



Publications





<https://doi.org/10.1038/s43856-024-00471-5>

A systematic pan-cancer study on deep learning-based prediction of multi-omic biomarkers from routine pathology images

Check for updates

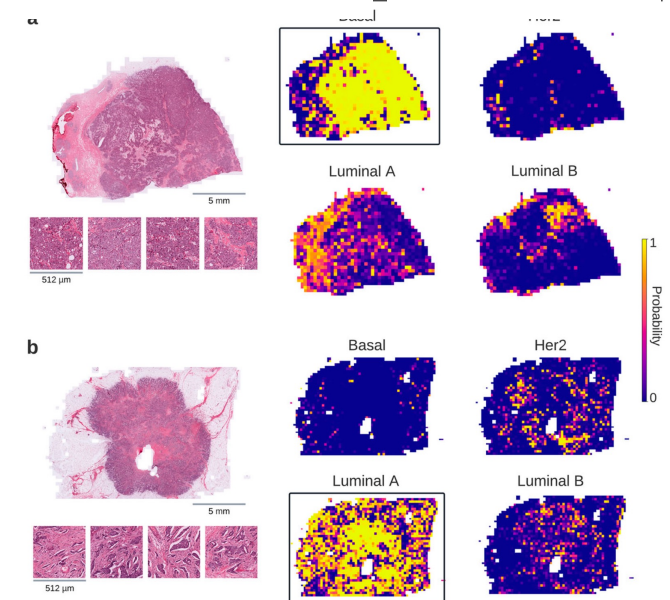
Salim Arslan¹✉, Julian Schmidt¹, Cher Bass¹, Debapriya Mehrotra^{1,2}, Andre Geraldes¹, Shikha Singhal^{1,3}, Julius Hense¹, Xiusi Li¹, Pandu Raharja-Liu¹, Oscar Maiques^{4,5}, Jakob Nikolas Kather^{6,7} & Pahini Pandya¹

Fig. 6 | Visualization of predictability with deep learning from histopathological images. Deep learning (DL)-based predictions for the molecular subtypes of breast cancer (i.e., Basal, HER2, Luminal A, and Luminal B) are visualized for two selected patients using heatmaps. The correctly-predicted subtype in each case is enclosed with a rectangle and the highest-ranking tiles from that class are given alongside the original whole slide image (WSI). The Basal type (a) shows sheets of tumor cells without any discernible gland formation, while the Luminal A patient's tumor (b) is composed of well-formed glands. Considering the heatmaps in both cases, one can notice that DL models can identify spatial regions that are relevant to the target class. Scale bar for WSIs: 5 mm. Scale bar for tiles: 512 μ m.

Table 1 | Average performance

Biomarker type/omic	Mean AUC \pm std.
Standard clinical biomarkers	0.742 \pm 0.120 ($n = 135$)
Clinical outcomes and treatment responses	0.671 \pm 0.120 ($n = 480$)
Under-/over-expression of proteins	0.666 \pm 0.108 ($n = 1728$)
Gene signatures and molecular subtypes	0.653 \pm 0.097 ($n = 810$)
Under-/over-expression of transcriptomes	0.637 \pm 0.108 ($n = 3090$)
Presence of single nucleotide variants (SNVs)	0.636 \pm 0.117 ($n = 5850$)

The table is sorted by the average performance.



IMAGING INFORMATICS AND ARTIFICIAL INTELLIGENCE

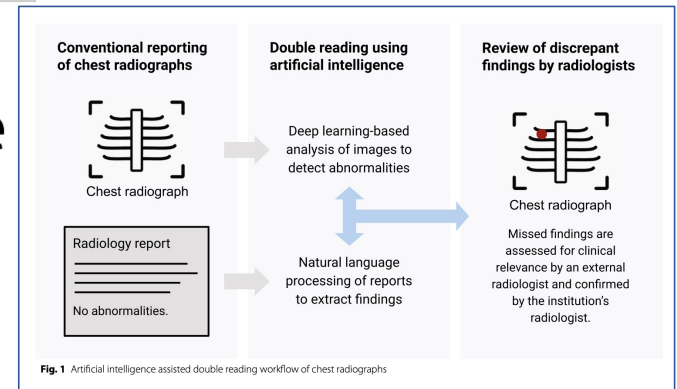
Artificial intelligence-assisted double reading of chest radiographs to detect clinically relevant missed findings: a two-centre evaluation

Laurens Topff^{1,2*}, Sanne Steltenpool^{3,4}, Erik R. Ranschaert^{5,6}, Naglis Ramanauskas^{7,8}, Renee Menezes⁹, Jacob J. Visser³, Regina G. H. Beets-Tan^{1,2†} and Nolan S. Hartkamp^{4†}

findings consisted of lung nodules (71.4%, 25 of 35), pneumothoraces (17.1%, 6 of 35) and consolidations (11.4%, 4 of 35).

Conclusion The AI-assisted double reading system was able to identify missed findings on chest radiographs after report authorisation. The approach required an external radiologist to review the AI-detected discrepancies. The number of clinically relevant missed findings by radiologists was very low.

Clinical relevance statement The AI-assisted double reader workflow was shown to detect diagnostic errors and could be applied as a quality assurance tool. Although clinically relevant missed findings were rare, there is potential impact given the common use of chest radiography.





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Utility of artificial intelligence in a binary classification of soft tissue tumors



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Table 3

Representative AI models metrics, classifying benign and malignant soft tissue tumors (Study arm 3).

Metric	AUC	Accuracy	Sensitivity	Specificity
Gradientboosting	0.664	0.667	0.579	0.75
Neuralnetwork	0.638	0.641	0.526	0.75
Xgboost	0.639	0.641	0.579	0.7
Randomforest	0.717	0.718	0.684	0.75
Bagging	0.666	0.667	0.632	0.7
Tabpfn	0.743	0.744	0.737	0.75
Histgradientboosting	0.664	0.667	0.579	0.75
Sgdclassifier	0.584	0.59	0.368	0.8
Logisticregression	0.768	0.769	0.737	0.8

Next-Generation Sequencing Trends among Adult Patients with Select Advanced Tumor Types



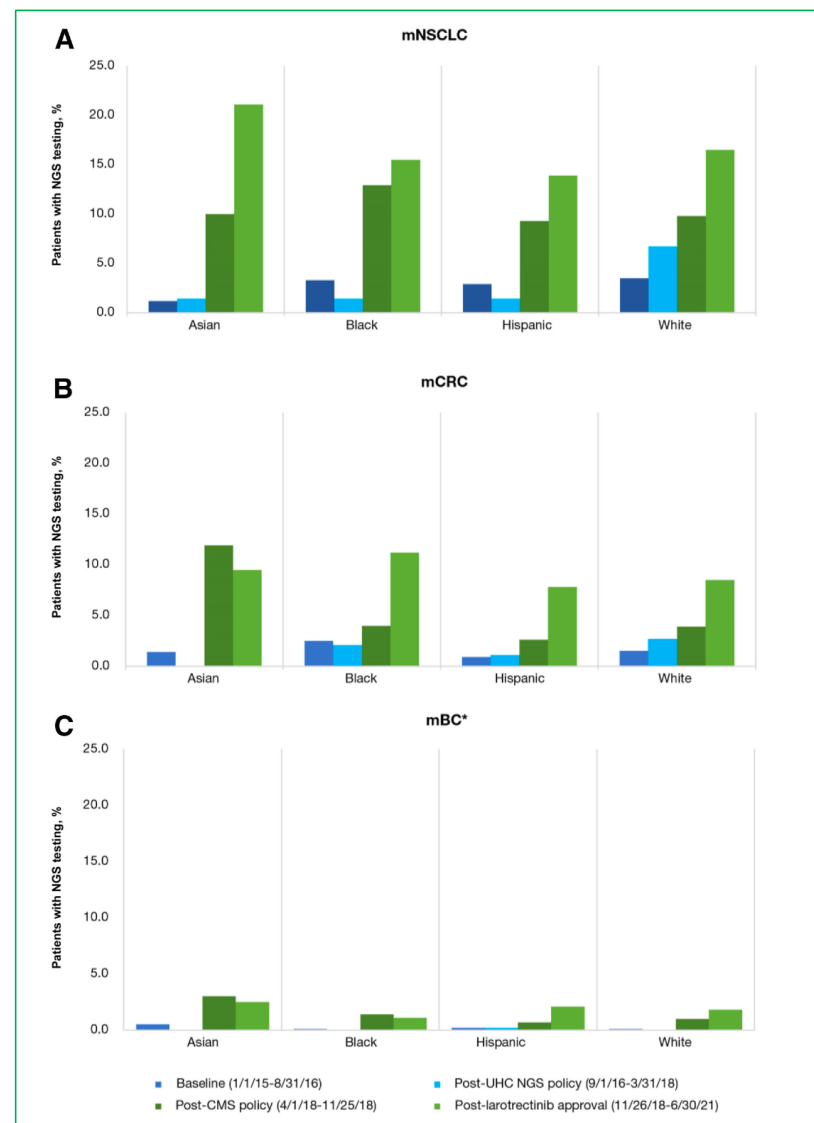
A Real-World Evidence Evaluation

Andrea Ferreira-Gonzalez,* Brian Hocum,† Gilbert Ko,† Sohul Shuvo,† Sreevalsa Appukkuttan,† and Svetlana Babajanyan†



From the Department of Pathology,* Virginia Commonwealth University, Richmond, Virginia; and Bayer HealthCare Pharmaceuticals, Inc.,† Whippany, New Jersey

Despite improving payer policies to expand coverage of NGS and molecular biomarker based therapy approvals, **NGS rates remained low across tumor types.**

Given the potential for improved patient outcomes with molecular biomarker based therapy, further efforts to improve NGS rates are warranted.



Strategies to Address the Clinical Practice Gaps Affecting the Implementation of Personalized Medicine in Cancer Care

Apostolia M. Tsimberidou, MD, PhD, FASCO, FAAAS¹ ; Anthony Sireci, MD, MSc²; Robert Dumanois³; and Daryl Pritchard, PhD⁴ 

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INTRODUCTION

Biomarker testing–based personalized medicine strategies can improve outcomes for patients with cancer at the individual and population levels.^{1,2} The identification of actionable molecular biomarkers and treatment with matched targeted therapies have been associated with favorable outcomes for individual patients. However, many patients with cancer do not undergo biomarker testing and do not receive targeted therapies.^{3–5} Ensuring that all patients with cancer have access to and receive biomarker–driven care remains a challenge.



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GENETICS

The molecular basis of cell memory in mammals: The epigenetic cycle

Mencía Espinosa-Martínez^{1,2,3†}, María Alcázar-Fabra^{1,2,3†}, David Landeira^{1,2,3*}

Cell memory refers to the capacity of cells to maintain their gene expression program once the initiating environmental signal has ceased. This exceptional feature is key during the formation of mammalian organisms and it is believed to be in part mediated by epigenetic factors that can endorse cells with the landmarks required to maintain transcriptional programs upon cell duplication. Here, we review current literature analyzing the molecular basis of epigenetic memory in mammals, with a focus on the mechanisms by which transcriptionally repressive chromatin modifications such as methylation of DNA and histone H3 are propagated through cell divisions. The emerging picture suggests that cellular memory is supported by an epigenetic cycle in which reversible activities carried out by epigenetic regulators in coordination with cell cycle transition create a phasic system that can accommodate both maintenance of cell identity and cell differentiation in proliferating stem cell populations.

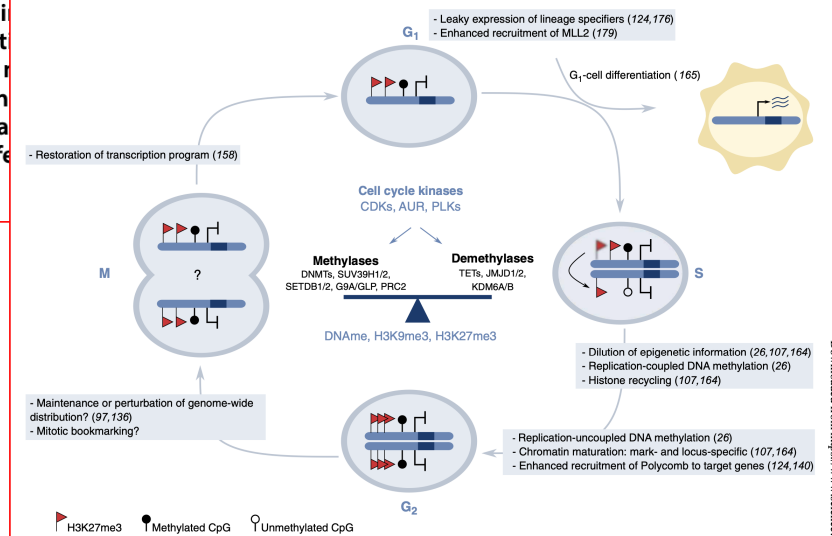
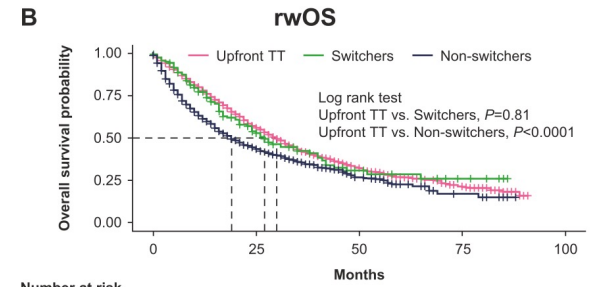
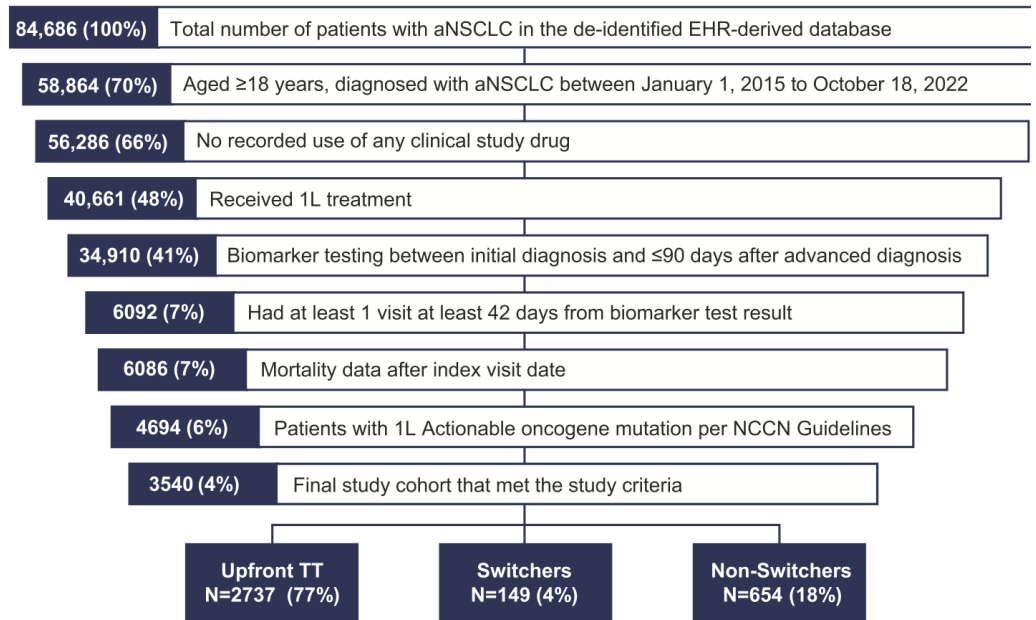


Fig. 3. Model of transmission of epigenetic memory in pluripotent cells: The epigenetic cycle. Undifferentiated cell nuclei during cell cycle transition (G₁, S, G₂, and M phases) are represented as light blue circles, while differentiated cells are depicted in yellow. Blue bars inside the nuclei represent a chromatid in which a gene encoding for a lineage-specifier protein is highlighted in dark blue. Methylated and unmethylated CpGs are represented as filled or empty lollipops, respectively. Red flags indicate H3K27me3.

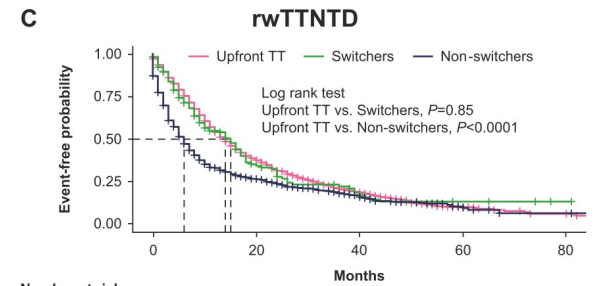


Clinical Value of Timely Targeted Therapy for Patients With Advanced Non–Small Cell Lung Cancer With Actionable Driver Oncogenes

Thomas Stricker^{*,1,2}, Neha Jain², Esprit Ma³, Elaine Yu³, Rongrong Wang³, Robert Schuldt³, Richard Price³, Tania Szado³, Jesse Sussell³, Sarika Ogale³, Victor Lin^{2,4}, Edward Arrowsmith^{1,2}, Dennis Slater^{2,5}, Daniel Vaena^{2,6}, Harry Staszewski^{2,7}, Bruno Fang^{2,8}, Lasika Seneviratne^{2,9}, Davey Daniel^{1,2}



	Duration of follow-up, median (IQR) months	rwOS, median (95% CI), months	Adjusted HRs
Upfront TT, n=2737	17 (8-32)	30 (28-32)	Reference group
Switchers, n=149	16 (8-33)	27 (21-40)	0.9697, P=0.8002
Non-switchers, n=654	11 (4-26.75)	19 (16-23)	1.3673, P=0.0000



	Duration of follow-up, median (IQR) months	rwTTNTD, median (95% CI), months	Adjusted HRs
Upfront TT, n=2737	10 (5-20)	14 (13-15)	Reference group
Switchers, n=149	10 (4-18)	15 (10-17)	0.9869, P=0.9008
Non-switchers, n=654	5 (1-13)	6 (5-7)	1.3308, P=0.0000

Work/ Technology & tools

GENOME DIAGNOSTICS IN THE FAST LANE

Streamlined workflows for DNA and RNA sequencing are helping clinicians to deliver prompt, targeted care to people in days – or even hours. **By Michael Eisenstein**

Sometimes good news arrives too late. About a decade ago, clinical geneticist Zornitza Stark and her colleagues at the Murdoch Children's Research Institute in Melbourne, Australia, set out to learn how genome sequencing might improve the care of young children with suspected hereditary disorders. The researchers sequenced the protein-coding regions in the genomes of 80 infants, looking for genetic changes to explain their conditions. For one nine-month-old boy with severe neurological symptoms, Stark's team homed in on a mutation that resulted in a crucial vitamin B1 deficiency, which could be readily treated with supplements for just under Aus\$150 per year (US\$136 at the time).

Unfortunately, it took six months from when the sample was taken to get that answer. Treatment with vitamin B1 safeguarded the boy's

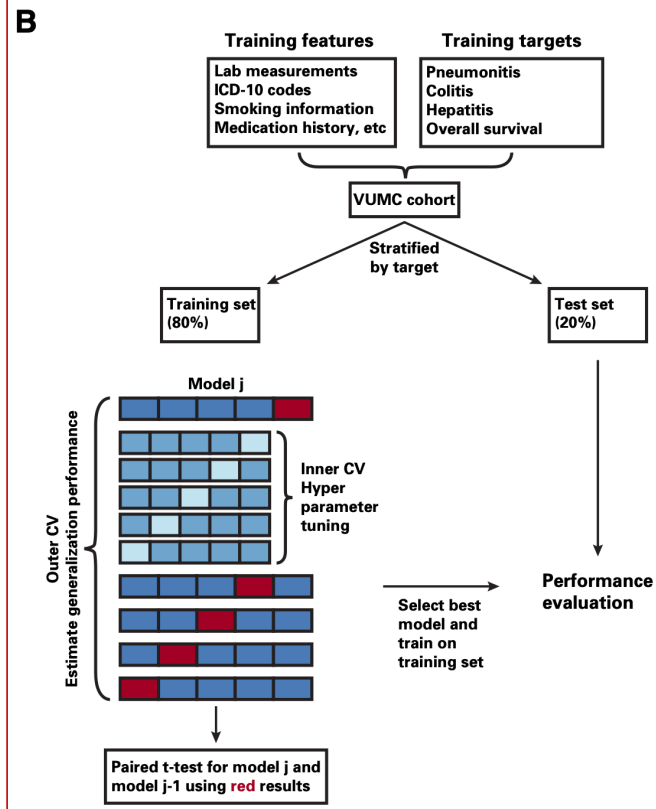
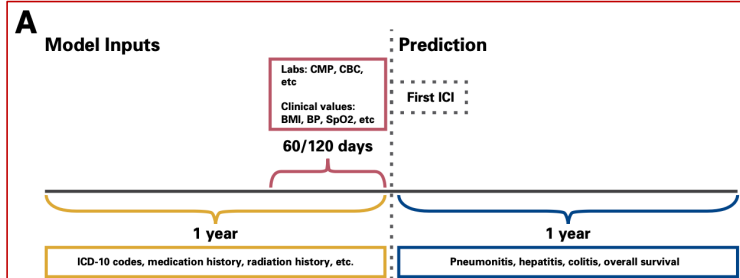
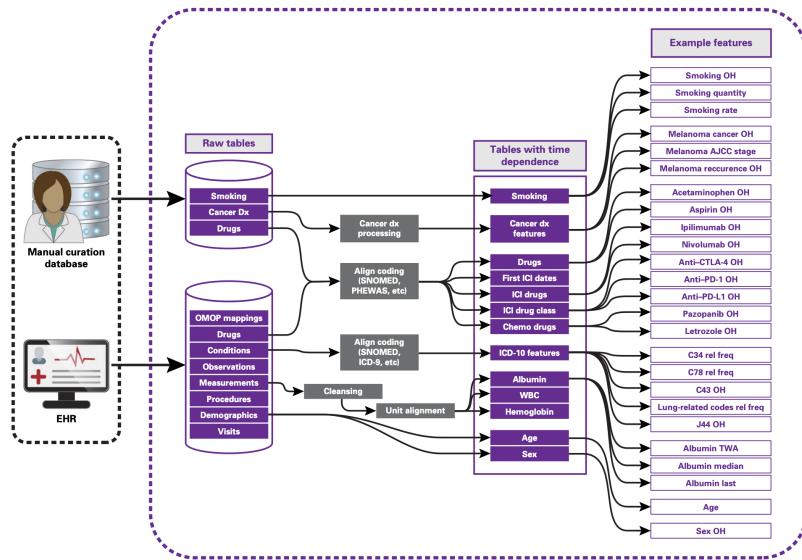


Prediction of Effectiveness and Toxicities of Immune Checkpoint Inhibitors Using Real-World Patient Data

Levente Lippenszky, MS¹; Kathleen F. Mittendorf, PhD²; Zoltán Kiss, MS¹; Michele L. LeNoue-Newton, PhD^{2,3}; Pablo Napan-Molina, MS¹; Protiva Rahman, PhD^{4,5}; Cheng Ye, PhD⁴; Balázs Laczi, MS¹; Eszter Csemnai, MS¹; Neha M. Jain, PhD^{2,6}; Marilyn E. Holt, PhD^{2,7}; Christina N. Maxwell, MS²; Madeleine Ball, BA^{2,8}; Yufang Ma, PhD, PharmD^{2,9}; Margaret B. Mitchell, MD, MHPE^{2,10}; Douglas B. Johnson, MD, MSCI^{2,11}; David S. Smith, PhD^{1,2}; Ben H. Park, MD, PhD^{2,11}; Christine M. Micheel, PhD^{2,11}; Daniel Fabbri, PhD⁴; Jan Wolber, PhD, MBA^{1,3}; and Travis J. Osterman, DO, MS^{2,4,11}

DOI | <https://doi.org/10.1200/JCO.2023.00207>

CONCLUSION To our knowledge, this is the first ML solution that assesses individual ICI risk-benefit profiles based predominantly on routine structured EHR data. As such, use of our ML solution will not require additional data collection or documentation in the clinic.



Outcome Modeled	Diagnosis (N)	AUC (95% bootstrap CI)
Pneumonitis 1y	All cancer types (n = 416)	0.739 (0.638 to 0.823)
	Melanoma (n = 166)	0.590 (0.353 to 0.841)
	Lung cancer (n = 111)	0.723 (0.600 to 0.840)
	GU cancer (n = 67)	0.845 (0.686 to 0.960)
Hepatitis 1y	All (n = 392)	0.729 (0.655 to 0.804)
	Melanoma (n = 136)	0.567 (0.373 to 0.777)
	Lung cancer (n = 107)	0.884 (0.792 to 0.965)
	GU cancer (n = 53)	0.639 (0.376 to 0.863)
Colitis 1y	All (n = 427)	0.755 (0.638 to 0.856)
	Melanoma (n = 161)	0.747 (0.631 to 0.850)
	Lung cancer (n = 112)	0.853 (0.717 to 0.964)
	GU cancer (n = 68)	0.560 (0.447 to 0.672)
OS 1y	All (n = 403)	0.752 (0.706 to 0.796)
	Melanoma (n = 158)	0.794 (0.716 to 0.861)
	Lung cancer (n = 115)	0.681 (0.580 to 0.781)
	GU cancer (n = 63)	0.741 (0.600 to 0.858)

<https://doi.org/10.1038/s41746-024-01071-2>

The lucent yet opaque challenge of regulating artificial intelligence in radiology

James M. Hillis, Jacob J. Visser, Edward R. Scheffer Cliff, Kelly van der Geest – Aspers, Bernardo C. Bizzo, Keith J. Dreyer, Jeremias Adams-Prassl & Katherine P. Andriole

**Table 1 | Summary of radiology AI/ML device**

Regulatory agency	United States Food and Drug Administration
Organizational structure for regulatory clearance	Centralized process through Health
Typical risk classification for radiology AI/ML device	Class II
Predicate pathway	510(k) pathway (for sub I/II device).
Product types / codes	Regulation numbers defined associated 'special control' multiple product codes have been used for radiology
Minimal device metrics	Defined for some products assisted prioritization so >0.95). Many product codes do
Model change process	Draft guidance to define Control Plan. Separate guidance software change to an e
Accelerated / conditional pathway	No; the Breakthrough Device still requires the application
Consideration of cost-effectiveness in clearance	No
Post-market surveillance	Yes
Database of approved devices	FDA website ²

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Comment | Published: 18 March 2024

New AI regulation in the EU seeks to reduce risk without assessing public benefit

[Barbara Prainsack](#)  & [Nikolaus Forgó](#)

[Nature Medicine](#) (2024) | [Cite this article](#)

580 Accesses | 66 Altmetric | [Metrics](#)

The European Union's new AI Act focuses on risk without considering benefits, which could hinder the development of new technology while failing to protect the public.

Article

Economics of Artificial Intelligence in Healthcare: Diagnosis vs. Treatment

Narendra N. Khanna ¹, Mahesh A. Maindarkar ^{2,3}, Vijay Viswanathan ⁴, Jose Fernando Sudip Paul ³, Mrinalini Bhagawati ³, Puneet Ahluwalia ⁶, Zoltan Ruzsa ⁷, Aditya Inder M. Singh ², John R. Laird ¹⁰, Mostafa Fatemi ¹¹, Azra Alizad ¹², Luca Saba ¹³, V. Aman Sharma ¹⁴, Jagjit S. Teji ¹⁵, Mustafa Al-Maini ¹⁶, Vijay Rathore ¹⁷, Subbaram Nair ¹⁸, Amer M. Johri ¹⁹, Monika Turk ²⁰, Lopamudra Mohanty ²¹, David W. Sobel ²², Martin Kludija Viskovic ²⁴, George Tsoulfas ²⁵, Athanasios D. Protogerou ²⁶, George D. K. Mostafa M. Fouda ²⁹, Seemant Chaturvedi ³⁰, Mannudeep K. Kalra ³¹ and Jasjit S. Su

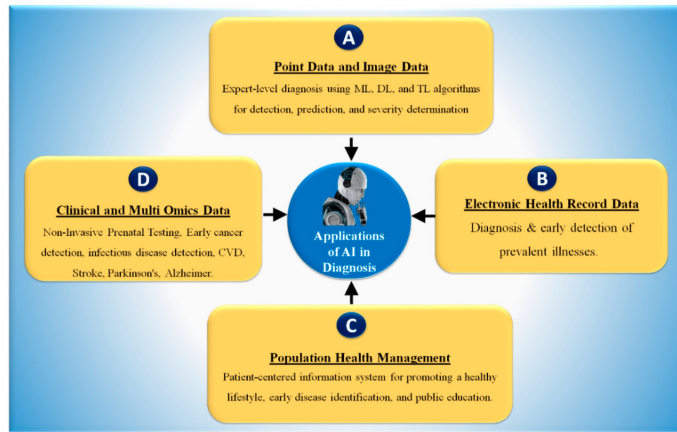


Figure 5. Applications of AI in healthcare diagnosis. AI: artificial intelligence, ML: machine learning, DL: deep learning, TL: transfer learning, CVD: cardiovascular diseases.

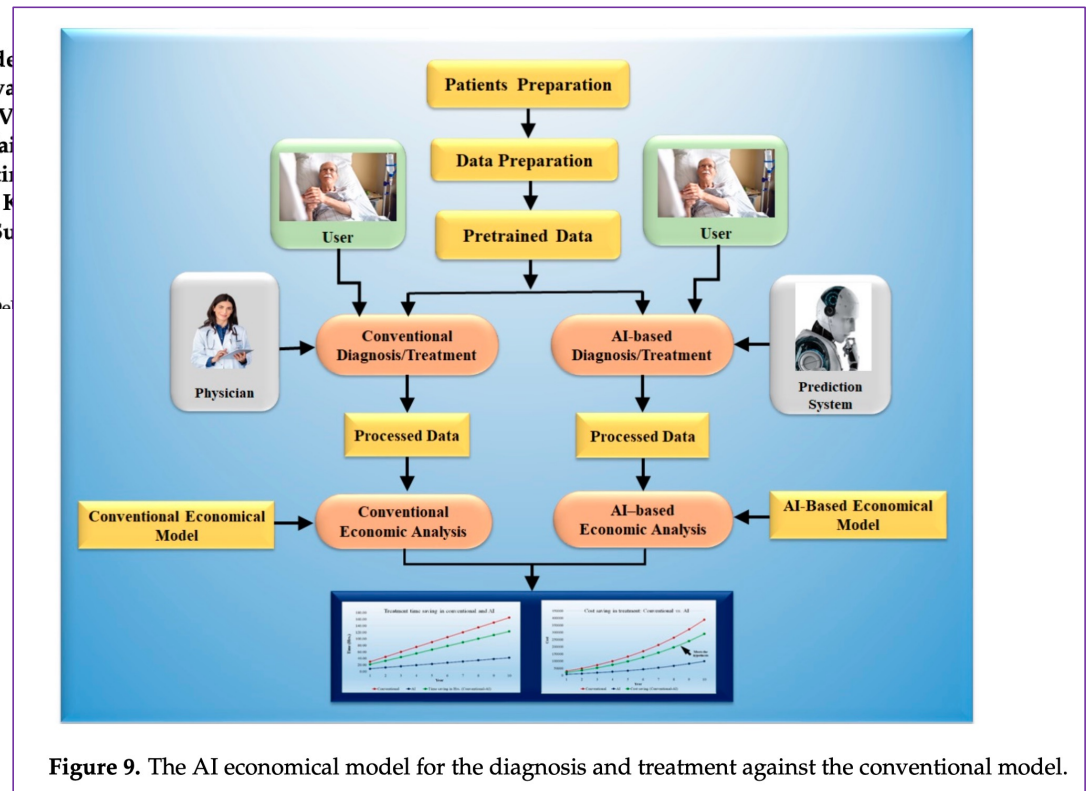


Figure 9. The AI economical model for the diagnosis and treatment against the conventional model.

Smart Healthcare in the Age of AI: Recent Advances, Challenges, and Future Prospects

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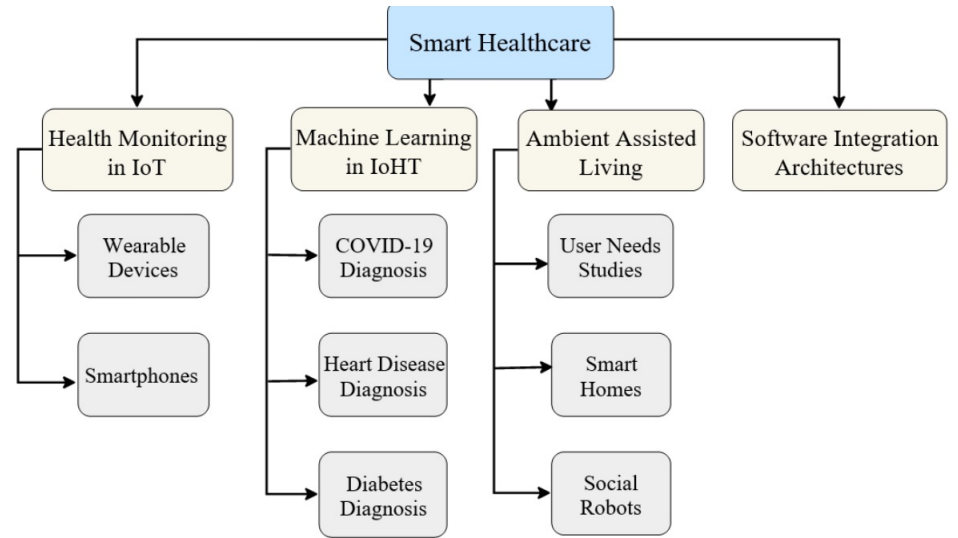


FIGURE 1. The overall workflow of the reviewed systems of smart healthcare.

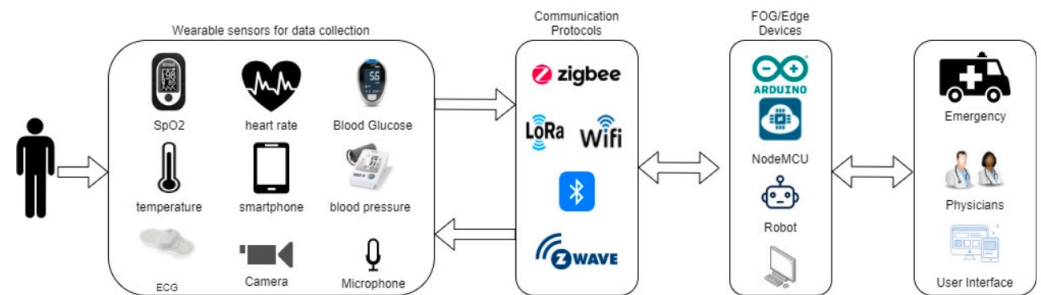


FIGURE 2. A general pipeline of a health monitoring system based on wearable devices.



Heterogeneity and predictors of the effects of AI assistance on radiologists

Received: 22 June 2023

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Feiyang Yu ^{1,2,5}, Alex Moehring ^{3,5}, Oishi Banerjee¹, Tobias Salz^{4,6},
Nikhil Agarwal^{4,6} & Pranav Rajpurkar ^{1,6} 

experience-based factors, such as years of experience, subspecialty and familiarity with AI tools, fail to reliably predict the impact of AI assistance. Additionally, lower-performing radiologists do not consistently benefit more from AI assistance, challenging prevailing assumptions. Instead, we found that the occurrence of AI errors strongly influences treatment outcomes, with inaccurate AI predictions adversely affecting radiologist performance on the aggregate of all pathologies and on half of the individual pathologies investigated. Our findings highlight the importance of personalized approaches to clinician–AI collaboration and the importance of accurate AI models. By understanding the factors that shape the effectiveness of AI assistance, this study provides valuable insights for targeted implementation of AI, enabling maximum benefits for individual clinicians in clinical practice.



An immunophenotype-coupled transcriptomic atlas of human hematopoietic progenitors

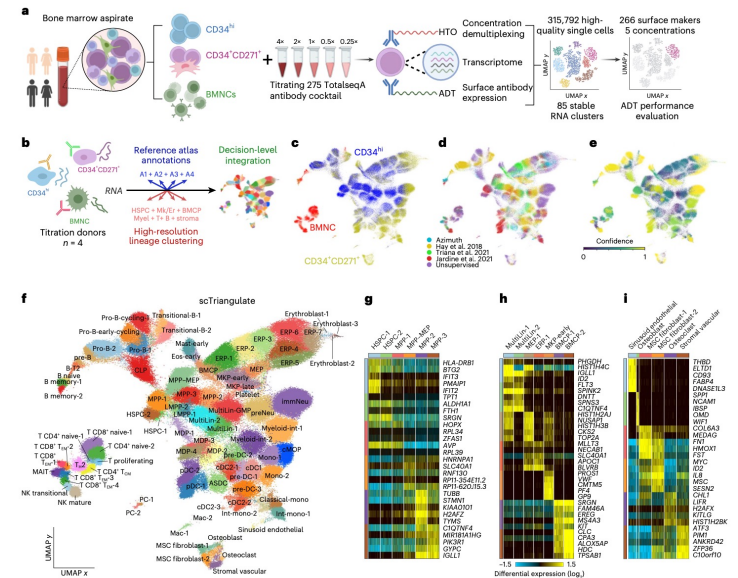
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Xuan Zhang^{1,14}, Baobao Song^{1,2,14}, Maximillian J. Carlino^{3,4}, Guangyuan Li⁵, Kyle Ferchen¹, Mi Chen^{3,4}, Evrett N. Thompson^{3,4,6}, Bailee N. Kain¹, Dan Schnell⁵, Kairavee Thakkar⁵, Michal Kouril⁵, Kang Jin⁵, Stuart B. Hay⁵, Sidharth Sen⁵, David Bernardicius¹, Siyuan Ma¹, Sierra N. Bennett¹, Josh Croteau⁷, Ornella Salvatori⁷, Melvin H. Lye⁸, Austin E. Gillen^{9,10}, Craig T. Jordan⁹, Harinder Singh¹¹, Diane S. Krause^{3,4,6}, Nathan Salomonis^{5,12} ✉ & H. Leighton Grimes^{1,12,13} ✉



Article

Evolutionary trajectories of small cell lung cancer under therapy

<https://doi.org/10.1038/s41586-024-07177-7>

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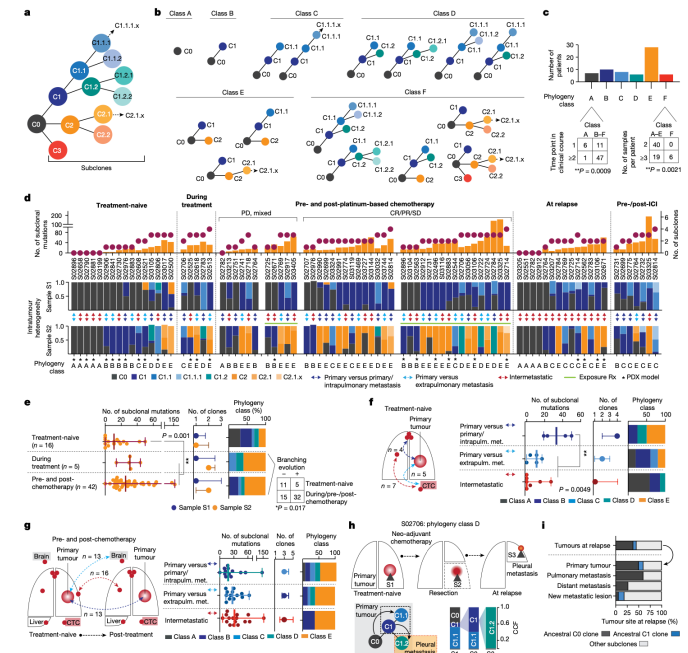
Published online: 13 March 2024

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Julie George^{1,2}, Lukas Maas¹, Nima Abedpour^{1,3,4}, Maria Cartolano^{1,5}, Laura Kaiser¹, Rieke N. Fischer⁶, Andreas H. Scheel⁷, Jan-Philipp Weber⁶, Martin Hellmich⁸, Graziella Bosco¹, Caroline Volz^{3,5}, Christian Mueller^{1,2}, Ilona Dahmen¹, Felix John⁶, Cleidson Padua Alves¹, Lisa Werr¹, Jens Peter Panse^{9,10}, Martin Kirschner^{9,10}, Walburga Engel-Riedel¹¹, Jessica Jürgens¹¹, Erich Stoelben¹², Michael Brockmann¹³, Stefan Grau^{14,15}, Martin Sebastian^{16,17,18}, Jan A. Stratmann^{16,17}, Jens Kern¹⁹, Horst-Dieter Hummel²⁰, Balazs Hegedüs²¹, Martin Schuler^{18,22}, Till Plönes^{22,23}, Clemens Aigner^{21,24}, Thomas Elter³, Karin Toepelt³, Yon-Dschun Ko²⁵, Sylke Kurz²⁶, Christian Grohé²⁶, Monika Serke²⁷, Katja Höpker²⁸, Lars Hagmeyer²⁹, Fabian Doerr^{21,30}, Khosro Hekmath³⁰, Judith Strapatsas³¹, Karl-Otto Kambartel³², Geothy Chakupurakal³³, Annette Busch³⁴, Franz-Georg Bauernfeind³⁴, Frank Griesinger³⁵, Anne Luers³⁵, Wiebke Dirks³⁵, Rainer Wiewrodt³⁶, Andrea Luecke³⁶, Ernst Rodermann³⁷, Andreas Diel³⁷, Volker Hagen³⁸, Kai Severin³⁹, Roland T. Ullrich^{3,5}, Hans Christian Reinhardt^{40,41}, Alexander Quaas⁷, Magdalena Bogus⁴², Cornelius Courts⁴², Peter Nürnberg⁴³, Kerstin Becker⁴³, Viktor Achter⁴⁴, Reinhard Büttner⁷, Jürgen Wolf⁶, Martin Peifer^{1,5} & Roman K. Thomas^{1,7,18}

genome duplications. Gene-damaging *TP53* alterations and co-alterations of *TP53* missense mutations with *TP73*, *CREBBP/EP300* or *FMN2* were significantly associated with shorter disease relapse following chemotherapy. In summary, we uncover key processes of the genomic evolution of SCLC under therapy, identify the common ancestor as the source of clonal diversity at relapse and show central genomic patterns associated with sensitivity and resistance to chemotherapy.





Tertiary lymphoid structures and B cells determine clinically relevant T cell phenotypes in ovarian cancer

PD1⁺ T cells. Spatial B-cell profiling identifies patterns of in situ maturation and differentiation associated with mTLSs. Moreover, B-cell depletion promotes signs of a dysfunctional CD8⁺ T cell compartment among tumor-infiltrating lymphocytes from freshly isolated HGSOE and NSCLC biopsies. Taken together, our data demonstrate that – at odds with NSCLC – HGSOE is associated with a low density of follicular helper T cells and thus develops a limited number of mTLS that might be insufficient to preserve a ICI-sensitive TCF1⁺PD1⁺ CD8⁺ T cell phenotype. **These findings point to key quantitative and qualitative differences between mTLSs in ICI-responsive vs ICI-irresponsible neoplasms that may guide the development of alternative immunotherapies for patients with HGSOE.**

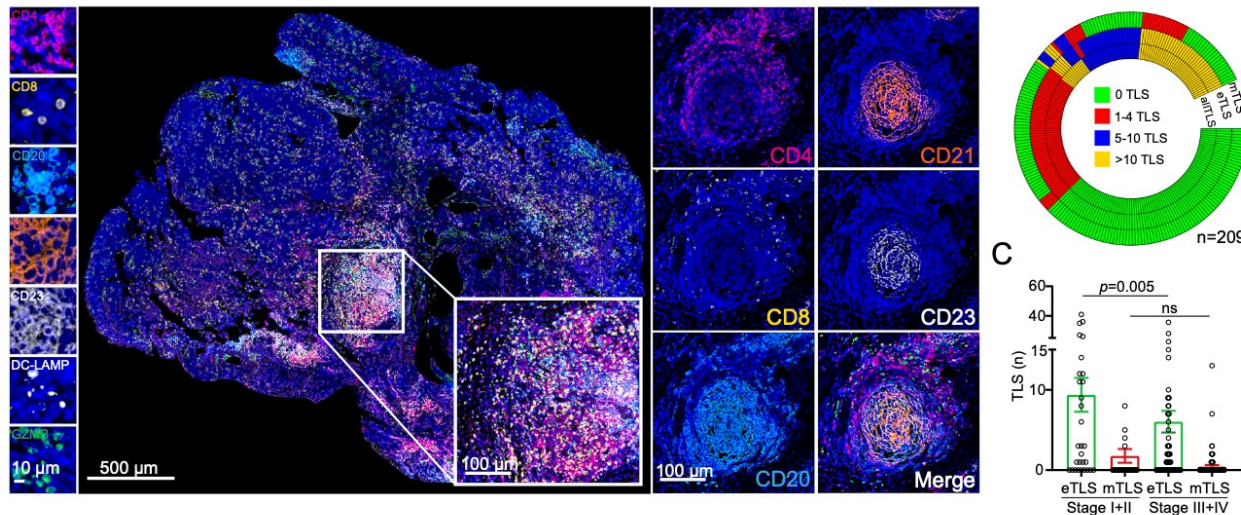
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A list of authors and their affiliations appears at the end of the paper

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Intratumoral tertiary lymphoid structures (TLSs) have been associated





Allele-specific transcriptional effects of subclonal copy number alterations enable genotype-phenotype mapping in cancer cells

Received: 18 January 2023

Hongyu Shi^{1,2}, Marc J. Williams¹, Gryte Satas¹, Adam C. Weiner^{1,3},
Andrew McPherson¹ & Sohrab P. Shah¹✉

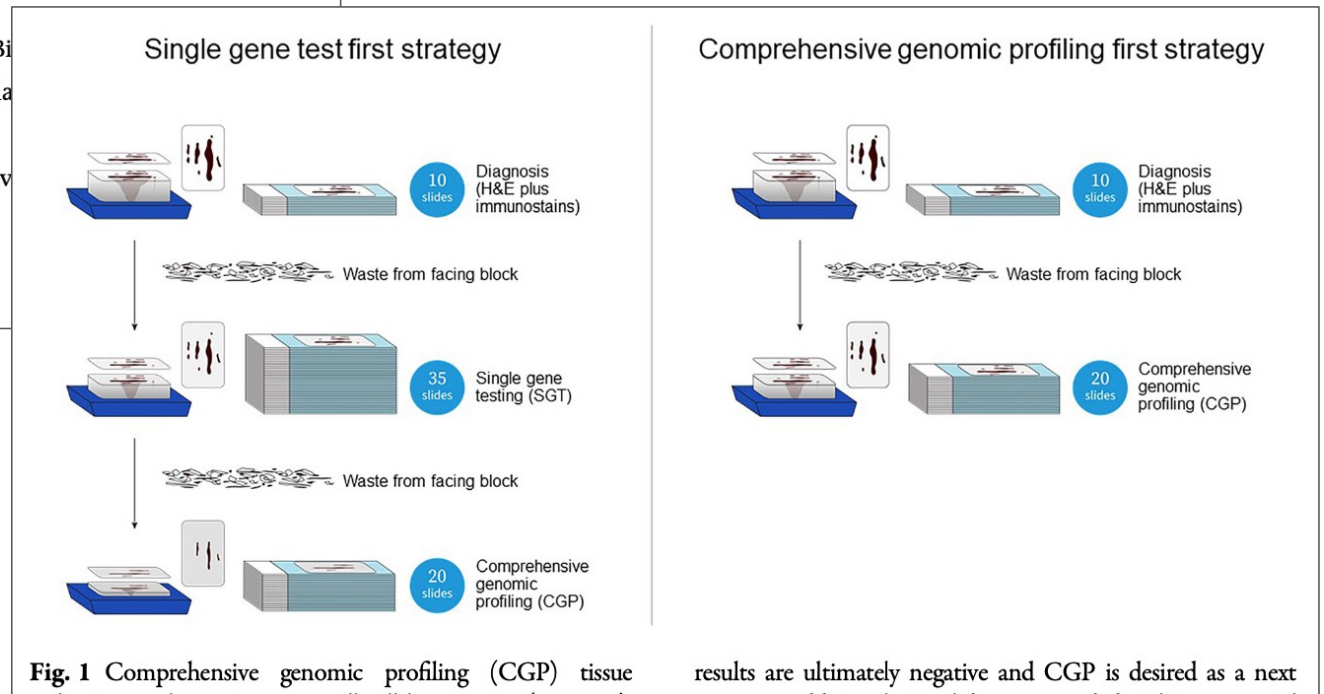
Accepted: 1 March 2024

transcription, and obviates the need to define genotypic clones from a phylogeny a priori, leading to highly granular definitions of clones with distinct expression programs. These improvements enable clone-clone gene expression comparisons with higher resolution and identification of expression programs that are genomically independent. Our approach sets the stage for dissecting the relative contribution of fixed genomic alterations and dynamic epigenetic processes on gene expression programs in cancer.

The Impact of Prior Single-Gene Testing on Comprehensive Genomic Profiling Results for Patients with Non-Small Cell Lung Cancer

Mary K. Nesline  · Vivek Subbiah · Rebecca A. Previs · Kyle C. Strickland · Heidi Ko · Paul DePietro · Michael D. Blum · Maureen Cooper · Nini Wu · Jeffrey Conroy · Sarabjot Pabla · Shengle Zhang · Zachary D. Wallen · Pratheesh Sathyan · Kamal Saini · Marcia Eisenberg · Brian Caveney · Eric A. Severson · Shakti Ramkissoon

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NEWS | 12 March 2024

How AI-powered handheld devices are boosting disease diagnostics - from cancer to dermatology

Nature Medicine explores the latest translational and clinical research news, with FDA approval of an AI-assisted optical reader to help in the diagnosis of skin cancer.

Digital and Computational Pathology Are Pathologists' Physician Extenders

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

"Physician extender" is a long-used term in medicine¹ that denotes a "non-medical healthcare provider who sees patients on behalf of or in conjunction with a lead physician or physician(s)."² Increasing physician demand requires continuing assessment of the value of physician extenders, including within pathology.^{3,4} During the COVID-19 pandemic, health care institutions and private practice groups across all medical fields felt the unprecedented demand for fast and accurate medical laboratory testing and diagnostics.⁵⁻⁷ Beyond the COVID-19 pandemic, the urgency for pathologists and medical laboratories across the world to continue to deliver

(often 4–6 years depending on location), and following medical school they complete residency training and fellowship (an additional 4–6 years). Many pathologists who practice in the United States have practiced previously in other countries and go through rigorous financial lengths to obtain US medical licensure, residency training, and legal citizenship to practice in the United States. Although recent pipeline efforts have focused on increasing US medical student and international medical graduate exposure to pathology (because many medical schools lack adequate exposure within their curricula),¹⁹⁻²² it will be many years



Events

Next steering
committee
meeting
April 24th 2024
at
3:00PM
(EST)