HIGH-DIMENSIONAL, MULTI-OMICS ANALYSES OF PROTEINS, METABOLITES, TRANSCRIPTS, AND GENES ENABLE BIOMARKER DISCOVERY IN EARLY- AND LATE-STAGE PANCREATIC CANCER

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INTRODUCTION

- Pancreatic cancer is the 3rd leading cause of cancer-related deaths in the United States[1]
- Most newly diagnosed cases are already at an advanced stage when prognosis is poor
- This highlights the need to develop tests with high sensitivity and specificity for early detection of pancreatic cancer[2]
- Blood-based tests that include multiple analytes may enable identification of biomarkers that provide high sensitivity and specificity for earlier detection and more selective treatment
- PrognomiQ has developed a multi-omics assay and analysis platform to comprehensively profile blood samples and detect proteins, metabolites, lipids, mRNA, miRNA, cfDNA fragments, and methylation at CpG sites
- This platform can provide deep insights into disease biology and may enable the development of high sensitivity and specificity tests for early detection of cancer

OBJECTIVE

- To explore the potential of multi-omics assays to detect and quantify pancreatic cancer biomarkers in the blood
- To determine if biomarkers from different assays represent different aspects of biological regulation

RESULTS

FIGURE 1. Biomarkers differentiating between non-cancer and pancreatic cancer cohorts span the full genotype-to-phenotype spectrum

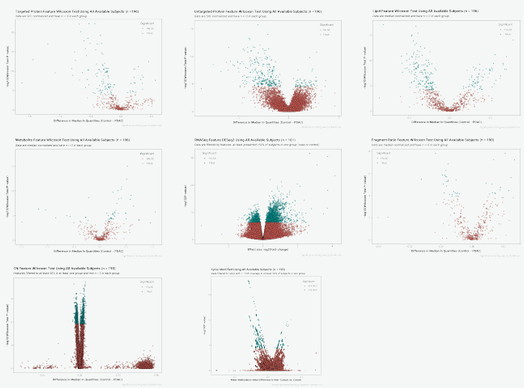
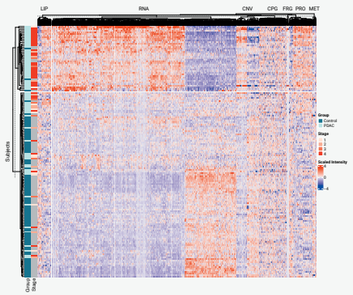


TABLE 1. Number of total and statistically significant features detected for each 'omic

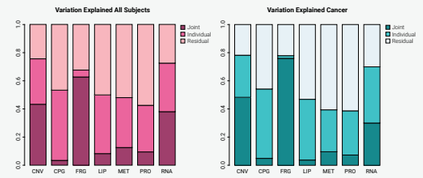
Analyte Type	# Subjects	Total # of Features	# Significant Features
Metabolites	196	377	49
Lipids	196	830	232
Untargeted Proteomics	196	17,093	296
Targeted Proteomics	195	766	160
CpG	190	59,958	542
RNA Transcript	161	203,014	3,385
CNV	190	28,949	727
Fragments	190	412	37

FIGURE 2. Unsupervised clustering on differential biomarkers shows heterogeneity across disease states



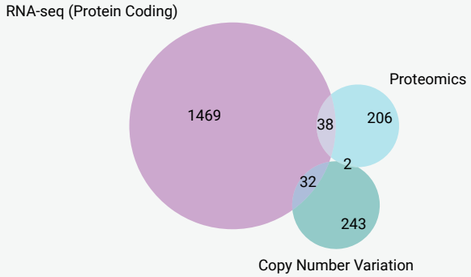
- *A substantial number of cancer individuals cluster with non-cancer individuals, even at late-stage. Supervised ML approaches may better separate these groups*
- *Different 'omics appear to pick up on different aspects of biological variation*

FIGURE 3. Variance decomposition illustrates that shared and unique aspects of biology are captured by each omic



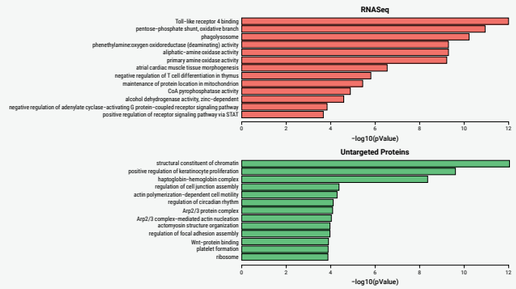
- *No single 'omic captures all the biological variance*
- *There is shared biology across the different 'omics (the joint component). We can look across them to uncover a shared biological signal*
- *There is also unique biology captured by each individual assay i.e. the individual component*

FIGURE 4. Multi-omics readouts can highlight biomarkers that are shared between them



- *Overlapping multi-omics assays can prioritize biomarker candidates*
- *The two proteins overlapping with copy number change are E and N cadherin and may be relevant for epithelial-to-mesenchymal transition in pancreatic cancer*

FIGURE 5. Different molecular assays are capturing analytes from distinct biological processes



CONCLUSIONS

- Multiple pancreatic cancer biomarkers were detected via blood-based assays in each omic type
- Biomarkers broadly separate cancer individuals from non-cancer individuals
- Cancer biological signals can be shared across omics readouts or be assay-specific
  - No single assay captures the breadth of biological variance seen in cancer
  - Individual assays can capture distinct aspects of cancer biology
  - Multiple assays can be used as multiple lines of evidence towards shared biology
- Multi-omic integration across assays can be done using a data-driven approach
- Results can inform ongoing work towards machine learning classification and diagnosis of pancreatic cancer

DISCLOSURES

Study funded by PrognomiQ. All employees are current or former employees of PrognomiQ.

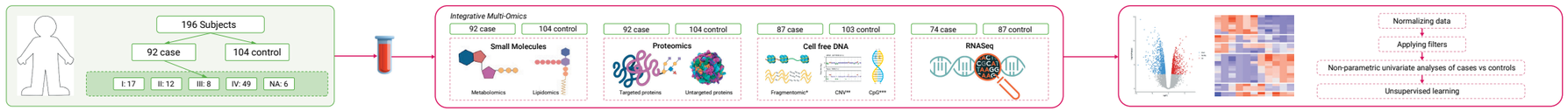
ACKNOWLEDGEMENTS

Funded by PrognomiQ (San Mateo, CA). Editorial and graphic assistance provided by Prescott Medical Communications Group (Chicago, IL).

REFERENCES

1. US Centers for Disease Control and Prevention, An Update on Cancer Deaths in the United States. Available at: https://www.cdc.gov/cancer/dcpc/research/update-on-cancer-deaths/index.htm. Accessed on Sept 6th 2022
2. Pereira, et al.,*Lancet Gastroenterol Hepatol.*; 4 (7): 698-710 (2020)
3. Lock et al. *Ann Appl Stat*; 7 (1): 523-542 (2013)

METHODS



Study Design and Sample Collection

- This was a cross-sectional, multi-center, case-control study enrolling 196 biopsy-confirmed, treatment-naive pancreatic ductal adenocarcinoma subjects with age- and gender-matched controls without cancer history in preceding 5 years (Figure 5)
- Blood was collected in assay-specific tubes for each subject following standardized protocols across all centers

Sample and Data Processing

- Individual assay samples were QC-ed, prepared, and processed using field-standard methods for their specific type
- Hemolyzed samples were excluded
- Quantitation and normalization were done using field-standard methods specific to each omics
- Confounding factors including batch and library size (genomics read-outs specific) were accounted for

*Fragment-length disorder
**Copy-number variation (CNV)
***CpG site methylation

Data Analyses

- Univariate analyses were performed to identify features differentiating cancer from non-cancer cohorts for each assay
- Multiple hypothesis testing was controlled using Bonferroni correction or Benjamini-Yekutieli procedure where appropriate
- Unsupervised clustering was used to investigate if subjects naturally grouped into clusters associated with disease status
- Gene set enrichment analysis was performed to understand associations with disease biology
- Overlapping and non-overlapping variance analysis was performed with JIVE[3] analytical tools