Outcome driven persona-typing for precision oncology: Beyond a genomics centered view of individualized therapy

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Abstract

Background: Precision oncology is currently being defined mainly by a genomics-oriented view to tumor biology. However, a multi-omic view to tumor biology and more accurate outcome prediction is emerging. Combining this with treatment history, clinical-epidemiological data, and outcomes data may provide patient-specific descriptors that in N-dimensional space constitute population based "personas" that share common outcome destinies and identify response predictors to any given therapy.

Methods: We utilized our database from 1,014 pancreatic adenocarcinoma patients within our ongoing registry study as a feasibility study. Commercial exome (321 genes by NGS) and proteomic data (24 proteins by IHC) as well as previous and current treatment history, epidemiological data and outcomes data were collected on every patient. Overall Survival (OS) was calculated and 10 individual outcome "personas" were created that spanned short-term survival (< 6 months) to long term survival (32-110 months). Statistical analysis of individualized gene, protein, specific treatment type, disease stage, location, age, gender, ethnicity, was used to determine key principal components that significantly ($p < 0.05$) described each outcome persona to create a unique persona-type identifier.

Results: Proteomic information was significantly associated with outcomes more frequently then genomic information ($p = 0.02$). Longest term outcome personas (OS > 32 months) were characterized by increased PD1 and decreased TS protein levels along with increased frequency of BRCA2 genomic alterations and treatment with off-label targeted therapy. Shorter term personas (OS < 6 months) were described by high TS protein levels along with genetic alterations in MYCL1, MYST3, VEGFA, ZNF703 and KEL.

Conclusions: Persona-typing can be used to define and map key characteristics that associate with outcome and specific treatment. In the future, individual patients can be mapped to pre-defined personas that could more accurately describe outcome destiny and optimized/personalized therapy options.

Background

- Integration of proteomic and clinical data can improve predictive biomarkers of treatment response relative to those based on genomics alone (1).
- Traditional methods for finding cancer subtypes have relied on transcriptomic data, but the subtype-specific treatment effects are typically not reported (2).
- Through a molecular profiling service and registry protocol, we have built a database of genomic, proteomic, clinical, and outcomes data for over 1,000 pancreatic cancer patients (3).

Methodologic Details

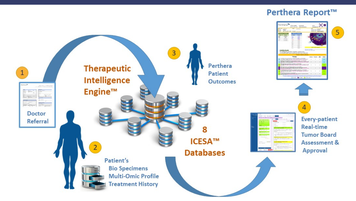


Figure 1: The Perthera Workflow: After referral and consent, Perthera facilitates the process of tumor biopsy, coordinates molecular testing, and reviews the results with the disease-specific medical review panel. A report is then delivered to the patient and treating oncologist, and patients are followed longitudinally for outcomes. Here, labs used were Foundation Medicine for next-gen sequencing and Caris Life Sciences or NeoGenomics for immunohistochemistry of a panel of proteins.

Group	N (%)	Median OS (months)	Log rank P-value
Gender			0.38
Male	520 (51%)	20.5	
Female	494 (49%)	22.9	
Age			0.72
≤ 64	535 (53%)	22.2	
> 64	479 (47%)	21.6	
Stage at diagnosis			**$< 10^{-6}$**
Metastatic	432 (44%)	16.2	
Localized/Loc. Adv.	550 (56%)	28.0	

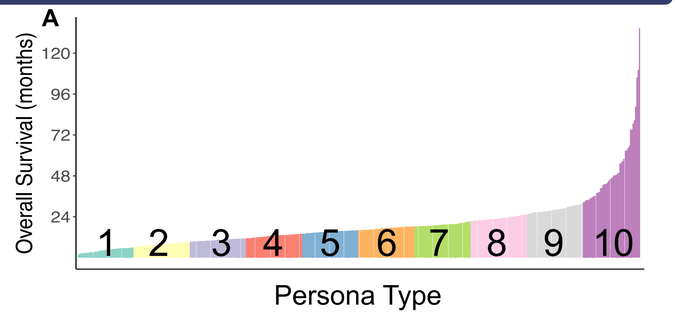
Table 1: Patient characteristics. The distribution of age and gender were relatively even in the cohort of 1,014 PDA patients. In 982 PDA patients with available staging information, 44% were diagnosed with metastatic disease. Median overall survival was calculated from Kaplan Meier estimates, and differences were assessed using the log rank test.

Clinical variables
Gender, Age, Ethnicity
Prior therapy, Therapy after profiling
Next-gen sequencing
321-gene FoundationOne panel, including KRAS, TP53, CDKN2A/B, SMAD4, ARID1A, STK11, BRCA1/2, ATM, MYC, RNF43, GNAS, ERBB2
Immunohistochemistry
TS, ERCC1, RRM1, TOPO1, PTEN, HER2, ALK, MLH1, PMS2, MSH2, MSH6, phospho-AKT

Table 2: Variables assessed.

Biomarkers Associated with OS Personas

Figure 3: Patient characteristics. (A) Patients were ordered according to overall survival and divided into 10 equal sized deciles, which served as outcome-driven "personas". **(B)** Characteristics associated with personas were identified using Fisher's exact test to determine which variables were significantly enriched or depleted in each persona. Each variable was equally weighted, and significant variables are listed for each persona, with upward arrows indicating that a variable is enriched in the persona and downward arrows indicating that a variable is depleted in the persona. All personas had at least one significantly associated NGS marker, while half of them had a significantly associated IHC marker. Age, gender, and ethnicity were not significantly associated with any of the personas.



B

Persona Type 1
NGS: ⬆ TP53, VEGFA, U2AF1, MYST3, ZNF703, MYCL1, KEL
IHC: ⬆ TS, RRM1
⬆ Metastatic at diagnosis
⬇ Prior response to Nab-P/Gem

Persona Type 2
NGS: ⬆ BRAF, KAT6A, ARID2, PAX5
IHC: ⬆ PD-L1
⬆ Metastatic at diagnosis

Persona Type 3
NGS: ⬆ FGFR1, ZNF703, PIK3CG
⬇ Prior response to FOLFIRINOX

Persona Type 4
NGS: ⬆ TP53
IHC: ⬇ PTEN, PD-1
⬇ Post-report off-label therapy

Persona Type 5
NGS: ⬆ KMT2D, SPTA1
IHC: ⬆ PGP
⬇ TS, EGFR

Persona Type 6
NGS: ⬆ CCNE1, TP53
⬇ Metastatic at diagnosis
⬇ Prior exposure to chemotherapy

Persona Type 7
NGS: ⬆ SLIT2

Persona Type 8
NGS: ⬆ SMAD2, SETD2

Persona Type 9
NGS: ⬆ BRCA2

Persona Type 10
NGS: ⬆ BRCA2
IHC: ⬆ PD-1
⬇ TS
⬆ Prior exposure to gemcitabine
⬆ Post-report off-label therapy
⬇ Metastatic at diagnosis

Multivariate OS Biomarkers

	$N_{altered}/N_{total}$ (%)	Fisher's test P-value
Assay		**0.001**
NGS	20/321 (6.2%)	
IHC	7/24 (29%)	

Table 3: Comparison of number of significant markers by assay type. The fraction of protein markers associated with personas was higher than the fraction of NGS markers associated with personas.

Conclusions and Future Directions

- **Outcome-driven persona-typing based on multi-parameter molecular--clin-epi-treatment data can identify n-dimensional signatures that associate with outcome.**
- **The high fraction of significant proteins that correlate with outcome supports the further exploration of protein testing in precision oncology. While conflicting evidence exists pertaining to the utility of protein data as biomarkers for chemotherapy response (4), our results suggest that the multivariate context should be taken into account.**
- **Generally, patients with better OS cluster in persona-types characterized by have decreasing levels of TS, increasing frequency of DNA repair alterations (e.g. BRCA2) and concomitant treatment with off-label therapies (e.g. PARPi) and have been treated with gemcitabine as well as reduced frequency of metastatic disease.**
- **Future development will include:**
  - **Validation through mapping of new patients onto existing personas**
  - **Application of advanced subtyping techniques such as topological data analysis**
  - **Ongoing collection of data and enrollment of new patients will allow for finer-grained subtyping using specific treatments, incorporating additional chart abstracted clinical/epidemiological data and new types of next-generation molecular profiling (e.g. phosphoproteomic, metabolomic, microbiome, etc).**

Citations and Acknowledgments

(1) Wulfkuhle et al. 2012 *Clinical Cancer Research* 18(23): 6426-35
(2) Bailey et al. 2016 *Nature* 531: 47-52
(3) Pishvaian et al. 2018 Under review
(4) Rao et al. 2017 *Oncotarget* 8(23): 37923-37934

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