



IX SIMPOSIO · SYMPOSIUM | 2024 **BIOPSIA LÍQUIDA · LIQUID BIOPSY**

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

COMPUTATIONAL BIOLOGY, MEDICAL REPORTING AND DATA AT FOUNDATION MEDICINE

Dr. Thomas Wieland

#SimposioBiopsiaLiquida
www.simposiobiopsialiquida.com

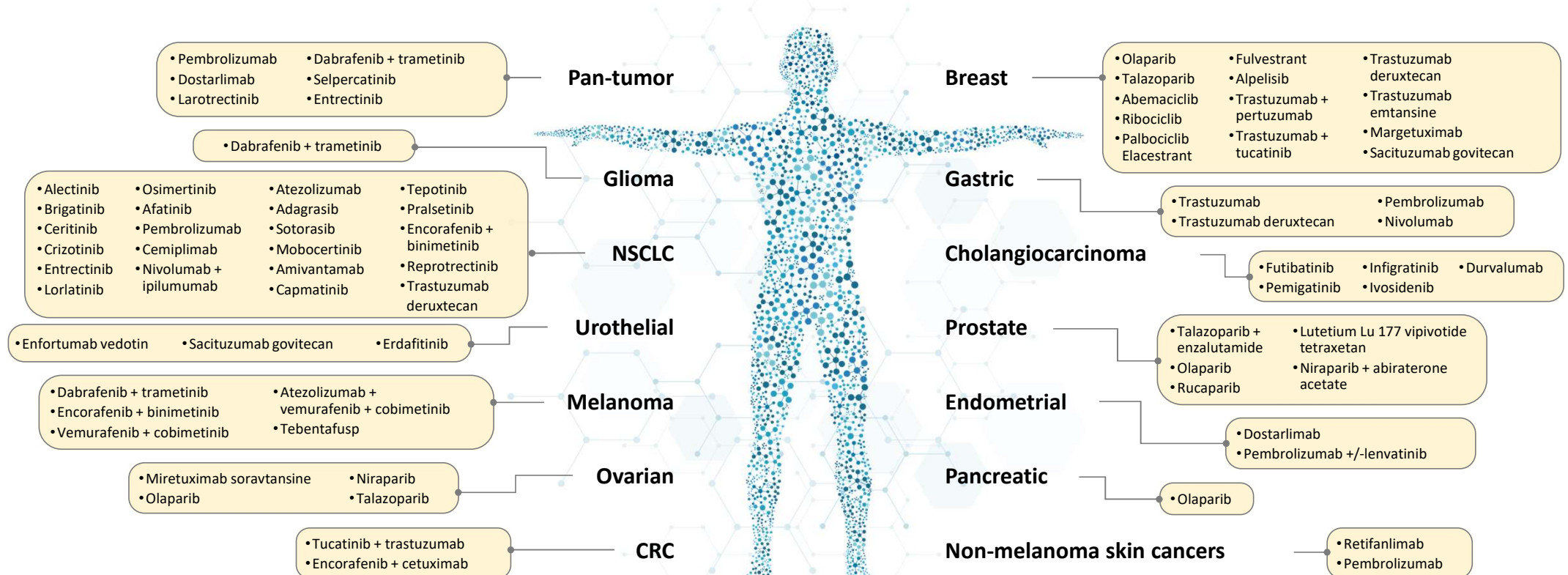
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PRECISION ONCOLOGY APPROVALS CONTINUE TO INCREASE

Selected targeted therapy and immunotherapy approvals in solid tumors*



*Current as of November 2023.

FDA. Oncology (Cancer) / Hematologic Malignancies Approval Notifications. Updated June 20, 2023. Accessed November 13, 2023. <https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications>.

FOUNDATION MEDICINE DRIVES PRECISION CANCER CARE

FDA-APPROVED

ALL SOLID TUMORS

TISSUE BIOPSY

LIQUID BIOPSY

 FOUNDATIONONE® CDx

- DNA (324 genes)
- TMB + MSI
- 25 CDx claims, 3 group CDx claims
- Option to add IHC testing for PD-L1

 FOUNDATIONONE® LIQUID CDx

- DNA (311 genes)*
- bTMB + MSI-H + tumor fraction**
- 9 CDx claims, 1 group CDx claim

HEMATOLOGIC MALIGNANCIES AND
SARCOMAS

 FOUNDATIONONE® HEME

- DNA (406 genes) + RNA (265 genes)
- For hematological malignancies, sarcomas, and solid tumors where RNA sequencing is desired
- TMB + MSI
- Laboratory developed test (LDT)

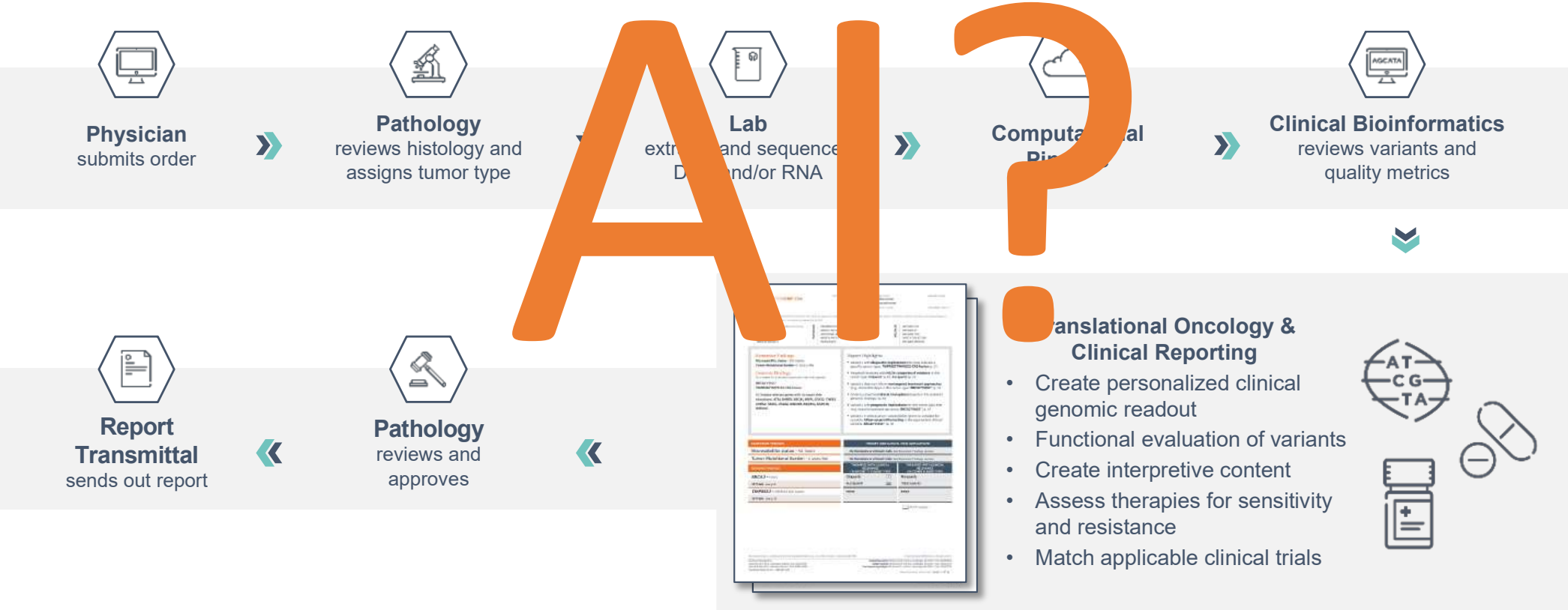
*FoundationOne@Liquid CDx is FDA-approved to report substitutions and indels in 311 genes, including rearrangements in ALK and BRCA1/2 and copy number alterations in BRCA1/2 and ERBB2 (HER2). Comprehensive results across all 324 genes are reported as a laboratory professional service which is not reviewed or approved by the FDA.

**bTMB, MSI-H status, and tumor fraction are reported as a laboratory professional service which is not reviewed or approved by the FDA.

The information in this slide is specific to the US only

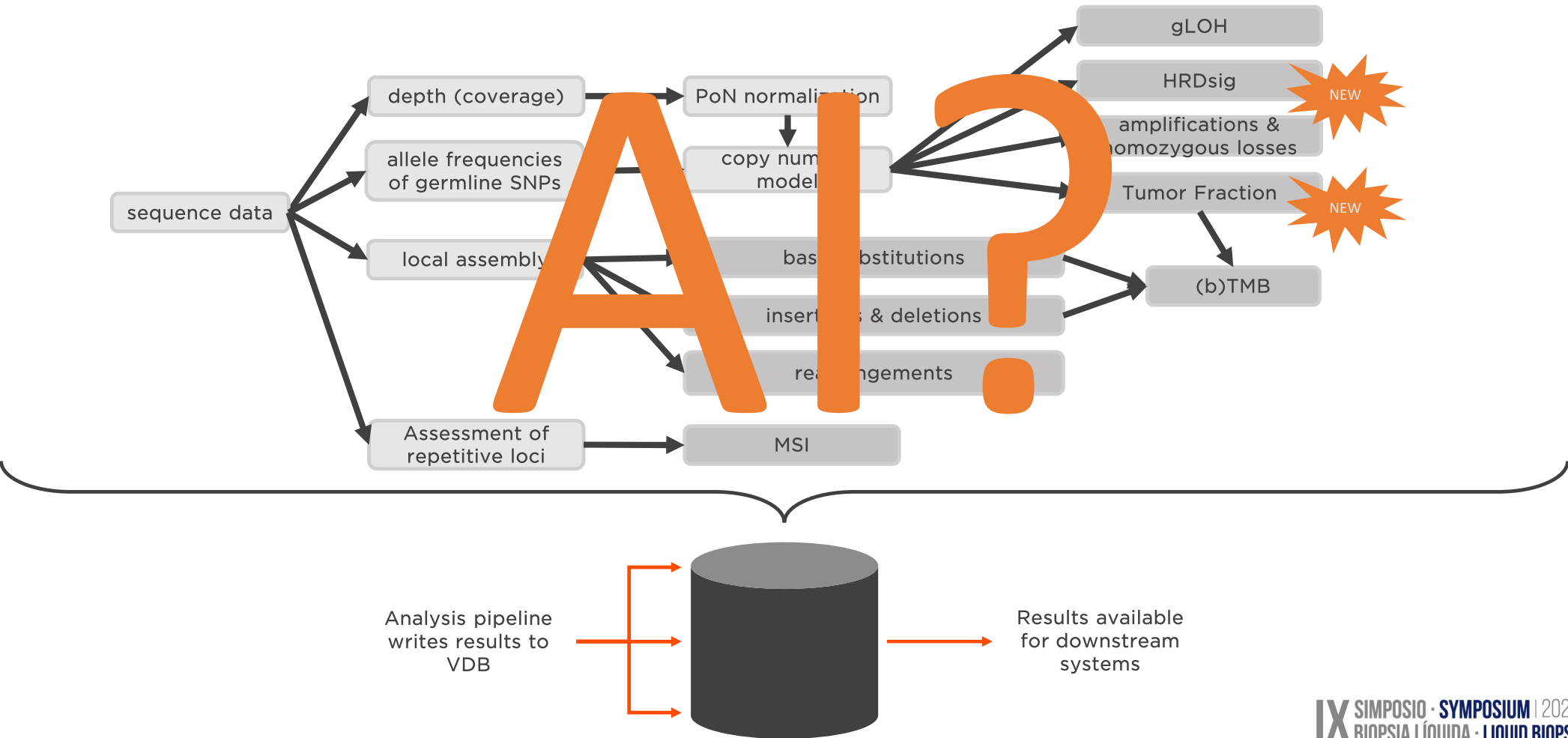
WORKFLOW OF FOUNDATION MEDICINE CGP WITH NGS

Multiple teams involved in the process



CGP = comprehensive genomic profiling, NGS = next-generation sequencing.

SEQUENCE DATA ARE ANALYZED BY MULTIPLE METHODS TO DETECT DIFFERENT TYPES OF ALTERATIONS



WHAT IS ARTIFICIAL INTELLIGENCE (AI)?

ARTIFICIAL INTELLIGENCE

Any technique which enables computers to mimic human behavior



MACHINE LEARNING

Ability to learn without being explicitly programmed



DEEP LEARNING

A subset of ML which make the computation of multi-layer neural network feasible



From Zhang B, Shi H, Wang H. Machine Learning and AI in Cancer Prognosis, Prediction, and Treatment Selection: A Critical Approach. J Multidiscip Healthc. 2023 Jun 26;16:1779-1791. doi: 10.2147/JMDH.S410301. PMID: 37398894; PMCID: PMC10312208.

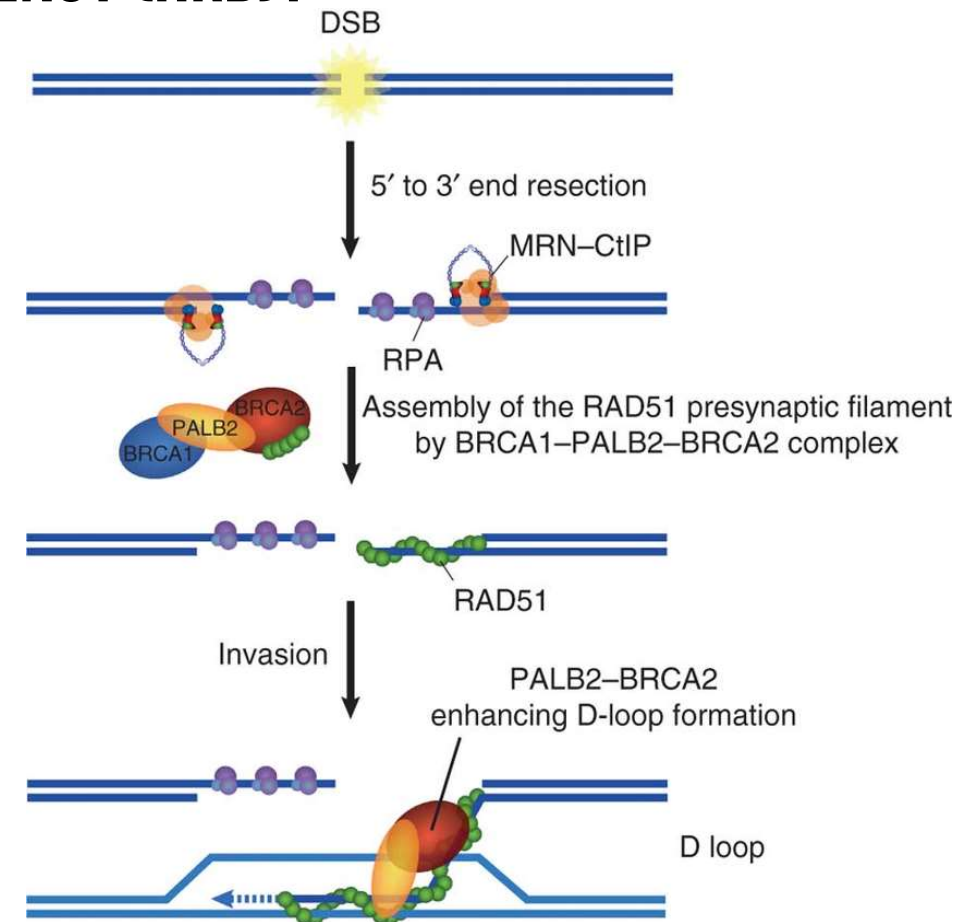
DEVELOPMENT OF A NOVEL HRD SIGNATURE - HRDSIG

WHAT IS HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD)?

- **Homologous Recombination Repair (HRR)** is a cellular pathway that repairs double strand breaks in DNA, ensuring chromosomal integrity and cell viability in healthy cells

KEY GENES IN THIS PATHWAY INCLUDE *BRCA1/2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1/2*, *FANCL*, *PALB2*, *RAD51B/C/D*, and *RAD54L*

- Tumors with *defective* HRR, are referred to as **H**omologous **R**ecombination **D**eficient (**HRD**)
- Mutation/loss of HRR genes is common in several cancer types, including breast, ovary, pancreas, and prostate cancer, commonly referred to as “BRCA-associated cancers”



Buisson R, Dion-Côté AM, Coulombe Y, et al. Cooperation of breast cancer proteins PALB2 and piccolo BRCA2 in stimulating homologous recombination. *Nature Structural & Molecular Biology*. 2010;17(10):1247-1254. doi:<https://doi.org/10.1038/nsmb.1915>

HRD AND PARP INHIBITORS

PRACTICE CHANGING CLINICAL TRIALS

HRD tumors are hypothesized to be more susceptible to DNA-damaging therapeutics through a process called **synthetic lethality**, confirmed through practice-changing trials with platinum chemotherapies and Poly (ADP-ribose) polymerase (PARP) inhibitors:

OVARIAN SOLO1 (maintenance olaparib, 2018), ARIEL3 (maintenance rucaparib, 2018), PRIMA (niraparib, 2020)

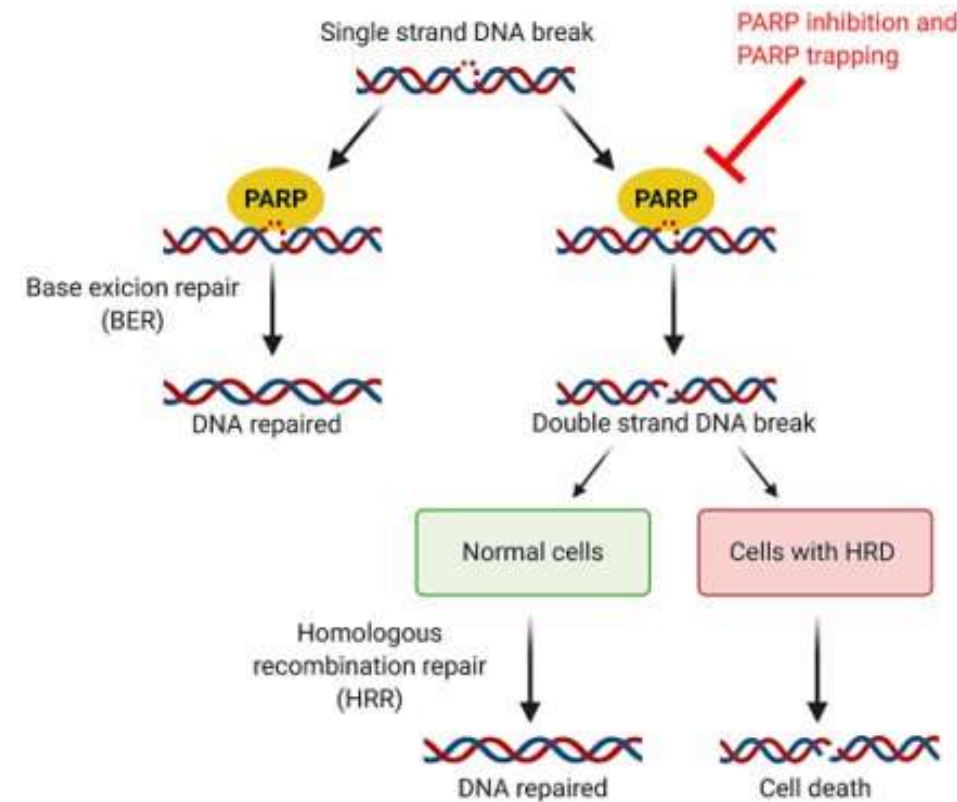
HER2 neg BREAST EMBRACA (talazoparib; 2018); OlympiAD (olaparib, 2018); OlympiA (adjuvant olaparib, 2022)

PANCREATIC POLO (maintenance Olaparib, 2019); Cis/Gem for mPDAC (O'Reilly et al., 2020); Rucapanc-2 (2021)

PROSTATE PROpel (olaparib, 2023), TALAPRO-2 (talazoparib, 2023), PROfound (olaparib, 2020), TRITON2 (rucaparib, 2020)

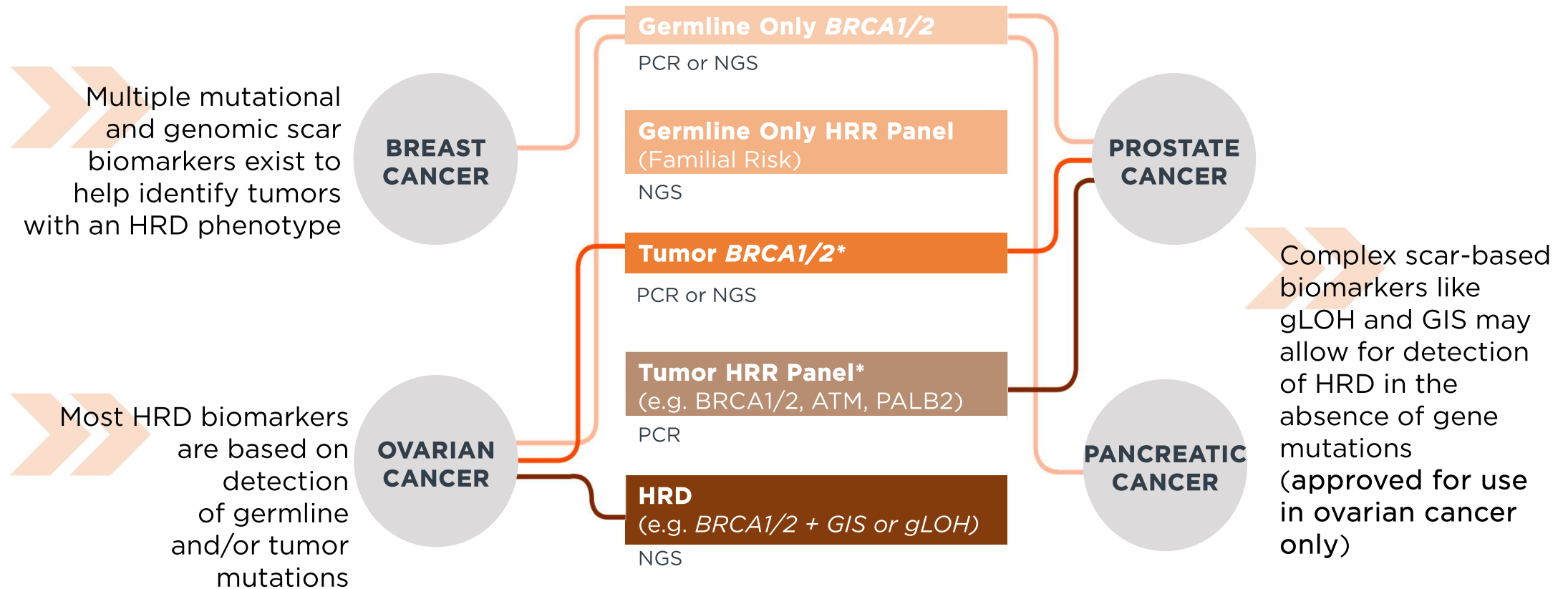
FUTURE

Pan-tumor | New therapies (e.g. PARP1, ATR inhibitors) | Earlier stage disease



Buisson R, Dion-Côté AM, Coulombe Y, et al. Cooperation of breast cancer proteins PALB2 and piccolo BRCA2 in stimulating homologous recombination. *Nature Structural & Molecular Biology*. 2010;17(10):1247-1254. doi:<https://doi.org/10.1038/nsmb.1915>

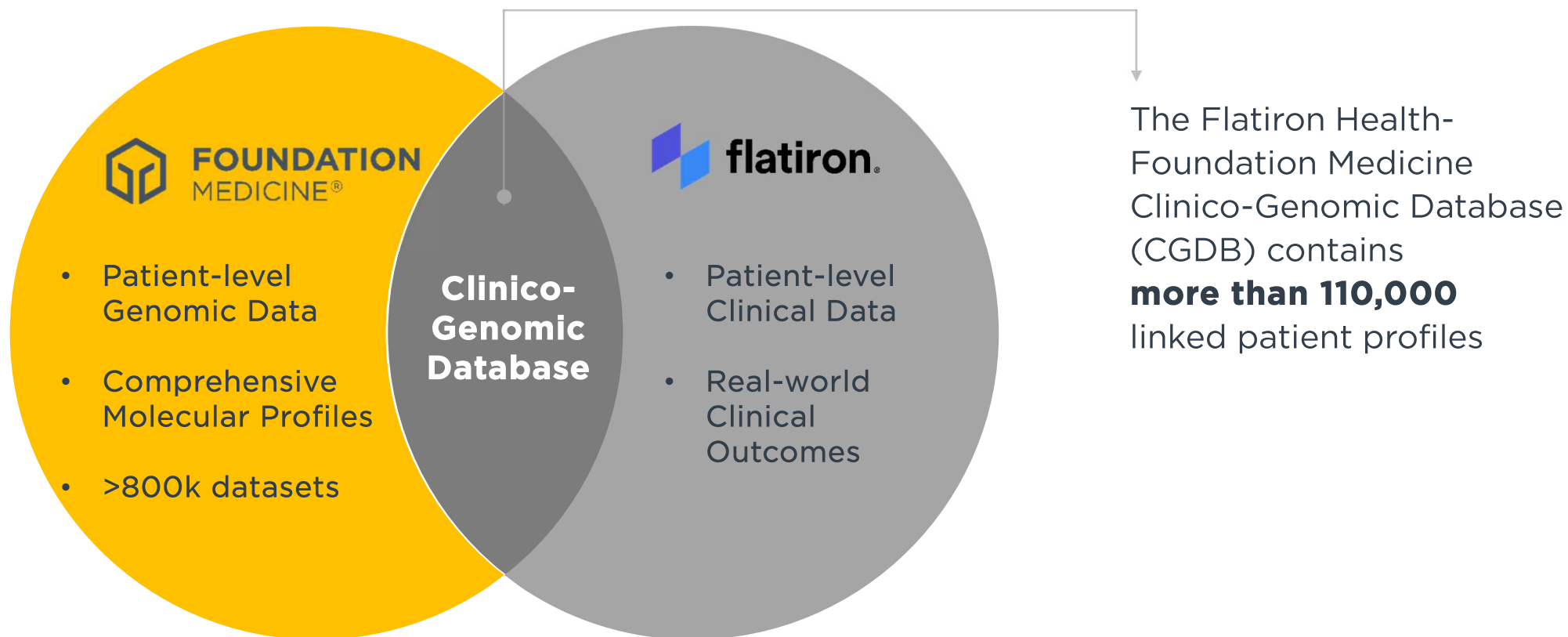
THE LANDSCAPE OF HRD BIOMARKERS IS COMPLEX



1. Stewart MD, Merino Vega D, Arend RC, et al. Homologous recombination deficiency: Concepts, definitions, and assays. *The Oncologist*. 2022;27(3):167-174. doi:10.1093/oncolo/oyab053

PCR = Polymerase Chain Reaction
NGS = Next Generation Sequencing

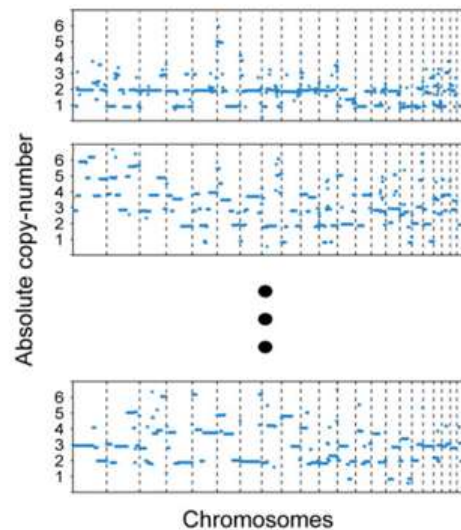
A TRANSFORMATIVE CLINICO-GENOMIC DATABASE (CGDB)



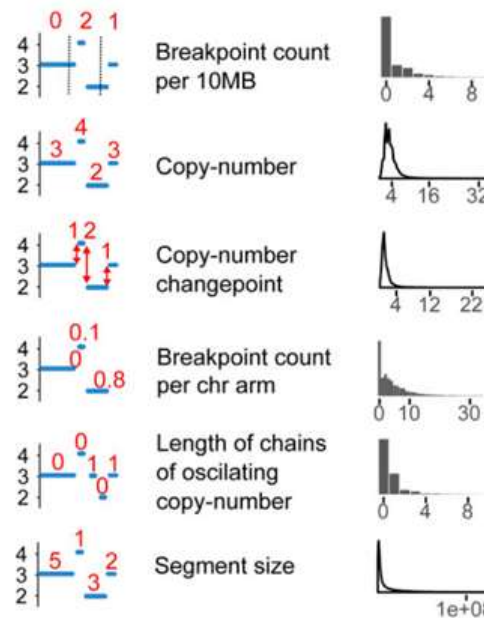
HRD SIGNATURE (HRDSIG) DEVELOPMENT

A machine learning comprehensive scar-based copy number signature that gives a functional HRD readout pan-cancer

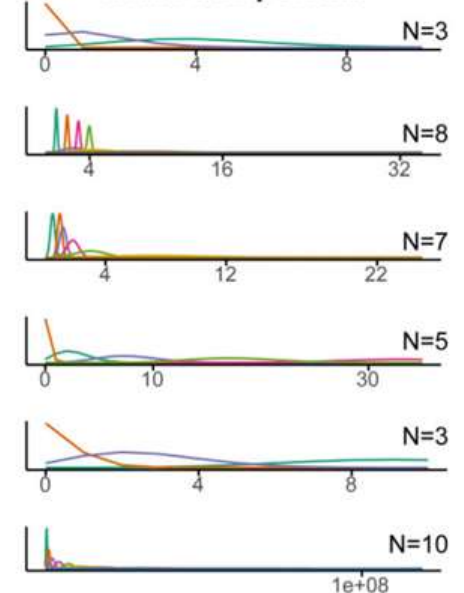
Compute absolute CN from shallow WGS



Derive CN feature distributions



Fit optimal number of mixture model components



- HRDsig was built with a diverse set of >100 CN features, expending upon Macintyre et al.

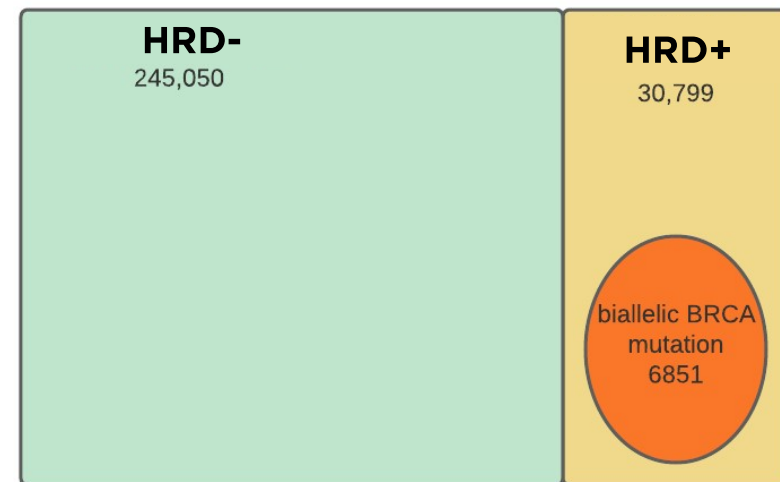
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Macintyre et al., Copy number signatures and mutational processes in ovarian carcinoma. Nature Genetics, 2018.

HRD SIGNATURE (HRDSIG) DEVELOPMENT

A machine learning comprehensive scar-based copy number signature that gives a functional HRD readout pan-cancer

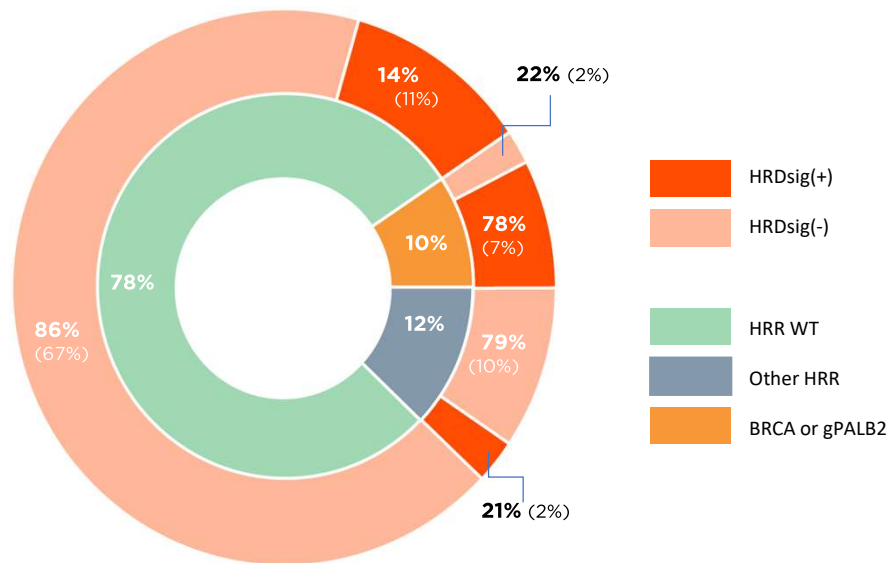
- Built with a diverse set of **>100 CN features**
- Trained using our large pan-tumor (>500,000 pt) genomic database
- Performance was examined in a set of approximated “true positive” and “true negative” samples:
 - “True positive”: Biallelic *BRCA1/2*
 - “True negative”: HRR WT
- Performance down to at least 20% tumor purity



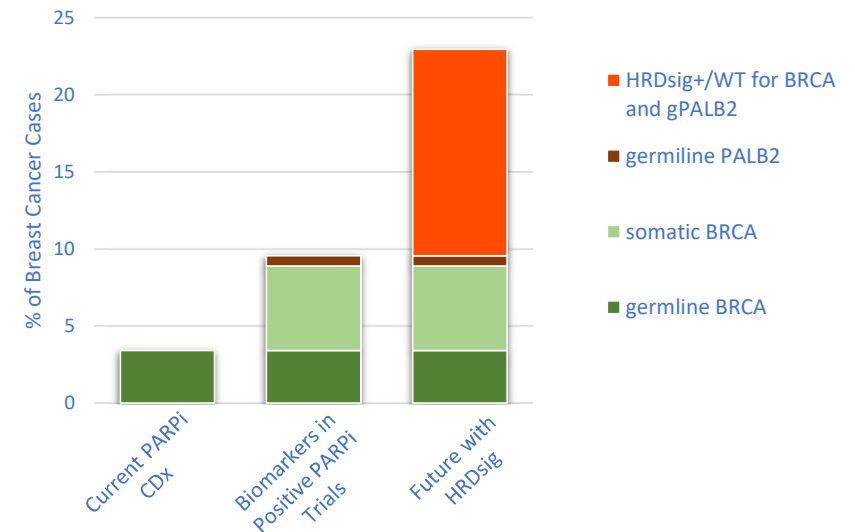
CLINICAL VALIDITY OF HRDSIG

HRDSIG IDENTIFIES BREAST CANCER PATIENTS BEYOND BRCA/PALB2

BREAST CANCER –FOUNDATION CORE



HRDsig captures most patients with *gBRCA* or *sBRCA/gPALB2* (which appear similarly predictive to *gBRCA*) as well as a subset of patients WT for HRR alterations

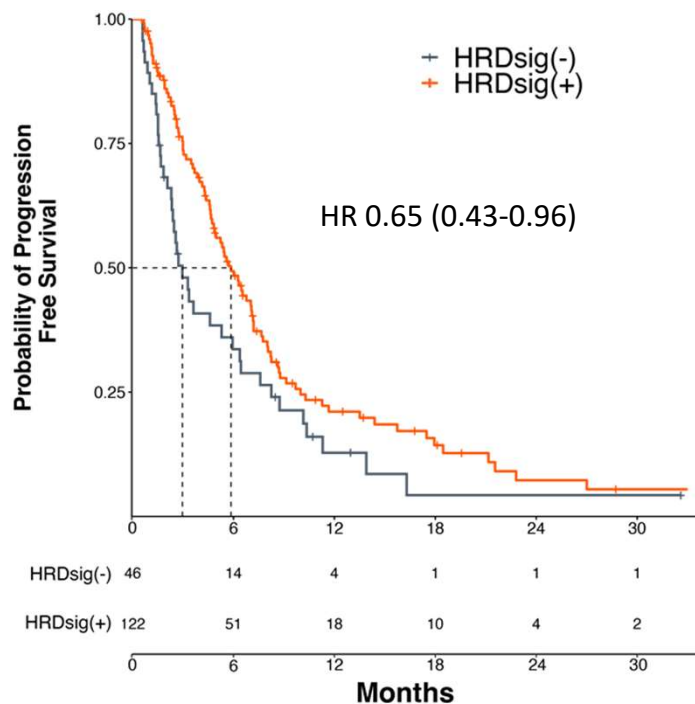


Breast cancers tested with CGP:

- 3.4% with *gBRCA* (current CDx)
- 9.6% with any *BRCA* or *gPALB2*
- 21% with HRDsig+
- 23% with any *BRCA*, *gPALB2* or HRDsig+

HRDSIG IDENTIFIES METASTATIC BREAST CANCER PATIENTS WHO BENEFIT FROM PARPI

BREAST CANCER – CGDB



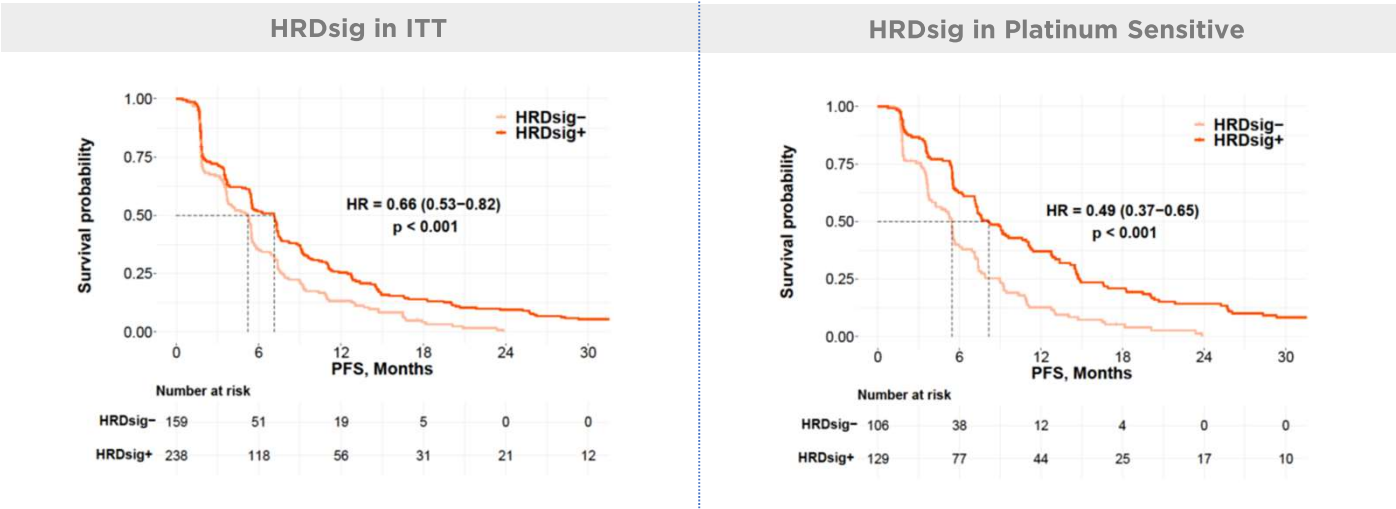
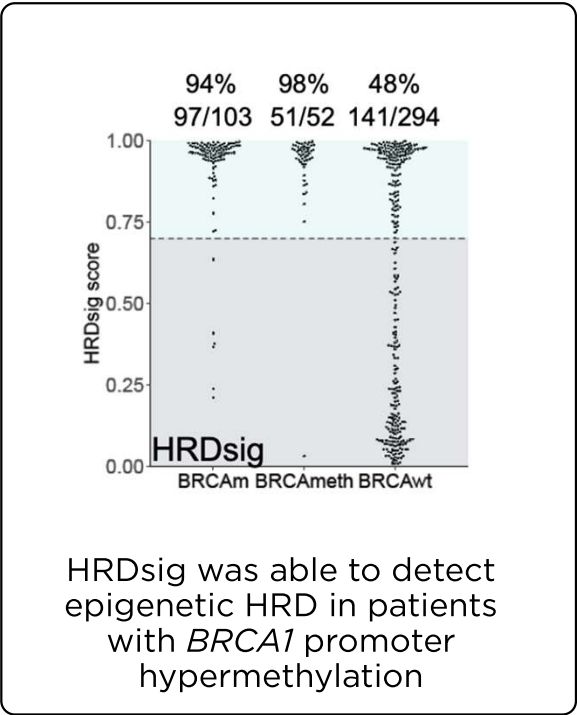
Patients with HRDsig(+) have longer median rwPFS and significantly reduced risk of progression (6.3 v 2.8 months) on PARPi compared to patients without HRDsig detected (similar trends were observed for rwOS)

» Opportunities for HRDsig to predict benefit from platinum chemo and PARPi in the neoadjuvant and adjuvant settings are being explored

HRDSIG+ AT BASELINE CORRELATED WITH BENEFIT FROM RUCAPARIB IN ARIEL2

OVARIAN CANCER– ARIEL2 TRIAL COHORTS

HRDsig POSITIVITY ACROSS *BRCA*wt, *BRCA*mut, AND *BRCA*1 PROMOTER METHYLATION



In ARIEL2, HRDsig positivity prior to rucaparib was associated with PFS benefit in the ITT (platinum resistant or sensitive) and the platinum sensitive population

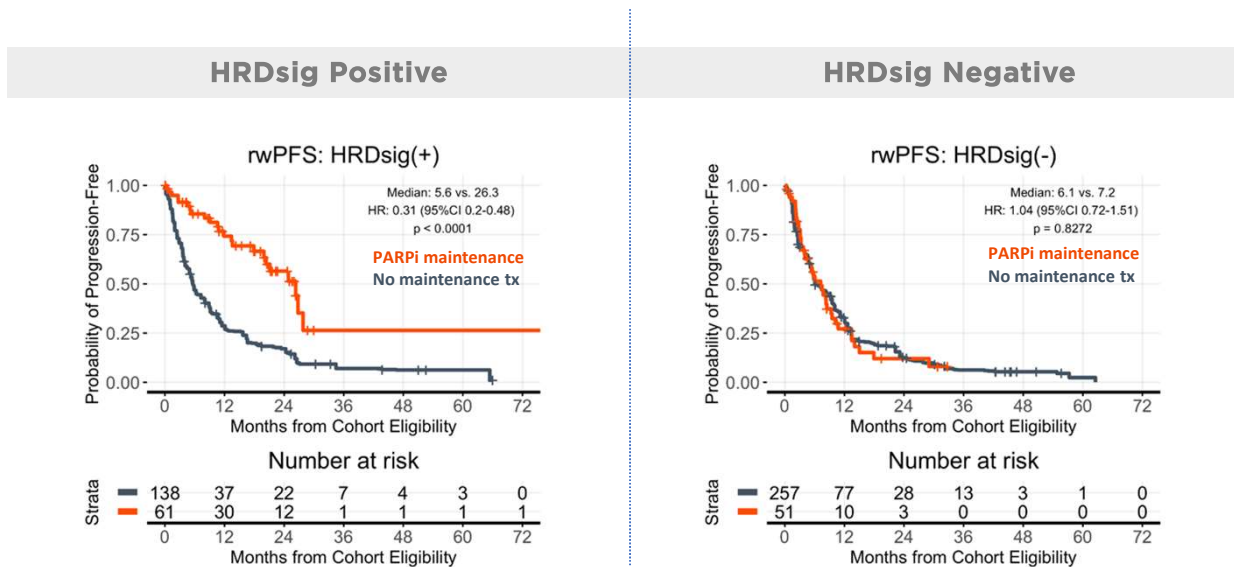
Sokol ES, Madison RW, Jin DX, et al. Abstract 966: Exploration of a novel HRD signature (HRDsig) as a biomarker for rucaparib benefit in ARIEL2. 2023;83(7_Supplement):966-966. doi:https://doi.org/10.1158/1538-7445.am2023-966

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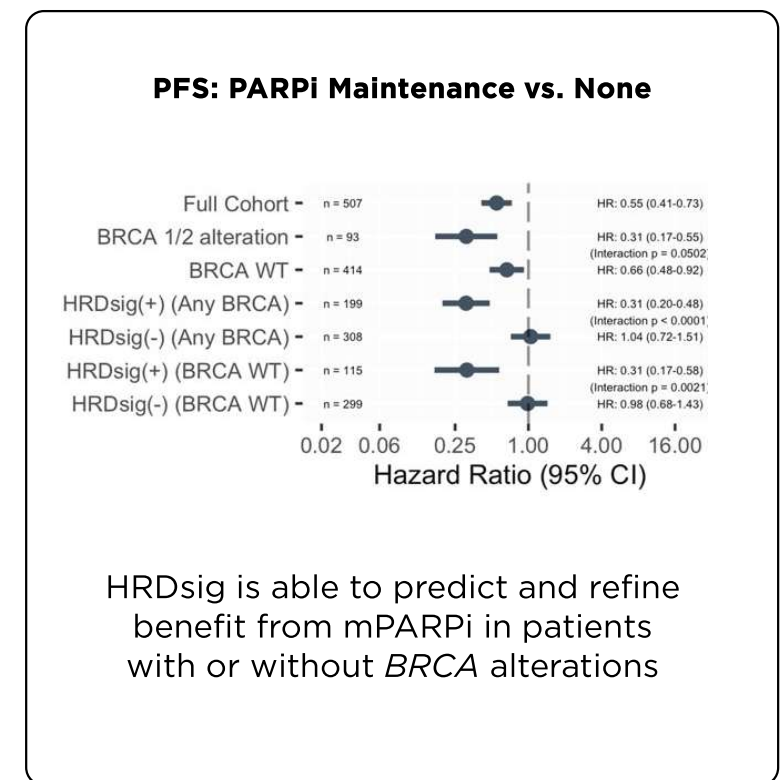
HRDSIG IDENTIFIES OVARIAN CANCER PATIENTS WHO BENEFIT FROM MAINTENANCE PARPI

OVARIAN CANCER– CGDB

HRDsig identifies more than 2x as many patients as BRCA mutation alone



HRDsig+ is predictive of improved PFS (HR of 0.31) to maintenance PARPi therapy regardless of *BRCA* status in real-world patients with advanced ovarian cancer



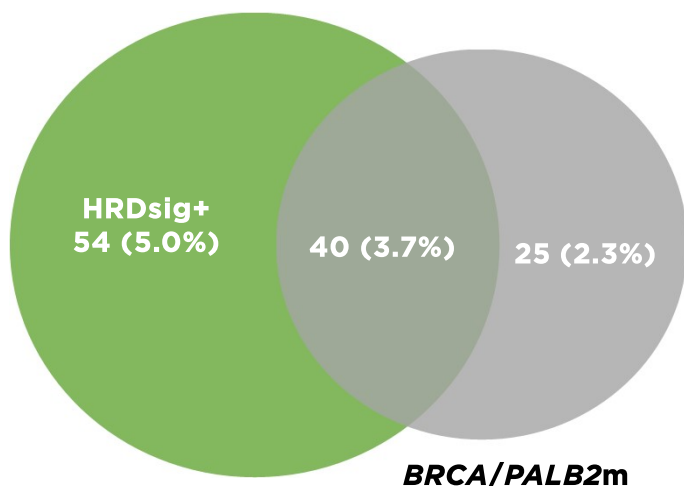
Richardson DL, Julia, Graf R, et al. Effectiveness of PARP inhibitor maintenance therapy (mPARPi) in advanced ovarian cancer (OC) by BRCA1/2 and HRD signature in real-world practice.. 2023;41(16_suppl):5583-5583. doi:https://doi.org/10.1200/jco.2023.41.16_suppl.5583

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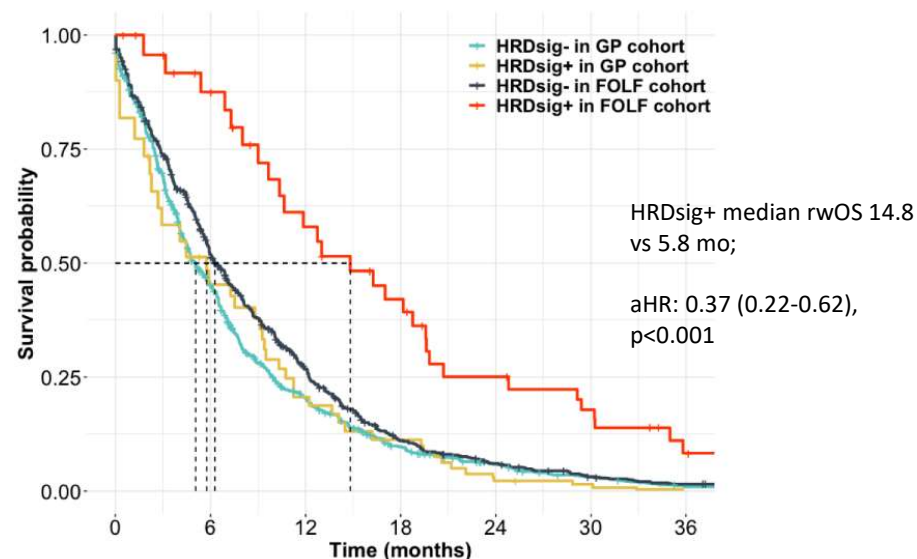
HRDSIG FOR 1L PLATINUM CHEMO SELECTION IN PANCREATIC CANCER

PANCREATIC CANCER– CGDB

Potential to complement professional guidelines recommending BRCA and PALB2 mutation testing



HRDsig positivity co-occurred with *BRCA* and *PALB2m* but was also present in a wild-type population



HRDsig has the potential to identify patients with HRD-associated genomic scars who are more likely to benefit from FOLF vs GP in this retrospective analysis

Kuei-Ting Chen and others, A Novel HRD Signature Is Predictive of FOLFIRINOX Benefit in Metastatic Pancreatic Cancer, The Oncologist, 2023; oyad178, <https://doi.org/10.1093/oncolo/oyad178>

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GP = gemcitabine-paclitaxel,
FOLF = FOLFIRINOX (containing oxaliplatin)

CLINICAL VALIDITY EVIDENCE FOR HRDSIG

Summary of published evidence

OVARIAN and PROSTATE

- CN signature methods and HRDsig initial CV in ovarian and prostate cancer
Antonarakis et al. AACR 2022 and Moore et al. *JCO-PO* 2023.
- HRDsig for PARPi maintenance therapy in ovarian cancer
Richardson et al. ASCO 2023.
- HRDsig as a PARPi biomarker in ovarian cancer (ARIEL2 trial)
Sokol et al. AACR 2023.

PANCREATIC

- HRDsig for FOLFIRINOX vs Gem/Pac in pancreatic cancer
Chen et al. *The Oncologist* 2023.

BREAST

- BRCA, PALB2 and HRDsig for PARPi therapy in advanced breast cancer
Batalini et al. *JCO-PO* 2023.
- Genomics of HRDsig in early vs advanced stage breast cancer
Jeon et al. ASCO 2023.

¡GRACIAS!

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