



CASCADe 2027 NON-CONFIDENTIAL SUMMARY »

HRDefine: A Clinical Test to Expand Treatment Options for Ovarian and Triple-Negative Breast Cancer Patients

Overview

PARP inhibitors are among the most effective precision therapies available for certain cancers, but current methods for identifying eligible patients often rely on genomic scar measurements that reflect historical DNA repair defects rather than a tumor's current biology. HRDefine is a molecular diagnostic developed at the University of Washington that combines mutation and methylation biomarkers associated with homologous recombination deficiency (HRD) to help identify patients who may benefit from PARP inhibitor therapy. By assessing biologically relevant drivers of HRD, HRDefine is intended to provide a clinically actionable assessment of a tumor's DNA repair status and identify patients not recognized through conventional BRCA mutation testing alone.

Description

HRDefine is a molecular diagnostic developed for oncology applications, initially focused on high-grade serous (tubo-)ovarian cancer, with active validation underway in triple-negative breast cancer (TNBC). The assay combines mutation profiling with quantitative methylation analysis to identify tumors with homologous recombination deficiency (HRD). By evaluating both genetic alterations and methylation-associated gene silencing, HRDefine can detect biologically relevant drivers of HRD that may not be identified through mutation testing alone. Integrating these complementary biomarkers is intended to provide a clinically actionable assessment of tumor DNA repair status and support patient selection for PARP inhibitor therapy.

Proof-of-concept evidence comes primarily from the ARIEL2 clinical trial, in which patients identified as HRD-positive by HRDefine criteria had treatment response measures statistically similar to those of patients with BRCA mutations when treated with a PARP inhibitor. In an independent cohort of several hundred ovarian cancer samples, methylation status measured by the assay showed high concordance with an earlier qualitative methylation test and correlated with an orthogonal genomic HRD measure. The research team has also shown that methylation status can change over the course of treatment. This may represent a mechanism of therapeutic resistance that static, scar-based tests are not designed to detect, underscoring the potential value of a real-time, quantitative assay such as HRDefine.

Current development is focused on completing laboratory validation of the assay, pursuing Washington State medical diagnostic licensure, and validating HRDefine's predictive value across

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several large, completed randomized controlled PARP inhibitor trials in ovarian cancer representing more than 3,000 patients. A parallel effort, led by Fred Hutch/UW Medicine breast oncology researchers Dr. Lynn Symonds and Dr. Jennifer Specht, is launching a validation study of HRDefine in hundreds of TNBC samples, with the goal of expanding PARP inhibitor eligibility beyond the small fraction of TNBC patients who carry inherited BRCA1/BRCA2 mutations.

Technology Readiness Level (TRL)

TRL 5 for the ovarian cancer application — System or subsystem components have been tested in a relevant environment that models real-world conditions. Analytical development has been completed and the assay has been evaluated using clinical and archival patient samples; additional validation and regulatory activities are ongoing prior to clinical deployment. The TNBC application is at an earlier stage, with a dedicated validation study in hundreds of samples now launching.

Value Proposition

- **Expands eligible patients:** Identifies additional ovarian cancer and TNBC patients who may benefit from PARP inhibitor therapy beyond those identified through BRCA mutation testing alone.
- **Real-time biology:** Is designed to reflect a tumor's current DNA-repair function rather than a historical “scar,” with the potential to improve accuracy as tumors evolve or develop resistance.
- **Practical and low-cost:** Uses a low-cost assay format compatible with routine clinical laboratory workflows and standard formalin-fixed tumor tissue already collected in clinical practice.
- **Addresses a significant underserved market:** Is intended to expand testing options in TNBC, where only about 5% of patients currently qualify for PARP inhibitor therapy despite evidence that HRD is present in a substantially larger fraction of TNBC tumors, and in ovarian cancer, where quantitative BRCA1/RAD51C methylation testing is not widely available.
- **Platform potential:** May have applicability beyond ovarian and breast cancer in other HRD-associated cancers, including prostate and pancreatic cancer, as supporting validation data emerge.

Intellectual Property Position

Patent application pending.

Market Opportunity

- **Primary customers:** Clinical and reference diagnostic laboratories, academic medical center pathology departments, and oncology practices seeking improved patient selection for PARP inhibitor and platinum chemotherapy treatment decisions.
- **Pharmaceutical partners:** Companies developing PARP inhibitors and other DNA-repair-targeted therapies represent a strategic partnership and licensing audience, given their need for patient-selection biomarkers.
- **Differentiation opportunity:** Existing HRD testing approaches rely largely on genomic scar measurements or research-use-only genomic algorithms, creating a potential differentiation opportunity for HRDefine as a clinically deployable, quantitative assay.

- **Unmet need in TNBC:** Oral PARP inhibitors are currently available only to the roughly 5% of TNBC patients with inherited BRCA1/BRCA2 mutations, despite most TNBC tumors carrying HRD, representing a substantial underserved patient population and commercial opportunity.
- **Future applications:** As PARP inhibitors and related DNA-repair-targeted drugs move toward expanded indications across ovarian, breast, prostate, and pancreatic cancers, demand for a more precise patient-selection biomarker is expected to grow.

References

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