Paige Predict

An AI-enabled digital pathology application for biomarker status prediction

Introduction

When a tissue sample is insufficient for sequencing (QNS), it can leave providers without the genomic results needed to inform the next steps in a patient's care. Reattempting sequencing requires significant tissue, and prioritizing targeted biomarker testing may be difficult.

To help inform testing prioritization and diagnostic yield, Tempus developed Paige Predict. This AI-enabled digital pathology application analyzes a hematoxylin-and-eosin (H&E) stained whole slide image (WSI), digitized as part of our standard lab process, to predict the likelihood of key biomarkers when a Tempus xT test results in a QNS. Powered by a state-of-the-art Paige Foundation Model pre-trained with three million diverse pathology slides, Paige Predict identifies the phenotypic signatures of 123 molecular biomarkers and oncogenic pathways across 16 cancer types.

For each molecular biomarker and oncogenic pathway, Paige Predict calculates the positive likelihood ratio, relative to the patient's specified disease cohort. The positive likelihood ratio, which measures the strength of the application's predictions, compares the probability that the relevant alteration is confirmed by subsequent definitive testing with the probability that alteration is not confirmed. Paige Predict then calculates a "Paige Prediction", which considers both the general prevalence of the alteration within the patient's cancer cohort, and the strength of the predictions as measured by positive likelihood ratio. The Paige Prediction reflects the revised expectations, after incorporating both prevalence and the Paige Predict results, that the patient's sample will have a positive result for the alteration in a confirmatory test. The results also categorize the molecular features into Elevated, Typical, and Reduced Likelihood groups relative to the patient's cohort based on the calculated likelihood ratio.

These predictions provide clinically relevant information to help inform confirmatory testing strategies, maximizing the likelihood of receiving an actionable result before exhausting tissue. Paige Predict results are probabilistic predictions, so they should not be used to determine treatment eligibility or as evidence of actual biomarker status.

Analytical validation and performance

The Paige Predict validation study cohort consisted of 7,717 H&E-stained WSIs from samples sequenced using the Tempus xT assay, representing a broad range of solid tumor types (see table in appendix). Each molecular feature was represented by a minimum of 20 positive and 20 negative quality-controlled samples, and is statistically representative of a larger cohort of Tempus real-world data.

Each biomarker and oncogenic pathway within each cancer cohort was evaluated across multiple experiments to evaluate analytical accuracy, analytical sensitivity and specificity, and analytical robustness. The analytical validation heavily focused on evaluating the performance of Paige Predict in samples with limited tumor content, so that it would be more representative of the subset of samples where tissue-based sequencing results in a QNS.

Each molecular feature within each cancer cohort met the following acceptance criteria:

- Minimum analytical accuracy criteria, for which each feature must demonstrate overall performance, measured using the area under the receiver operating characteristic curve (AUC), of ≥0.70 when evaluated against ground truth from the Tempus xT assay.

- Limited performance regression and model stability, within defined bounds, when evaluated on samples with limited tumor content. These experiments defined the limit of detection (LoD) and specimen requirements for Paige Predict.

- Tumor content, including both tumor area and the ratio of tumor tissue to normal tissue, was evaluated for each sample. As tumor content decreased, Paige Predict's performance (AUC) was re-measured to confirm a performance difference of no more than 5% compared to the full slide reference AUC, and prediction root mean square error (RMSE) of less than 0.1.

- Across the assay, the LoD was established as a combination of a minimum tumor area of ≥1.5 mm² with a tumor-to-tissue ratio of ≥ 20%. All biomarkers and molecular features meet the defined acceptance criteria at the established LoD.

- Robustness to potential interferences, including blur or scanning artifacts, and concordance between multiple different WSI scans generated from different scanning machines of the same type.

- Each slide was initially reviewed by a qualified pathologist to confirm the WSI was interpretable. For slides passing pathology QC, all samples generated Paige Predict results.

- To evaluate reproducibility of the predictions across scanning machines, a subset of 300 samples, with representation from each cancer cohort, was rescanned on a different scanner machine of the same type; RMSE remained <0.1 for all molecular features.

Clinical validity of H&E-based digital biomarkers

Recently, studies have shown successful deployment of H&E-based digital biomarkers in real-world clinical trial settings to identify actionable alterations, such as FGFR mutations in urothelial cancer and EGFR mutations in lung adenocarcinoma, for the purpose of selecting appropriate testing and/or quickly identify clinical trial options.[1,2]

At Tempus, we previously validated a high-performance predictor for MSI-H status in prostate cancer,[3] demonstrating that these models can predict the likely presence or absence of rare but therapeutically actionable biomarkers from H&E images. These studies confirm that AI-based histopathology models provide a reliable, efficient, and clinically actionable bridge between routine morphology and definitive molecular profiling.

Appendix

Paige Predict demonstrates the following performance across molecular features and cancer cohorts:

Cancer Cohort	Molecular Feature	Average AUC
Bladder Cancer	CCNE1 amplification	0.79
	ERBB2 amplification	0.81
	FGFR3 alterations	0.70
	FGFR3 fusions	0.85
	HRAS alterations	0.84
	KRAS alterations	0.75
	MDM2 amplification	0.72
	TP53 alterations	0.77
	RTK pathway	0.81
Breast Cancer	AKT1 alterations	0.70
	CCNE1 amplification	0.88
	ERBB2 alterations	0.80
	ERBB2 amplification	0.80
	ERBB2 SNV/INDEL	0.77
	ESR1 alterations	0.86
	ESR1 SNV/INDEL	0.83
	ESR1 amplification	0.80
	MDM2 amplification	0.74
	MTAP deletion	0.75
	PTEN deletion	0.80
	TP53 alterations	0.89
	DNA damage response pathway	0.90
	RTK pathway	0.85

Cancer Cohort	Molecular Feature	Average AUC
Brain/CNS Cancer	mTOR pathway	0.75
	RTK pathway	0.96
Colorectal Cancer	ARID1A alterations	0.79
	BRAF alterations	0.82
	ERBB2 amplification	0.77
	FBXW7 alterations	0.73
	KRAS alterations	0.82
	MSI-H	0.97
	PIK3CA alterations	0.76
	PTEN alterations	0.85
	TMB-H	0.85
	TP53 alterations	0.85
	mTOR pathway	0.83
Endometrial Cancer	AKT1 alterations	0.81
	ARID1A alterations	0.85
	CCNE1 amplification	0.91
	ERBB2 amplification	0.90
	FGFR2 alterations	0.71
	KRAS alterations	0.79
	MSI-H	0.88
	NF1 alterations	0.71
	PPP2R1A alterations	0.71
	PTEN alterations	0.90
	TMB-H	0.85
	TP53 alterations	0.93
	DNA damage response pathway	0.87
	HRD pathway	0.76
	TGF beta pathway	0.73
Gastroesophageal Cancer	ARID1A alterations	0.77
	CCNE1 amplification	0.77
	EGFR amplification	0.81
	ERBB2 amplification	0.85
	FBXW7 alterations	0.76
	FGFR2 amplification	0.76
	MDM2 amplification	0.79
	MSI-H	0.88
	PIK3CA alterations	0.73
	PTEN alterations	0.77
	TMB-H	0.78
	TP53 alterations	0.80

Cancer Cohort	Molecular Feature	Average AUC
Hepatobiliary Cancer	ERBB2 alterations	0.78
	ERBB2 amplification	0.86
	FGFR2 fusions	0.86
	IDH1 alterations	0.91
	KRAS alterations	0.89
	TP53 alterations	0.89
Melanoma	BRAF alterations	0.75
	KIT alterations	0.79
	NF1 alterations	0.70
	TMB-H	0.76
	TP53 alterations	0.85
Non-small cell lung cancer	ALK fusions	0.85
	CCNE1 amplification	0.74
	EGFR alterations	0.90
	ERBB2 amplification	0.75
	FGFR1 amplification	0.86
	KRAS alterations	0.85
	MDM2 amplification	0.74
	MET alterations	0.90
	MET amplification	0.87
	PTEN alterations	0.82
	SMARCA4 alterations	0.81
	STK11 alterations	0.93
	TMB-H	0.73
	TP53 alterations	0.85
Ovarian, Fallopian Tube & Primary Peritonial Cancer	ARID1A alterations	0.89
	BRCA1 alterations	0.76
	CCNE1 amplification	0.81
	ERBB2 amplification	0.80
	KRAS alterations	0.89
	PIK3CA alterations	0.89
	PPP2R1A alterations	0.72
	PTEN alterations	0.88
	TMB-H	0.83
	TP53 alterations	0.95
Pancreatic Cancer	CCNE1 amplification	0.81
	KRAS alterations	0.91
	PIK3CA alterations	0.73
	TIMB-H	0.77
	TP53 alterations	0.80
	HRD pathway	0.72
Prostate Cancer	CDK12 alterations	0.84
	MSI-H	0.91
	PTEN alterations	0.72
	TMB-H	0.86
	TP53 alterations	0.76
	mTOR pathway	0.85
Renal Cell Carcinoma	PTEN alterations	0.73
	TP53 alterations	0.83
Soft Tissue Sarcoma	CDK4 amplification	0.85
	MDM2 amplification	0.86
	MTAP deletion	0.84
	TMB-H	0.77
	TP53 alterations	0.84
	mTOR pathway	0.83
Thyroid Cancer	BRAF alterations	0.88
	NRAS alterations	0.90
	TP53 alterations	0.91
	mTOR pathway	0.84
Tumor of Unknown Origin	TGF beta pathway	0.83

For Paige Predict validation, oncogenic molecular pathways are defined by alterations detected in any of these variants:

DNA damage response (DDR) (N=23): ATM, ATR, ATRX, BRCA1, BRCA2, BRIP1, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL, MDM2, MDM4, MLH1, MUTYH, NPM1, PALB2, PPP2R1A, RAD50, RAD51, STAG2

Receptor tyrosine kinase (RTK) (N=34): ALK, CBL, CSF1R, DDR2, EGFR, EPHA3, EPHA5, EPHB1, ERBB2, ERBB3, ERBB4, FGF19, FGF3, FGF4, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT3, FLT4, HGF, IGF1R, KIT, MET, NF1, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PTPN11, RET, ROS1

Homologous recombination deficiency (HRD) (N=11): BRCA1, BRCA2, PALB2, ATM, CHEK1, CHEK2, RAD51, FANCA, CDK12, RAD51B, RAD51C

mTOR pathway (N=16): AKT1, AKT2, AKT3, CRKL, IRS2, MTOR, PIK3CA, PIK3CG, PIK3R1, PIK3R2, PTEN, RICTOR, RNF43, RPTOR, TSC1, TSC2

TGF-β pathway (N=5): SMAD2, SMAD3, SMAD4, TGFBR1, TGFBR2

References

1. Ramon AJ, Parmar C, Carrasco-Zevallos OM, et al. Development and deployment of a histopathology-based deep learning algorithm for patient prescreening in a clinical trial. *Nat Commun.* 2024;15(1).

2. Campanella G, Kumar N, Nanda S, et al. Real-world deployment of a fine-tuned pathology foundation model for lung cancer biomarker detection. *Nat Med.* Published online July 9, 2025.

3. Hu Q, Rizvi AA, Schau G, et al. Development and validation of a deep learning-based microsatellite instability predictor from prostate cancer whole-slide images. *NPJ Precis Oncol.* 2024;8(1).