The Homologous Recombination Deficiency (HRD) Project
In normal cells, proteins like PARP1 and BRCA help repair DNA. In cells with mutated BRCA, DNA repair is altered leading to genetic instability and cancer. Use of a PARPi causes the cell to recognize the damage and go through cell death (apoptosis). There are other proteins besides BRCA involved in the HRR pathway that, if altered, may benefit from treatment with PARPi. Identifying patients whose tumors foster these alterations, also called Homologous Repair Deficiency (HRD), will lead to improved response. Currently, assays measure HRD differently.
Homologous recombination deficiency (HRD) is a complex biomarker that helps identify whether patients may respond to certain treatments.

Currently, there is no standardized way to define, measure, and report HRD.

A unique research partnership to develop alignment strategies among different methods for measuring HRD and aligning around its use as a biomarker in clinical care.

<table>
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<th>The Definition</th>
<th>The Problem</th>
<th>The Solution</th>
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<td>This type of biomarker has promise in identifying patients with certain cancers who are more likely to benefit from PARP inhibitors and additional DNA repair targeting drugs.</td>
<td>A few NGS-based HRD assays are currently available, and these use different approaches to measure HRD. But there is no agreement on what parameters contribute to the determination of a sample’s HR status.</td>
<td>Friends has assembled a consortium of project partners from key healthcare sectors to address concerns about the lack of consistency in determining HRD status, its prognostic value, and its use as a predictive biomarker.</td>
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HRD Harmonization Project

**Overall Goal:** To harmonize the way HRD is defined, measured, and reported to better identify and care for patients who are most likely to benefit from targeted therapies.

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<th>Workflow</th>
<th>Phase 1: Discovery and Definition</th>
<th>Phase 2: Assay Alignment</th>
<th>Phase 3: Clinical Contextualization</th>
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| **Objectives** | • To refine the way HRD is utilized  
• To better understand how HRD calls are determined  
• To propose common language around the use of HRD | • To understand the level of variability across HRD assays  
• To identify opportunities for harmonization  
• To propose best practices for HRD assay alignment and use | • To explore how disease context impacts association between HRD and clinical outcome  
• To identify approaches for the development of clinical evidence to evaluate HRD |
| **Approach** | Developed a landscape analysis of HRD aimed to identify how HRD is used, define how HRD calls are made, and propose common language around the use of HRD. | Working through an analysis plan including multiple diagnostics companies to identify variability in HRD assays and opportunities for harmonization. | Report findings from Phase 2 for clinicians and patients, and develop an analysis plan to evaluate impacts of HRD testing on clinical efficacy. |
## Project Approach

### HRD Harmonization Project

*Do HRD assays report different HR statuses? If so, why might this variation exist?*

- Describe the variation in HRD assays, then explore potential sources of variation

### TCGA– In Silico Analysis

- 348 ovarian cancer files
- DNA Nexus deidentified files and shared with diagnostics developers
- Developers ran their HRD assays on in silico files
- NCI stats team compared assays

### Patient Sample Analysis

- ~125 freshly sectioned ovarian cancer samples
- Fredrick National Laboratory will extract and distribute DNA/RNA
- Developers will run their HRD assays on samples
- NCI stats team will compare assays

*We lack a “gold standard” for HRD – focus on observed variability in assays*
Analysis Strategy Overview

**Primary Analysis**

**Descriptive analysis describing concordance**
HRd vs. HRp

**Secondary/Exploratory Analysis**

- Model based analyses
  Association of assay factors with HR Status

- Analysis of continuous scores
  HRD & %gLOH

- Clinical performance
  Platinum sensitivity
  *(Patient samples only)*

**Additional General Analyses**

- Gene-specific mutation analysis
  A descriptive, qualitative analysis considering how gene mutations relate to HR status calls
  *(Patient samples only)*

- BRCA 1/2 mutation status
  Report the frequency of mono vs. biallelic BRCA mutations