Development and Validation of a Computational Histology Artificial Intelligence–Powered Predictive Biomarker for Selection of Chemotherapy in Advanced Pancreatic Cancer

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DOI https://doi.org/10.1200/JCO-25-02199

ABSTRACT

PURPOSE Predictive biomarkers to guide selection of first-line chemotherapy for advanced pancreatic ductal adenocarcinoma (PDAC) are an unmet clinical need. This study used the Computational Histology Artificial Intelligence (CHAI) platform to develop and validate a histomorphology-based G-chemo versus F-chemo (GvF) biomarker that predicts benefit from first-line fluoropyrimidine-based (F-chemo) versus gemcitabine-based (G-chemo) regimens.

METHODS The CHAI platform extracted quantitative histomorphologic features from whole-slide images of hematoxylin and eosin–stained diagnostic biopsies. In a multi-institutional development cohort, features associated with differential outcomes as measured by time to next treatment or death (TNTD) between F-chemo–treated and G-chemo–treated patients produced continuous biomarker scores, which were dichotomized into G-pref or F-pref results. The biomarker and threshold were locked. An independent validation cohort from the prospective COMPASS and Know Your Tumor studies assessed differential treatment outcomes by TNTD and overall survival (OS).

RESULTS There were 477 patients (development: 178; validation: 299). In validation, among 173 F-pref patients, those treated with F-chemo had significantly better outcomes than G-chemo for both TNTD ($P = .035$; median TNTD: F-chemo 8.6 months; G-chemo 7.5 months) and OS ($P = .003$; median OS: F-chemo 14.4 months; G-chemo 11.7 months). Among 126 G-pref patients, G-chemo had significantly superior TNTD ($P = .038$; median TNTD: F-chemo 7.2 months; G-chemo 9.6 months), but no difference in OS ($P = .5$; median OS: F-chemo 12.4 months; G-chemo 14.3 months). In propensity score–weighted analysis, the biomarker predicted treatment effect (biomarker-treatment interaction TNTD $P < .001$; OS $P = .005$). RNA subtypes were associated with TNTD and OS but did not predict differential treatment effects ($P = .3$).

CONCLUSION The histomorphology-based GvF biomarker predicted differential treatment benefit of first-line GvF. This biomarker can guide optimal treatment selection for first-line therapy in advanced PDAC.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Accepted January 9, 2026
Published February 11, 2026

J Clin Oncol 00:1-11

View Online Article

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer death, and outcomes are particularly poor with unresectable disease.[1] Detection of somatic or germline alterations amenable to targeted therapies or immunotherapy is infrequent, rendering cytotoxic chemotherapy the mainstay of management. Two chemotherapy regimens, the fluoropyrimidine-based triplet regimen (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin; FOLFIRINOX) and the gemcitabine-based doublet regimen (gemcitabine with nab-paclitaxel [GnP]), represent primary first-line systemic therapy alternatives.[2,3] To our knowledge, no trials conducted to date have clearly shown either regimen to

CONTEXT

Key Objective

To use a computational histology artificial intelligence (AI) platform to develop and validate a biomarker from digitized whole-slide images from pancreatic cancer biopsy specimens.

Knowledge Generated

The biomarker predicts for treatment benefit from first-line fluoropyrimidine-based (F) versus gemcitabine-based (G) chemotherapy. Multi-institutional real-world data were used for development, and data from two prospective cohorts were used for validation. In the validation cohort, the biomarker-treatment interaction between biomarker status and chemotherapy regimen was statistically significant for the end points of time to next treatment or death and overall survival.

Relevance *(R.B. Parikh)*

While further prospective validation is necessary prior to clinical adoption, this and future AI-based pathology biomarkers should be considered as correlative biomarkers or in enrichment strategies in trials of first-line therapies in metastatic pancreatic cancer.*

*Relevance section written by *JCO* Associate Editor Ravi B. Parikh, MD, MPP, FACP.

be superior, resulting in treatment selection that is governed by performance status, side-effect profiles, and physician and patient preference. The randomized phase II PASS-01 trial found progression-free survival was similar between GnP and modified FOLFIRINOX (mFFX); however, overall survival (OS) and safety trends favored GnP.[4] Consequently, there is a need for predictive biomarkers to help guide individual treatment selection.

Artificial intelligence (AI)–based computational histopathology methods can analyze hematoxylin and eosin (H&E)–stained pathology whole-slide images (WSI) and identify features of the tumor and its microenvironment, representing an avenue for oncology biomarker development.[5,6] The Computational Histology Artificial Intelligence (CHAI) platform detects cell and tissue types and quantifies interpretable features from WSIs.[7,8] This platform was previously used to develop a histomorphologic signature from PDAC resection specimens associated with adjuvant gemcitabine treatment outcomes.[9]

In this study, we applied the CHAI platform in unresectable PDAC to develop a signature from pretreatment H&E-stained biopsy specimen WSIs to predict treatment benefit from first-line fluoropyrimidine- versus gemcitabine-based regimens. We then tested the hypothesis that this biomarker would predict treatment efficacy in a validation cohort consisting of patients from two prospective cohort studies.

METHODS

Patient Cohorts and Clinical Characteristics

We assembled multiple cohorts of patients with unresectable PDAC treated with standard first-line chemotherapy, specifically fluoropyrimidine- (F-chemo) or gemcitabine-based (G-chemo) regimens. The study cohort was divided into a development cohort and an independent validation cohort, the latter consisting of data that had not been used in the development of the biomarker (Fig 1A). The development cohort included patients from two comprehensive cancer centers: Cedars-Sinai Medical Center (Cedars) and University of Pittsburgh Medical Center (UPMC). The independent validation cohort consisted of patients from two independent, prospectively collected nonrandomized data sets: (1) the Know Your Tumor (KYT) pancreatic cancer precision medicine molecular profiling initiative of the US-based Pancreatic Cancer Action Network (PanCAN), and (2) the Comprehensive Molecular Characterization of Advanced PDAC for Better Treatment Selection (COMPASS) trial (ClinicalTrials.gov identifier: NCT02750657), a Canadian prospective clinical sequencing study of advanced PDAC.[10,11] The cohort assembly, model development, and validation processes are outlined in Figure 1 and additional details related to cohorts and inclusion criteria are described in Supplementary Methods (online only). Institutional review board approval was obtained for each participating data set. Given all patient information was deidentified, the study was considered IRB exempt and consent waived. Information on the COMPASS trial is available on ClinicalTrials.gov under NCT02750657.

Study End Points

The primary end point for this first-line treatment predictive biomarker was time to next treatment or death (TNTD), defined as the time from treatment initiation to the start of second-line therapy of a different backbone or death. TNTD is a routinely used real-world end point with known correlation to progression-free survival and was selected as the

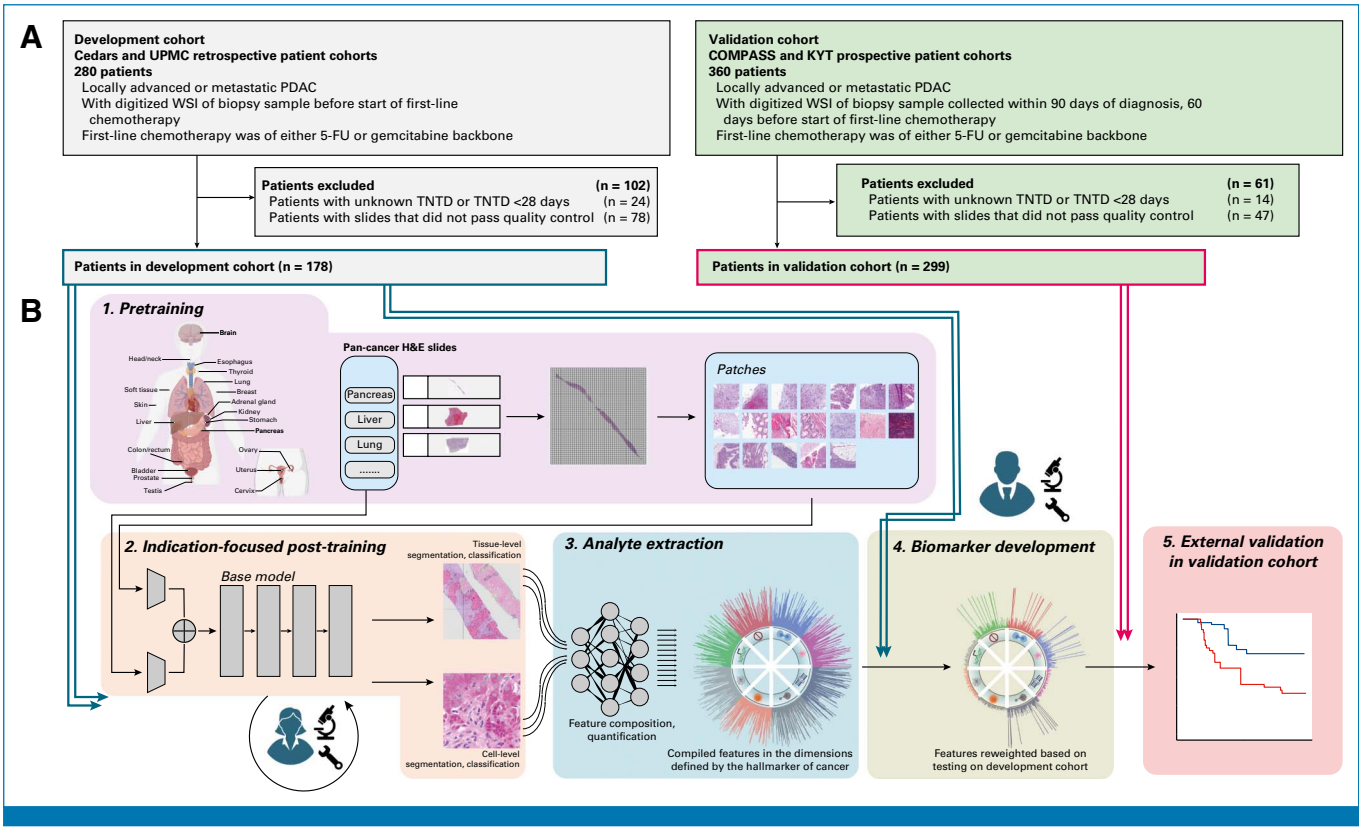

FIG 1. Study overview. (A) Assembly of development and validation cohorts. (B) CHAI platform workflow can be described in five steps. (1) Pretraining: pan-cancer H&E slides are patched and merged with indication labels to form the base model for cell and tissue classification. (2) Post-training: for the indication of interest (in this case, PDAC), the base model is iteratively fine-tuned with human supervision with data sets enriching for that indication. (3) Analyte extraction: from an H&E-stained slide, the fine-tuned base model quantifies histomorphologic features of the cancer and its microenvironment in dimensions defined by the hallmarks of cancer. (4) Biomarker development: under human supervision, the quantified histomorphologic features are weighted based on testing on development cohort for statistical performance and form the biomarker. (5) External validation: the locked biomarker is tested on an independent external validation cohort for patient stratification. 5-FU, 5-fluorouracil; Cedars, Cedars Sinai Medical Center; CHAI, Computational Histology Artificial Intelligence; H&E, hematoxylin and eosin; KYT, Know Your Tumor; PDAC, pancreatic ductal adenocarcinoma; TNTD, time to next treatment or death; UPMC, University of Pittsburgh Medical Center; WSI, whole-slide image.

primary end point, given it was readily available for the prospective validation trial cohorts and is not subject to the confounding treatment effect of second-line treatments (eg, crossover or contamination) when assessing a predictive biomarker.[12,13] The secondary end point was OS, defined as the time from the initiation of first-line chemotherapy treatment to death.

Development of a Pathology-Based Predictive Biomarker

We applied the previously described CHAI platform to develop a pathology-based predictive biomarker for differential treatment benefit between fluoropyrimidine-based and gemcitabine-based chemotherapy.[7,9] Briefly, digitized H&E-stained diagnostic slides were processed through deep learning models to segment tissue and cell regions. The models were trained on approximately 25,000 pan-cancer H&E-stained slides including 500,000 nuclei annotations and 100 million μm^2 of tissue annotated by board-certified pathologists. Models were trained to accurately segment various cell and tissue types relevant to cancer biology and to identify over 30,000 histomorphologic features related to phenotypic attributes, including, but not limited to, nuclei size, nuclei morphology, cell spatial orientation, immune infiltration, and stroma density, that are hallmarks of cancer pathology (Fig 1B, Steps 1-3).[14] The macro area under the curve was 0.999 for tumor nuclei segmentation and 0.997 for tissue segmentation across both primary and metastatic PDAC samples.

Using the development cohort, predictive feature selection and weighting was performed to construct a signature using univariable Cox proportional hazards (CPH) analysis with the TNTD end point, with subsequent refinement using multivariable CPH models and chunk tests (Fig 1B, Step 4). The signature yielded a continuous score (Data Supplement, Fig S1, online only), ranging from those with most benefit from gemcitabine-based to those with most benefit from fluoropyrimidine-based regimens. The G-chemo versus

F-chemo (GvF) biomarker was formed by identifying the threshold at which there was the greatest differential in the hazard ratio (HR) for patients receiving gemcitabine-based chemotherapy and the HR of patients receiving fluoropyrimidine-based chemotherapy.

Validation of a Pathology-Based Predictive Biomarker

A power calculation for validation cohort size was performed using NCSS PASS 2025 v25.0.3 (Supplementary Methods).

The GvF biomarker was locked and then applied to the validation cohort. The biomarker classified each case into either favoring a gemcitabine-based chemotherapy regimen (G-pref) or favoring a fluoropyrimidine-based chemotherapy regimen (F-pref; Fig 1B, Step 5).

Statistical Analysis

The association of the GvF biomarker with TNTD and OS was evaluated using multivariable CPH models and likelihood ratio (LR) tests. Statistical tests of interaction between subgroups and treatment were performed to test the hypothesis that the subgroup is significantly associated with differential treatment effects.

To minimize confounding from baseline clinical characteristics between patients receiving F-chemo and G-chemo, a propensity score–weighted analysis—including variables age, Eastern Cooperative Oncology Group (ECOG) performance status, presence of liver metastasis, number of metastatic sites, and cohort—was applied on the validation cohort. Inverse probability of treatment weighting (IPTW) was then applied to create a weighted cohort for survival analysis. Further details related to variable selection and the approach for propensity score matching are described in Supplementary Methods.

Because treatment assignment was not randomized in the validation cohort, a target trial emulation (TTE) framework was also used to assess the performance of the biomarker in the validation cohort.[15] Further details related to the specifications of a hypothetical randomized controlled trial comparing mFFX to GnP and data mapping are provided in Supplementary Methods.

A prespecified P value <.05 was considered significant. Statistical analysis was performed with R v4.2.0 (R Foundation, Vienna, Austria). Study design and execution aimed to meet standards for studies evaluating AI models in oncology (Data Supplement, Table S1).[16] Further details around statistical analysis are described in Supplementary Methods.

RNA Sequencing and Analysis

Methods for sequencing and identification of RNA subtypes have previously been described for the COMPASS cohort.[11] For KYT, RNA-seq methods are provided in Supplementary Methods. PurIST[17] was used to assign basal-like versus classical subtypes for each tumor.

To study the molecular underpinnings of the GvF biomarker, BayesPrism deconvolution[18] was used to isolate the tumor component from bulk RNA-seq data. DEseq2[19] was used for differential expression (DE) analysis comparing F-pref against G-pref, controlling for batch effects possibly created by data originating from two different studies (COMPASS and KYT). Finally, gene set enrichment analysis (GSEA)[20] was used to extract pathways enriched for DE between F-pref and G-pref.

RESULTS

Patient Characteristics

The development cohort included 280 patients with 24 excluded for incomplete end points and 78 excluded for sample quality, leaving 178 patients in the development analysis cohort: 83 (46.6%) from Cedars and 95 (53.4%) from UPMC (Table 1). One hundred and thirty-seven patients had biopsy slides obtained from the primary tumor, 22 had slides obtained from metastases, and 19 had biopsy slides from both primary tumor and metastases. The validation cohort included 360 patients with 14 excluded for incomplete end points and 47 excluded for sample quality, leaving 299 patients in the validation analysis cohort: 155 (51.8%) from COMPASS and 144 (48.2%) from KYT. One hundred and eighty-seven patients had biopsy slides obtained from primary tumor and 112 had slides obtained from metastatic sites. Among the validation cohort, 292 (97.6%) received first-line mFFX or GnP regimens; seven patients had other fluoropyrimidine- or gemcitabine-based regimens.

Clinical Characteristics Based on Biomarker Status

Median follow-up time for the validation cohort was 11.5 months with a median TNTD of 8.0 months and a median OS of 12.5 months. Those treated with GvF showed similar TNTD (Fig 2A, HR, 1.01 [95% CI, 0.78 to 1.32]; P = .9) and OS (Fig 2B, HR, 1.24 [95% CI, 0.93 to 1.65]; P = .13). In the IPTW CPH regression, F-chemo and G-chemo groups had similar TNTD (HR, 1.07 [95% CI, 0.70 to 1.66]; P = .7) and OS (HR, 0.97 [95% CI, 0.63 to 1.51]; P = .9).

In the validation cohort, 173 (57.9%) patients were classified as F-pref and 126 (42.1%) as G-pref. Baseline clinical and tumor variables, including age, sex, ethnicity, ECOG status, CA 19-9 pretreatment serum level, presence of germline homologous recombination repair deficiency (HRD) mutation, and RNA subtypes, were similar across biomarker status (Data Supplement, Table S2). The group characterized as G-pref by the biomarker harbored more locally advanced (34% *v* 23%) cases than those designated as F-pref.

TABLE 1. PDAC Patient Clinical Characteristics, Split by Development and Validation Cohorts

Characteristic	Development Cohort (n = 178)	Validation Cohort (n = 299)	Two-Sided, *P*[a]
Biomarker status, No. (%)			.002
F-pref	76 (43)	173 (58)	
G-pref	102 (57)	126 (42)	
Age, years, median (IQR)	68.0 (61.2-74.0)	64.0 (58.0-70.0)	<.001
Sex, No. (%)			>.9
Male	105 (59)	175 (59)	
Race, No. (%)			.3
Non-White	30 (17)	48 (16)	
White	148 (83)	177 (59)	
Unknown	0 (0)	74 (25)	
ECOG, No. (%)			.002
0	46 (26)	57 (19)	
1	96 (54)	109 (36)	
2	13 (7.3)	1 (0.3)	
3	2 (1.1)	1 (0.3)	
4	1 (0.5)	0 (0)	
Unknown	20 (11)	131 (44)	
Extent of disease, No. (%)			.1
Locally advanced	37 (21)	83 (28)	
Metastatic	141 (79)	216 (72)	
CA 19-9 pretreatment level U/mL, median (IQR)	1,344.6 (95.5-6,594.0)	1,325.0 (176.5-8,516.0)	.5
First-line chemotherapy backbone, No. (%)			<.001
5-Fluorouracil	71 (40)	196 (66)	
Gemcitabine	107 (60)	103 (34)	
Site of biopsy, No. (%)			
Primary	137 (77)	187 (62)	<.001
Metastasis	22 (12)	112 (38)	
Primary + metastasis	19 (11)	0 (0)	

NOTE. Tabulated patient characteristics are reported between the development and validation cohorts. For continuous variables, medians and quartiles (Q1 and Q3) are provided; for categorical variables, counts of observations and their proportions in the corresponding populations are provided.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PDAC, pancreatic ductal adenocarcinoma.

[a]Fisher exact test *P* values exclude missing data counts.

Predictive Biomarker Performance

In the validation cohort, among G-pref patients (n = 126), those treated with G-chemo (n = 43, 34%) had superior TNTD (log-rank *P* = .038, Fig 2C) and no significant difference in OS than those treated with F-chemo (n = 83; log-rank *P* = .52, Fig 2D). The median TNTD for G-chemo patients was 9.6 months (95% CI, 7.1 to 13.6) compared with 7.2 months (95% CI, 6.1 to 8.7) for the F-chemo patients. Therefore, a 2.4-month improvement in TNTD is expected for 34% of the G-pref patients. The median OS for G-chemo patients was 14.3 months (95% CI, 9.0 to 21.3) compared with 12.4 months (95% CI, 11.1 to 14.5) for F-chemo patients.

Similarly, in the validation cohort, among F-pref patients (n = 173), those treated with F-chemo (n = 113, 65%) had superior TNTD (log-rank *P* = .035, Fig 2E) and OS (log-rank *P* = .003, Fig 2F) compared with those treated with G-chemo (n = 60, 35%). The median TNTD for the F-chemo patients was 8.6 months (95% CI, 7.4 to 11.3) compared with 7.5 months (95% CI, 5.8 to 8.7) for the G-chemo patients. Therefore, a 1.1-month improvement in TNTD is expected for 65% of the F-pref patients. Similarly, the median OS for F-chemo patients was 14.4 months (95% CI, 11.3 to 16.7) compared with 11.7 months (95% CI, 7.8 to 12.7) for the G-chemo patients. Therefore, a 2.7-month improvement in OS is expected for 65% of the F-pref patients. Combined, 48% of patients' treatment decisions would have changed by biomarker status in the validation cohort.

Using CPH regression, the predictive test for biomarker-treatment interaction was significant for both TNTD (*P* = .003) and OS (*P* = .015), suggesting that the biomarker is

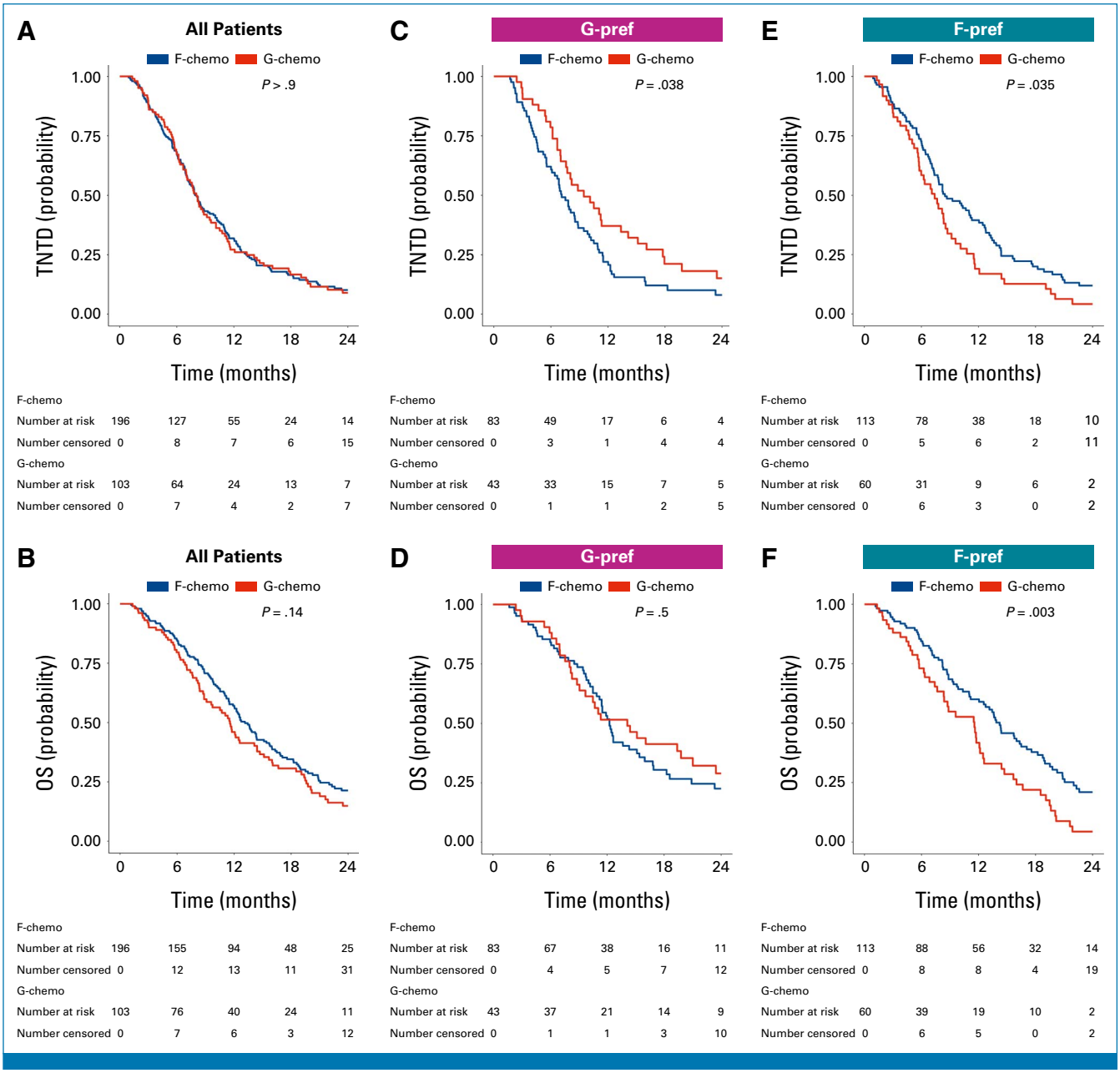

FIG 2. Validation cohort outcomes by end point, treatment group, and GvF biomarker status. Validation cohort survival comparison between first-line chemotherapy (GvF), for (A) TNTD and (B) OS. Based on multivariable CPH regression, the predictive test for biomarker-treatment interaction was significant for both TNTD (P = .003) and OS (P = .015). This interaction can be seen from the Kaplan-Meier survival curves. Among patients with PDAC classified as G-pref, those treated with G-chemo had (C) significantly better TNTD (log-rank P = .038) and (D) no significant difference for OS (log-rank P = .52) than those treated with F-chemo. Among patients with PDAC classified as benefitting from fluoropyrimidine-based chemotherapy (F-pref), those treated with F-chemo had significantly better (E) TNTD (log-rank P = .035) and (F) OS (log-rank P = .003) than those treated with G-chemo. P values reported are from log-rank tests. F-chemo, fluoropyrimidine-based chemotherapy; F-pref, F-chemo-preference; GvF, G-chemo versus F-chemo; G-chemo, gemcitabine-based chemotherapy; G-pref, G-chemo-preference; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; TNTD, time until next treatment or death.

predictive of differential treatment benefit (Fig 3). The treatment interaction terms for age and presence of liver metastasis were not significant. In the IPTW CPH regression, the GvF biomarker-treatment interaction remained significant for TNTD (P < .001) and OS (P = .005). Similar results were seen among the subset of patients (n = 292) who had received mFFX or GnP specifically (Data Supplement, Figs S2A-S2D; interaction P = .039 for TNTD; P = .018 for OS, Data Supplement, Fig S3). Additionally, we employed a TTE framework using data from the validation cohort (n = 115; Data Supplement, Table S3). The biomarker-treatment interaction terms remained significant under this framework (Data Supplement, Fig S4; interaction P < .001 for TNTD; P = .002 for OS, Data Supplement, Fig S5).

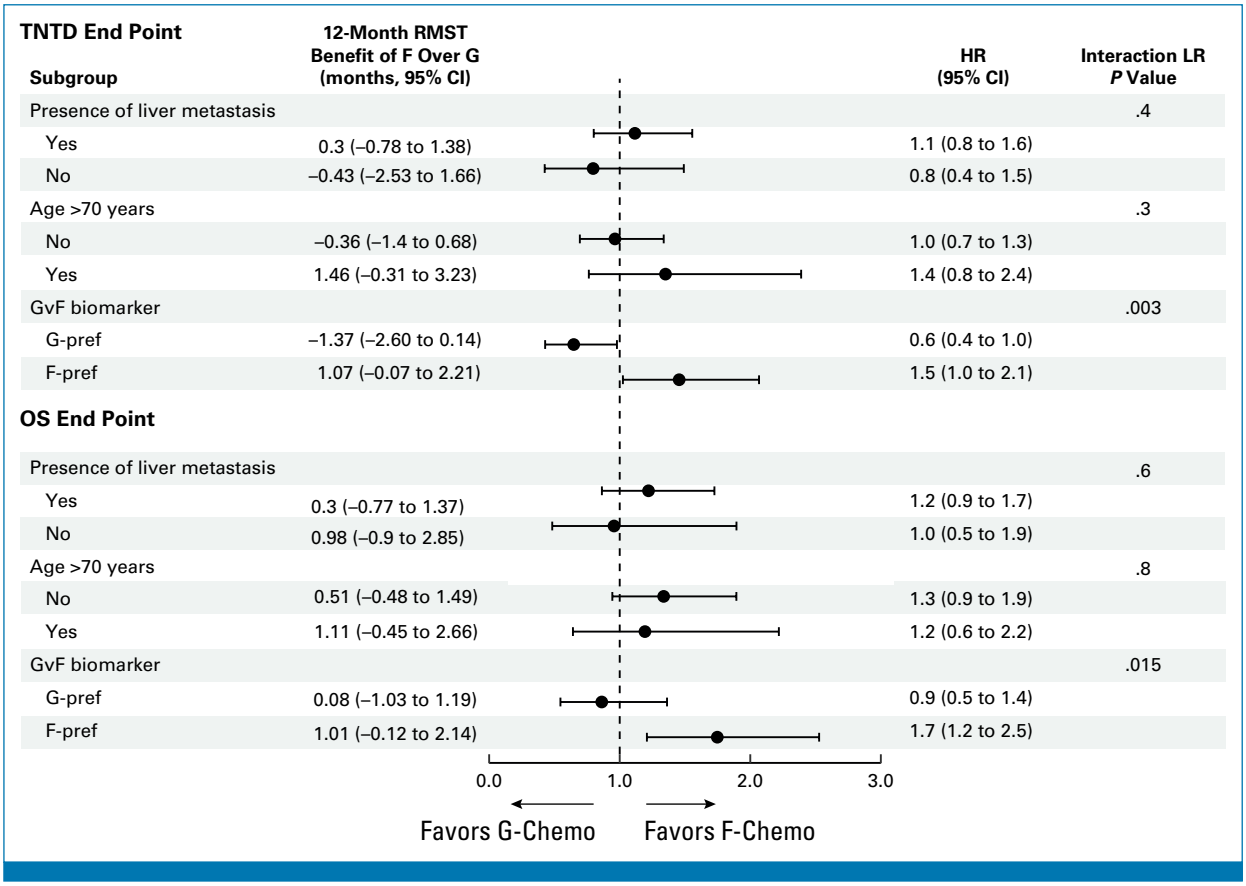

FIG 3. Forest plots among subgroups of the validation PDAC cohort for TNTD and OS end points. The 12-month RMST benefit of F over G within the patient subgroup, at 12 months, describes the benefit of F-chemo over G-chemo measured in restricted mean survival times; a negative value indicates that F-chemo was at disadvantage compared with G-chemo. HRs and two-sided 95% CI for the differential treatment effects between G-chemo and F-chemo are reported per subgroups and the associated interaction term *P* values from a CPH regression are reported. CPH, Cox proportional hazards; F over G, F-chemo over G-chemo; F-chemo, fluoropyrimidine-based chemotherapy; F-pref, F-chemo-preference; G-chemo, gemcitabine-based chemotherapy; G-pref, G-chemo-preference; HR, hazard ratio; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; RMST, restricted mean survival time; TNTD, time until next treatment or death.

Finally, the biomarker significantly stratified F-chemo patients by TNTD (log-rank *P*: 0.04) and G-chemo patients by TNTD (log-rank *P*: 0.026) and OS (log-rank *P*: 0.007; Data Supplement, Fig S6).

Association of the Biomarker With Molecular Markers

Among the 299 patients in the validation cohort, RNA subtypes were available for 226 (76%): 146 from COMPASS and 80 from KYT. The RNA basal and classical subtyping was associated with both TNTD and OS in the validation cohort (Data Supplement, Figs S7A and S7B, classical subtype HR, 0.48 [95% CI, 0.34 to 0.70]; $P < .0001$ for OS), but not associated with treatment effect as evidenced by a nonsignificant RNA subtype-treatment interaction ($P = .3$ for TNTD and $P = .8$ for OS, Figs 4A-4D). GvF biomarker status was not correlated with RNA subtyping (Fig 4E, Fisher's exact test $P = .3$) and interaction with treatment remained significant in a multivariable CPH model that adjusted for RNA subtype ($P < .05$). Finally, we explored the DE across tumors classified by the GvF biomarker as F-pref versus G-pref through DESeq2.[18] GSEA suggested that F-pref was markedly enriched for cell cycle and metabolic programs (Data Supplement, Fig S8). The top F-pref–enriched hallmark pathways included E2F targets (normalized enrichment score [NES] = 3.78, Padj = 1.7×10^{-50}), MYC targets V1 (NES = 3.75, Padj = 3.7×10^{-46}), and G2M checkpoint (NES = 3.45, Padj = 7.1×10^{-37}), indicating enhanced proliferative signaling. Additional enrichment was observed for MTORC1 signaling (NES = 2.51, Padj = 3.2×10^{-15}), oxidative phosphorylation (NES = 2.34, Padj = 2.6×10^{-11}), and glycolysis (NES = 1.69, Padj = 1.9×10^{-4}), suggesting metabolic reprogramming toward both anabolic growth and energy production. By contrast, hallmark pathways enriched for G-pref included epithelial-mesenchymal transition (NES = −1.49, Padj = 3.4×10^{-3}), Hedgehog signaling (NES = −1.54, Padj = 0.054), and myogenesis (NES = −1.41, Padj = 0.031), indicating enhanced stromal and differentiation programs.

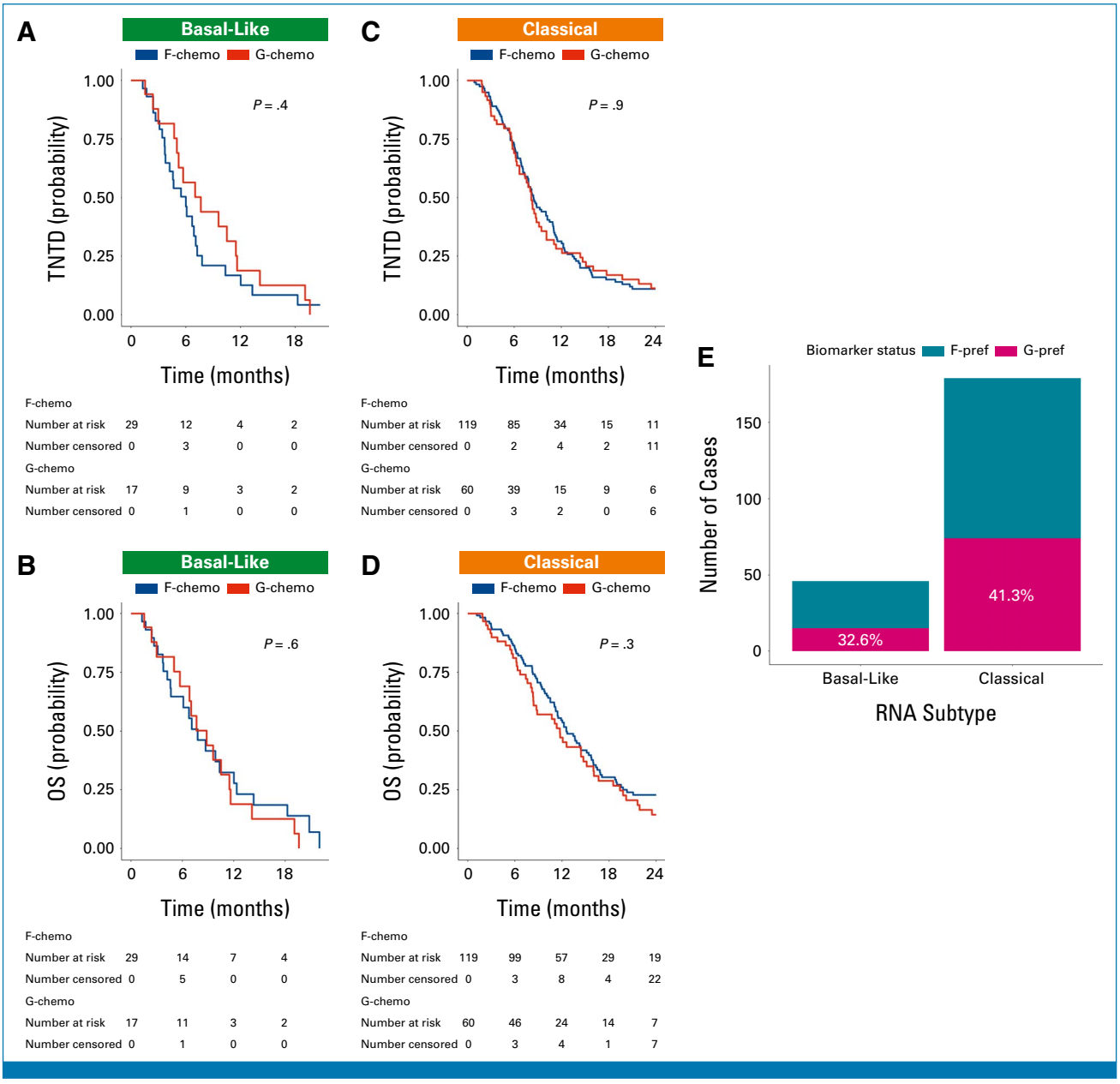

FIG 4. Validation cohort outcomes by RNA basal and classical subtyping for each end point: distribution of GvF biomarker by RNA basal and classical subtyping. Among cases classified as basal-like, those that received G-chemo had no difference in (A) TNTD (HR, 0.75 [95% CI, 0.40 to 1.42]; $P = .4$) or (B) OS (HR, 1.19 [95% CI, 0.62 to 2.29]; $P = .6$) versus F-chemo. Among cases classified as classical, there was no difference between G-chemo and F-chemo for (C) TNTD (HR, 1.03 [95% CI, 0.73 to 1.45]; $P = .9$) and (D) OS (HR, 1.22 [95% CI, 0.85 to 1.76]; $P = .3$). (E) Bar chart of biomarker calls within each RNA subgroup (basal-like and classical). Fisher's exact test $P = .3$. *P* values reported are from log-rank tests. F-chemo, fluoropyrimidine-based chemotherapy; G-chemo, gemcitabine-base chemotherapy; GvF, G-chemo versus F-chemo; OS, overall survival; TNTD, time until next treatment or death.

DISCUSSION

In this study, we developed and validated a computational histology artificial intelligence–powered signature that predicts benefit of first-line fluoropyrimidine-based versus gemcitabine-based regimens in advanced PDAC. Developed from a real-world multi-institutional cohort and validated in an international cohort derived from two pooled prospective studies, the histomorphologic assay–based biomarker dichotomized patients into those who experienced improved outcomes with fluoropyrimidine-based regimens and those with improved outcomes with gemcitabine-based regimens. The biomarker predicted differential treatment effect with significant biomarker-treatment interaction terms for both end points, TNTD and OS.

The incremental benefit in median TNTD (G-pref: 2.4 months; F-pref: 1.1 months) and median OS (G-pref: 1.8 months; F-pref: 2.6 months) with the biomarker-predicted preferred regimen represent a comparable or larger magnitude of improvement to those seen in the pivotal phase III studies MPACT (median OS and PFS benefit were both 1.8 months) and NAPOLI-3 (OS and PFS benefit of 1.9 months and 1.8 months, respectively) that led to US Food and Drug Administration (FDA) metastatic pancreatic cancer indication approvals of GnP and NALIRIFOX, respectively.[3,5] The observed differences in median OS in cases treated with the biomarker-suggested chemotherapy regimen versus the alternative regimen exceeded the 1- to 2-month gain in survival deemed clinically meaningful by treating clinicians.[21] The differential treatment effect of the GvF biomarker exceeded that of commonly used clinical variables such as age and the presence of liver metastasis. Moreover, on the basis of the frequency of G-pref patients among those receiving F-chemo (83/196, 42%) and the frequency of F-pref patients among those receiving G-chemo (60/103, 58%) in the validation cohort, more than 40% of patients may have benefitted from biomarker-directed selection of an alternate therapy.

Advanced PDAC has proven challenging to treat despite extensive efforts to optimize systemic therapies. Although novel small molecule inhibitors targeting RAS are being investigated and have demonstrated promise, the primary systemic therapy for PDAC in the first line remains cytotoxic chemotherapy.[2,3] Optimal systemic therapy with RAS inhibitors may ultimately involve combination of RAS inhibitors with backbone cytotoxic chemotherapy. Patients with PDAC often present at an advanced stage of disease and frequently receive only one line of therapy, emphasizing the importance of optimal first-line systemic therapy selection.[22,23] This AI pathology assay uses pretreatment biopsies without consuming additional tissue specimens, with a typical turnaround time of under 72 hours, thus offering the clinical care team an opportunity to expeditiously select the most appropriate first-line chemotherapeutic regimen. A tool with such practical benefits addresses an unmet clinical need for treatment-predictive biomarkers that enhance rational, personalized therapy decision making in PDAC. An evolving regulatory framework is creating the space for digital pathology-based biomarkers to be used clinically per standards set forth by the FDA and Clinical Laboratory Improvement Amendments.[24]

Biomarkers associated with differential treatment benefit to fluoropyrimidine- versus gemcitabine-based regimens are of significant interest as they could potentially facilitate personalized oncologic care and, on a population level, drive improved outcomes. To date, perhaps most well known are multiple transcriptomic classification schemes, which converge around classifying PDAC into classical or basal-like subtypes based on bulk RNA sequencing, with the basal-like subtype associated with worse prognosis and response to FOLFIRINOX.[16,25,26] However, this study did not find RNA subtyping to predict differential response to specific chemotherapeutic regimens with statistical significance. Based on RNA-seq data, the F-pref tumors seemed to demonstrate increased proliferation and metabolic transcriptomic programs, while the G-pref tumors showed increased signatures of epithelial-mesenchymal transition, hedgehog signaling, and myogenesis. But, the GvF biomarker did not significantly correlate with basal/classical subtypes and remained significantly predictive while adjusting for the subtypes, suggesting that it captures distinct facets of phenotypic PDAC biology not otherwise captured by RNA subtyping.

In addition, greater hENT1 expression is associated with outcomes in patients treated with gemcitabine,[27] and the GemPred biomarker, an RNA-based assay developed in preclinical models, has been reported to associate with adjuvant gemcitabine sensitivity.[28] Notably, such molecular assays require a significant amount of tissue for testing, and the low tumor cellularity of PDAC biopsy specimens result in high failure rates and technical variability, both of which are significant challenges to clinical application of these assays.[29]

Patients with germline mutations in the homologous recombination repair pathway and corresponding HRD have been shown to respond to platinum-based therapies. Although identification of patients with HRD may be feasible and could inform use of FOLFIRINOX, its utility is limited to a small subset (approximately 5%-8%) of the PDAC population and cannot identify patients who may respond to gemcitabine-based regimens.[30,31]

Consequently, there is a continuing need for biomarkers that can fit existing clinical workflows, are optimized for rapid test turnaround times, and can effectively identify the optimal first-line therapy for patients with PDAC. The predictive biomarker described in this study can distinguish the most effective treatment between fluoropyrimidine- versus gemcitabine-based regimens, which is in contrast to other biomarkers under investigation predictive of only a single chemotherapy modality. CHAI's upstream quality control primary exclusion were cases with low cellularity, which further supports the utility of core needle biopsies in PDAC.[32] This study was performed on fine and core needle biopsy specimens; future work should evaluate performance on fine-needle aspiration specimens. Additionally, the described histologic biomarker can easily embed within existing clinical workflows and critical treatment decision-making windows with rapid typical processing times of under 72 hours.

Limitations of this study include data missingness for certain clinical covariates such as performance status. In addition, the validation data set, while prospective, was not a randomized assignment to treatment groups, which can introduce unknown confounding. For instance, favorable OS outcomes in F-chemo-treated patients in the validation cohort could be related to the utilization of F-chemo in patients with more robust performance status. Although we

used techniques (eg, propensity scores and TTE) to offset such effects, future efforts are warranted for additional validation studies of the predictive biomarker on prospective randomized cohorts. It should be noted that there was potential for immortal time bias to have affected the composition of patients in the KYT cohort, given that patients could enroll at any point in their disease course; cohort was controlled for in the propensity score analysis. In addition, although widely accepted in real-world data studies, the primary end point was limited to TNTD, rather than true PFS, on the basis of available clinical data. One additional challenge in our analysis was the limited number of patients in the validation cohort with performance status of ECOG 2 or greater, complicating generalization to real-world populations. Future studies include additional validation in various patient populations, including those treated with other contemporary regimens such as NALIRIFOX, and further exploration of molecular mechanisms associated with the GvF biomarker to offer new insights into pancreatic cancer tumor biology. For example, future work is planned to understand the effects of the GvF biomarker in the context of HRD to enhance optimal therapy selection. Finally, it is possible that with additional cases available for development, the performance of the model discrimination could be further improved; however, this study design allowed the prospective cohorts to be held out solely for validation.

In conclusion, this study reports an AI-powered composite histomorphologic signature that can predict the preferred first-line chemotherapy regimen in advanced PDAC, validated on a prospectively collected cohort. The clinical application of this biomarker appears practically feasible, without tissue consumption or prolonged turnaround time, and it can facilitate treatment selection in a patient population with high unmet need, with the potential to improve patient outcomes.

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PRIOR PRESENTATION

Presented in part at the ASCO Gastrointestinal Cancers Symposium, San Francisco, CA, January 9, 2026.

SUPPORT

Supported in part by the Pancreatic Cancer Action Network (PanCAN - Know Your Tumor), the University Health Network, Toronto (COMPASS trial), and Valar Labs, Inc.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-02199.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-02199.
The H&E slides and RNA data will be made available to approved requesting collaborators by the COMPASS and PanCAN organizations. Genomic data generated from the COMPASS trial is available at the European Genome-phenome Archive (EGA; https://ega-archive.org/, https://ega-archive.org/studies/EGAS00001002543, and https://ega-archive.org/datasets/EGAD00001009409), which includes BAM files from whole-genome and transcriptome sequencing. Interested researchers can request access to the data by contacting OICR-DAC@oicr.on.ca or by downloading the Data Access Agreement form from EGA. Once the Data Access Agreement has been executed, data release can be expected within three business days. The period during which data can be downloaded is flexible according to the downloader's needs. Data access is approved on a limited use and project-specific basis. These data are available under restricted access in accordance with the ethical data regulations followed by the COMPASS trial, ensuring patient privacy is respected. Corresponding clinical data for the COMPASS trial can be publicly accessed within the supplementary materials of previous publications. If additional variables are needed, a data sharing agreement may be requested by contacting Jennifer J. Knox, Princess Margaret Cancer Centre, University Health Network, 700 University Avenue, 7-724, Toronto, ON, Canada M5G 1Z5. Phone: 416-946-2399; fax: 416-946-6546; Jennifer.Knox@uhn.ca. Data from panCAN's Know Your Tumor initiative are available for qualified researchers and can be obtained by completing and submitting a Data Use Agreement at www.pancan.org/spark. Specific inquiries related to the data and/or access can be sent to spark@pancan.org. In addition, the source code may be made available, subject to intellectual property

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ACKNOWLEDGMENT

The authors are grateful for the Pancreatic Cancer Action Network programs and the COMPASS trial team, and acknowledge their efforts and support. In addition, the authors thank the patients with pancreatic cancer whose journeys contributed to these insights. Finally, the authors thank Vineeta Agarwala, MD, PhD, and Patrick Doherty, MBA, MS, for their contributions.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Development and Validation of a Computational Histology Artificial Intelligence–Powered Predictive Biomarker for Selection of Chemotherapy in Advanced Pancreatic Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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No other potential conflicts of interest were reported.