Functional precision medicine: Uncovering high actionability in rare cancers beyond genomics

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INTRODUCTION

Precision medicine relies on mutational profiling, yet the clinical actionability remains limited for many cancer patients, especially for rare cancers. Rare cancers—those with fewer than 6 new cases per 100,000 people each year—collectively make up about 25% of all cancer diagnoses. Patients with rare cancers face significantly worse outcomes, with 5-year survival rates of only about 49% compared to 63% for more common cancers. Here, we evaluated the feasibility and actionability of ex vivo drug sensitivity testing across solid tumors using the Personalized Automated Robotics Informatics Sequenced (PARIS®) CLIA-certified test, assessing patient-derived tumor cells (PDTCs) responses to a broad oncology drug panel.

METHODS

- We cultured 91 PDTCs from 85 patients with rare cancer types.
- Organoid derivation time averaged 23 days (median: 12 days), with the extended timeline attributed to the development of bespoke culture conditions and, often, to account for prior treatment washout (approximately 3 weeks).
- Following successful derivation, the PDTCs were seeded evenly in 384-well plates.
- The PARIS workflow then proceeded with the addition of a customizable drug panel (median: 46 compounds) using high-throughput robotics capable of precisely delivering nanoliters of drugs via sound wave technology on the subsequent day.
- Organoids were cultured with drugs for 6 days.
- The readout of the PARIS assay is based on ATP production (CellTiter-Glo).
- Algorithmic analysis provided a clinical report for oncologists, ranking drugs by their effectiveness.
- A CLIA-certified report guided oncologists toward personalized, patient-oriented therapeutic decisions.

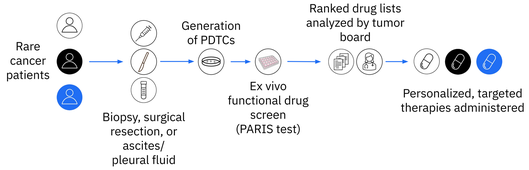

Figure 1. Description of PARIS assay workflow

RESULTS

Rapid TAT enhances the actionability and clinical utility of PDTC-based drug testing

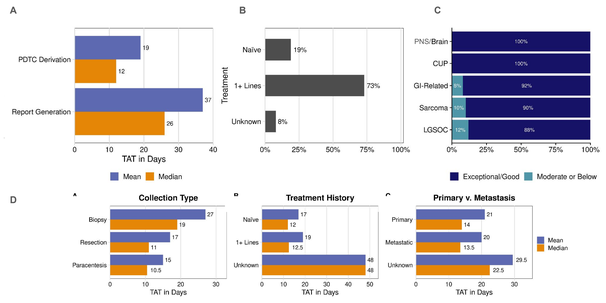

Figure 2. Overall turnaround time (TAT) for organoids and report generation, treatments exposure prior to PARIS test and test actionability. A) Median and average TAT of PDTC establishment were calculated and compared to median and average TAT for CLIA report delivering. B) Stats of treatments exposure. Most samples had seen one or more line of treatment prior to getting the PARIS test. C) PARIS test actionability in each cohort; with 88% capability of identifying an exceptional to good drug (chemo or targeted) for LGSOC, 90% for any sarcoma, 92% for gastrointestinal-related cancer and 100% for either brain/PNS cancer or cancer of unknown primary (CUP). Moderate or below includes the response categories moderate, low and none. D) Across sample collection types, PDTC derivation time was shorter for paracentesis or surgical resections compared to biopsy collection (10.5 and 11 vs. 19 days, respectively). Previous treatment exposure did not delay TAT compared to treatment naive samples. PDTCs could be derived from metastatic and primary samples in approximately similar times.

SUMMARY

The **PARIS** assay enables clinically applicable drug sensitivity profiling for rare cancers with **high actionability** and a **clinically relevant turnaround time** empowering personalized treatment implementation:

- Using this assay, we identified drugs with exceptional/good responses in 88% of rare cancer cases (49% of cases for chemotherapeutic agents)
- PDTCs can be generated from both treatment-naïve and pre-treated samples with a median of 12 days, with drug profiling and reporting completed within 26 days
- The assay identified therapeutic sensitivities to unique targeted agents that would not have been identified by standard molecular profiling, and PTDCs recapitulated known chemoresistance

RESULTS

Table 1. Rare cancer cohort profile

Cohort Characteristics	Number	
Total number of patients	85	
Total number of samples	91	
Total number of screens	111	
Age		
Median Age at Diagnosis	48 (n=72)	4 pt had 2 collections; 1 pt had 3 collections; 13 unknown
Median Age at screening	51 (n=74)	3 pt had 2 collections; 1 pt had 3 collections, 9 unknown
Gender: (exception one unknown)	**Number**	**Percentage**
Male	36	40%
Female	54	59%
Clinical Diagnosis		
Ampullary/Appendiceal	5	6%
Bladder	2	2%
Brain (Astrocytoma, GBM, Nervous System)	3	3%
Cancer of Unknown Primary (CUP)	4	4%
Cholangiocarcinoma/Gallbladder	26	29%
Esophageal/Gastric Cancer	6	7%
Gynecological Cancer (Clear Cell, Müllerian, Vulvar)	3	3%
Low Grade Serous Ovarian cancer (LGSOC)	15	17%
NUT Midline Carcinoma	2	2%
Primary Peritoneal Carcinoma	2	2%
Salivary Gland Tumor	1	1%
Sarcoma	19	21%
Thymic Tumor	2	2%
Uveal Melanoma	1	1%
Stages		
I	4	4%
II	4	4%
III	13	14%
IV	48	53%
Unknown	22	24%
Specimen Source		
Primary Tumor	31	34%
Distant Metastasis	55	60%
Unknown	5	6%
Specimen Anatomical Site		
Abdomen	11	12%
Ascites/Pleural Effusion	6	7%
Bladder	2	2%
Bone	2	2%
Brain/Spine	6	7%
Colorectal/Small bowel/Appendix	5	6%
GE Junction/Stomach	3	3%
Liver/Gallbladder	25	28%
Lung	5	6%
Omentum	2	2%
Ovary/Vulva	2	2%
Peritoneum	5	6%
Others/Unknown	17	19%

PDTC-based drug screening for Brain and Peripheral Nervous System Cancer, Cancer of Unknown Primary and Sarcomas

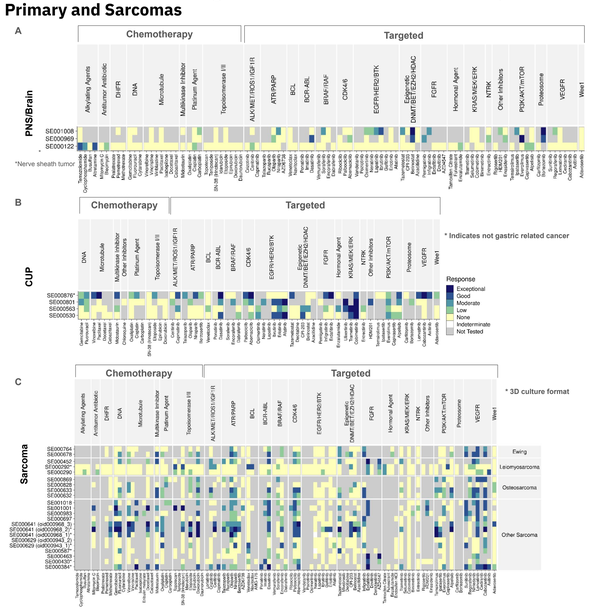

Figure 3. Distinctive drug sensitivity landscapes in PNS/brain, CUP, and sarcomas
A. PNS/Brain: Three treatment naïve samples showed distinct response patterns. A PNS-derived sample (SE000122) showed sensitivity to chemotherapies and moderate response to PI3K/AKT inhibitors. In contrast, both CNS-derived samples were chemoresistant but highly sensitive to targeted therapies (proteasome, PI3K/AKT/mTOR, FGFR, and ATR/PARP inhibitors). **B.** CUP: All samples were pretreated. Three gastric-related CUP samples showed clustered sensitivities to EGFR/HER2 and MAPK pathway inhibitors. The fourth sample (bladder cancer-related) displayed chemosensitivity alongside responsiveness to VEGFR, FGFR, and CDK4/6 inhibitors. Showing diagnosis based stratification. **C.** Sarcoma: Drug sensitivity profiling revealed common vulnerability to FGFR and VEGFR inhibitors across subtypes, while highlighting subtype-specific differences. Ewing sarcoma, leiomyosarcoma, and osteosarcoma samples were predominantly chemoresistant except to topoisomerase inhibitors. Ewing and osteosarcoma subtypes showed particular sensitivity to PARP inhibitors. VEGFR inhibitor sensitivity was most pronounced in 2D-cultured sarcoma samples.

Drug sensitivity profiling of Low grade serous ovarian cancers and gastrointestinal related cancers

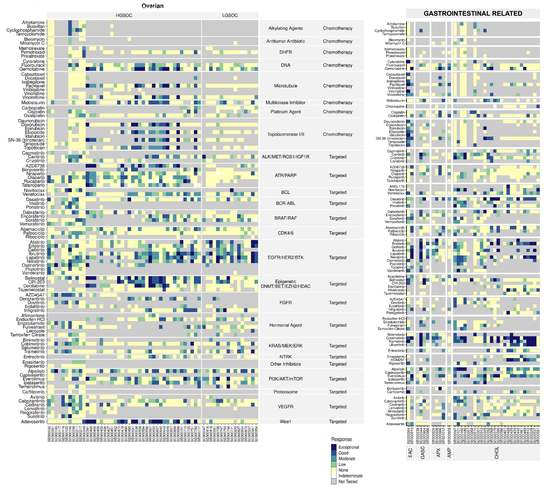

Figure 4.
A. Ovarian Cancers. Heatmap of PARIS test comparing 15 low-grade serous ovarian carcinomas (LGSOC) obtained at distinct time points against a representative group of high-grade serous ovarian carcinomas (HGSOC). While most LGSOC demonstrated sensitivity to various targeted therapies, only 3 exhibited any chemotherapy response, all with moderate sensitivity to gemcitabine. Common targeted pathway sensitivities included EGFR/HER2, BTK, MEK, mTOR, PI3K/AKT, BET, and BCL. These results demonstrate that the PARIS test not only recapitulates the known clinical resistance of LGSOC to most chemotherapies and PARP inhibitors (compared to HGSOC) but can also identify multiple targeted treatment options for nearly all patients.
B. GI-related Cancers. Heatmap showing ex vivo responses to all targeted drugs and chemotherapies tested in at least three organoid cultures. A total of 92% of organoid cultures exhibited a good to exceptional response (SPM 15-12) to at least one, and often more than one, FDA-approved targeted agent. In contrast, only very few cases and 10 chemotherapies showed good to exceptional responses, which include the standard of care BTC treatments cisplatin and gemcitabine. Gray rectangles indicate drugs that were not tested in that screen.

Case example of two distinct NUT midline carcinomas

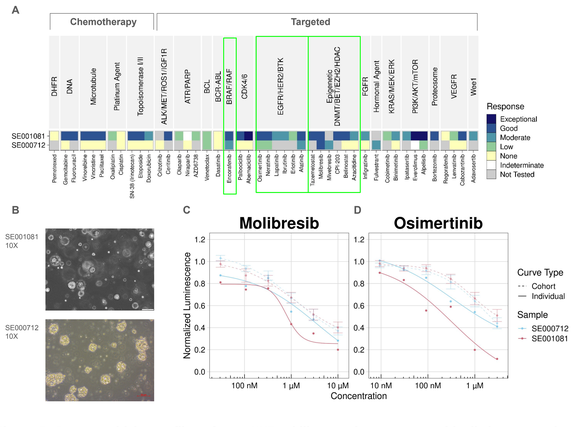

Figure 5. Drug sensitivity profiles of two NUT midline carcinoma cases with distinct genomic alterations. A. A heatmap demonstrates unique drug response patterns, with both cases showing sensitivity to EGFR inhibitors, RAF inhibitors, PI3K inhibitors, and epigenetic-targeting BET inhibitors. The heavily pretreated sample (SE000712, BRD3-NUTM1 fusion, which got SBRT radiation first, then secondary Carboplatin + Paclitaxel (replaced with Nab-Paclitaxel) + Ipilimumab + Nivolumab and thirdly before PARIS testing Ifosfamide + Etoposide + Vorinostat) displayed no chemotherapy responses compared to SE001081 (BRD4-NUTM1 fusion), which received only adjuvant therapies (Pembrolizumab + Cisplatin + Etoposide) and had still multiple chemotherapy response. **B.** Brightfield microscopy images of patient-derived tumor organoids from both cases at 10X magnification. Despite the limited sample size, two significant trends were observed for both stage IV, pretreated cases exhibited: **C.**marked sensitivity to BET inhibitors such as Molibresib, correlating with their genomic fusion profiles, and **D.** strong responsiveness to EGFR inhibitors, including Osimertinib, an irreversible EGFR-TKI capable of crossing the blood-brain barrier.

Case example of stage IV LGSOC

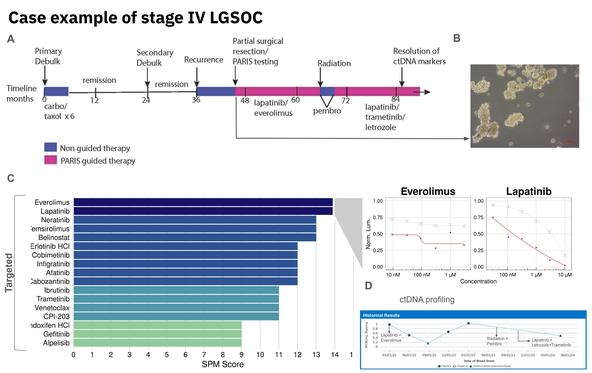

Figure 6. PARIS Test indicated future treatment options for a LGSOC case. A 40-year-old female was diagnosed with LGSOC (stage IIIB) involving the omentum and peritoneum. Four years after diagnosis and initial treatments, tissue was obtained via surgical resection for PARIS testing. Sequencing revealed no actionable alterations. The patient has been on PARIS-guided treatment for >34 months except for a brief 3-month pause to receive radiation and immunotherapy. Currently the patient's ctDNA is undetectable, consistent with near complete response. **A.** The patient's disease timeline indicating the PARIS Test and prospective treatments. **B.** Bright field images of PDTC. **C.** Drug sensitivity assay indicates multiple top scoring drugs as potential treatments. Lapatinib and Everolimus drug curves were shown here. **D.** A recent ctDNA test report indicates a level below the analytical range, that correlates with the personalized treatments exposure.

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