HRD Harmonization Project Findings

February 1, 2024

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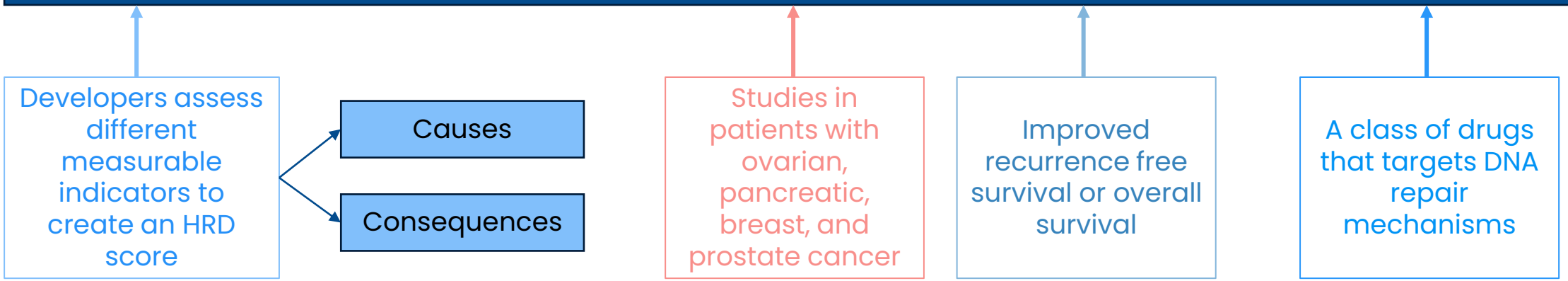
Friends of Cancer Research

Homologous Recombination Deficiency

A complex biomarker that helps identify patients who might benefit most from a PARP inhibitor.



Challenges

- The complexity of the biomarker leads to different definitions of what constitutes HRD
- Different assays have different cutpoints or thresholds leading to inconsistency in how HRD is measured and interpreted
- Variability in HRD measurements may impact treatment decisions and ultimately patient outcomes

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HRD Harmonization Project

Are HRD assay results consistent across different assays, and what factors contribute to any observed variability?

Phase 1
Discovery and Definition

Landscape assessment published in the *Oncologist*

JOURNAL ARTICLE

Homologous Recombination Deficiency: Concepts, Definitions, and Assays

Mark D Stewart, Diana Merino Vega, Rebecca C Arend, Jonathan F Baden, Olena Barbash, Nike Beaubier, Grace Collins, Tim French, Negar Ghahramani, Patsy Hinson ... Show more

The Oncologist, Volume 27, Issue 3, March 2022, Pages 167–174, https://doi.org/10.1093/oncolo/oyab053

Published: 27 January 2022 **Article history**

Phase 2
Assay Alignment

Analysis of HRD assays assessing shared datasets

- In Silico Analysis
- Clinical Analysis

Phase 3
Clinical Contextualization

Interpreting and sharing findings

- AMP Conference 2022
- AACR OvCa Conf. 2023
- *Friends* Public Meeting
- Publication forthcoming

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Study Design

Distribute freshly extracted nucleic acids from 90 archival ovarian cancer samples

↓

Assay developers *independently sequenced* samples then measured and reported HRD

↓

NCI Biometric Research Program compared results to determine level of agreement

↓

The HRD Harmonization Working Group reviewed and aligned on findings

We lack a "gold standard" for HRD – focused on observed variability in assays

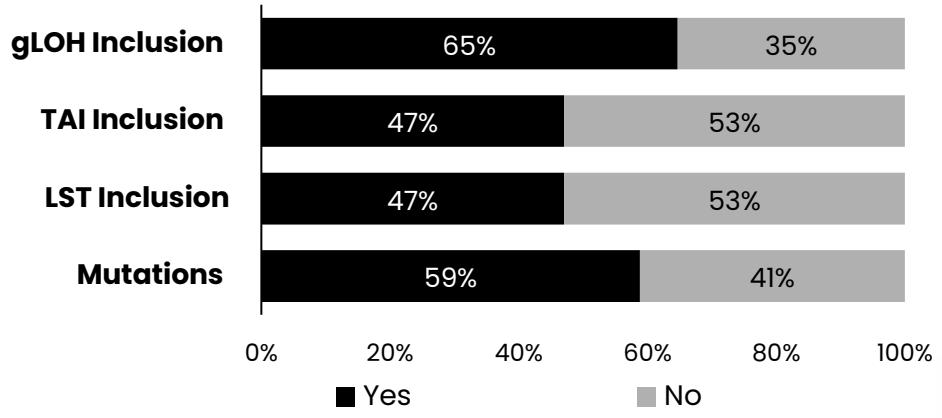
Sample Characteristics (n=90)

- Stage III or IV high grade serous ovarian cancer
- Treatment-naïve, subsequently treated with platinum-based chemotherapy

Assay Characteristics (n=17)

- All assessed *BRCA1* and *BRCA2* mutations to define HRD
- Cutoffs for HRD and range of values reported varied

Distribution of Assay Factors Used to Define HRD



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Assessing Concordance

Positive Percent Agreement (PPA)

The percentage of samples that test ***positive*** by one test (Assay A) that are found ***positive*** by a second test (Assay B).

Also calculated:

Negative Percent Agreement (NPA)

Average Positive percent Agreement (APA)

Average Negative percent Agreement (ANA)

HRD = Positive
Not HRD = Negative

EXAMPLE

Patient	1	2	3	4	5	6	7
Assay A	HRD	HRD	Not	HRD	HRD	Not	Not
Assay B	HRD	HRD	HRD	Not	Not	Not	Not
Assay C	HRD	HRD	Not	Not	Not	HRD	Not

Agreement analyses performed over all possible combinations of samples and assays.

Comparison	PPA
A to B	50%
B to A	66%
A to C	50%
C to A	66%
B to C	66%
C to B	66%

FDA Guidance: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

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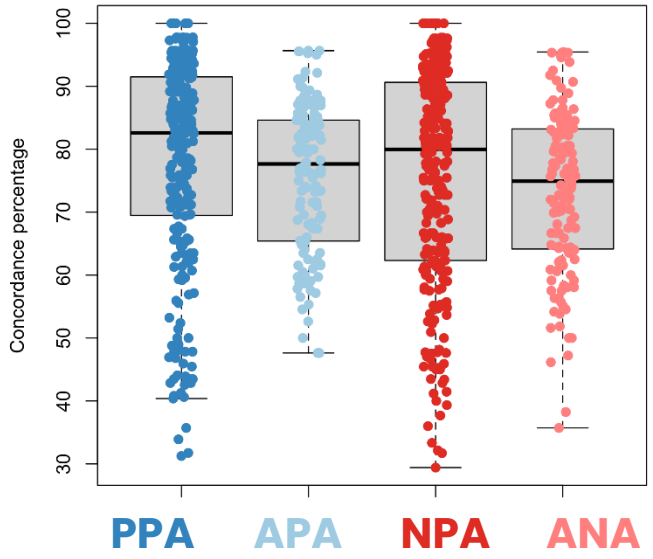
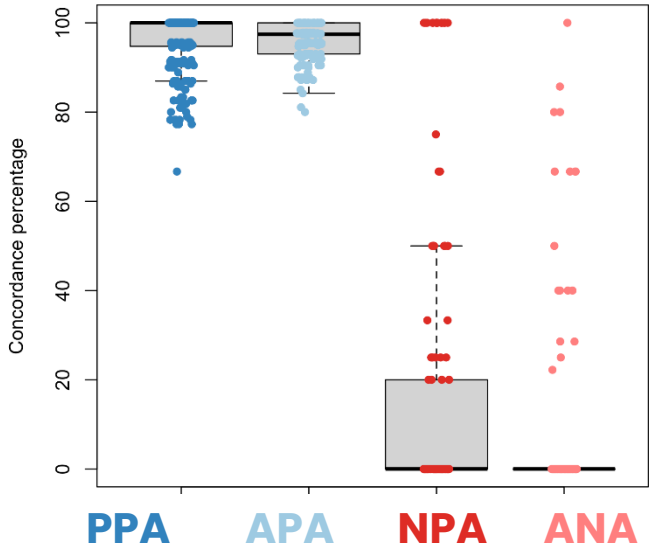
Concordance for HRD Calls

All Samples (n=90)



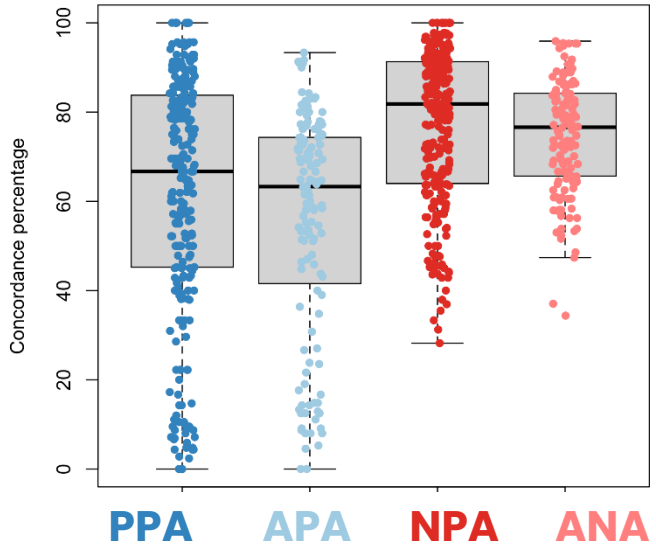
	PPA	APA	NPA	ANA
Median (IQR)	83 (71-91)	78 (65-85)	80 (62-91)	75 (64-83)

Mutated *BRCA1* and *BRCA2* (n=23)



PPA	APA	NPA	ANA
100 (95-100)	97 (93-100)	0 (0-20)	0 (0-0)

Wild-Type *BRCA1* and *BRCA2* (n=67)



PPA	APA	NPA	ANA
67 (45-84)	63 (42-74)	82 (64-91)	77 (66-84)

Agreement is moderate overall.

Agreement is better for samples with mutated *BRCA1* and *BRCA2* compared to WT *BRCA1* and *BRCA2*.

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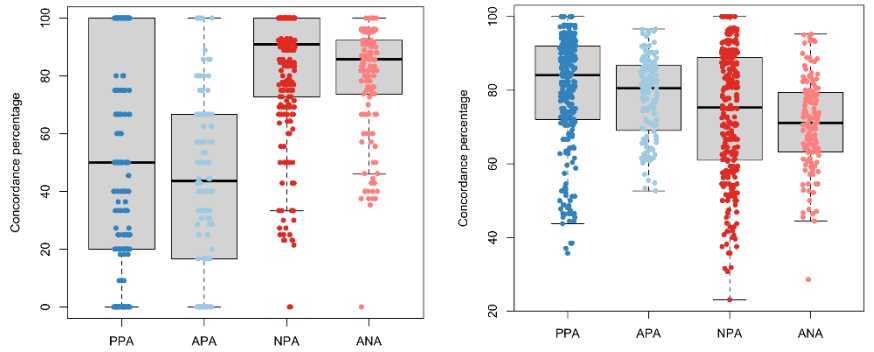
Factors Associated with Agreement

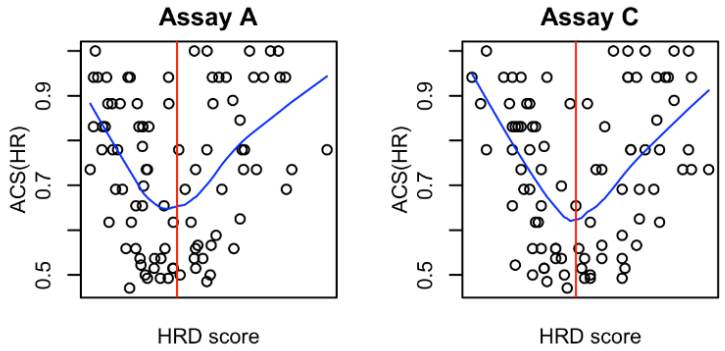
Category	Factors Assessed
Clinical	CCNE1 Amplification
	Race
	Debulking Status
Sample	Tumor Purity
	DNA Quality
	Age of Block
Assay	Use (RUO vs. Clinical)
	HRD Cutoff

CCNE1 Amplified (n=14 samples)

CCNE1 Non-Amplified (n=76 samples)



Samples with CCNE1 amplification have better agreement for not HRD calls.



Less agreement near HRD cutoff.

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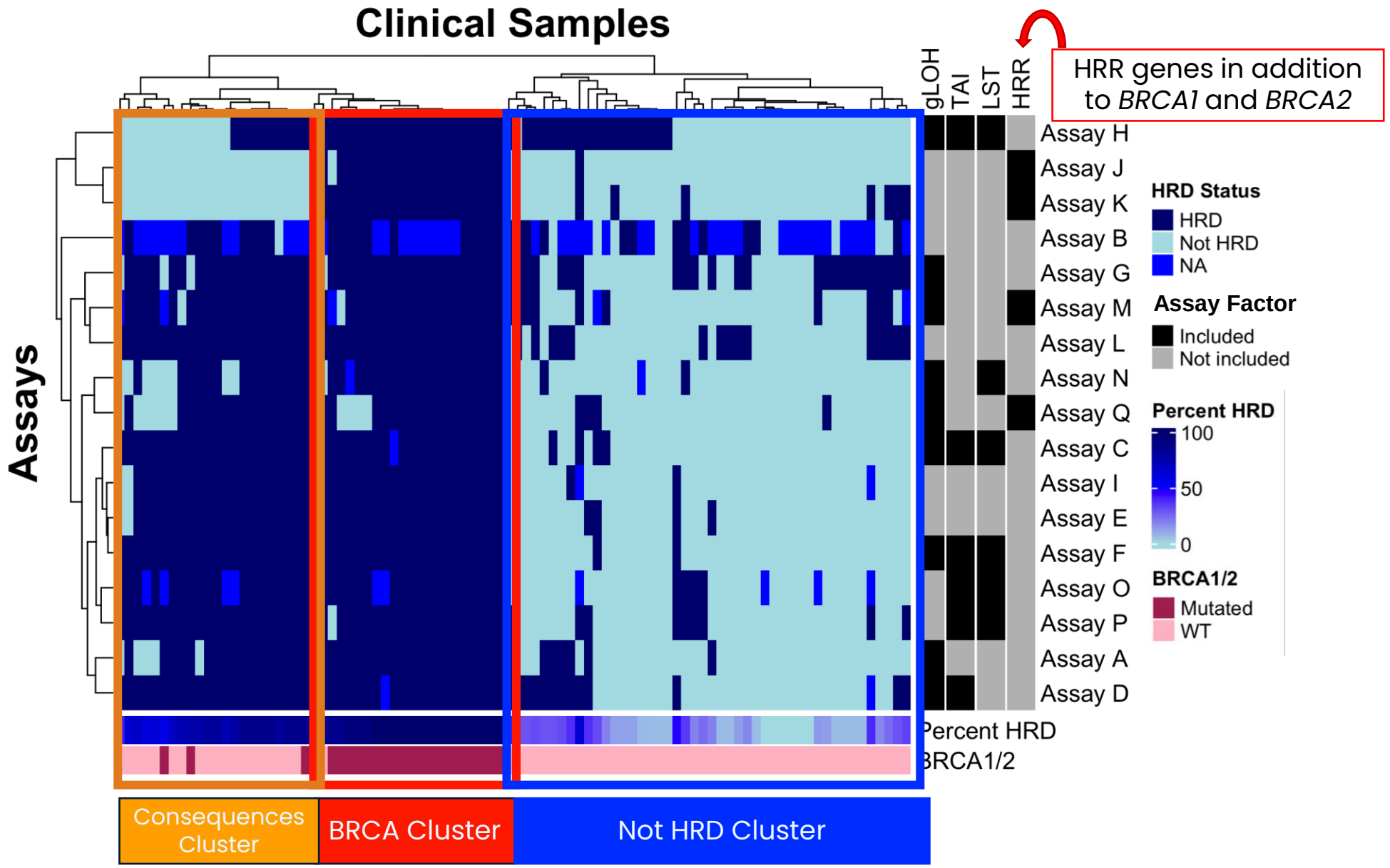

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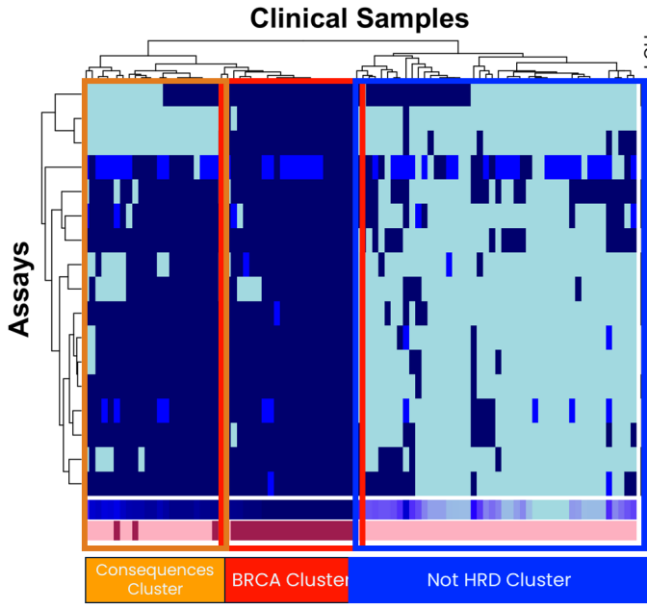
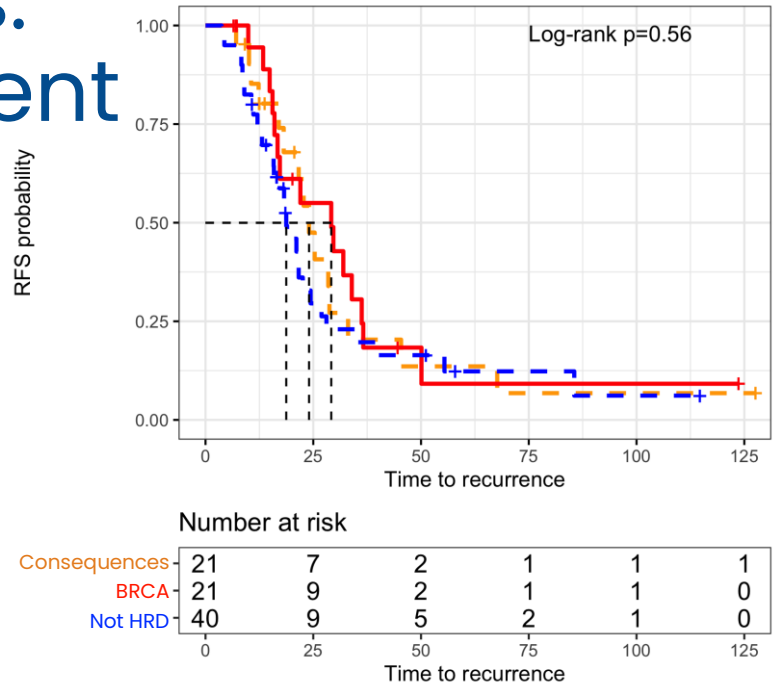
Survival Analyses: Platinum Treatment

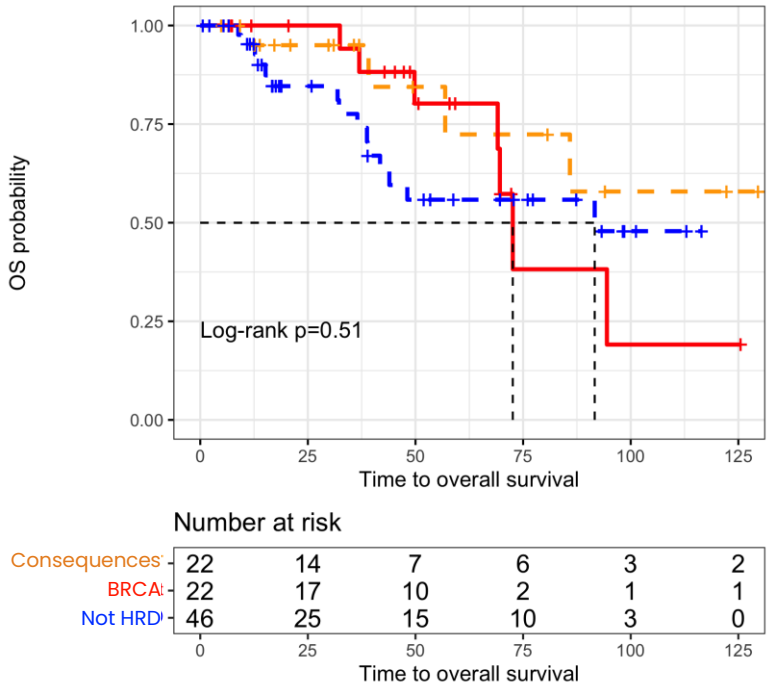


	Consequences Cluster
	BRCA Cluster
	Not HRD Cluster

Recurrence Free Survival



Overall Survival



	Consequences Cluster	BRCA Cluster	Not HRD Cluster
Median RFS	24.0 months	29.2 months	18.7 months
Median OS	NA	72.6 months	91.6 months

"HRD clusters" trend towards improved OS over "Not HRD cluster" (not statistically significant)

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Conclusions

- Moderate level of agreement observed for HRD calls across assays
- Patient and sample characteristics do not account for the variability between assays

Recommendations for assay development:

- Identify the best approach for assays to report HRD to enhance consistency
- Align on expectations for analytical validation
- Consider approaches for developing a "gold standard," including use of a reference material

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Thanks to our project partners!

Special thanks to:

- NCI Biometric Research Program (Led by Dr. Lisa McShane)
- University of Alabama Birmingham (Dr. Rebecca Arend)
- Molecular Characterization Lab at Frederick National Laboratory
- Diagnostic developers who participated

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