Biomarker Testing in Ovarian Cancer

Bradley Monk, MD
Honor Health

Disclosures

- 2 Year Disclosure of Financial Relationships for Dr. Bradley Monk June 2023

- Sponsors involved in producing, marketing, selling, re-selling, or distributing products

Cancer Type	Commercial Interest	What was received	Role
Cervical, uterine, ovarian	AstraZeneca	Honorarium	Speaker/Consultant
Uterine, ovarian	Eisai	Honorarium	Speaker/Consultant
Cervical, uterine, ovarian	Genmab/Seagen	Honorarium	Consultant
Ovarian	ImmunoGen	Honorarium	Speaker/Consultant
Uterine	Karyopharm	Honorarium	Consultant
Cervical, uterine, ovarian	Merck	Honorarium	Speaker/Consultant
Cervical, uterine, ovarian	Myriad	Honorarium	Speaker/Consultant
Ovarian	Novocure	Honorarium	Consultant
Ovarian	Roche/Genentech	Honorarium	Speaker/Consultant
Cervical, uterine, ovarian	TESARO/GSK	Honorarium	Speaker/Consultant

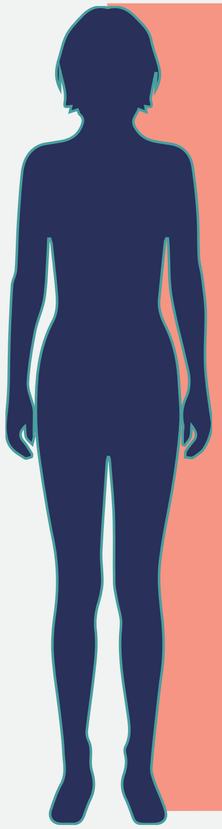
What kind of biomarkers? Clinical Trial Definitions

- **Integral markers** are essential for conducting the study as they define eligibility, stratification, disease monitoring or study endpoints.

- **Integrated markers** test a hypothesis based on preexisting data and not simply generating hypotheses. Such integrated markers need to be performed ideally on all patients in a trial and the assay should already have been tested in human subjects with the disease in question and demonstrated reproducible analytic qualities.

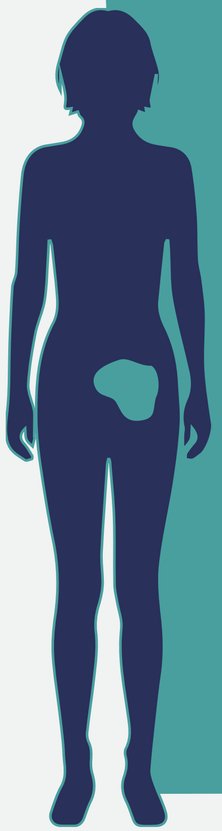
- **Exploratory markers** are used to generate testable hypotheses

Germline versus somatic mutations



Germline mutation[1-3]

- Mutation inherited from parental gametes and can be passed on to offspring
- Mutation present in every cell in the body
- Some germline mutations may confer increased risk for cancer (eg, *BRCA1/2* mutations)



Somatic mutation[1-3]

- Mutation not inherited from parental gametes and cannot be passed to offspring
- Mutation is present only in affected cells (eg, tumor)

1. Randall LM, et al. *Gynecol Oncol*. 2017;146:217-24; 2. NCI. BRCA Mutations: Cancer Risk and Genetic Testing. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#what-other-cancers-have-been-linked-to-mutations-in-brca1-and-brca2. Reviewed January 30, 2018. Accessed March 6, 2020; 3. Alldredge J, et al. *Obstet Gynecol Clin North Am*. 2019;46:37-53.

Molecular Profiling is becoming increasingly complex

Analyzing DNA, RNA and proteins to reveal a more complete molecular blueprint to guide precise and individualized treatment decisions.

DNA

Whole Exome Sequencing
SNVs, Indels & Copy Number Alterations

RNA

Whole Transcriptome Sequencing
Fusions & Varian Transcripts

Protein

Immunohistochemistry
Tumor-expressed antigens

Standard of Care + Clinical Trial Biomarkers

Immunotherapy	Targeted Therapy	Chemotherapy/Hormonal Therapies	Clinical Trials

Next-Generation Sequencing
DNA
– Illumina NovaSeq System –

~22,000 full gene coverage
(whole exome coverage)
719+ clinically-relevant genes at 1,000x
Point mutations, indels, and
copy number alterations
~250,000 exonic/intronic/intergenic SNPs –
LOH, gene loss or amplification
Genomic Signatures: HLA Genotyping, LOH,
MSI, and TMB
Cancer-associated pathogen panel

Next-Generation Sequencing
RNA
– Illumina NovaSeq System –

~22,000 full gene coverage
(whole transcriptome coverage)
60 million read count
Gene fusions and variant transcripts
Novel translocation detection independent of
intronic breakpoint

Immunohistochemistry
Protein
– Ventana & Dako IHC –

Up to 13 clinically relevant IHCs (optimized
across 25 tumor types)
Multiple FDA approved CDx PD-L1 tests for
different disease types (per label)
Controls on every IHC
4 µm cuts to preserve tissue

The Importance of RNA Sequencing

Fusion genes are an emerging class of highly important targets for cancer diagnosis and treatment

- **Clinical Setting:** **High quality clinical care requires screening for RNA fusions, which are rare but with efficacy in the 70%+ range**
- **Biopharma Setting:** **Compelling need to find responsive patients for both clinical trials and commercial purposes**

NTRK Gene Fusions Across Various Cancers

<5%	**Colon cancer** **Melanoma** **Various sarcomas** **Cholangiocarcinoma** **Glioma** **Pancreatic cancer** **Appendiceal cancer** **Lung adenocarcinoma**
5-75%	**Thyroid cancer** **GIST**
>75%	**Secretory carcinoma of the salivary gland** **Secretory breast carcinoma**

Other Gene Fusions: ***RET*, *FGFR*, *ALK*, *ROS1*, *RSPO3*...**

Mounting evidence of higher fusion detection through RNA-based analysis over DNA-based analysis.

Memorial Sloan Kettering Cancer Center

(Benayed, et al.)

RNA-based analysis identifies more fusions than DNA-based analysis

-- Study based on MSK-IMPACT (DNA) and MSK-Fusion (RNA) (April 2019)

Direct comparison between DNA and RNA shows RNA is the superior method for fusion analysis

-- Caris internal data based on 10x the size of the of Benayed, et al. study

NCCN National Comprehensive Cancer Network®

NCCN Guidelines (i) recommend RNA-based NGS for patients with no identifiable driver oncogenes to maximize detection of fusion events; and (ii) state that RNA-based NGS may be considered to assess for fusions as DNA-based NGS may not detect some *NTRK1* and *NTRK3* fusions

-- NCCN updated guidelines for NSCLC (May 2020)

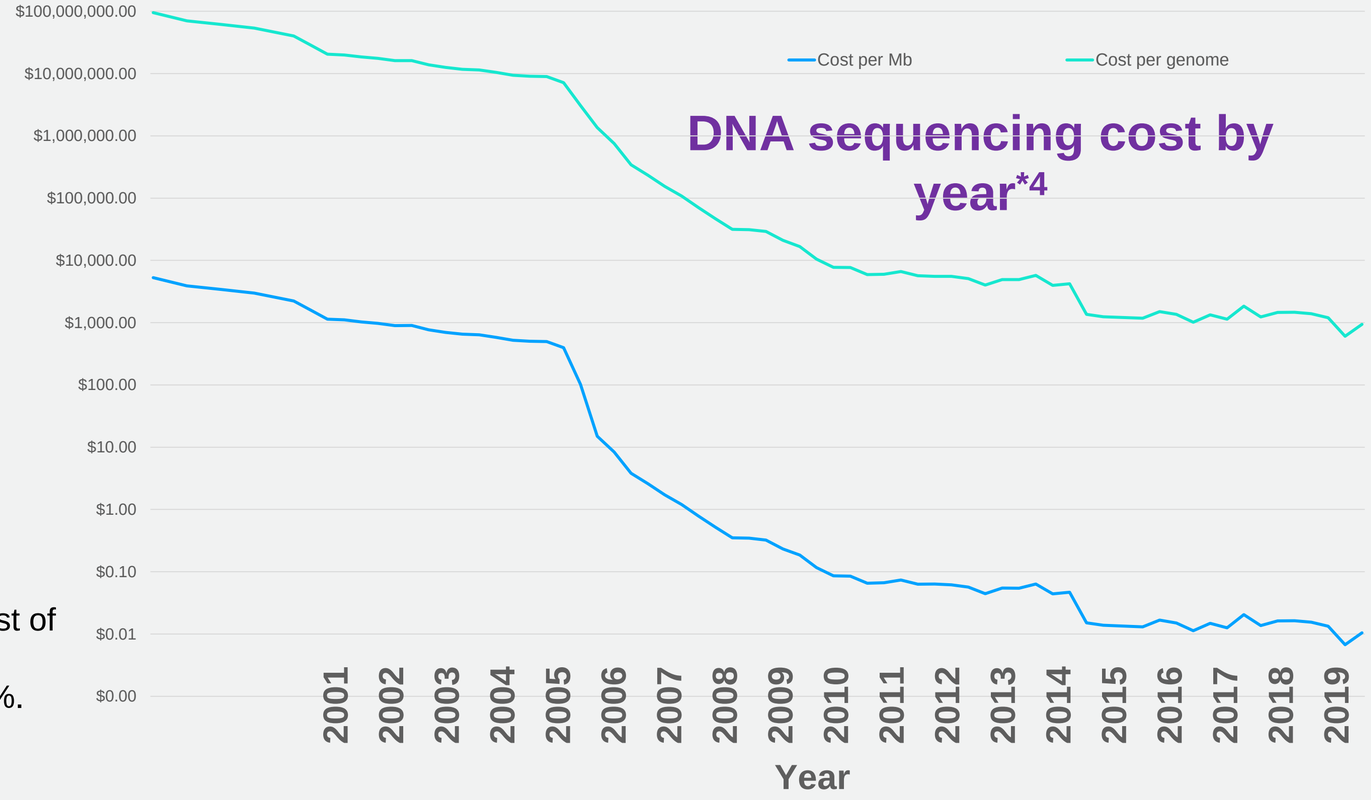
GOG FOUNDATION®

6

The biomarker testing is becoming less expensive and more cost effective

Technological advances have led to increased options for biomarker testing[1,2]
Testing is expected to become more accurate, faster, and less costly[1-3]

The cost of DNA sequencing has decreased dramatically over the past 10 years[4]



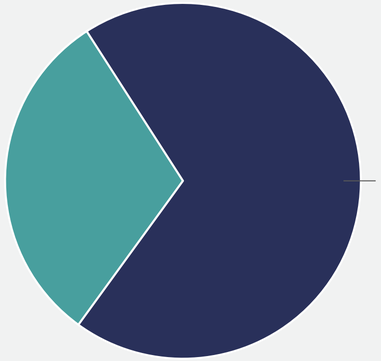
* Sequencing costs represent production costs associated with DNA sequencing performed at sequencing centers funded by the National Human Genome Research Institute. Cost per Mb is defined as the cost of determining 1 million bases of DNA sequence with a minimum quality score of Phred20 (or Q20), which represents an error probability of 1%. Cost per genome is defined as the cost of sequencing a human-sized genome.

1. Kamps R, et al. *Int J Mol Sci.* 2017;18(2). pii: E308; 2. Lynce F, et al. *Am Soc Clin Oncol Educ Book*. 2016;35:e72-8; 3. Frey MK, et al. *Gynecol Oncol Res Pract*. 2017;4:4; 4. National Human Genome Research Institute. DNA Sequencing Costs: Data. https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data. Updated October 30, 2019. Accessed March 9, 2020.

GOG FOUNDATION

Biomarker testing rates in ovarian cancer have historically been low

Only ~30% of patients diagnosed with ovarian cancer between 2013 and 2014 received genetic testing, despite guidelines recommending testing for >10 years*[1]



Out of 6001 patients

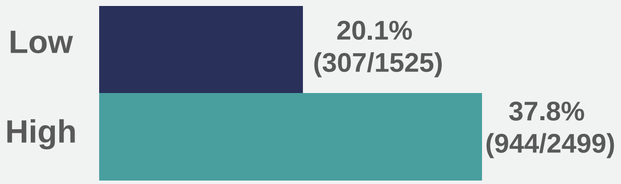
~70% had no germline genetic testing results[1]

Study overview

- All female patients with breast and ovarian cancer diagnosed between 2013 and 2014 from the Georgia Cancer Registry and the California Cancer Registry were linked with germline genetic testing information from four laboratories that performed the majority of testing†[1]
- All other variables (including socioeconomic and demographic factors) were captured from SEER registries[1]

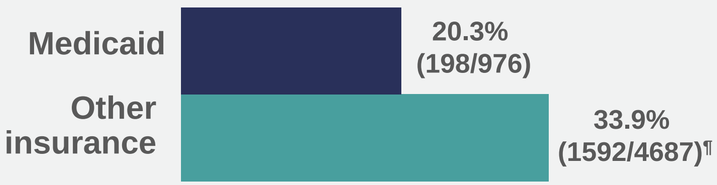
Testing rates varied with socioeconomic and demographic factors, including‡[1]:

Poverty level,§ % (n/N)



Race/ethnicity, % (n/N)

Insurance, % (n/N)



* These data predate the availability of PARP inhibitors.[2] † Germline genetic testing results were collected from Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; Myriad Genetics, Salt Lake City, UT. ‡ Testing rates also varied by age, stage/grade, and marital status. § Poverty level determined based on data from the 2010 US census for area-based residential poverty: high poverty level corresponds to residential areas where poverty was <10%, and low poverty level corresponds to residential areas where poverty was ≥20%.1 ¶ Other is defined as patients who were insured or insured/no specifics.

1. Kurian AW, et al. *J Clin Oncol*. 2019;37:1305-15; 2. FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications. www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm. Accessed March 9, 2020.

Strategies have been proposed to overcome barriers to biomarker testing

Factors contributing to low biomarker testing rates in ovarian cancer may include[1]:

- Lack of awareness or knowledge
- Failure to recommend testing
- Barriers to receipt of testing, such as:

Lack of access to genetic counselors

Out-of-pocket costs to patients

Patient attitudes and perceptions

A variety of strategies have been suggested to improve testing rates, including[2,3]:

Increased awareness among health care providers and patients

Innovative genetic counseling services (telehealth or collaborative care)

Improved genetic counseling referral process

Improved access to care for patients within disadvantaged communities

1. Childers CP, et al. *J Clin Oncol.* 2017;35:3800-6; 2. Hoskins PJ, et al. *CA Cancer J Clin.* 2017;67:493-506; 3. Cohen SA, et al. *Am Soc Clin Oncol Educ Book.* 2019;37:1305-15.

NCCN Guidelines® include recommendations for biomarker testing throughout the disease trajectory for patients with ovarian cancer*

Timeline for biomarker testing in women with or who are at high risk for ovarian cancer

Before diagnosis[1]

- Testing for high-penetrance ovarian cancer susceptibility genes (such as *BRCA1/2*) is clinically indicated in individuals who meet specific criteria
- Testing criteria include:
  - Having a blood relative with a known pathogenic/likely pathogenic variant
  - Family history of ovarian cancer

After diagnosis[2]

- All patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation[1] and germline and somatic testing†
- Germline and/or somatic *BRCA1/2* status may inform maintenance therapy
- In absence of *BRCA1/2* mutation, HRd status may provide information on magnitude of benefit of PARPi

At relapse[2]

- Validated molecular testing should be performed in a CLIA-approved facility using most recently available tumor tissue
- Testing is recommended to include at least *BRCA1/2* and MSI/dMMR†
- Evaluation of HRd can be considered
- Consider additional somatic tumor testing to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic treatment options exist

*All recommendations are category 2A unless otherwise indicated. † If not previously done. *BRCA,* breast cancer susceptibility gene; CLIA, Clinical Laboratory Improvement Amendments; dMMR, mismatch repair deficient/deficiency; FDA, US Food and Drug Administration; HRd, homologous recombination deficiency; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network; PARPi, poly (ADP-ribose) polymerase inhibitor.

GOG FOUNDATION®

What kind of biomarkers?

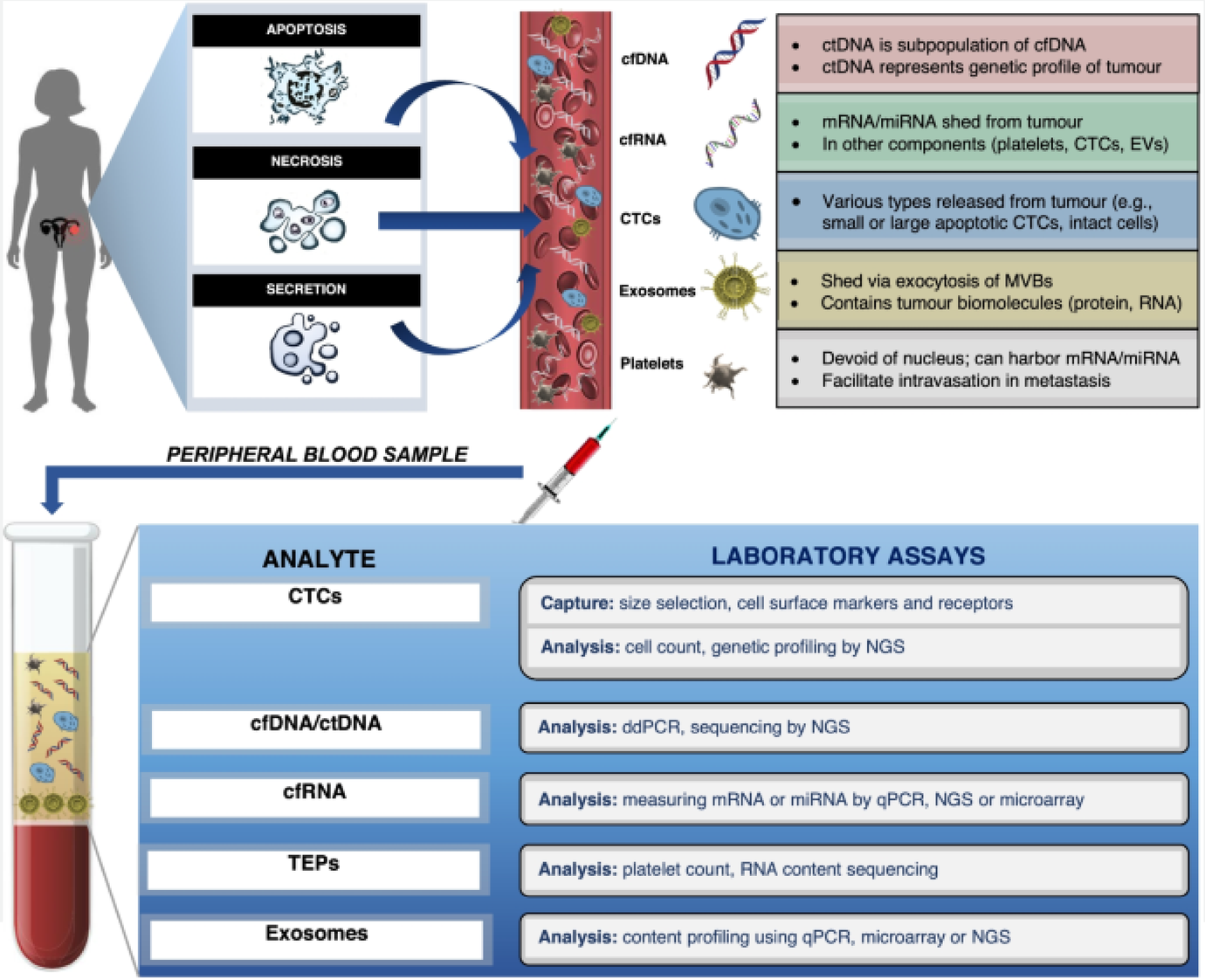
- **Early Detection**
  - Markers with sensitivity and specificity to identify cancers at a stage where they are curable

- **Diagnostic**
  - Markers which accurately determines the diagnosis and presence of the cancer

- **Prognostic**
  - Markers which predict patient outcome

- **Predictive**
  - Markers which predict clinical event i.e. response, toxicity etc.
  - CDx, IVD, IDE, CDRH, PMA

Potential clinical utility of liquid biopsies in ovarian cancer: Screening, minimal residual disease (MRD), molecular profiling



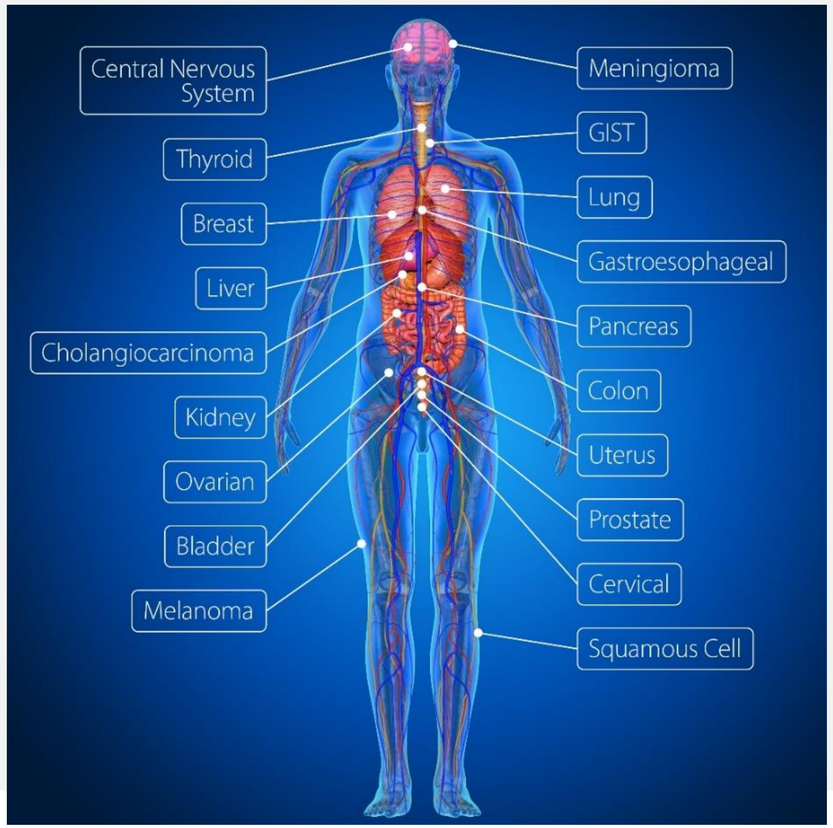
Zhu JW et. al. Mol Cancer. 2022 May 11;21(1):114.

GOG FOUNDATION®

“Genomic Prevalence Score” Informs and Corrects Diagnoses

6559 Machine learning models

MI GPSai™ 2.0

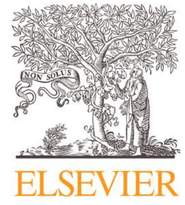


MI GPSai™ is a Cancer Type Similarity Score

- **Analyzes a tumor’s molecular signature and provides the prevalence of that signature against the clinico-genomic database across 21 cancer categories**

Clinical Utility

- **Diagnostic Verification on Every Case, Cancer of unknown primary (CUP) and Atypical clinical presentation or cases with clinical ambiguity**
- **> 4000 CUP Calls to Date**



Machine learning analysis using 77,044 genomic and transcriptomic profiles to accurately predict tumor type

Jim Abraham[a,b], Amy B. Heimberger[c], John Marshall[d], Elisabeth Heath[e], Joseph Drabick[f], Anthony Helmstetter[a], Joanne Xiu[a], Daniel Magee[a], Phillip Stafford[a], Chadi Nabhan[a,g], Sourabh Antani[a], Curtis Johnston[a], Matthew Oberley[a], Wolfgang Michael Korn[a,h], David Spetzler[a,b,*]

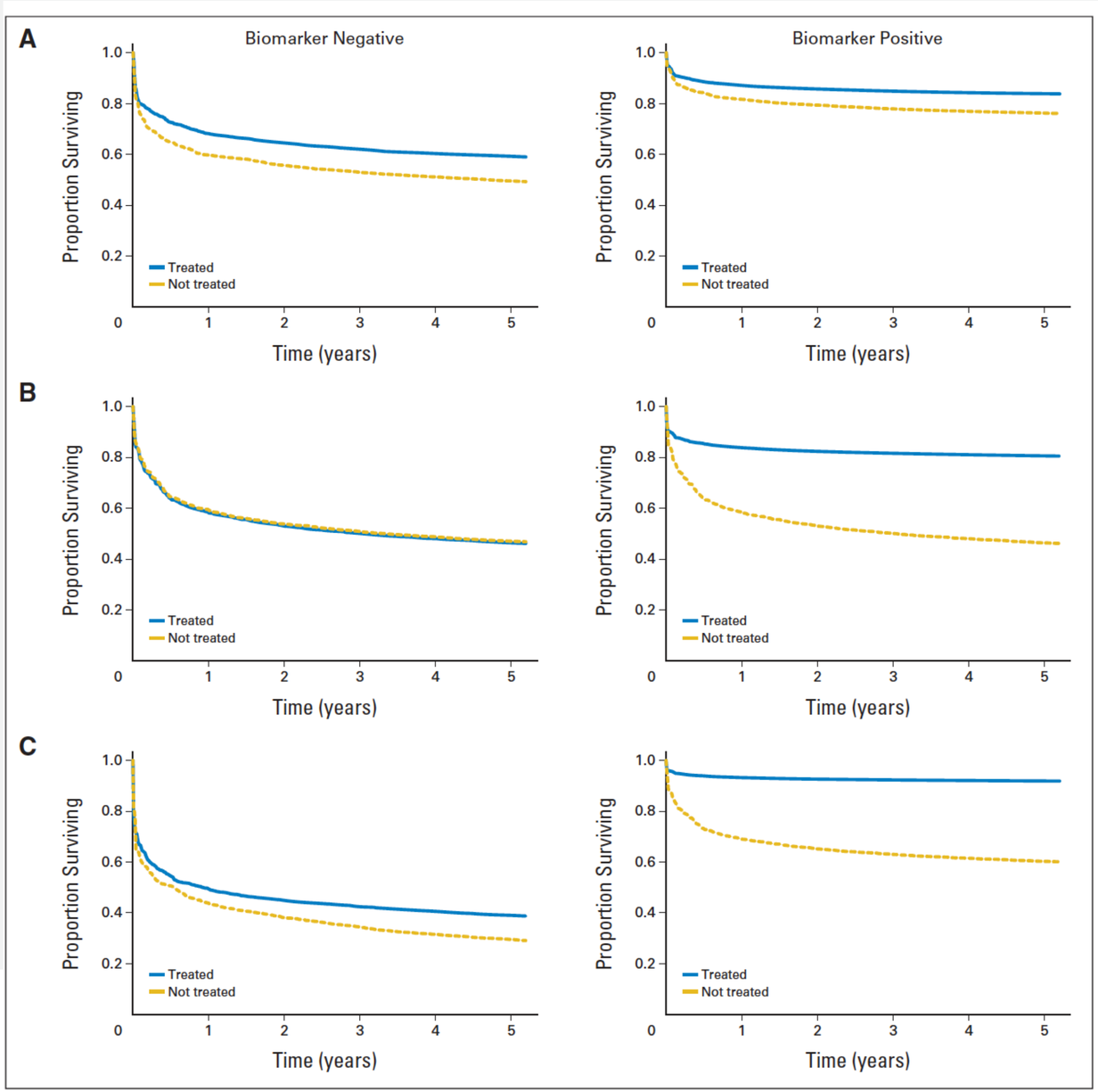
ELSEVIER

Development and Accuracy

- **Trained on genomic data from 34,000+ cases and transcriptomic data on more than 23,000+ cases**
- **In a validation set of 19,000+ cases, GPS predicted the cancer category with an accuracy of over 94%**

Assay	Cancer Categories	N Independent Test Set	Accuracy (%)	Cases Called (%)
Caris MI GPSai 2020	21	13,661	94.7	93
PCAWG 2020	14	1,436	88	100
MSK IMPACT 2019	22	11,644	74.1	100
Cancer Genetics Tissue of Origin 2012	9	27	94.1	89
Biotheranostics CancerTYPE ID 2011	30	187	83	100
Park SY 2007	7	60	75	78
Dennis JL 2005	7	130	88	100
Brown RW 1997	5	128	66	86
Gamble AR 1993	14	100	70	100

Biomarker: Predictive or prognostic?



A) Purely **prognostic** biomarker: The biomarker-positive patients have a better survival than biomarker-negative patients, independent of treatment group.

B) Purely **predictive** marker: There is only a treatment effect for biomarker-positive patients.

C) Biomarker that is **both predictive and prognostic**. This is also an example of a quantitative interaction.

Ballman KV. J Clin Oncol. 2015 Nov 20;33(33):3968-71.

GOG FOUNDATION

Companion Diagnostics (CDx)

- In 2014, the FDA issued a regulatory guidance document on **CDx**, which defines this **type of assay** as an in vitro diagnostic device (**IVD**) that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of a CDx is stipulated in both the assay instructions for use (**IFU**) and in the labeling of the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.

1) Identify patients who are most likely to **benefit** from a particular therapeutic product;
2) Identify patients likely to be at increased risk for **serious side effect**;
3) **Monitor response** to treatment

- ✓ Requires an Investigational Device Exemption (**IDE**) in a clinical trail.
- ✓ Regulated by Center for Devices and Radiological Health (**CDRH**).
- ✓ Premarket approval (**PMA**) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics
https://www.fda.gov/media/81309/download
https://www.fda.gov/media/99030/download
https://www.fda.gov/about-fda/fda-organization/center-devices-and-radiological-health
https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma

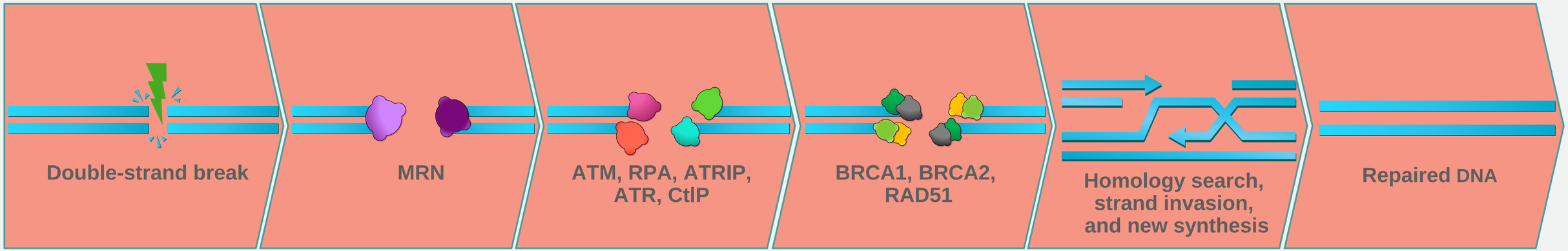
Ovarian Cancer: Histology specific biomarkers

- High grade serous and endometrioid:
  - HRD, *BRCA1/2,* other HRR genes, *TP53*, *AXL*, Folate receptor-α, *MAPK*, *MYC*, *CCNE1,* HER2
  - Deletions and large genomic rearrangements
- Ovarian cancer-mucinous:
  - *KRAS*, HER2, *CDX2, MSI, TMB*
- Ovarian cancer low grade:
  - *KRAS*, *NRAS*, *ESR1, HER2, MSI, TMB*
- Ovarian cancer-clear cell
  - *CDKN2A*, *ARID1A*, *ESR1, MSI, TMB*
- Others?

Approximately 50% of ovarian cancers are characterized by HRD[1]

- HRd cells cannot accurately repair double-strand breaks
- HR is the only high-fidelity pathway for DSB repair[2]
- Germline, somatic mutations or other unknown factors in components of the HR pathway can cause HRd[1,2]
- Cells with HRd rely on NHEJ, an error-prone process, to repair DSBs[1,2]

HR pathway overview[3]



HRd is associated with accumulation of mutations and other genomic alterations[1,2]

ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; ATRIP, ATR interacting protein; BRCA, breast cancer susceptibility gene; CtIP, C-terminal binding protein interacting protein; DSB, double-strand break; HR, homologous recombination; HRd homologous recombination deficient/deficiency; MRN, Mre11/Rad50/Nbs1 complex; NHEJ, nonhomologous end joining; RAD51, DNA repair protein RAD51 homolog 1; RPA, replication protein A.

1. Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137-54; 2. Curtin NJ. *Nat Rev Cancer*. 2012;12:801-17; 3. Peng G, et al. *World J Clin Oncol*. 2011;2:73-9.

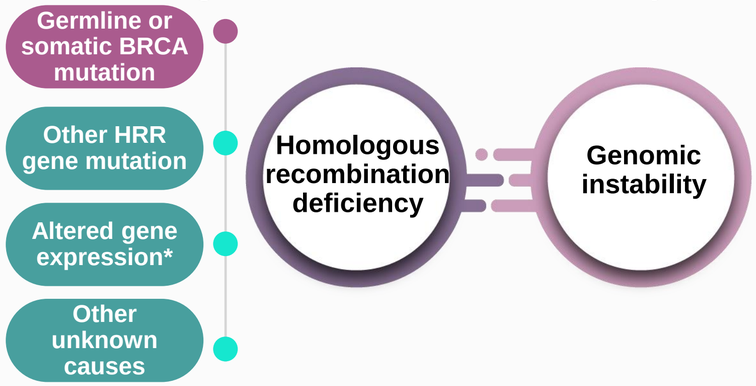
What is homologous recombination deficiency?

Homologous recombination deficiency describes the phenotype (or characteristic) of a cell/tumour that has impaired ability to conduct homologous recombination repair (HRR)[1]

Cells that are homologous recombination deficient (HRD-positive) are unable to perform HRR to accurately repair DNA double-strand breaks (DSBs)[1,2]

Many different events can impair the HRR pathway, resulting in homologous recombination deficiency[1]

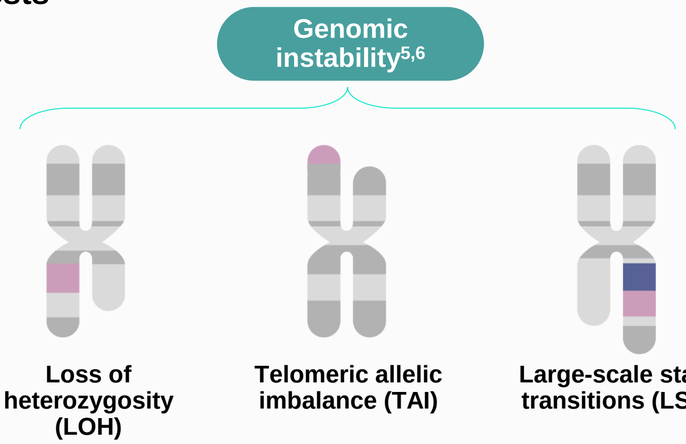
BRCA mutations are the archetypal cause of homologous recombination deficiency[3]



Adapted from Konstantinopoulos 2015

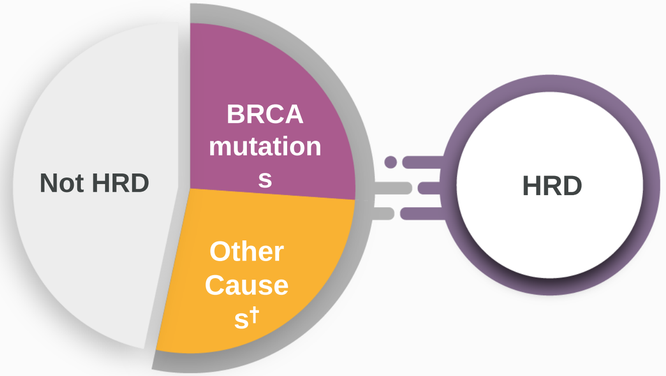
HRD-positive cells rely on error-prone repair pathways which results in genomic instability and increases the risk of acquiring a mutation that leads to malignant transformation[1,4]

Repair of DSBs by error-prone pathways leads to characteristic DNA aberrations such as: loss of heterozygosity (LOH), telomeric allelic imbalance (TAI) and large-scale state transitions (LST), which can be identified in genomic instability tests[5,6]



HRR gene panels (such as BRCA testing) look for the 'cause' of HRR loss, whereas HRD genomic instability tests look for the 'effect' of HRR loss[7]

BRCA testing alone does not identify all ovarian cancer patients with homologous recombination deficiency as many can have high genomic instability from alternative causes[8]



Adapted from Konstantinopoulos 2015

*For example, epigenetic silencing of *BRCA1* via promoter hypermethylation has been reported in ovarian cancer. †Other HRR gene mutation, altered gene expression, other unknown causes

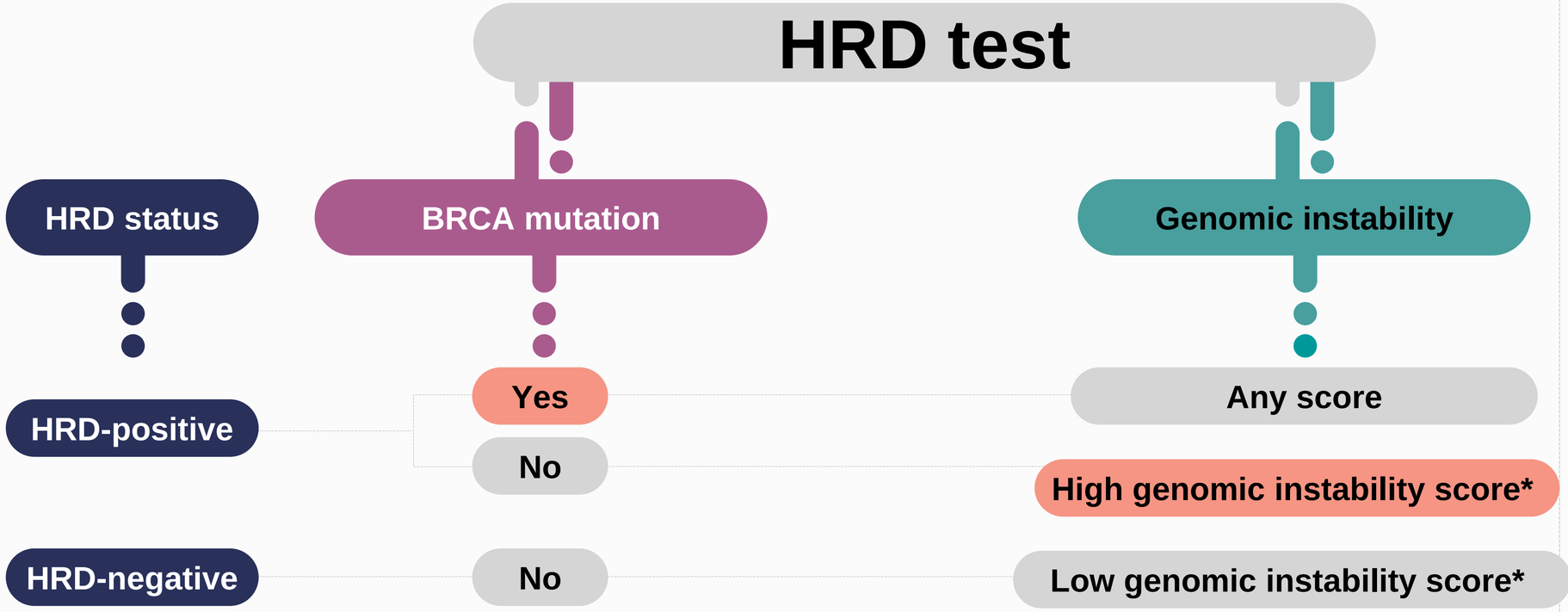
DSB=double-strand break; HRD=homologous recombination deficiency; HRR=homologous recombination repair; LOH=loss of heterozygosity; LST=large-scale state transition; TAI=telomeric allelic imbalance

1. Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5:1137–1154; 2. O'Connor MJ. *Mol Cell*. 2015;60:547–560; 3. Bonadio RRCC, et al. *Clinics (Sao Paulo)*. 2018;73(Suppl 1):e450s; 4. Frey MK and Pothuri B. *Gynecol Oncol Res Pract*. 2017;4:4; 5. Watkins JA, et al. *Breast Cancer Res*. 2014;16(3):211; 6. Timms KM, et al. *Breast Cancer Res*. 2014;16(6):475; 7. Pellegrino B, et al. *ESMO Open*. 2019;4(2):e000480; 8. Ray-Coquard I, et al. Presented at ESMO Annual Congress 2019. 27 September–1 October. Barcelona, Spain. Presentation LBA2_PR

GOG FOUNDATION

What is a HRD test and how is BRCA testing involved?

Clinically validated methods to detect HRD in newly diagnosed ovarian cancer require BRCAm testing and scoring of genomic instability[1,2] HRD tests require tumour tissue samples[1]



If a patient has a BRCAm they will be HRD-positive[1,2]

Commercially available HRD tests often determine BRCA status and measure genomic instability. Separately, if a BRCAm is detected, it is common for a patient to also receive reflex germline testing to identify if the mutation is of germline origin, which may have familial implications[3]

If a HRD test does not detect a BRCAm, a patient can still be HRD-positive if they have a high genomic instability score (for example, genomic instability score ≥42 in the Myriad myChoice® CDx assay)[1,2]

*For example, a HRD cut-off score of 42 is used in the Myriad myChoice® CDx assay. HRD cut-off scores differ depending on the HRD test used

CDx=companion diagnostic; BRCAm=BRCA mutation; CDx=companion diagnostic; HRD=homologous recombination deficiency

1. Myriad myChoice HRD Technical Specifications. Available at: https://myriad-web.s3.amazonaws.com/myChoice/downloads/myChoiceHRDTechSpecs.pdf. Accessed February 2022; 2. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416–2428; 3. Sundar S, et al. *Int J Gynecol Cancer*. 2021;31(2):272–278

GOG FOUNDATION®

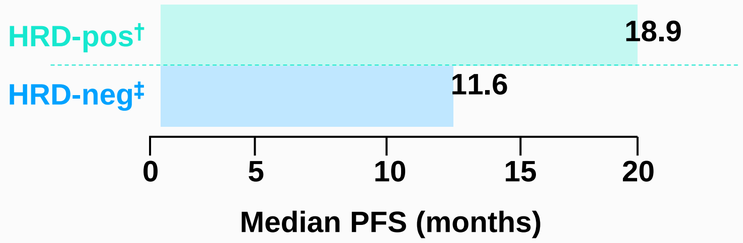
Why is detecting HRD important for people with ovarian cancer?

HRD status has both prognostic and predictive implications for the patient[1]
Understanding a person's HRD status can optimise patient care through eligibility for, and potential access to, treatments that target underlying biological drivers of disease[1]

Prognostic value[2–4]

People with ovarian cancer with high levels of genomic instability display longer PFS and OS with treatment than those with low levels of genomic instability[2]

Upon receiving HRD test results, subsequent reflex gBRCA testing can also inform both personal risk to future cancers,[3] and family members at risk to cancer[4]

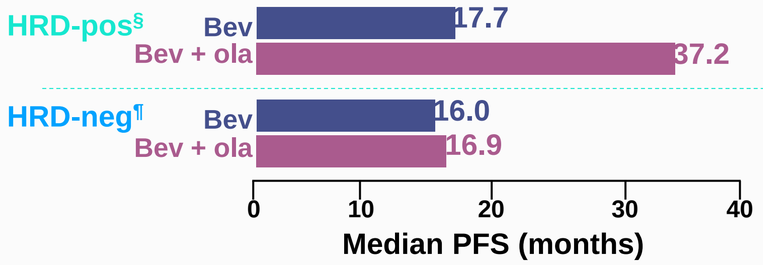


Survival outcomes following 1L carboplatin monotherapy per HRD status in people with aOC in SCOTROC4[*5]

Predictive value[6,7]

HRD is present in ~50% of newly diagnosed high-grade epithelial ovarian cancers.[1,7] Tumours with HRD are sensitive to PARP inhibition[4]

Identification of HRD predicts for magnitude of benefit for PARPi therapy; for example, in the Phase III PAOLA-1 trial of olaparib + bevacizumab vs. bevacizumab alone as maintenance treatment in 1L ovarian cancer[7]



PFS by HRD status in people with aOC in PAOLA-1[7]

Eligibility for, and potential access to, certain treatments

Testing for HRD should be considered at diagnosis to inform treatment decisions for people with ovarian cancer[8,9]

Olaparib, a PARPi agent, in combination with bevacizumab has been approved by the FDA and EMA for the 1L maintenance treatment of people with newly diagnosed advanced ovarian cancer[10,11]

Countries outside the remit of the FDA and EMA may have different approvals. Reimbursement via insurance or national health systems is different between individual countries and regions

GOG FOUNDATION®

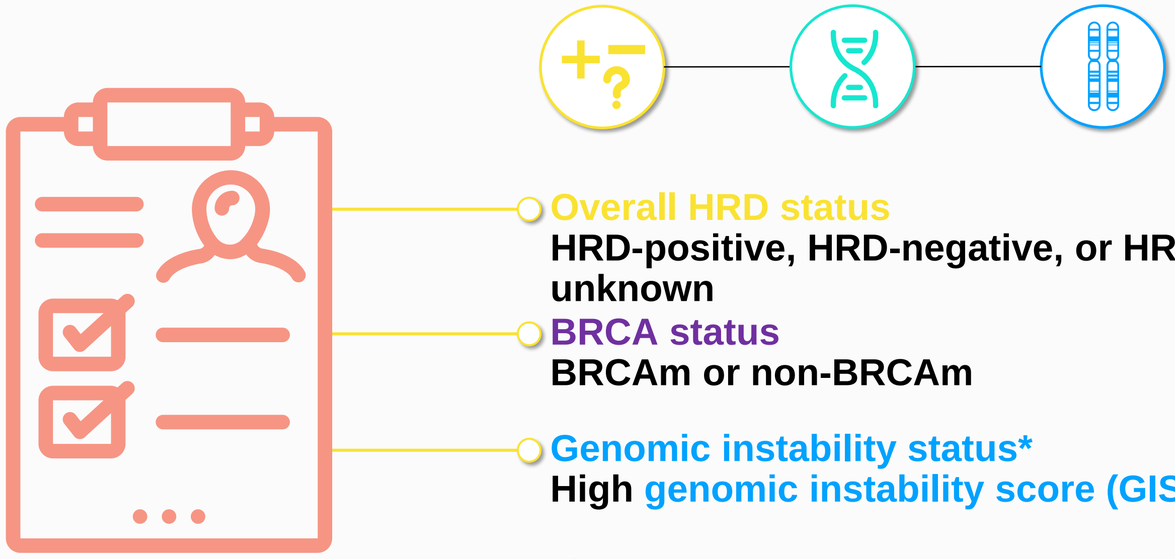
How are HRD test results interpreted?

Testing for HRD assesses both: mutations in *BRCA1* or *BRCA2* and genomic instability[1]

Commercially available tests, such as the Myriad myChoice® CDx assay, will test for both of these parameters and provide the results on the same report.

Please note that the exact format for HRD testing outputs vary between the specific tests and locations[1]

A HRD test report should contain three main results:



Overall HRD status
HRD-positive, HRD-negative, or HRD-unknown

BRCA status
BRCAm or non-BRCAm

Genomic instability status*
High genomic instability score (GIS) or low GIS†

The GIS and associated cut-off score may be provided as additional information depending on the HRD test used

Example HRD test report form: Myriad myChoice® CDx HRD test

Myriad HRD Status: POSITIVE

GIS Status: **POSITIVE**

The Genomic Instability Score (GIS) is a measurement of three biomarkers (loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions) associated with homologous recombination deficiency.

Tumor Mutation *BRCA1/BRCA2* Status: **NEGATIVE FOR A CLINICALLY SIGNIFICANT MUTATION**

ASSAY DESCRIPTION

Intended Use: Myriad myChoice® CDx is a next generation sequencing-based *in vitro* diagnostic test that assesses the qualitative detection and classification of single nucleotide variants, insertions and deletions, and large rearrangement variants in protein coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes and the determination of Genomic Instability Score (GIS) which is an algorithmic measurement of Loss of Heterozygosity (LOH), Telomeric Allelic Imbalance (TAI), and Large-scale State Transitions (LST) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The results of the test are used as an aid in identifying ovarian cancer patients with positive homologous recombination deficiency (HRD) status, who are eligible, because of a positive test result for deleterious or suspected deleterious mutations in *BRCA1* or *BRCA2* genes, or may become eligible, because of a positive test result for deleterious or suspected deleterious mutations in *BRCA1* or *BRCA2* genes or a positive Genomic Instability Score, for treatment with the targeted therapy listed in Table 1 in accordance with the approved therapeutic product labeling.

TABLE 1: Companion diagnostic indications

Tumor Type	Biomarker	Therapy
Ovarian Cancer	Myriad HRD, defined as: • deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes and/or • positive Genomic Instability Score	Lynparza® (olaparib)‡ Zejula® (niraparib)

‡ Refer to the drug label for HRD definition for olaparib monotherapy or combination therapy.

Detection of deleterious or suspected deleterious *BRCA1* and *BRCA2* mutations and/or positive Genomic Instability Score in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib) maintenance therapy. This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, Inc., a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108

THE FOLLOWING INFORMATION HAS NOT BEEN REVIEWED AND APPROVED BY THE FDA.

COMPREHENSIVE GENE ANALYSIS

Genes Fully Analyzed: *BRCA1, BRCA2*

Genes Partially Analyzed †:

Genes Not Analyzed:

† Complete analysis was not able to be performed on limited regions of specific genes, which shall be provided upon request.

Patient Genomic Instability Score: 67
A Genomic Instability Score (GIS) of 42 or greater confers a positive GIS status.

VARIANT CLASSIFICATION AND ANALYSIS DESCRIPTION

Myriad's myVision® Variant Classification Program performs ongoing evaluations of variant classifications. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report. The classification and interpretation of all variants identified in this assay reflects the current state of Myriad's scientific understanding at the time this report was issued. Variant classification and interpretation may change for a variety of reasons, including but not limited to, improvements to classification techniques, availability of additional scientific information, and observation of a variant in more patients. For more detailed information including Performance Characteristics, please find the complete Technical Information at: bit.ly/myChoiceCDxSpecs.

*GIS may also be provided by some laboratories. †For example, a HRD cut-off score of 42 is used in the Myriad myChoice® CDx assay. HRD cut-off scores differ depending on the HRD test used
BRCAm=BRCA mutation; CDx=companion diagnostic; GIS=genomic instability score; HRD=homologous recombination deficiency

1. Myriad myChoice® HRD Technical Specifications. Available at: https://myriad-web.s3.amazonaws.com/myChoice/downloads/myChoiceHRDTechSpecs.pdf. Accessed February 2022

GOG FOUNDATION®

Current Landscape of HRD Testing in Ovarian Cancer

Myriad myChoice

- GIS = LOH + TAI + LST
  - Loss of Heterozygosity (**LOH**) – 26,000 SNPs
  - Telomeric Allelic Imbalance (**TAI**)
  - Large-scale State Transition (**LST**)
- Somatic BRCA1/2 Status
- **Positive**: BRCA1/2 Pathogenic **or** GIS>=42
- Companion diagnostic for Olaparib and niraparib in ovarian cancer

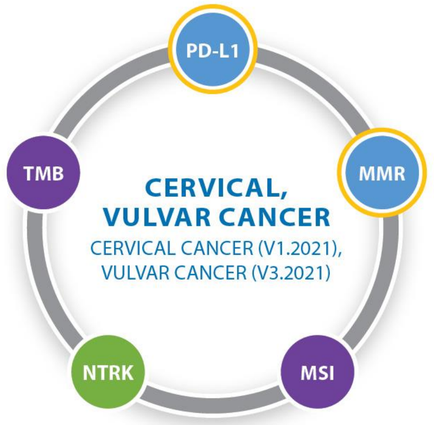
FoundationOne CDx BRCA+LOH

- LOH regions are inferred across 22 autosomal chromosomes using genome-wide copy number profile and minor allele frequencies of the single nucleotide polymorphisms (SNPs)
- LOH regions spanning across >=90% of a whole chrome/arm excluded
- BRCAmut, BRCAwt/LOHhigh (LOH ≥16%)
- Companion diagnostic for rucaparib

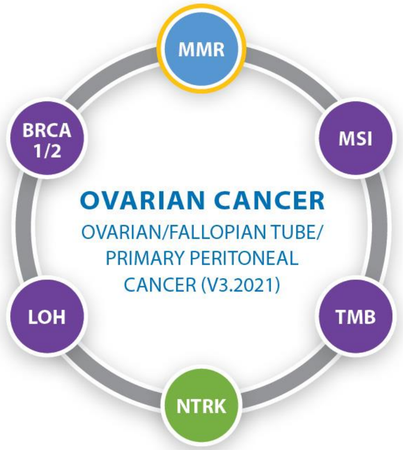
Trial	Drug	Setting	Test	Outcome
NOVA	Niraparib	Platinum-sensitive after response, maintenance	myChoice	Efficacy regardless of HRD, greater benefit in HRD+
PRIMA	Niraparib	1st line maintenance	myChoice	Efficacy regardless of HRD, greater benefit in HRD+
PAOLA	Olaparib	1st line maintenance	myChoice	Efficacy regardless of HRD, greater benefit in HRD+
ATHENA-M	Rucaparib	1st line maintenance	Foundation One CDx	Efficacy regardless of HRD, greater benefit in HRD+
Study 1	Olaparib	≥3 line	BRACAnalysis CDx	Efficacy in germ line BRCA 1 and 2
QUADRA	Niraparib	≥3 line	myChoice	Efficacy in HRD
ARIEL2	Rucaparib	≥2 line	FoundationFocus	Higher efficacy in BRCA1/2 and/or LOH high compared to LOH low
ARIEL3	Rucaparib	Platinum-sensitive after response, maintenance	Foundation One CDx	Efficacy regardless of LOH. Magnitude of benefit dependent on LOH

https://myriad.com/oncology/mychoice-cdx/
https://www.foundationmedicine.com/test/foundationone-cdx

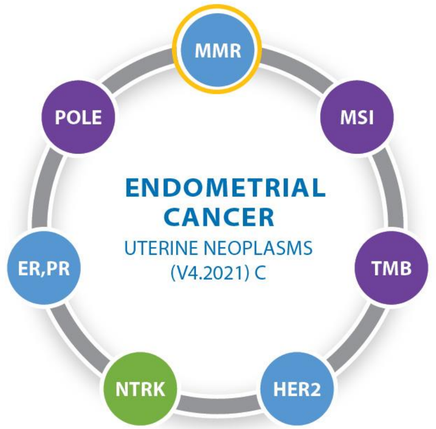
NCCN Guidelines: Gynecological Cancers Overview



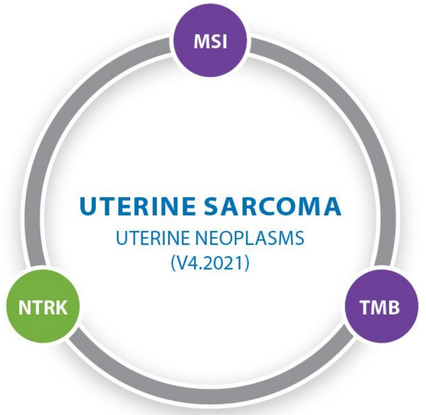
- FDA-approved PD-L1 (22c3) CDx in cervical cancer, NCCN recommended PD-L1(22c3) in vulvar cancer
- Genomic signatures TMB and MSI via WES
- Unbiased NTRK gene fusion detection via WTS



- Tumor molecular testing may be considered in the appropriate setting
- BRCA1/2 and HRD testing via WES
- gLOH as a measure of genomic instability via WES
- MMR deficiency assessed by IHC
- Genomic signatures TMB and MSI via WES
- Unbiased NTRK gene fusion detection via WTS
- **FRα**



- ER, PR, MMR based on IHC.
- HER2 IHC/ISH for serous endometrial cancer using appropriate cut-off.
- POLE mutations via WES
- Genomic signatures TMB and MSI via WES
- Unbiased NTRK gene fusion detection via WTS



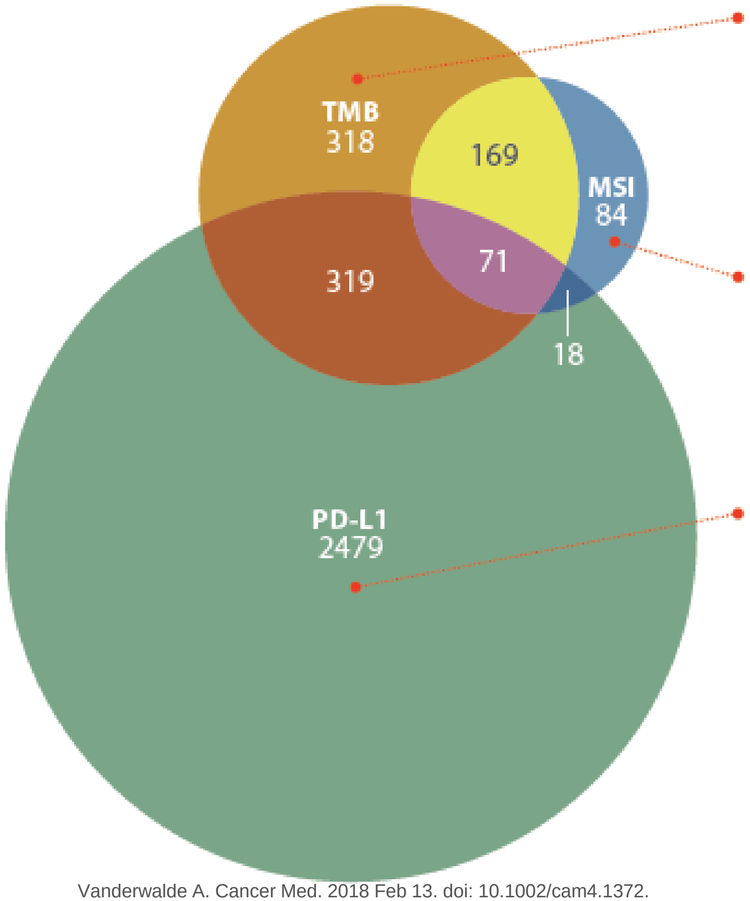
- Comprehensive genomic profiling is informative and should include at least NTRK, MSI, and TMB.
- Relevant molecular findings (e.g. EPC1/2, FGFR2, FGFR4, JAZF1, PTEN, *et cetera*) for uterine sarcomas can be evaluated using WES, WTS.

WTS | RNA **IHC/ISH** | Protein/Gene **NGS** | DNA **FDA approved CDx**

Update as per NCCN 2023

GOG FOUNDATION®

Unlock the Power of Immune Checkpoint Inhibitors



Vanderwalde A. Cancer Med. 2018 Feb 13. doi: 10.1002/cam4.1372.

Tumor mutational burden (TMB) measures the total number of non-synonymous somatic mutations identified per megabase of the genome coding area. Tumors with high TMB likely harbor neoantigens and may respond more favorably to immunotherapies.[4-5,7]

Microsatellite instability (MSI) is caused by failure of the DNA mismatch repair (MMR) system.[3] MSI-High correlates to an increased neoantigen burden, which may indicate the tumor is more likely to respond favorably to immunotherapies.

~~Programmed death ligand-1 (PD-L1)~~ is among the most important checkpoint proteins that mediate tumor-induced immune suppression through T-cell downregulation.[5,8] PD-L1 expression may indicate a more likely response to immunotherapies.[2,9-11]

1. Topalian SL. N Engl J Med. 2012;366(26):2443-2454. doi:10.1056/NEJMoa1200690. – 2. Patel SP and Kurzrock R. Mol Cancer Ther. 2015;14(4):847-856. doi:10.1158/1535-7163.MCT-14-0983. – 3. Le DT. N Engl J Med. 2015;372:2509-2520. doi:10.1056/NEJMoa1500596. – 4. Rizvi NA. Science. 2015; 384(6230):124-128. doi:10.1126/science.aaa1348. – 5. Rosenberg JE. The Lancet. 2016; 387(10031):1909-1920. doi:10.1016/S0140-6736(16)00561-4. – 6. Motzer RJ. N Engl J Med. 373:1803-1813. doi:10.1056/NEJMoa1510665. – 7. Snyder A. N Engl J Med. 2014; 371:2189-2199. doi:10.1056/NEJMoa1406498. – 8. Mellman I. Nature. 2011;480:480-489. doi:10.1038/nature10673. – 9. Borghaei H. N Engl J Med. 2015;373:1627-39. doi:10.1056/NEJMoa1507643. – 10. Garon EB. N Engl J Med. 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824. – 11. Taube JM. Clin Cancer Res. 2014;20(19):5064-5074. doi:10.1158/1078-0432.CCR-13-3271.
12. Vanderwalde A. Cancer Med. 2018 Feb 13. doi: 10.1002/cam4.1372.

FRα: An Actionable Therapeutic Target in Platinum-Resistant Ovarian Cancer [1]

New Addition to NCCN

Prevalence of FRα expression[2-4]

- **FRα is a folate transport protein that is expressed in 90% of patients with ovarian cancer and has limited expression on normal tissue—making it an attractive therapeutic target**

~35% of patients with ovarian cancer have high levels of FRα expression[5]

- **Because FRα levels remain relatively unchanged following chemotherapy, expression can be tested upon diagnosis or at progression[5,6]**

With the approval of mirvetuximab - soravtansine-gynx, FRα is now an actionable target for platinum-resistant ovarian cancer[1]

FRα, folate receptor alpha.

1. ELAHERE. Package insert. ImmunoGen, Inc.; 2022. 2. Toffoli G, et al. *Int J Cancer*. 1997;74(2):193–198. 3. Markert S, et al. *Anticancer Res*. 2008;28(6A):3567–3572. 4. Parker N,

FRα: An Actionable Therapeutic Target in Platinum-Resistant Ovarian Cancer [1]

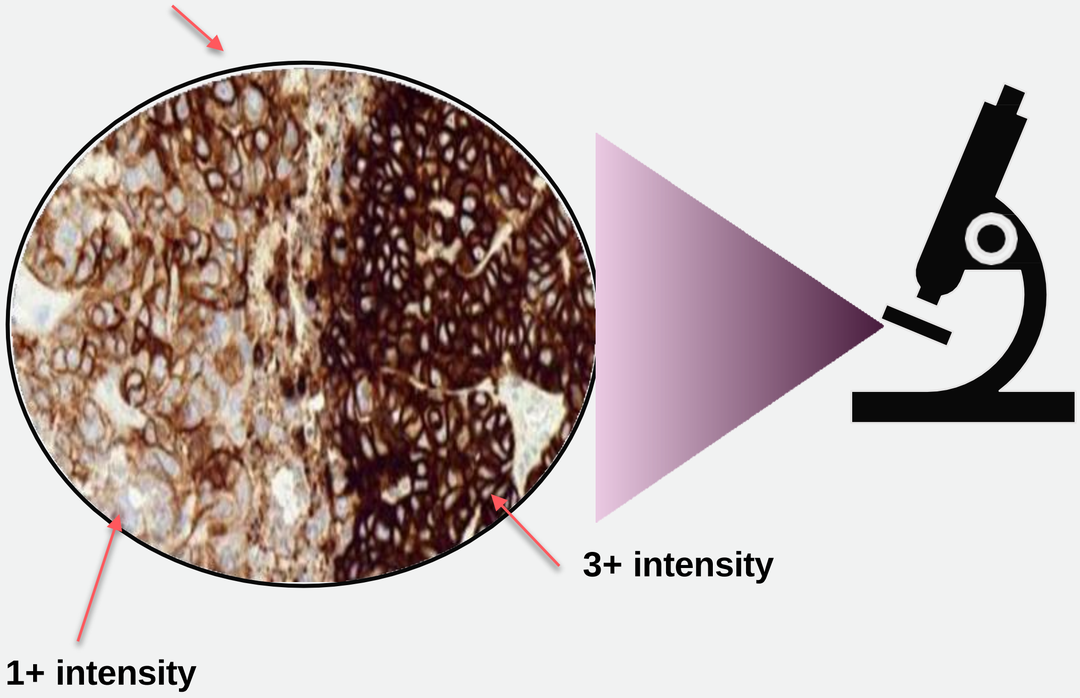
Testing for FRα expression

- The VENTANA FOLR1 IHC[a] assay is the first FDA-approved companion diagnostic test for determining FRα expression[2]
  - This test can be run on fresh or archival tissue[3]
- Platinum-resistant patients who test positive by the VENTANA FOLR1 IHC[a] assay are candidates for treatment with ELAHERE[1,2]
  - FRα positivity is defined as ≥75% of tumor cells staining with 2+ intensity

Test all patients with ovarian cancer for FRα at diagnosis to be ready to treat at first sign of platinum resistance[1,4]

FRα-high[5]

≥75% of viable tumor cells with 2+ intensity



FRα, folate receptor alpha; FOLR1, folate receptor 1; IHC, immunohistochemistry.
[a]VENTANA FOLR1 (FOLR1-2.1) RxDx Assay.

1. ELAHERE. Package insert. ImmunoGen, Inc.; 2022. 2. VENTANA FOLR1 (FOLR1–2.1) RxDx Assay. Prescribing Information. Roche; 2022. 3. Data on file. ImmunoGen, Inc. Waltham, MA.
4. Despierre E, et al. *Gynecol Oncol*. 2013;130(1):192–199. 5. Matulonis UA, et al. Abstract presented at: 2022 Society of Gynecologic Oncology Annual Meeting; March 19-22, 2022;

Ovarian Cancer: Histology specific biomarkers

- High grade serous and endometrioid:
  - HRD, *BRCA1/2,* other HRR genes, *TP53*, *AXL*, Folate receptor-α, *MAPK*, *MYC*, *CCNE1,* HER2
  - Deletions and large genomic rearrangements
- Ovarian cancer-mucinous:
  - *KRAS*, HER2, *CDX2, MSI, TMB*
- Ovarian cancer low grade:
  - *KRAS*, *NRAS*, *ESR1, HER2, MSI, TMB*
- Ovarian cancer-clear cell
  - *CDKN2A*, *ARID1A*, *ESR1, MSI, TMB*
- Others?

Thank You

HONORHEALTH. Virginia G. Piper Cancer Center

AZCCC Arizona Center for Cancer Care

THE UNIVERSITY OF ARIZONA

Creighton University School of Medicine

Patient Care
Teaching
Research

GOG FOUNDATION®

HONORHEALTH®

Research Institute

bmonk@gog.org