The PASS-01 Challenge to Validate Treatment Selection Algorithms in Advanced Pancreatic Cancer (**PASS-01 Challenge**)

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1.0 Background Information

By the end of this decade, pancreatic ductal adenocarcinoma (PDAC) will become the second most common cause of cancer death[1]. Most PDACs present at an advanced incurable stage, which is treated with palliative-intent systemic therapy. Outcomes remain dismal, with a median survival of approximately one year[2–4]. Novel approaches to improving outcomes are urgently needed.

Biomarker-guided treatment selection can improve outcomes by matching patients to the most effective available treatment. In the first-line setting, consensus-based guidelines[5, 6] recommend three multi-agent chemotherapy regimens for metastatic PDAC: modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FFX), the same regimen with nanoliposomal irinotecan substituted for irinotecan (NALIRIFOX), or gemcitabine with nab-paclitaxel (GNP). Clinical trials and meta-analysis show these regimens yield similar outcomes on average[2–4, 7]. However, biomarkers have been proposed that identify subgroups that may uniquely benefit from specific treatments. For example, basal-like and classical transcriptomic subtypes may derive differential benefit from GNP and FFX, respectively[8–11]. Predictive biomarkers can range from hypothesis-driven single-gene tests, such as *hENT1* RNA expression[12], to machine-learning algorithms that can be multimodal, incorporating clinical, pathological, DNA, and RNA features. While several biomarkers show promise in PDAC, none have been validated in randomized clinical trials. Randomization is required for unbiased evaluation of differential treatment effect (DTE) predictions.

The PASS-01 trial (JCO 2025) offers an unprecedented opportunity to evaluate predictive biomarkers in PDAC[3]. Patients with metastatic PDAC were randomized to GNP or FFX. Clinical data, digitized whole-slide histopathology images, and whole-genome and transcriptome sequencing after laser-capture microdissection were collected for correlative analysis. Similar input data are available from the COMPASS trial of advanced PDAC[13]; however, in COMPASS, treatment was assigned by the physician and patient choice. Therefore, COMPASS holds value for training algorithms but cannot be used to test DTE algorithms.

We have trained multimodal machine learning algorithms to predict outcomes in PDAC patients treated with FFX or GNP in the COMPASS trial. The resulting system was named MULTIPL. Next, we designed the PASS-01 Challenge, in which biomarkers and algorithms of DTE and prognosis can be formally tested in a randomized trial. In this challenge, participating groups from other institutions will submit predictions for evaluation in the PASS-01 trial, which randomized participants to FFX or GNP. The PASS-01 Challenge presents an opportunity to rigorously evaluate predictive biomarkers for treatment selecting in advanced PDAC.

2.0 Study Objectives

2.1 Primary objective

We have specified the primary objective of the challenge in alignment with the PASS-01 trial design, specifically to assess the differential treatment effects on progression-free survival in the per-protocol population.

2.2 Secondary objectives

Secondary objectives and metrics are also pre-specified in the table below.

Objective Category	**Population**	**Endpoint**	**Prediction**	**Primary metric**	**Secondary metrics**
Primary	PP[a]	PFS[c]	DTE[f]	C4B[h]	Qini[k], hazard ratio[l]
Secondary		OS[d]			
		OR[e]			
	ITT[b]	PFS	O[g]	CI[i]	AUC, hazard ratio, calibration[m]
		OS			
		OR		AUC[i]	AUPRC[n], odds ratio[n], calibration
	PP[a], FFX	PFS	O[g]	CI	AUC, hazard ratio, calibration
		OS			
		OR		AUC	AUPRC, odds ratio, calibration
	PP[a], GNP	PFS	O[g]	CI	AUC, hazard ratio, calibration
		OS			
		OR		AUC	AUPRC, odds ratio, calibration

[a]PP: per-protocol
[b]ITT: intention to treat

[c]PFS: Progression-free survival, measured from randomization to progressive disease, according to RECIST 1.1, censored at last follow-up.
[d]OS: Overall survival, , measured from randomization to death, censored at last follow-up.
[e]OR: Objective response, measured using the best confirmed objective response according to RECIST 1.1
[f]DTE: Differential treatment effects. Here, algorithms will predict a continuous scalar value, where higher values indicate a predicted benefit of FFX versus GNP, anchored at 0 where neither regimen is preferred. Algorithms can also propose a treatment, either "FFX", "GNP", or "Undecided".
[g]O: outcome. Here, algorithms will predict a continuous scalar value, where higher values indicate a better outcome, calibrated on the outcome itself i.e. survival days or probability of response. Algorithms can also propose a binary classification of "Better", "Worse", or "Undecided".
[h]C4B: Concordance-statistic for benefit (*J Clin Epi,* 2018), implemented with the CForBenefit function the R package EpiForsk with default parameters. .
[i]CI: Concordance index, implemented with the concordance.index function in the R package survcomp with default parameters.
[j]AUC: Aread under the curve
[k]Qini will be estimated from tools4uplift package
[l]Hazard ratio will compare outcomes between concordant treatment (*i.e.*, when the predicted label FFX versus GNP matches the treatment received) *versus* discordant treatments, excluding "Undecided".
[m]Calibration: estimated using the integrated calibration index
[n]AUPRC: area under the precision-recall curve
[o]Odds ratio: odds ratio for response, comparing concordant versus discordant treatments as with hazard ratio.

2.0 Study Design

We propose to organize an algorithm challenge to validate prognostic and predictive large language models in advanced pancreatic cancer using existing PASS-01 data. External academic, commercial, and other qualified groups will receive a restricted de-identified baseline dataset that links clinical variables and digital pathology images from UHN with tumour genomic and transcriptomic data accessed through the controlled access European Genome Phenome Archive where genomic data is uploaded by the Ontario Institute for Cancer Research. The clinical dataset will exclude all direct identifiers and will not include outcome variables such as treatment response, progression free survival, or overall survival. Each group will run this dataset through its own existing algorithms and return only patient level prediction outputs to the PASS-01 team, which will then link these predictions to centrally held outcome data and calculate performance metrics. All groups will sign data use and participation agreements that limit use of the dataset to generating and submitting predictions for this challenge, prohibit using the clinical data to train or further adapt artificial intelligence models or to develop unrelated tools or products, and prohibit any attempt at re-identification. This data will be used for algorithm validation purposes only. These activities will

expand on the analysis of existing PASS-01 data, involve no additional patient contact or procedures, and present only a theoretical risk of re-identification that is mitigated through coding and variable minimization, secure technical and organizational safeguards, and strict contractual limits on use.

3.1 Retrospective data

This project will use previously collected clinical and tumour genomic and transcriptomic data from 170 patients included in the PASS-01 study (CAPCR ID: 20-5105). The the data to be used in this study was collected between 1-Oct-2020 to 1-Mar-2025.

The limited clinical data variables to be used in the study include:

- Age
- Gender
- Race
- Baseline ECOG
- Baseline CA19-9
- Treatment arm
- Site of biopsy
- Metastatic sites

3.2 Challenge details

1. Participating groups wishing to enter the challenge will apply on the challenge website and sign a template DTA with UHN.
2. Participants will obtain IRB approval if necessary, according to institutional guidelines.
3. Participants will apply for data access on EGA.
4. Limited clinical data will be provided to the participants by the PASS-01 Challenge team.
5. Participants will generate predictions using their algorithm.
6. Participants will email a CSV file to the PASS-01 Challenge team.
7. A manuscript will be published describing the results of the challenge within six months of completion on medrxiv, followed by a peer-reviewed journal.

3.3 Timeline

- 9 months to collect algorithms
  - Authors can publish their results once received
- 3 months to compare algorithms and publish results

4.0 Ethics

4.1 Consent waiver

Consent is not obtained for this study because it involves only the retrospective use of previously collected study data from the PASS-01 trial. All data have

already been collected and this study does not involve direct contact with individuals or any change in clinical care, and presents no more than minimal risk. Use of retrospective data proceeds under a waiver of consent, with safeguards for privacy and confidentiality as described in this protocol. Obtaining individual consent is not possible as nearly all patients in the retrospective PASS-01 cohort are deceased.

5.0 Data Security

Participants entering the challenge will sign a template DTA with UHN. Limited de-identified clinical data will be transferred securely to participants in an encrypted Excel file through institutional email.

Data generated from this study will be stored within secure institutional repositories with full encryption at rest and in transit. Files will be retained for 10 years after study completion in accordance with institutional data governance policies and securely deleted or archived following project completion.

6.0 Statistical Analysis

The performance of prognostic algorithms will be assessed using the area under the receiver operating characteristic curve (AUC) for ORR and the concordance index (CInd) for PFS and OS. The performance of predictive algorithms for differential treatment benefits will be assessed using the concordance for benefit (C4B) metric, which was adapted for PFS and OS. Survival estimates will be calculated using Kaplan-Meier curves. ORR will be compared between recommendation-treatment concordant and discordant cases using odds ratios from a logistic regression, while PFS and OS will be compared using Cox proportional hazard regressions.

References

1. Rahib L, Smith BD, Aizenberg R, et al: Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 74:2913–2921, 2014
2. Wainberg ZA, Melisi D, Macarulla T, et al: NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial. Lancet 402:1272–1281, 2023
3. Knox JJ, O'Kane G, King D, et al: PASS-01: Randomized phase II trial of modified FOLFIRINOX versus gemcitabine/nab-paclitaxel and molecular correlatives for previously untreated metastatic pancreatic cancer. J Clin Oncol JCO2500436, 2025
4. Ohba A, Ozaka M, Mizusawa J, et al: Modified fluorouracil, leucovorin, irinotecan, and oxaliplatin or S-1, irinotecan, and oxaliplatin versus nab-paclitaxel + gemcitabine in metastatic or recurrent pancreatic cancer (GENERATE, JCOG1611): A randomized, open-label, phase II/III trial. J Clin Oncol 43:3345–3354, 2025
5. Conroy T, Pfeiffer P, Vilgrain V, et al: Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 34:987–1002, 2023
6. Guidelines Detail [Internet]. NCCN [cited 2025 Nov 10] Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455
7. Nichetti F, Rota S, Ambrosini P, et al: NALIRIFOX, FOLFIRINOX, and gemcitabine with nab-paclitaxel as first-line chemotherapy for metastatic pancreatic cancer: A systematic review and meta-analysis: A systematic review and meta-analysis. JAMA Netw Open 7:e2350756, 2024
8. O'Kane GM, Grünwald BT, Jang G-H, et al: GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. Clin Cancer Res 26:4901–4910, 2020
9. Wenric S, Sangli C, Guittar J, et al: Real-world validation of the purity independent subtyping of tumors classifier for informing therapy selection in pancreatic ductal adenocarcinoma. JCO Precis Oncol 9:e2500197, 2025
10. Singh H, Xiu J, Kapner KS, et al: Clinical and genomic features of classical and basal transcriptional subtypes in pancreatic cancer. Clin Cancer Res 30:4932–4942, 2024
11. Rashid NU, Peng XL, Jin C, et al: Purity Independent Subtyping of Tumors (PurIST), A clinically robust, single-sample classifier for tumor subtyping in pancreatic cancer. Clin Cancer Res 26:82–92, 2020

12. Perera S, Jang GH, Wang Y, et al: HENT1 expression predicts response to gemcitabine and nab-paclitaxel in advanced pancreatic ductal adenocarcinoma. Clin Cancer Res 28:5115–5120, 2022
13. Knox JJ, Jang GH, Grant RC, et al: Whole genome and transcriptome profiling in advanced pancreatic cancer patients on the COMPASS trial. Nat Commun 16:5919, 2025