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Short communication

Beyond genomics: functional precision medicine for personalized cancer therapy

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Introduction

Precision medicine has revolutionized cancer care by enabling the selection of treatments based on the molecular characteristics of individual tumors. Despite major advances in genomic profiling technologies, actionable genomic alterations are identified only in a subset of patients, and genomic information alone often fails to accurately predict treatment response. Functional precision medicine (FPM) has emerged as a complementary approach that directly measures the sensitivity of patient-derived cancer cells to therapeutic agents, providing real-time information on drug efficacy at the individual patient level.

FPM involves exposing patient-derived tumor cells to a panel of approved and investigational small molecules and quantifying cellular responses. The resulting drug response patterns provide information about tumor vulnerabilities that may not be apparent from genomic analyses alone, capturing the integrated effect of all genomic and non-genomic factors on drug sensitivity to support personalized therapeutic decision-making. This strategy is particularly attractive in hematological malignancies, where viable patient samples can be readily obtained and analyzed. Recent technological developments have enabled the implementation of high-throughput drug screening platforms capable of evaluating hundreds of compounds and drug combinations within clinically relevant timeframes at single-cell resolution.

Clinical evaluation of FPM demonstrates feasibility and survival benefit

EXALT-1

Over the past decade, functional drug screening technologies have advanced from experimental platforms to clinically applicable decision-support tools. The EXALT clinical trial program was established to evaluate the feasibility and clinical utility of FPM in patients with aggressive hematological malignancies.

The prospective EXALT-1 trial represented the first interventional study demonstrating clinical benefit from FPM-guided therapy selection in advanced blood cancers (Kornauth et al., 2022). Treatment recommendations were generated using ex vivo functional drug sensitivity testing of patient-derived tumor cells and reviewed by a multidisciplinary molecular tumor board. The primary endpoint of the study was the progression-free survival (PFS) ratio, defined as the ratio between PFS achieved on the FPM-guided treatment (PFS2) and PFS achieved on the patient's most recent prior therapy (PFS1). A PFS ratio greater than 1.3 was considered indicative of meaningful clinical benefit, allowing each patient to serve as their own control.

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Approximately 200 patients were screened, 143 tested, of which 76 were evaluable, and 56 were treated based on FPM results. Importantly, 30 out of 56 patients (54%) from the primary analysis set reached a PFS ratio of ≥1.3 with a median PFS ratio of 3.4. Twelve patients exhibited an exceptional response (defined as tripled PFS duration compared to the expected response duration of the respective disease entity). EXALT-1 was the first precision medicine cancer trial using a direct functional test to instruct n-of-one therapies.

EXALT-2

Building on the results of EXALT-1, the multicentric prospective randomized EXALT-2 trial was initiated to directly compare FPM, genomic precision medicine, and physician-guided treatment decisions in patients with relapsed or refractory blood cancers (Kazianka et al., 2025). The study represents one of the first efforts to systematically evaluate different precision medicine strategies within a single clinical framework. Recent feasibility analyses demonstrated successful implementation of the precision medicine workflow across multiple academic centers. Diagnostic profiling was completed in nearly all enrolled patients, generating clinically actionable treatment recommendations in the majority of cases. Importantly, both functional and genomic approaches proved feasible within clinically relevant timelines, supporting their integration into routine clinical workflows. The study aims to enroll 150 patients.

The EXALT-2 study assesses the potential of functional drug testing to guide personalized treatment decisions in real-world clinical practice. While comprehensive genomic profiling identifies molecular alterations and potential therapeutic targets, functional drug screening directly measures treatment response at the phenotypic level. The integration of these methodologies may provide a more complete understanding of tumor biology and therapeutic vulnerabilities than either approach alone.

Future perspectives

The transition from EXALT-1 to EXALT-2 illustrates the rapid development of FPM from proof-of-concept studies toward multicenter international clinical implementation. Future efforts will focus on prospective validation of clinical benefit, integration of multimodal molecular and functional datasets, and development of standardized in vitro diagnostic platforms capable of supporting routine therapeutic decision-making.

As precision oncology continues to evolve, functional drug sensitivity testing may become an essential component of personalized cancer care, particularly for patients with advanced cancer where conventional treatment options remain limited.

Conclusion

We and others have demonstrated that FPM can be successfully integrated into clinical decision-making for patients with advanced hematological malignancies. The EXALT-2 trial confirmed the feasibility of implementing FPM in a multicenter setting and provided a framework for comparing functional and genomic precision medicine strategies. Together, these studies support the clinical utility of functional drug screening while underscoring the need for larger prospective trials to generate high-level evidence required for routine implementation.

Beyond treatment selection, FPM can uncover unexpected therapeutic vulnerabilities and opportunities for drug repurposing, revealing clinically relevant applications for existing compounds outside their conventional indications. As functional and molecular approaches become increasingly integrated, FPM has the potential to become an important component of personalized cancer care and to accelerate the translation of biological insights into improved patient outcomes.

References

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