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#3655

Leveraging alternative AI/ML technologies to identify predictive biomarkers for chemotherapy selection: An analysis of the COMPASS trial evaluating chemotherapy response in advanced PDAC

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains a highly lethal malignancy with limited effective treatments, where first-line therapy often involves Gemcitabine + *nab*-Paclitaxel (GnP) or FOLFIRINOX (FFX). Substantial disease heterogeneity and the lack of reliable predictive biomarkers contribute to variable therapeutic responses.

OPPORTUNITY:

AI/ML have the potential to analyze complex genomic and transcriptomic data to help identify predictive biomarkers to guide more accurate, personalized treatment strategies.

OBJECTIVES:

1. Analyze PDAC trial data to identify mutational and transcriptional biomarkers predictive of patient response to GnP or FFX.
2. Develop robust molecular signatures that inform personalized treatment strategies and improve clinical outcomes in PDAC.

METHODOLOGY

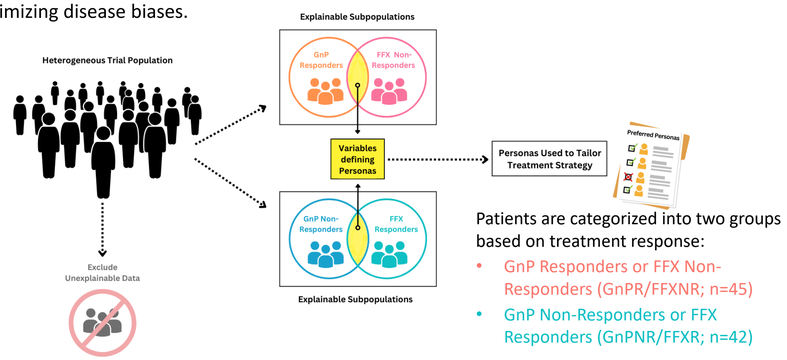
DATASET:

COMPASS dataset (n=87, ~25,000 SNVs and transcriptomic elements) evaluating PDAC patients who received GnP or FFX as first-line chemotherapy, with tumor responses evaluated based on standard criteria:

- Stable Disease (20% growth to 30% reduction)
- Partial Response (30% to 100% tumor reduction)
- Complete Response (Disappearance of tumor)

NETRAAI APPROACH:

NetraAI is an advanced, mathematically-augmented AI/ML technology developed to identify explainable patient subpopulations by distinguishing causal, high-effect-size "Personas" defined by 2-4 variables and specific ranges with respect to the endpoint, avoiding overfitting and minimizing disease biases.

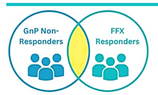


Patients are categorized into two groups based on treatment response:

- GnP Responders or FFX Non-Responders (GnPR/FFXNR; n=45)
- GnP Non-Responders or FFX Responders (GnPNR/FFXR; n=42)

RESULTS

1 MODELS OF FFX PREFERENTIAL RESPONSE



n=42 GnPNR/FFXR

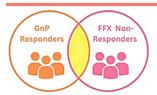
Variables that *simultaneously* characterize FFX Response and GnP Non-Response can be used to identify patients most likely to benefit from FFX.

Persona 1: n=26 (16 FFXR/GnPNR; 10 GnPR/FFXNR), p=0.008, Cohen's D=1.086 characterized by:
- C3AR1 (Complement C3a Receptor 1) < 3
- MIEF1 (Mitochondrial Elongation Factor 1) < 8
- HOXB6 (Homeobox B6) < 20

Persona 2: n=25 (13 FFXR/GnPNR; 12 GnPR/FFXNR), p=0.007, Cohen's D=1.129 characterized by:
- SUV39H1 (Suppressor of Variegation 3-9 Homolog 1) 1.5-3.2
- MBNL1 (Musclebind-like Splicing Regulator 1) < 40
- PHACTR4 (Phosphatase and Actin Regulator 4) < 50

Persona 3: n=25 (15 FFXR/GnPNR; 10 GnPR/FFXNR), p=0.008, Cohen's D=1.097 characterized by:
- DDTL (Doublecortin Domain-Containing Protein 1-Like) < 10
- YBX3 (Y-Box Binding Protein 3) < 125
- FRMD4A (FERM Domain Containing 4A) ≤ 5

2 MODELS OF GNP PREFERENTIAL RESPONSE



n=45 GnPR/FFXNR

Variables that *simultaneously* characterize GnP Response and FFX Non-Response can be used to identify patients most likely to benefit from GnP.

Persona 4: n=28 (17 FFXR/GnPNR; 11 GnPR/FFXNR), p=0.003, Cohen's D=1.200 characterized by:
- TRIM25 (Tripartite Motif Containing 25) 25-55
- RAB40B (Member of the RAS Oncogene Family) < 10
- NUTF2 (Nuclear Transport Factor 2) < 35

Persona 5: n=26 (16 FFXR/GnPNR; 10 GnPR/FFXNR), p=0.008, Cohen's D=1.280 characterized by:
- MVP (Major Vault Protein) < 180
- AC004980.7 (Long Non-Coding RNA) < 13

Persona 6: n=26 (16 FFXR/GnPNR; 10 GnPR/FFXNR), p=0.0006, Cohen's D=1.490
- DENND3 (DENN Domain Containing 3) < 26
- PDE8A (Phosphodiesterase 8A) < 52
- MMP15 (Matrix Metalloprotease 15) < 22

Lower levels of MVP were found to be associated with response to chemotherapy in both regimens, particularly favoring GnP response when combined with other variables.

3 C-FOR-BENEFIT TO EVALUATE AI-DERIVED MODELS FOR GNP AND FFX PREFERENTIAL RESPONSE

STANDARD ML ANALYSIS:

Using the full COMPASS dataset (83 patients, ~22,000 SNVs), univariate filtering selected the top 15 SNVs via ANOVA F-test to train classifiers predicting treatment benefit.

The best model – **Gradient Boosting with Nested 5-fold CV** achieved modest performance:

Accuracy	F1 Score	Sensitivity	Specificity	AUC
0.530	0.562	0.610	0.452	0.569

Models trained on the raw high-dimensional SNV space demonstrated limited separability of treatment preference, poor generalization, and failed to align directionally with actual tumor shrinkage.

NETRAI-AI ENHANCED ANALYSIS:

NetraAI identified a subpopulation (n=13 FFX, 10 GnP) characterized by 3 key SNVs (ZFYVE20, LOC389043, MIR30D) that perfectly differentiated treatment outcomes.

Training models using these three features and labels (FFX-Preferred, GnP Preferred, No Call) demonstrated *perfect generalization*:
- All Models (**Gradient Boosting, SVM, Deep Net, Naïve Bayes**): AUC = 1.00, Accuracy = 1.00
- **Binary** (0 vs 1) and **Multiclass** (0, 1, 2) **tasks**: Completely separable.

NetraAI successfully isolated the only generalizable subpopulation within the clinical trial data, discovering a minimal, explainable SNV signature that perfectly captures treatment-specific responses.

C-FOR-BENEFIT EVALUATION:

C-for-benefit was computed to assess whether the NetraAI findings are aligned with clinical benefit.
- **Setup:** A Gradient Boosting classifier used the three NetraAI-selected SNVs, focusing on patients with confidently predicted treatment preferences (FFx-Preferred vs GnP-Preferred).
- **Method:** For each matched pair (using Euclidean distance in the SNV feature space), the predicted benefit difference was compared to the actual tumor shrinkage difference.
- **C-for Benefit:** 0.923

92.3% of paired comparisons correctly reflected the actual benefit in tumor shrinkage, reinforcing the validity of the NetraAI-derived biomarker signature in guiding treatment decisions.

CONCLUSIONS & SIGNIFICANCE

PREDICTIVE BIOMARKERS: Specific transcriptional and mutational biomarkers can predict preferential response to therapy in oncology.

ENHANCED PATIENT STRATIFICATION: Successfully identified distinct patient subpopulations based on a small set of variables, enabling clear separation of treatment outcomes.

EFFICACY OF NETRAAI: Validation through the C-for-Benefit analysis (0.923), confirms the predictive power and clinical relevance of these persona-based models.

PRECISION MEDICINE: AI/ML techniques have the potential to drive precision medicine by informing personalized treatment strategies.

CLINICAL IMPACT: This integrated approach transforms abstract AI models into trustworthy, practical tools for clinical decision-making.

BIOMARKER DISCOVERY: The discovery of robust biomarkers, may extend beyond PDAC and enhance treatment efficacy across other cancers.

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