Understanding treatment response in pancreatic cancer: NetraAI provides genetic differentiation in FOLFIRINOX and Gemcitabine response

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BACKGROUND

Pancreatic cancer is known as a "silent killer" due to vague symptoms, late diagnosis, rapid progression, and poor response to therapy. Pancreatic cancer is the 14th most common cancer and 7th leading cause of cancer-associated deaths.

CURRENT STANDARD OF CARE:

Combination chemotherapy using FOLFIRINOX (FFX) or Gemcitabine with nab-paclitaxel (GnP).

CHALLENGES:

- Pancreatic cancer is a complex disease that is highly malignant in nature.
- Prolonging progression-free survival (PFS) and overall survival (OS) has remained a challenge due to disease heterogeneity.

OPPORTUNITY:

The COMPASS trial was the first prospective evidence of the potential predictive power of molecular profiling showing that there are unique advanced pancreatic ductal adenocarcinoma (PDAC) genomic and transcriptomic subtypes with molecular heterogeneity between individuals and differing responses to chemotherapy.

OBJECTIVES:

Identify causal genomic and transcriptomic factors that characterize molecular subtypes that capture heterogeneity between individuals and differing response to chemotherapy (GnP vs FFX) & elucidate how our methodology could improve clinical trial endpoint significance.

METHODOLOGY & WORKFLOW

COMPASS TRIAL DATASET:

- 208 pancreatic ductal adenocarcinoma (PDAC) patients.
- Whole genome sequencing (WGS) and RNA sequencing (RNASeq) prior to first-line combination therapy.
- **Primary Endpoint**: ≥30% reduction of tumor size following GnP or FFX.

Table 1. COMPASS Trial treatment program and response.

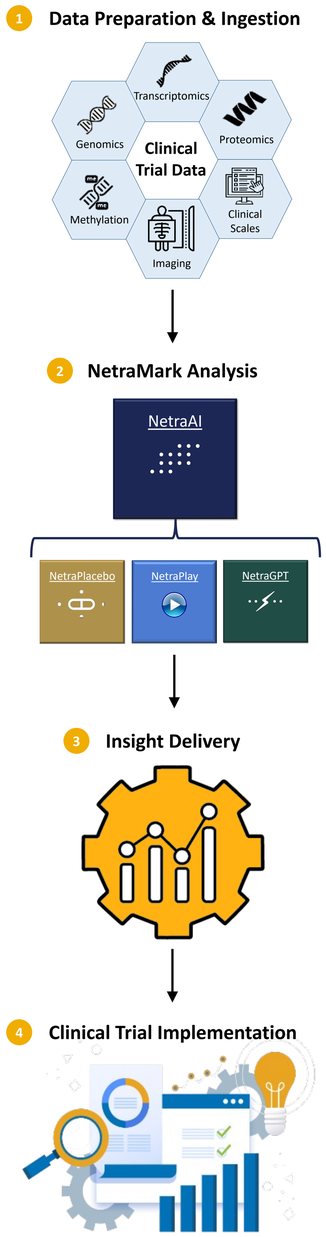
	Complete Response	Partial Response	Stable Disease	Progressive Disease
TOTAL	1	70	98	49
FFX	0	41	55	33
GnP	1	29	43	16

PERSPECTIVE ANALYTICS & HYPOTHESIS-GENERATION:

NetraAI has the ability to extract meaningful insights from multi-dimensional and highly heterogeneous patient population datasets to discover causal factors that affect patient response to FFX and GnP.

- Causal feature set discovery methodology.
- Generated hypotheses to discover unknown subpopulations that are defined by multiple genes and provide explanations for underlying driving mechanisms behind each subpopulation.
- Identify which patients are explainable to improve pancreatic survival through a precision medicine approach.

NetraMark Workflow
Generative Clinical Trial Decision Support



RESULTS

NetraMark AI Analysis: Uncovering hypotheses associated with pancreatic cancer response to standard of care protocols FFX and GnP

Genetic mechanisms differentiating FFX and GnP response in stable disease PDAC patients.
Using NetraAI, we identified key drivers of differentiation between responses to FFX and GnP treatment in stable disease patients (between a 30% loss and 20% growth of tumor) to reveal 3 distinct subpopulations (***Figure 1***).

- **Loop 1:** (9 GnP responders) characterized by downregulated *LRRC8E* and *UGT1A5.*
- **Loop 3:** (13 FFX, 4 GnP responders) characterized by downregulated *LRRC8E, PTPRH,* and *SORT1.*

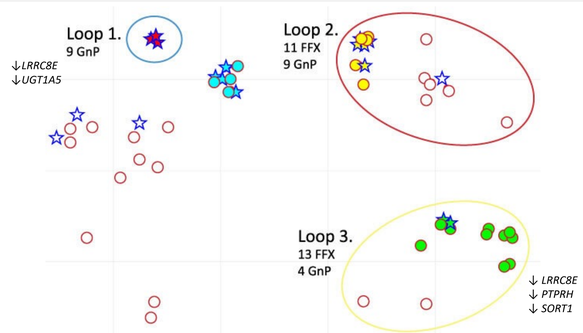


Figure 1. NetraAI identified PDAC subpopulations of stable disease patients responding to GnP and FFX. Star = GnP responder; Circle = FFX responder.

The NetraAI identified genes (*LRRC8E, PTPRH, UGT1A5,* and *SORT1)* that drive these distinct subpopulations are related to:

- Neuron death and regulation
- Neurotrophin signaling
- Neuron apoptotic processes

These pathways are not surprising considering the mechanism of chemotherapy and its induction of apoptosis.

Genetic mechanisms differentiating FFX and GnP response in stable disease, partial response, and complete response PDAC patients.
To extract more information from the COMPASS trial dataset, using NetraAI we:

- Generated a map that identified drivers of differentiation between FFX and GnP responders with stable disease, partial response (>30% but <100% loss of tumor), and complete response (complete disappearance of tumor) (***Figure 2***).
- **Loop 1:** 19/24 patients responded well to treatment with FFX. Characterized by higher expression of *CLEC19A* and *LRRC29*.
- **Loop 2:** 84 patients, 44 responded to FFX and 40 responded to GnP. 78% of the individuals who responded well to GnP are within Loop 2.

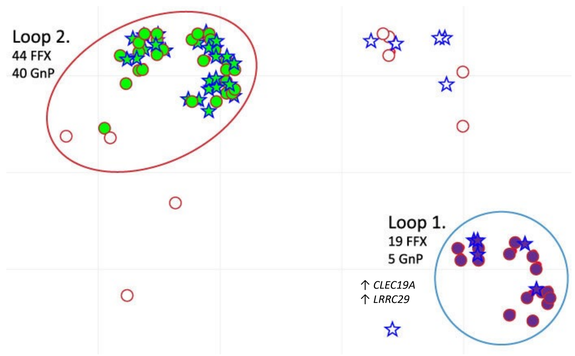


Figure 2. NetraAI identified PDAC subpopulations of stable disease, partial disease, and complete response patients responding to GnP and FFX. Blue star = GnP responder; Red circle = FFX responder.

A gene interaction network shows that *LRRC29* relates to *HOOK1* (***Figure 3***). *HOOK1* negatively regulates epithelial-to-mesenchymal transition (EMT) by inhibiting *SHP2* activity and is decreased in PDAC.

Simultaneous decreased *HOOK1* and *SHP2* levels are associated with a better patient response to GnP in NSCLC. These results suggest that response to chemotherapy may be cancer agnostic and may depend on the chemotherapeutic agent and genetic factors involved in disease progression, with *LRRC29* expression acting as a biomarker to choose between GnP and FFX treatment.

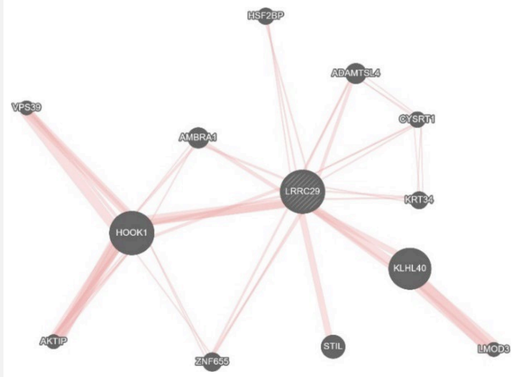


Figure 3. Gene interaction network generated using NetraAI identified genes for FFX and GnP responders.

NetraMark Insight Delivery and Clinical Trial Implementation: Enhancing effect size by characterizing patients based on drug response

Shifting effect size for patient drug response.
Using the characterization of patient drug response identified with NetraAI, it is possible to significantly increase the effect size of GnP and FFX response in subsequent clinical trials (**Figure 4**).

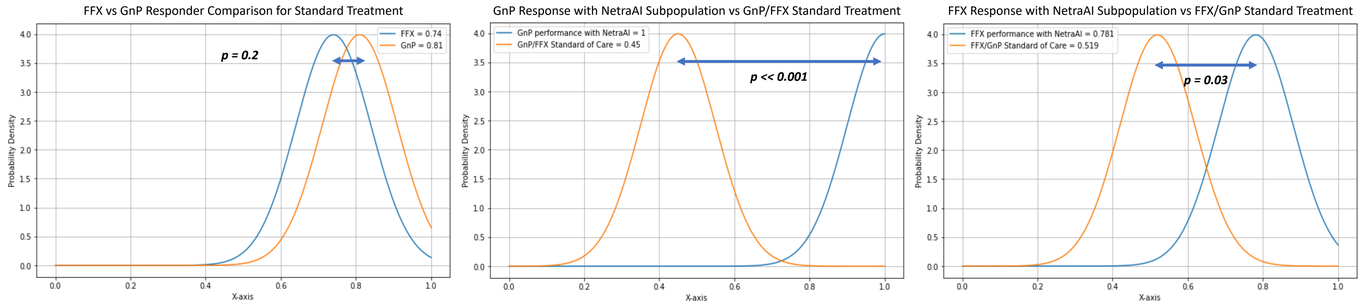


Figure 4. Maximizing effect size by incorporating NetraAI precision patient characterization with respect to GnP and FFX response hypotheses related to patient response.

CONCLUSIONS & SIGNIFICANCE

SUMMARY OF KEY FINDINGS

Using NetraAI, an augmented intelligence approach, we were able to identify:

- Several distinct signatures within a small dataset (n=208) that would allow oncologists to more confidently choose between FFX or GnP treatment for approximately 20% of patients.
- PDAC patients with decreased *HOOK1* and *SHP2* expression may better respond to GnP while FFX may be better for those with increased *LRRC29* expression.
- *SORT1,* an emerging target for pancreatic cancer invasion as a characterization of PDAC patients responding to FFX.

SIGNIFICANCE OF METHODOLOGY & FINDINGS

State of the art AI methods rely on strong effect sizes. The NetraAI brings next generation capabilities to discover subpopulation insights where hidden statistical significance and clinical trial de-risking live. By finding those patients that can be explained, the NetraAI drives clinical innovation.

FUTURE USE & APPLICATION

- Clinical trials can benefit by understanding which patient subpopulations are best aligned with the mechanism of action of their drug to improve drug response signal as evidenced by a significant shift in effect size. Our process can identify those patients which collectively define a response persona that can alter the outcomes of clinical trials.
- This process can also be used for biomarker discovery and for identifying the underlying role of specific genes and pathways involved in regulating the patient response to therapy.

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