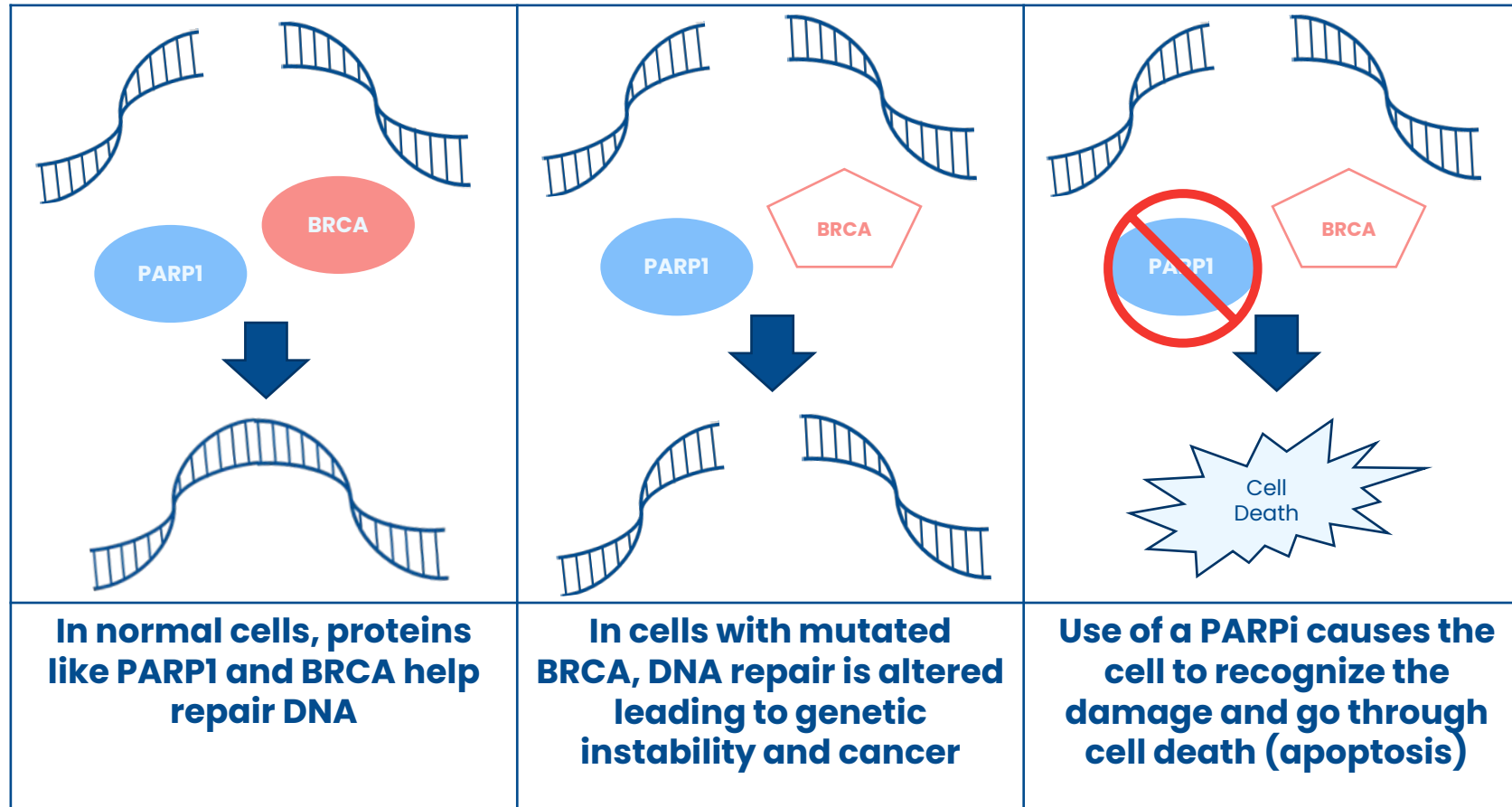




# The Homologous Recombination Deficiency (HRD) Project

# HRD Harmonization Project

## BRCA is involved in Homologous Recombination Repair (HRR)



There are other proteins besides BRCA involved in the HRR pathway that if altered cancer, 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.**

# HRD Harmonization Project

The Definition	The Problem	The Solution
<p><b>Homologous recombination deficiency (HRD) is a complex biomarker that helps identify whether patients may respond to certain treatments.</b></p> <p>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.</p>	<p><b>Currently, there is no standardized way to define, measure, and report HRD.</b></p> <p>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.</p>	<p><b>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.</b></p> <p><i>Friends</i> 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.</p>

# 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.

Workflow	Phase 1 Discovery and Definition	Phase 2 Assay Alignment	Phase 3 Clinical Contextualization
<b>Objectives</b>	<ul style="list-style-type: none"> <li>• To refine the way HRD is utilized</li> <li>• To better understand how HRD calls are determined</li> <li>• To propose common language around the use of HRD</li> </ul>	<ul style="list-style-type: none"> <li>• To understand the level of variability across HRD assays</li> <li>• To identify opportunities for harmonization</li> <li>• To propose best practices for HRD assay alignment and use</li> </ul>	<ul style="list-style-type: none"> <li>• To explore how disease context impacts association between HRD and clinical outcome</li> <li>• To identify approaches for the development of clinical evidence to evaluate HRD</li> </ul>
<b>Approach</b>	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

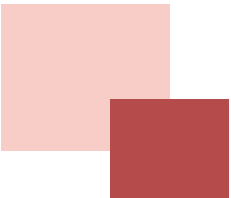
## TCGA- In Silico Analysis

- 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

