February 2024

How AI and Digital Pathology are Shaping Drug Development

Applications from Pioneers in Drug Discovery and Clinical Development

PathAI

Introduction

"If we proceed with everything in this stepwise, bespoke, almost handcrafted way, we can't proceed fast enough and on enough problems. We have to find ways to work at a different scale." — Aviv Regev, EVP Genentech Research and Early Development, interview with *Endpoints News*. [1]

Today's Life Sciences professionals face a multifaceted challenge: enhancing the precision, speed, and accessibility of research and development while keeping up with an expanding list of new technology and research discoveries. Many teams are also being asked to do more with less. Innovators must carefully balance incorporation of new technology and evidence with reliance on trusted approaches to research and drug development.

This ebook contextualizes these challenges within key use cases. We also explore case studies from a growing number of research teams leveraging AI-powered digital pathology to meet program objectives differently in this environment.

[1] In this interview, Aviv Regev shared her vision for Genentech's broader artificial intelligence strategy across solutions and objectives. This quote is not directly in reference to the Genentech, PathAI collaboration.
Dunn, A. (2023, December 6). Aviv Regev leads Genentech's next revolution with AI. Endpoints News. https://endpts.com/aviv-regev-leads-genentechs-next-revolution-with-ai/

Discovering novel biomarkers

Novel biomarker discovery requires identification and validation of measurable indicators associated with a biological state. Researchers must generate hypotheses, collect data and conduct analyses in early development before considering validation and potential impact to patient care.

Histopathology can reveal known disease patterns and signatures. It may even serve as the basis for novel biomarker discovery. However, widely available hematoxylin and eosin (H&E) whole slide images go underutilized for these purposes today.

AI-driven tissue and cell classification models in digital pathology unlock the potential of these images for rapid and scalable biomarker discovery. Leveraging machine learning, these models extract actionable insights by identifying hundreds of histological features in both biologically transparent and more “black box” ways. This approach unbridles hypothesis generation from pre-existing ideas and paradigms.

Discovering novel biomarkers

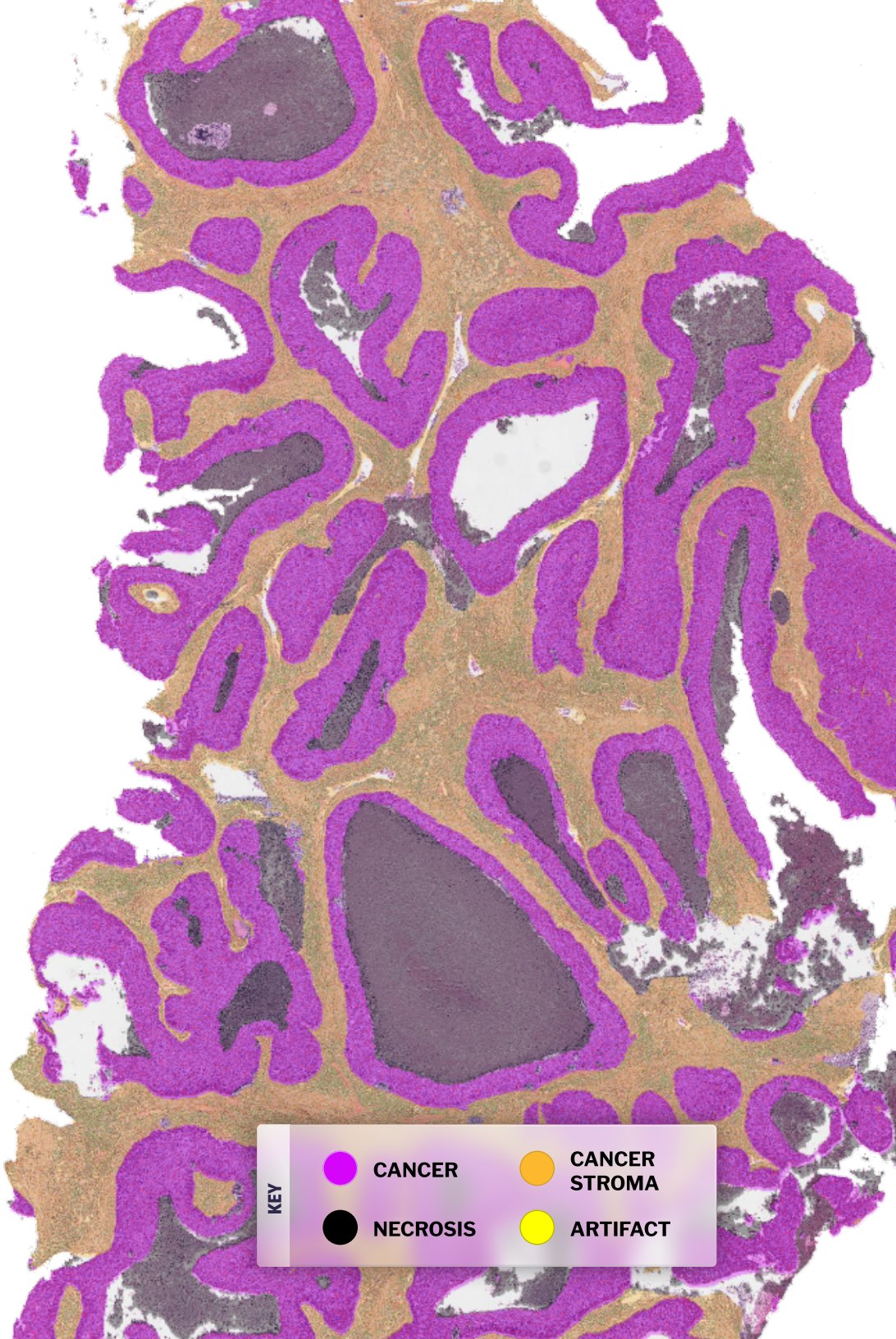
TILs as a potential predictive or prognostic measure

Tumor-infiltrating lymphocytes (TILs) play a prominent role in cancer prognosis and treatment decision-making.

In a poster presented at SITC 2023, researchers demonstrated a correlation between PathAI's lymphocyte-associated Human Interpretable Features (HIFs) and established lymphocyte markers from molecular measurement (e.g., CD8A) as well as complex immune signatures (e.g., lymphocyte infiltration).

These HIFs also successfully predict a potential novel biomarker, a predictive/prognostic inflammatory signature.

Download the SITC poster



Conway, J., et al. (2023). Quantification of tumor infiltrating lymphocytes (TILs) from pathology slides reflects molecular immune phenotypes [Poster presentation]. Society for Immunotherapy in Cancer, San Diego, CA.

Discovering novel biomarkers

Predictive biomarker for high-grade serous ovarian carcinoma

Manual pathology techniques can fall short in understanding the underlying disease biology of aggressive cancers. In a poster presented at ESMO, researchers used PathExplore™ to determine whether patient outcomes may be predicted from histological features of the tumor microenvironment (TME).

Their analysis uncovered a link between cancer cell nuclear size variability and overall survival, showcasing the potential of HIFs derived from H&E whole slide images as powerful predictors of patient response.

Download the ESMO poster

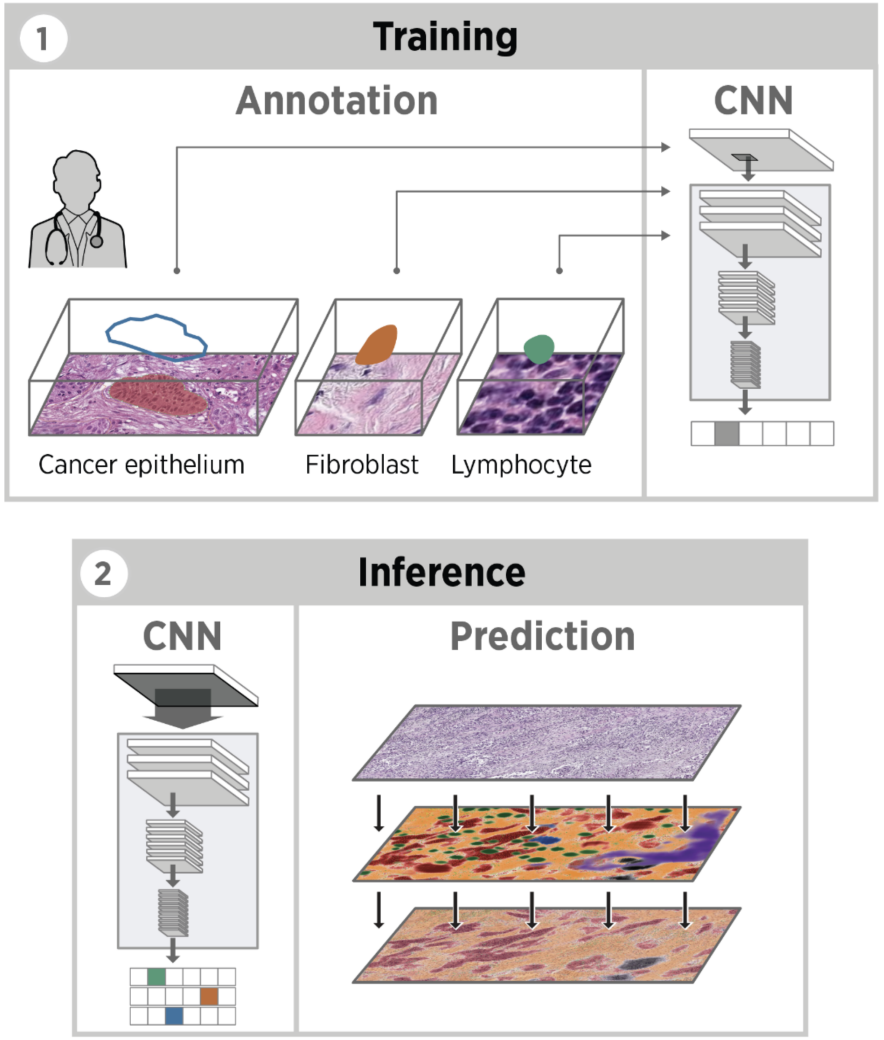


FIGURE 1

Schematic illustrating convolutional neural network (CNN) model development approach for pixel-level feature predictions.

Michener, C.M, et al. (2022). AI-powered analysis of nuclear morphology associated with prognosis in high-grade serous carcinoma [Poster presentation]. The European Society for Medical Oncology Congress, Paris, France.

Exploring histological features of molecular biomarkers

Histological examination of molecular biomarkers aids in understanding the pathological basis of diseases at a cellular level.

A deep understanding of the biological underpinnings of molecular biomarkers is crucial for developing targeted therapies that can effectively combat specific disease mechanisms, tailoring patient treatment strategies and improving diagnostic accuracy.

Over the last several years, numerous studies have demonstrated the ability of AI-powered pathology to rapidly quantify histological features from H&E whole slide images, such as the cell and tissue composition of the tumor microenvironment. Such studies have illuminated relationships between histological features and factors such as genomic variants and patient outcomes. Features of the TME have even been found to predict the biomarker status of patient samples.

CONTEXT

Patient diagnosis and prognosis often consider the biomarker status of a patient sample, which may be described in a binary or categorical fashion (e.g., “positive”, “negative”, “high”, “low”).

Exploring histological features of molecular biomarkers

TGFb-CAF status explained and predicted

In a poster presented at AACR Molecular Targets, researchers leveraged a bespoke machine learning model (additive multiple instance learning (aMIL)) to accurately predict TGFb-CAF-high versus -low status from whole slide images. The biological underpinnings of such predictions were then quantified using PathExplore HIFs. Tissue enriched for cancer stroma, as well as cancer-infiltrating and stromal fibroblasts, contributed most to ML-based high prediction.

These findings suggest that not only can complex molecular information be detected in routine pathology specimens, but predictions from otherwise black-box models can be biologically explained leveraging PathExplore.

Download the AACR poster

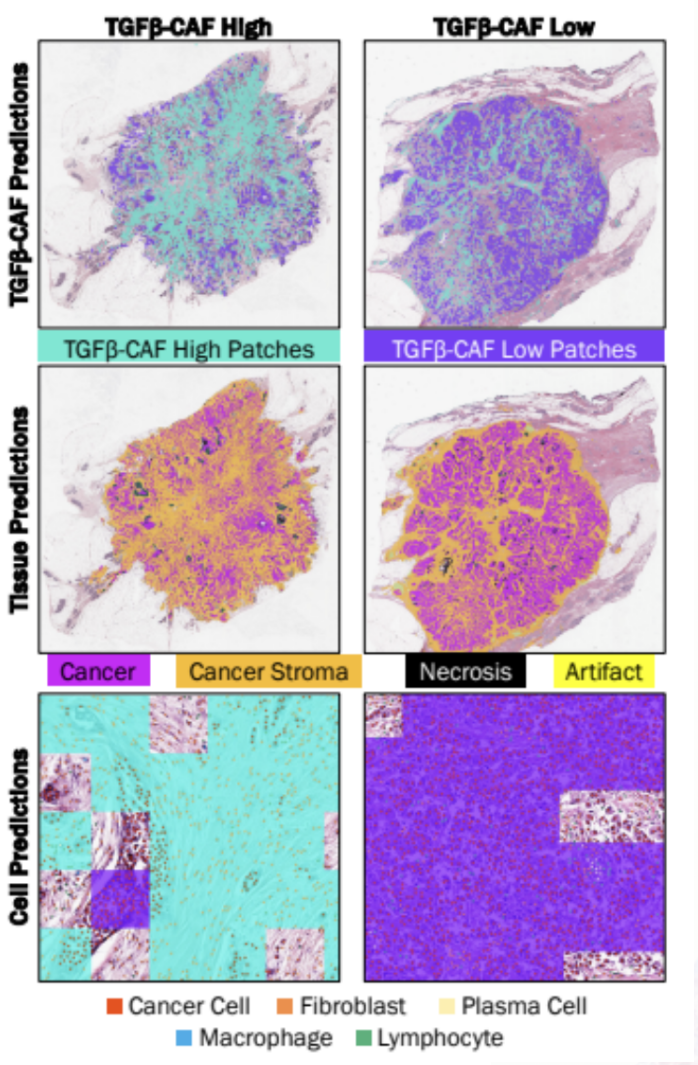


FIGURE 5

Overlays in BRCA tissue depicting predictions of TGFβ-CAF levels, tissue regions, and cell types in slides predicted to be TGFβ-CAF-high and TGFβ-CAF-low.

Markey, M, et al. (2023). Spatially-resolved prediction of gene expression signatures in H&E whole slide images using additive multiple instance learning models [Poster presentation]. AACR Conference on Molecular Targets and Cancer Therapeutics, Boston, MA.

“The AIML team is collaborating with PathAI to develop advanced computational pathology approaches. This includes the use of proprietary models and algorithms developed ...to capture more continuous and quantitative information about the unique biology of cancerous tumors, providing critical insights to support clinical decision making and increase our probability of success.”

— Danielle Belgrave, Vice President of AI/ML, GSK [2]

[2]Danielle Belgrave posted this quote to her LinkedIn upon sharing a blog post from GSK.ai outlining the increasing role of computational pathology, including PathAI solutions., in GSK strategy.

Belgrave, D. (2023, December). I'm excited to share some work we've been doing at GSK in the space of computational pathology for precision oncology. [LinkedIn post]. LinkedIn. https://www.linkedin.com/posts/danielle-belgrave-704157107_gsk-and-pathai-computational-pathology-for-activity-7141465096655949824-oEGn?

GSK.ai. (n.d.). GSK and PathAI: Computational Pathology for Precision Oncology in the Clinic. Retrieved January 25, 2024, from https://www.gsk.ai/blogs/gsk-and-pathai-computational-pathology-for-precision-oncology-in-the-clinic/

Exploring histological features of molecular biomarkers

TME features associated with ODX scores

Early stage breast cancer accounts for the majority of diagnoses and a large proportion of cases are HR+/HER2- subtype. The Oncotype DX (ODX) Breast Recurrence Score assay is a commonly used genomic test for this population to predict recurrence risk and benefit from chemotherapy, but requires significant tissue, time, and expense.

Researchers from Cleveland Clinic and PathAI identified correlations between individual HIFs and ODX scores using a univariate linear regression model, highlighting how cellular composition and morphology in the TME may inform risk of various ODX statuses. A multivariable model was also used to predict ODX score with high accuracy.

Download the SABCS poster

Univariate Regression Analysis

Cluster ID	Cluster name	Corrected group p-value	Mean effect size
1	Cancer cell density	2E-8	0.2
2	Density of fibroblast cells	5E-4	-1.7
3	Density of macrophage cells	4E-5	0.7
4	Density of immune cells	3E-17	2.5
5	Variations in cancer nuclear size	1E-6	1.5
6	Mean and variations in nuclear shape	0.03	0.1
7	Variations in nuclear size	0.001	0.3
8	Variations in non-cancer nuclear shape	0.01	-0.1
9	Variations in non-cancer nuclear color	0.02	-0.8
10	Other cell nuclear features	0.02	0.8
11	Variations in cancer nuclear color	6E-4	1
12	Covariate: Estrogen receptor positivity	4E-16	-3.1
13	Covariate: Progesterone receptor positivity	5E-21	-6.3
14	Covariate: HER2 positivity	0.9	-0.06
15	Covariate: Tumor Stage	0.01	1.4

TABLE 1 **Univariate regression analysis showed significant positive correlations between ODX scores and feature clusters (highlighted in red).**

Le, N, et al. (2023) Artificial Intelligence-Based Prediction of Oncotype DX Score from whole slide images using human-interpretable features and breast biomarkers [Poster presentation]. San Antonio Breast Cancer Symposium, San Antonio, CA.

Re-envisioning approaches to biomarker testing

Molecular biomarkers, such as genetic variants, transcriptional changes, and proteomic signatures, play a critical role in the diagnosis and prognosis of cancer. Surmounting testing gaps requires a paradigm shift.

Genomic testing remains the predominant approach to identifying patients for biomarker-based treatment. This approach, while valuable, comes with inherent limitations.

AI-powered algorithms have swiftly predicted biomarker status from routinely-available H&E whole slide images. Implementing this capability as a novel biomarker testing tool necessitates not only new methodologies and specialized technology but also robust collaboration across the healthcare ecosystem, involving providers, labs, regulators, and patients.

An effective commercialization strategy should account for integrated laboratory technologies, streamlined operations, and crucially, adhere to stringent data privacy standards.

CONTEXT

Access to genomic testing is often hindered by testing gaps arising from logistical challenges such as extended turnaround times, prohibitive costs, and substantial tissue sample requirements, which may not always be feasible or available.

Re-envisioning approaches to biomarker testing

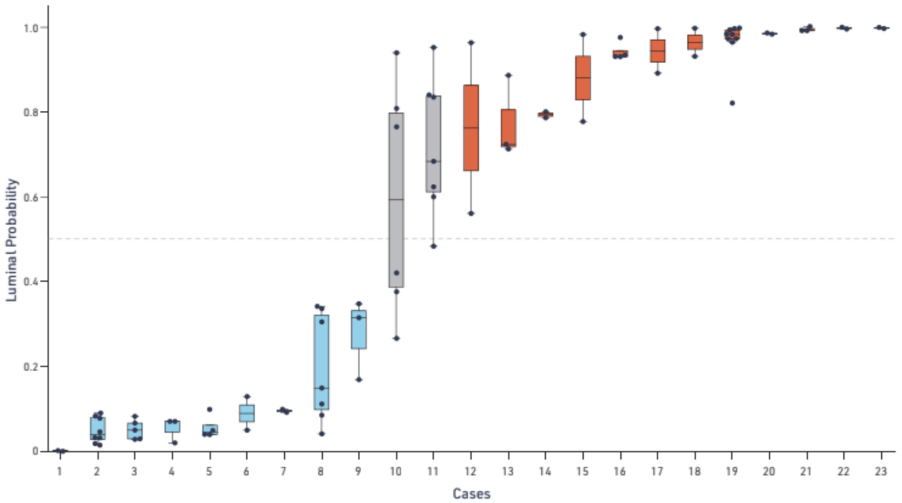
PPARG-targeted therapy in Luminal MIUC

In a recent AACR poster, Flare Therapeutics and PathAI researchers apply AI-driven analyses of H&E whole slide images to correctly identify tumors with luminal (PPARG-dependent) MIUC. These tumors may demonstrate response to PPARG-targeted therapy.

A future H&E and whole slide image based approach to biomarker testing has the potential to broaden access by enabling faster patient evaluation at a lower cost.

Download AACR poster

Consistency of model-predicted luminal status across multiple slide from the same case.



The model demonstrated high sensitivity (0.96) and specificity (0.82) across multiple WSIs for the same patient case. Only two of 23 cases had inconsistent luminal/non-luminal scoring.

CONTEXT

Identification of Luminal Muscle-Invasive Urothelial Carcinoma (MIUC) was previously only possible through use of RNA sequencing, known for its high cost and propensity to delay treatment decision-making.

Kirov, S., et al. (2023). Artificial intelligence (AI) analysis of histological images accurately identifies luminal subtype urothelial carcinomas characterized by high Peroxisome Proliferator-Activated Receptor Gamma (PPARG) expression [Poster presentation]. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Boston, MA.

Re-envisioning approaches to biomarker testing

Addressing the testing gap: c-MET over-expression

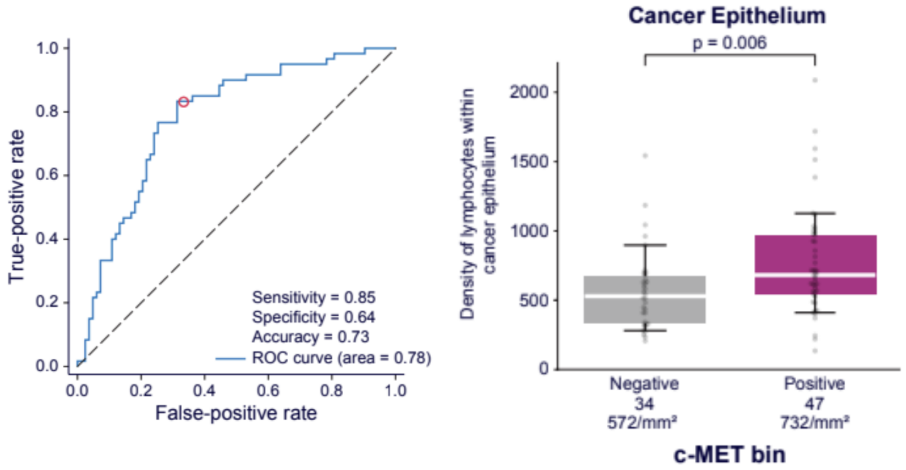
In a WCLC poster, AbbVie and PathAI researchers identified tumors with overexpressed c-MET directly from H&E whole slide images.

An H&E-based biomarker testing tool could utilize the existing access and capabilities of laboratories to enable more rapid identification of tumors exhibiting c-MET over-expression while also conserving patient tissue samples.

The numerous emerging treatments targeting the c-MET pathway are not yet supported by an established testing infrastructure, a gap that may otherwise limit and delay patient access.

Download the WCLC poster

cMET Overexpression is predicted by GNN model from the H&E WSIs with high sensitivity. HIFs shoes novel insight on the TME features.



Performance of the model is high at various classification thresholds, as shown by the ROC curve (left). PathAI derived human interpretable features also show correlation between c-MET status and lymphocyte infiltration as represented in the box plot (right).

CONTEXT

c-MET dysregulation is a known proto-oncogene presented as protein overexpression and gene mutation or amplification in 3-50% of NSCLC cases.

Rajan, D. et al. (2022). Deep-learning–based prediction of c-MET status from digitized H&E-stained non-small cell lung cancer tissue samples [Poster presentation]. IASLC 2022 World Conference on Lung Cancer, Vienna, Austria.

Targeting appropriate patient populations

In the quest for effective treatments, aligning potential therapies with the right patient populations is paramount. Despite intensive research and investment, many promising therapies falter.

Therapeutic candidates may unexpectedly encounter:

- Absence of therapeutic response
- Therapeutic resistance
- Late-stage adverse events

These issues may stem from intrinsic efficacy shortcomings or the over-precision or over-breadth in defining target populations, possibly overlooking patients who could benefit from novel treatments.

Insights into these challenges often lie hidden within the tumor microenvironment (TME), observable in standard H&E whole slide images. Leveraging AI, researchers can swiftly dissect these images to uncover cellular dynamics and molecular pathways indicative of potential therapeutic responses or resistance. By integrating supplementary data sources, like treatment history and patient outcomes, analyses can be further refined. Such enriched insights are instrumental in fine-tuning the effectiveness of therapeutic approaches and in minimizing associated risks.

Targeting appropriate patient populations

Immune checkpoint inhibitors in NSCLC

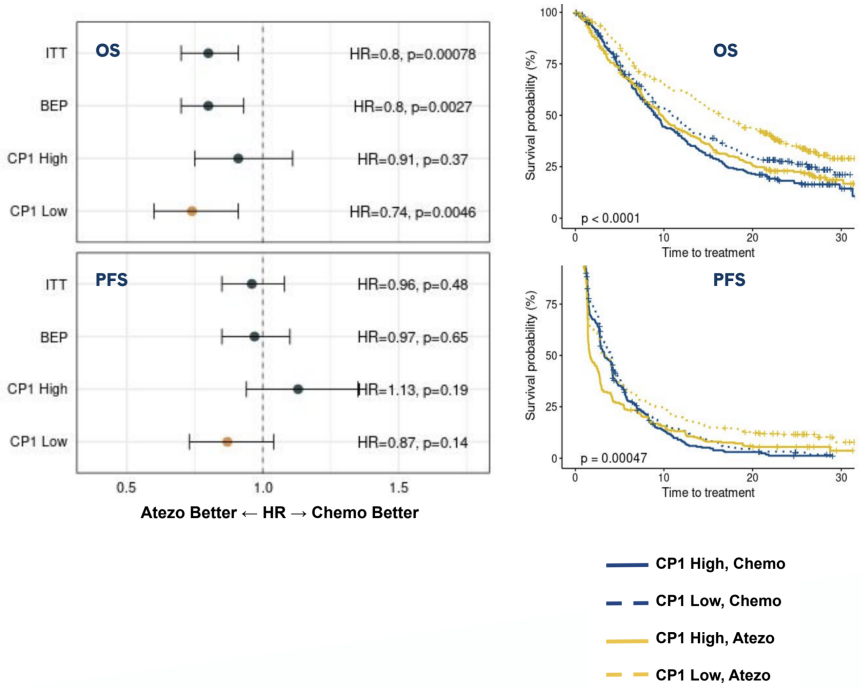
With further validation, findings could warrant expansion of the targetable patient population.

"Using a deep learning-based assay for quantifying pathology features of the TME from H&E images in two NSCLC trials, we identified a novel biomarker predictive of outcome to PD-L1 targeting therapy, even in PD-L1 low & negative patients."

In a 2023 AACR presentation, Genentech researchers explored a relationship between the tumor microenvironment (TME), PD-L1 targeting therapy (Atezolizumab) and patient outcomes in a retrospective analysis. Their work, leveraging PathAI HIFs, uncovered a composite feature (CP1) from H&E whole slide images not previously identified by pathologists or bulk RNA-sequencing. CP1 was predictively associated with improved overall survival, for both PD-L1 positive and negative patients.

View the AACR Abstract

CP1 low patients showed improved survival on Atezo compared to chemo



Qamra, A et al. (2023). Abstract 5705: Digital pathology-based prognostic & predictive biomarkers in metastatic non-small cell lung cancer. Cancer Research, 83(7 Supplement), 5705. https://aacrjournals.org/cancerres/article/83/7_Supplement/5705/722854/Abstract-5705-Digital-pathology-based-prognostic

Targeting appropriate patient populations

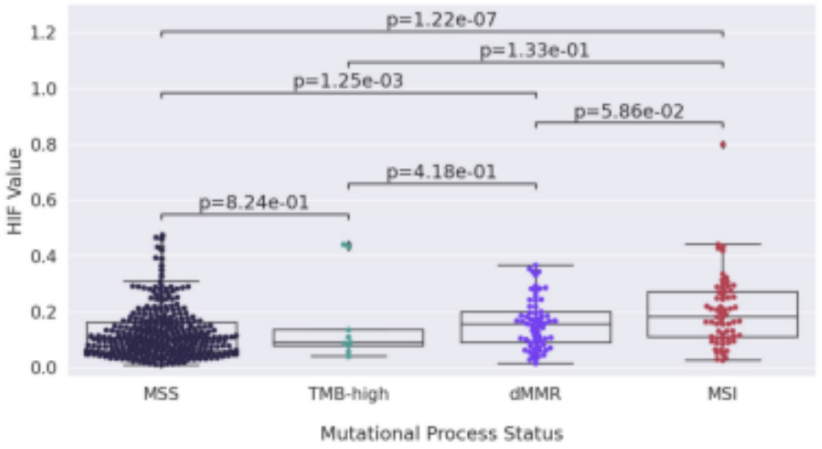
MSS/dMMR targeted immunotherapy

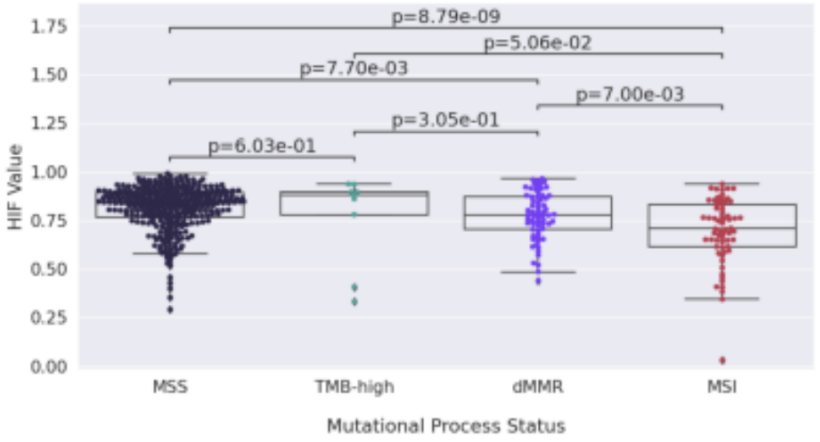
"Our results suggest that MSS/dMMR patients may also be considered for immunotherapy, thus expanding the population of amendable patients."

In a poster presented at SITC this year, researchers used PathExplore to quantitatively characterize the tumor microenvironment of MSS (microsatellite stable)/dMMR tumors, MSI tumors and MSS/TMB-H (Tumor Mutation Burden-High) tumors.

Their findings suggest it may be reasonable to leverage H&E whole slide images to identify patients with MSS/dMMR tumors, and potentially as a pre-screening tool for MSI and dMMR testing. Researchers may also consider MSS/dMMR status as an exploratory biomarker for immunotherapy given similarities between the TME composition of MSS/dMMR tumors and MSI/TMB-high tumors.

Download the SITC poster





CONTEXT

Mismatch repair deficiency (dMMR) leads to microsatellite instability (MSI), a predictive biomarker for immunotherapy in solid tumors. However, dMMR tumors historically have only been identifiable through complex molecular diagnostics.

Conway, J. et al. (2023). Quantifying the effect of microsatellite instability and mismatch repair deficiency on the tumor microenvironment [Poster presentation]. Society for Immunotherapy in Cancer. San Diego, CA.

PathExplore™

PathExplore eliminates the tradeoff between resolution and scalability, offering unparalleled resolution and quantification of the tumor microenvironment from routinely collected whole slide images (H&E).

CONTEXT

Machine Learning models are only as good as their training data and methods. PathAI training datasets include 50 million whole slide images with over 10 million annotations. Model evaluation methods have been rigorously and publicly evaluated.

PathExplore is a proprietary algorithm with integrated visualization tools. The model identifies cell types and tissue regions within your whole slide images, extracting over 600 human interpretable features. These metrics capture counts, densities and spatial relationships across cell types and tissue regions.

- **Speed of insight:** Receive results in days or weeks
- **Superior data and model development:** Benefit from the largest and highest quality training datasets and machine learning methods
- **Collaborative:** Share features and insights across departments using a single, cloud based software, AISight™
- **Designed for advanced spatial analytics:** Interact with PathExplore features in AISight alongside your proprietary algorithms and/or export outputs (.CSV) for analysis and linking to other data evidence sources

PathAI stands out as the sole digital pathology partner capable of seamlessly integrating algorithms and insights from PathExplore and custom projects into various contexts, including clinical trials, diagnostics, and laboratory operations. This integration is facilitated through the versatile digital pathology platform AISight, comprehensive analytic services, and a well-established laboratory network.

Gerardine, Y. (2023). Improved statistical benchmarking of digital pathology models using pairwise frames evaluation. arXiv. https://arxiv.org/abs/2306.04709

Enabling single and multi-tumor analysis across 14 indications

PathAI

PathAI is the only digital pathology partner with the ability to integrate algorithms and findings seamlessly into the clinical trial, diagnostics and lab contexts.

Contact Us

Email

bd@pathai.com

Website

www.pathai.com