Clinical Utility and Accessibility of Functional Precision Medicine for Relapsed/Refractory Pediatric and Adult Cancers

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BACKGROUND

Pediatric and adult patients with rare, relapsed, or refractory cancers often have few treatment options. Precision medicine approaches are often used to identify options when standard treatments fail. Despite the significant clinical benefit to advanced cancer patients, genomics precision medicine trials have revealed important constraints for patients that lack treatments matched to biomarkers, highlighting challenges in drug accessibility associated with novel targeted therapies. Current clinical findings from large-scale studies show ~10% of cancer patients receive benefit from genomics-guided therapies - in part due to limited insight into the complex relationship between molecular characteristics and patient response. Implementing functional precision medicine (FPM)—the integration of ex vivo drug screening and mutation profiling—can provide treatment options complementary to or independent of genomics-informed biomarkers. We have completed enrollment of FPM studies through three studies, and we are currently enrolling advanced cancer patients for FPM feasibility studies from pediatric/adolescent populations through Nicklaus Children's Hospital (NCT05857969, n = 65 patients) and adult populations through Cleveland Clinic Florida (NCT06024603, n = 36 patients).

METHODS

Overview of the Functional Precision Medicine (FPM) Program

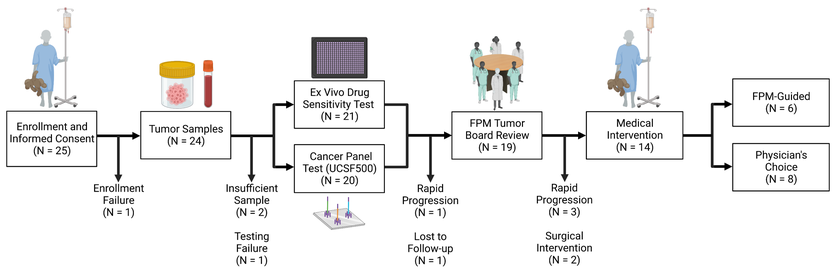

Figure 1: Functional precision medicine in the management of recurrent childhood cancers. Illustration of our functional precision medicine program depicting workflow, beginning with sample collection and processing, followed by establishment of patient-derived tumor cells that are subjected to single drug testing. In parallel, DNA is sent for targeted gene sequencing (UCSF500). Drug Sensitivity Scores (DSS) are reported back to the Molecular Tumor Board (MTB) within 5-10 days while sequencing data take up to 3 weeks. The MTB review the data, likely off-label availability for candidate drugs, prior experience with candidate drugs, and treatment history of each patient. A final list of therapeutic options (ranked in order of preference together with suggested doses and schedules) is issued, and patients are treated with the "best" recommendations whenever possible. 25 participants were enrolled, and tumor was excised from 24 participants. Drug testing was performed using a comprehensive drug library encompassing 40 formulary drugs frequently used at Nicklaus Children's Hospital, 47 non-formulary drugs approved by the U.S. Food and Drug Administration (FDA) for cancer treatment, as well as drugs from phase III/IV clinical trials. The library can be adapted to the formulary at any hospital or treatment center.

FPM Feasibility Study Testing Results

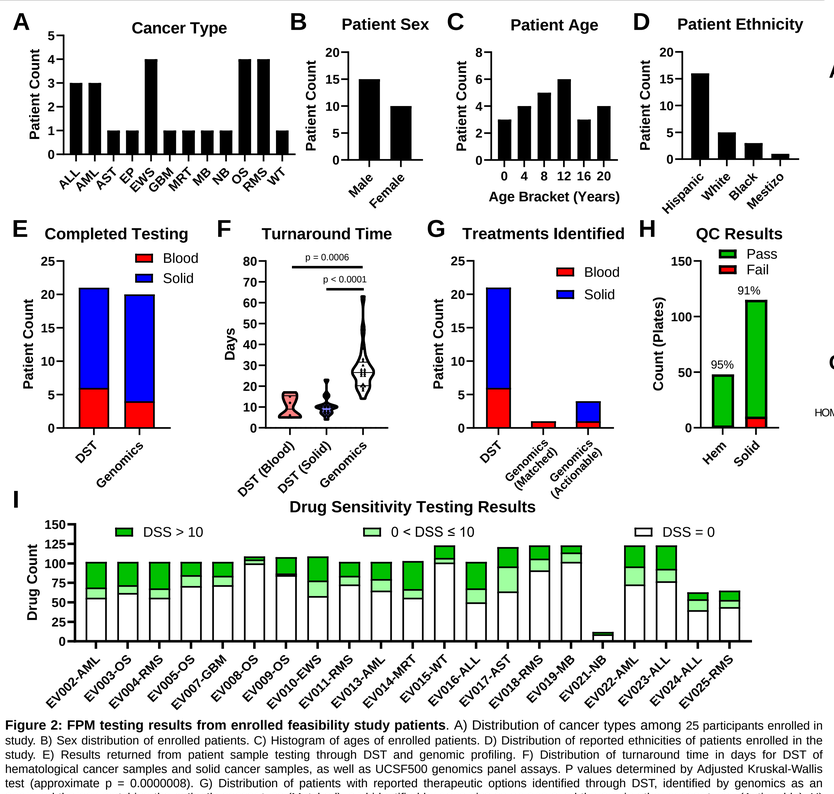

Figure 2: FPM testing results from enrolled feasibility study patients. A) Distribution of cancer types among 25 participants enrolled in study. B) Sex distribution of enrolled patients. C) Histogram of ages of enrolled patients. D) Distribution of reported ethnicities of patients enrolled in the study. E) Results returned from patient sample testing through DST and genomic profiling. F) Distribution of turnaround time in days for DST of hematological cancer samples and solid cancer samples, as well as UCSF500 genomics panel assays. P values determined by Adjusted Kruskal-Wallis test (approximate p = 0.0000008). G) Distribution of patients with reported therapeutic options identified through DST, identified by genomics as an approved therapy matching the patient's cancer type (Matched), and identified by genomics as an approved therapy in other cancer types (Actionable). H) Number and percent of DST plates that passed QC analysis for hematological and solid cancers. I) Distribution of DSS for each patient (ineffective, DSS = 0 [white]; moderately effective, 0 < DSS ≤ 10 [light green]; effective, DSS > 10 [dark green]).

RESULTS

FPM-Guided Treatment Regimens Resulted in Improved Responses

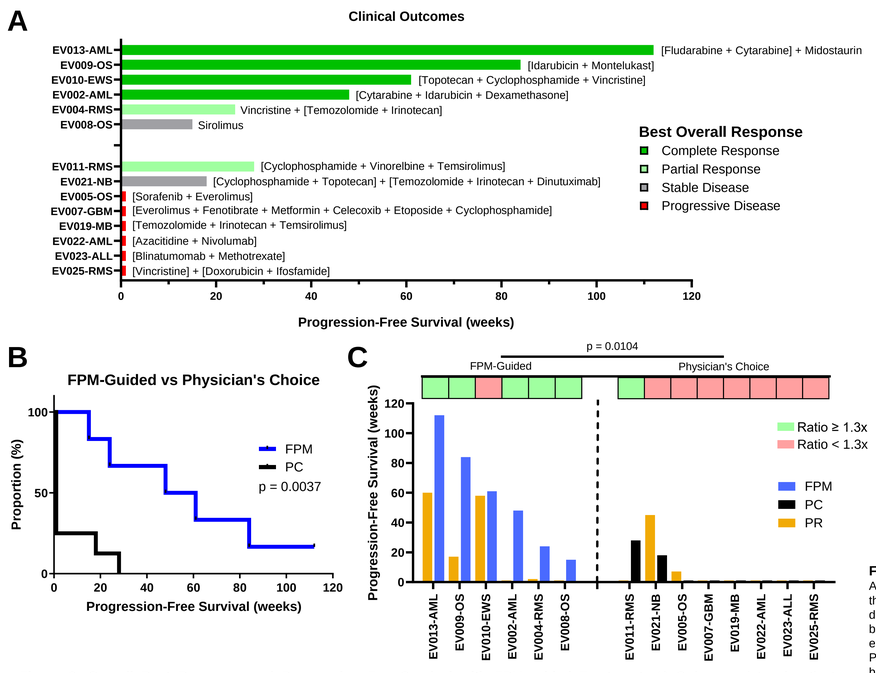

Figure 3: Overall Best Response and Progression Free-Survival with FPM-guided Treatment. A) Swimmer plots of patient progression-free survival, objective response, and associated treatment provided during the study. B) Kaplan-Meier plots showing progression-free survival of patients provided standard of care (black) compared to FPM-guided regimens (blue). Patients guided by FPM data had significantly improved progression-free survival vs. standard of care patients (p = 0.0037). C) Progression-free survival for previous regimen (yellow) vs. treatment provided during trial enrollment for FPM-guided patients (blue) and patients guided by standard of care (black). Green squares indicate patients with ≥ 1.3x PFS2/PFS1 ratio. Significantly more patients received PFS2/PFS1 ≥ 1.3x (p = 0.0104), with the median PFS2/PFS1 ratio = 8.5x.

Multi-Modal Validation of Patient-Derived Culture Models

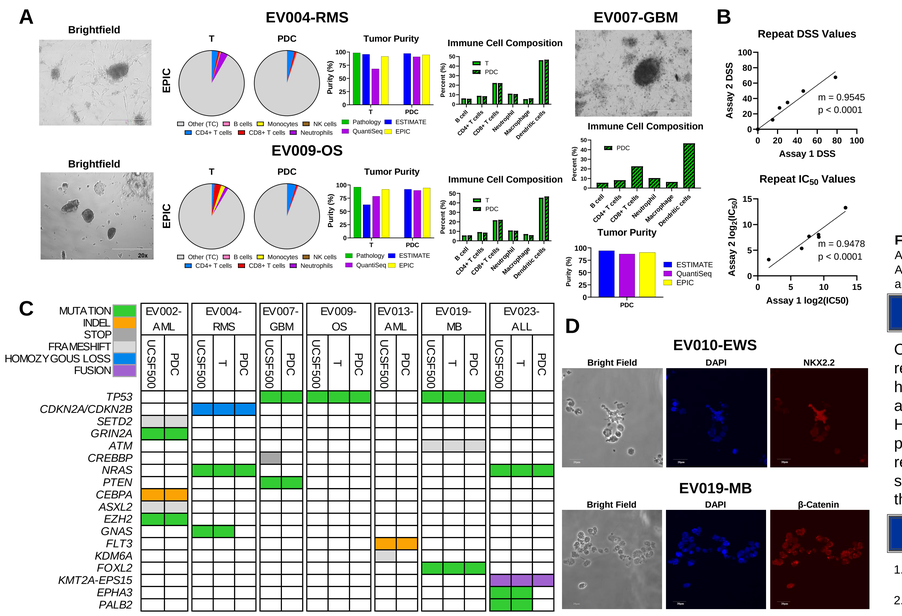

Figure 3: Characterization and validation of patient-derived cultures. A) Brightfield, immune cell analysis, tumor purity analysis and immune cell composition of patient-derived cultures. Patient-derived cultures retain immune cell populations present in the original tissue analyzed at time of tumor sampling and pathology review. Tumor purity measures through multiple bioinformatics pipelines demonstrates concordance of tumor purity of patient-derived cultures with tumor cell content at time of pathology review Cultures develop both two-dimensional and three-dimensional characteristics representing the complex morphology and environment of solid cancers. Cultures represent patient-derived models of RMS, OS, and GBM. B) DSS and IC50 values from repeated drug sensitivity testing experiments. Repeated experiments demonstrate high correlation, showing consistency of drug sensitivity testing results. C) Molecular profiling of patient-derived cultures to validate retention of genetic characteristics identified through UCSF500 tumor panel sequencing. Derived models show molecular characteristics consistent with tumors at time of sampling. D) Immunofluorescence analysis of patient-derived cultures to identify presence of key pathology markers identified during pathology review.

RESULTS (cont)

Patient Sample Characteristics and Clinical Correlations

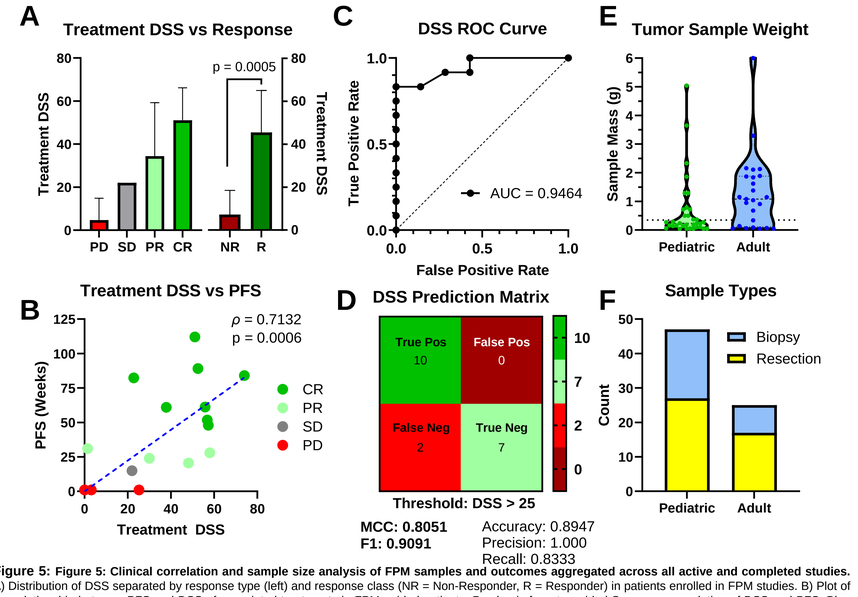

Figure 5: Figure 5: Clinical correlation and sample size analysis of FPM samples and outcomes aggregated across all active and completed studies. A) Distribution of DSS separated by response type (left) and response class (NR = Non-Responder, R = Responder) in patients enrolled in FPM studies. B) Plot of the relationship between PFS and DSS of associated treatments in FPM-guided patients. P value is from two-sided Spearman correlation of DSS and PFS. Blue dashed line represents a line of simple linear regression. C) Receiver operating characteristic (ROC) curve of true positive rate and false positive rate of DSS-based response prediction at optimal threshold (DSS > 25). D) Confusion matrix and associated statistical values of DSS predicted and actual OR in patients enrolled and tracked in FPM studies at optimal threshold (DSS > 25). Prediction performance metrics (Accuracy, Precision/Positive Predictive Value, Negative Predictive Value, Recall, MCC, F1) are provided below the confusion matrix. E) Sample sizes of patient solid tumor tissues by mass. F) Count of patients providing biopsy and resection samples across all clinical studies.

The Evolution of FPM through Deep Sequencing and AI/ML Analysis

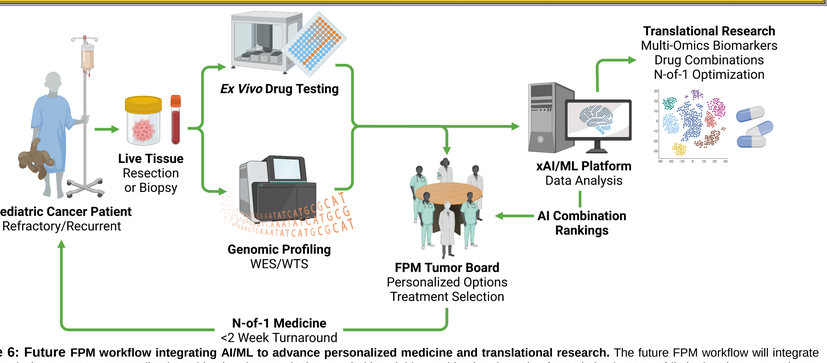

Figure 6: Future FPM workflow integrating AI/ML to advance personalized medicine and translational research. The future FPM workflow will integrate AI/ML analysis to support personalized combination therapy design to prioritize viable combination therapies for optimized usage of limited patient tumor tissue. AI/ML analysis will be performed both on individual patient datasets and will leverage prior patient FPM data in future advancements to the FPM workflow. AI/ML analysis will support translational research around biomarker development, combination therapy development, and advancement of n-of-1 therapeutic strategies.

CONCLUSIONS

Our study shows technical feasibility of integrating functional precision medicine approaches for patients with refractory/relapsed pediatric cancers. Routine clinical integration of FPM for treatment selection is technically feasible and has led to improved outcomes in pediatric cancer patients with refractory disease in an initial patient cohort. We are enrolling advanced cancer patients for FPM feasibility studies from pediatric/adolescent populations through Nicklaus Children's Hospital (NCT05857969, n = 65 patients) and adult populations through Cleveland Clinic Florida (NCT06024603, n = 36 patients). Inclusion of patient tissue samples procured via fine-needle or core biopsy techniques, in addition to surgical resections, enables access to FPM approaches for patients where surgical resection is not viable or considered part of standard of care. We are currently undergoing CLIA validation for the drug sensitivity testing assay in the FPM program, with the goal of initiating large-scale randomized clinical trials, and provide treatment options to patients nationally and globally.

REFERENCES

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2. Acanda De La Rocha AM, Fader M, Coats ER, et al. Clinical utility of functional precision medicine in the management of recurrent/relapsed childhood rhabdomyosarcoma. *JCO Precis Oncol.* 2021;5:PO.20.00438. doi:10.1200/PO.20.00438. PMC8563073.

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