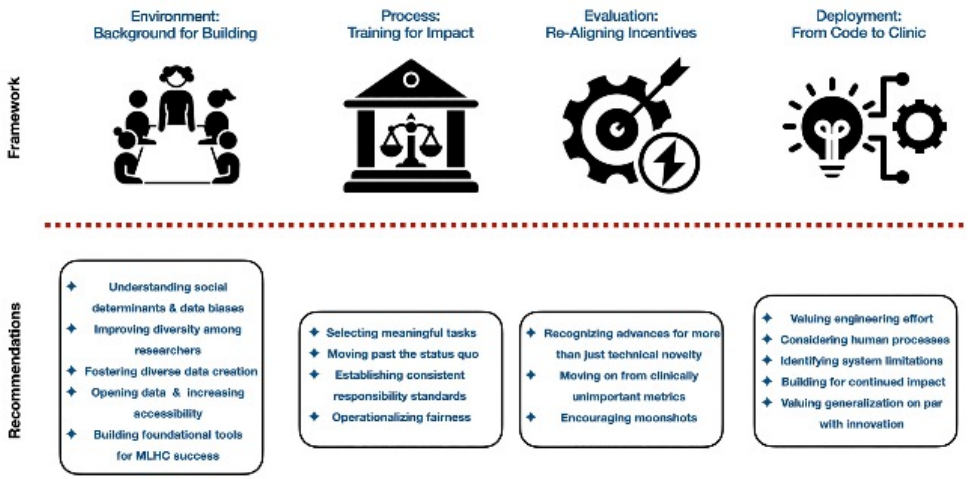

Fig 1. Machine learning for healthcare impact framework and recommendations.

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DATASETS, BENCHMARKS, AND PROTOCOLS

GPT versus Resident Physicians — A Benchmark Based on Official Board Scores

Uriel Katz, M.D.,[1] Eran Cohen, M.D.,[2,3] Eliya Shachar, M.D.,[2,4] Jonathan Somer, B.Sc.,[5] Adam Fink, M.D.,[6] Eli Morse, M.D.,[7] Beki Shreiber, B.Sc.,[8] and Ido Wolf, M.D.[2,3,4]

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Abstract

BACKGROUND Artificial intelligence (AI) is a burgeoning technological advancement, with considerable promise for influencing the field of medicine. As a preliminary step toward integrating AI into medical practice, it is imperative to ascertain whether model

Events

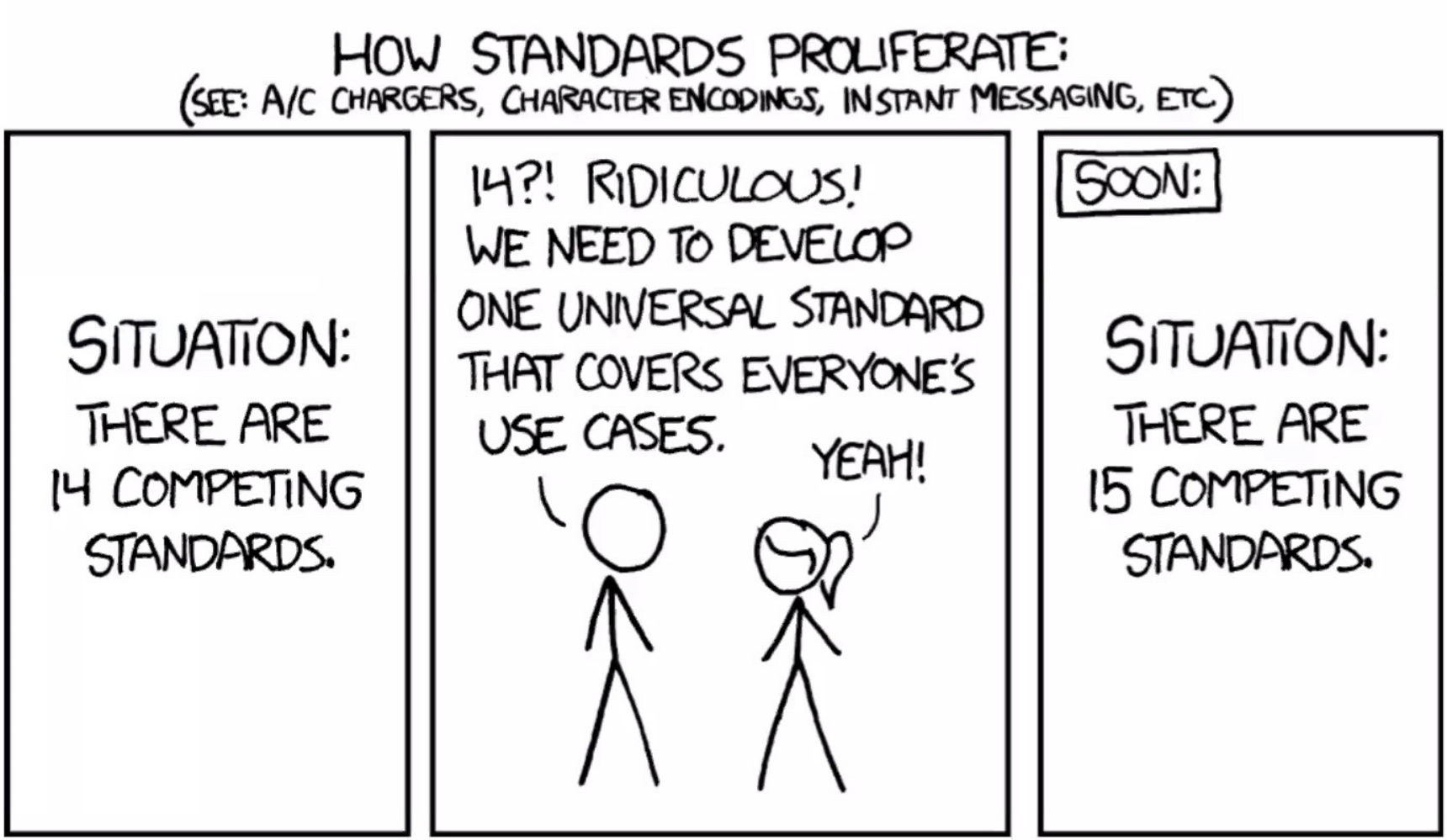
Next steering committee meeting

May 29th 2024

at

3:00PM

(EST)


HOW STANDARDS PROLIFERATE:
(SEE: A/C CHARGERS, CHARACTER ENCODINGS, INSTANT MESSAGING, ETC.)
SITUATION: THERE ARE 14 COMPETING STANDARDS.
14?! RIDICULOUS! WE NEED TO DEVELOP ONE UNIVERSAL STANDARD THAT COVERS EVERYONE'S USE CASES.
YEAH!
SOON:
SITUATION: THERE ARE 15 COMPETING STANDARDS.

Source: [xkcd]