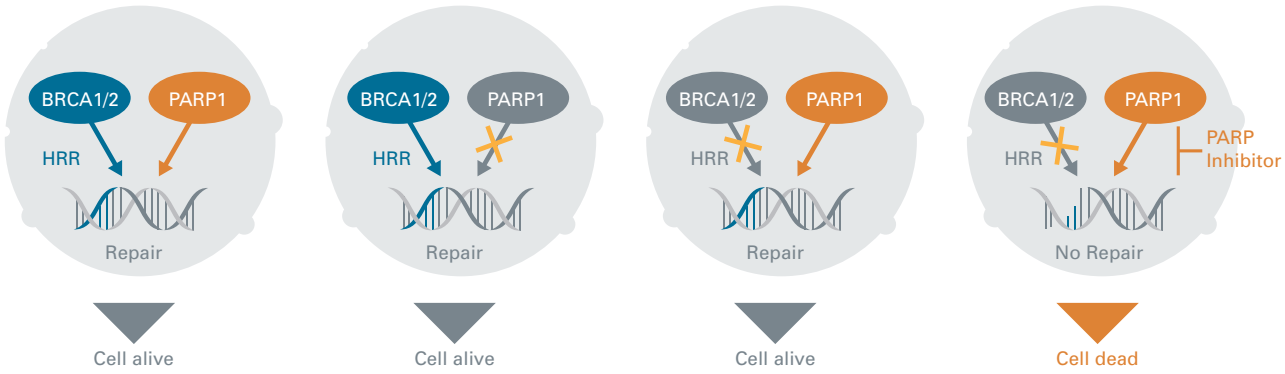
INTRODUCTION

An estimated 21,750 women will receive a new diagnosis of ovarian cancer in 2020 in the U.S.[1] Due to the subtlety of ovarian cancer symptoms and also a lack of an effective screening strategy, most women are diagnosed at an advanced stage (III or IV), and have a five-year survival rate of approximately 30%.[2] Ovarian cancer is also notoriously difficult to treat, with a high risk of recurrence even after surgery and chemotherapy. These factors have left women with few options in the late stage treatment setting.

An exciting new class of drugs, poly (ADP-ribose) polymerase (PARP) inhibitors, has shown meaningful clinical results in multiple studies, as both a late-line treatment and first line maintenance therapy. PARP inhibitors, such as Zejula® (niraparib) and Lynparza® (olaparib), work by blocking the PARP enzymes from helping to repair single stranded DNA breaks in cancer cells. This class of drugs works best when there is also damage to the repair mechanisms in the double strand break repair pathway – the highest fidelity repair mechanism being homologous recombination (HR). The HR pathway includes the *BRCA1* and *BRCA2* genes. Patients with homologous recombination deficiency (HRD) status and/or abnormal BRCA genes are most likely to respond to targeted therapy from PARP inhibitors. The single strand (PARP) and double strand (HRD) repair pathways both need to be broken to see the best results from parp inhibitor therapy. See Figure 1.

Figure 1: HRD and Impact on PARP Inhibitors

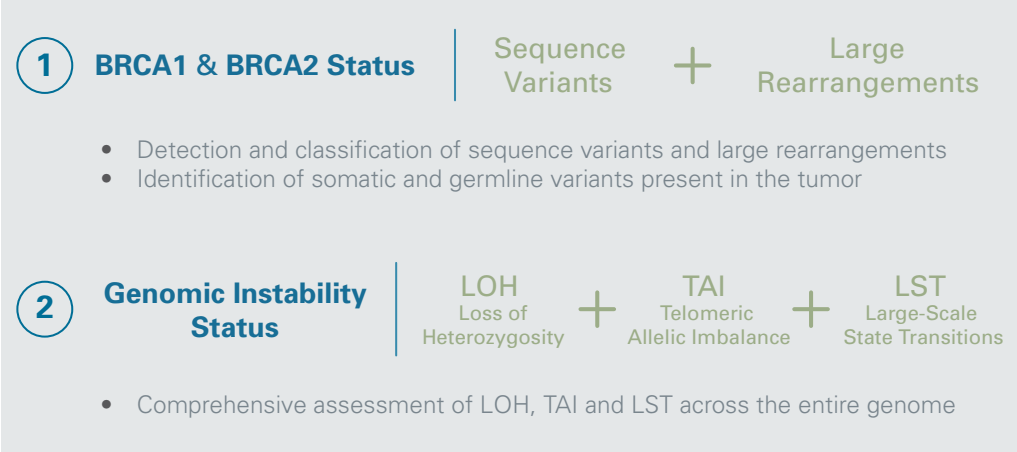


BRCA1 and BRCA2 allele are relatively resistant to PARP inhibition, while cells with BRCA1 or BRCA2 dysfunction lacking wild-type BRCA1 or BRCA2 (homologous recombination deficient mutant cells) are profoundly sensitized to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis.[4,5]

myChoice® CDx from Myriad Genetics, Inc., is the first and only FDA-approved tumor test that determines (HRD) status using two individual methods: 1) detecting deleterious or suspected deleterious BRCA gene mutations and 2) assessing genomic instability. (See Figure 2.) Most diagnostic tests on the market analyze only *BRCA1/2* sequencing status – myChoice provides the most comprehensive analysis of *BRCA1/2* by also including full large rearrangement testing to detect an additional 10% of mutations. While mutations in *BRCA1/2* is the most common cause of HRD, myChoice also looks for the downstream effects of HRD by measuring three critical biomarkers across the entire tumor genome: loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions. myChoice's unique methodology allows clinicians to quickly and accurately identify

which patients would preferentially benefit from treatment with Zejula® (niraparib), or Lynparza® (olaparib) in combination with bevacizumab.

Figure 2: myChoice's proprietary algorithm identifies which patients are most likely to benefit from the therapy.



TEST DESCRIPTION

The myChoice CDx test is performed on an ovarian tumor sample submitted to Myriad on formalin-fixed paraffin-embedded tumor blocks or slides that contain at least 40 microns of tumor (20% tumor by cellularity). Results are typically available in 14 days or less. Samples are returned to the ordering pathologist.

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 myChoice 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 Figure 3 in accordance with the approved therapeutic product labeling.

Figure 3: 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)

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.

CLINICAL TRIALS

PAOLA Study Summary

Olaparib has shown significant clinical benefit as maintenance therapy in women with newly diagnosed advanced ovarian cancer with a BRCA mutation. This randomized, double-blind, international phase 3 trial evaluated the clinical effect of combining maintenance olaparib and bevacizumab in newly diagnosed advanced ovarian cancer patients, regardless of BRCA mutation.

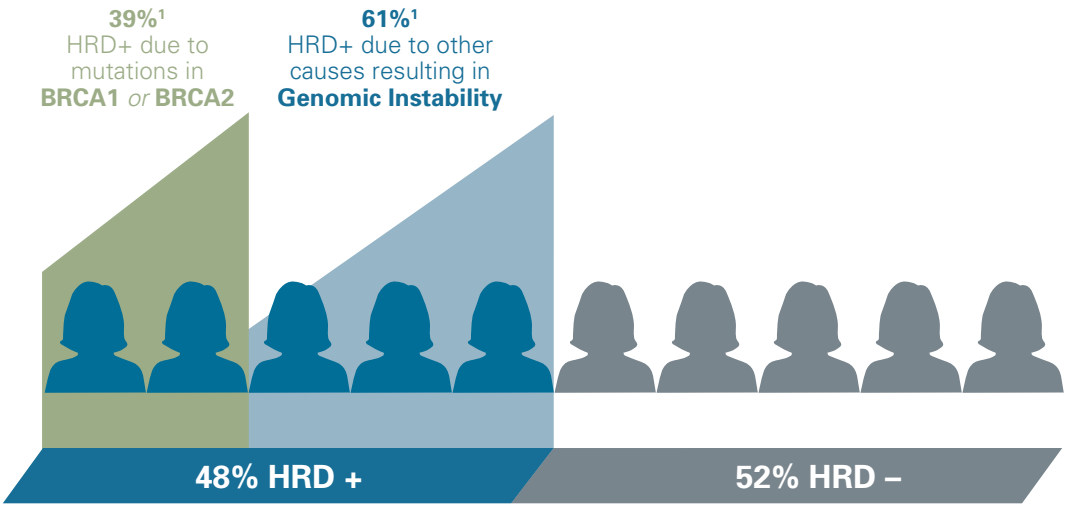
The study found that in patients with advanced ovarian cancer receiving first-line standard therapy including bevacizumab, the addition of maintenance olaparib provided a significant progression-free survival benefit, which was substantial in patients with HRD-positive tumors, including those without a BRCA mutation. Additionally, the data showed that women with HRD Negative tumors saw no benefit from olaparib and bevacizumab compared to bevacizumab alone.[3]

QUADRA Study Summary

> *"Ovarian cancer has a high rate of recurrence, so there is a real need for therapies for women whose cancer has progressed through multiple lines of treatment and who have few or no options left. It's meaningful to see that Zejula has been approved as a late-line treatment for women including those with and without BRCA mutations."*[4]
>
> Dr. Kathleen Moore, Lead Investigator of the QUADRA study; Director, Oklahoma TSET Phase 1 Program, and Associate Professor, Section of Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma.

The QUADRA study evaluated the safety and activity of niraprib in adult women with relapsed, advanced (grade 2 or 3) ovarian, fallopian tube, or primary peritoneal cancer, who have undergone three or more lines of chemotherapy. The results demonstrated clinically meaningful activity of niraparib, especially in women with HRD-positive platinum-sensitive disease, which includes patients with and without BRCA mutations.[3] In summary, the researchers found the data supported expanding the treatment indication for poly (ADP-ribose) polymerase inhibitors to include patients with HRD-positive ovarian cancer beyond those with BRCA mutations.[5]

Figure 3: myChoice CDx identifies more ovarian tumors with HRD than other testing methods



myChoice found 48% of women tested to be HRD+, including those who were platinum sensitive, resistant, and refractory.
1. Moore et al, Lancet Oncol 2019

FDA REVIEW PROCESS

The initial myChoice CDx PMA submission was granted priority review by the U.S. Food and Drug Administration due to unmet medical need for treatment of ovarian cancer. It was approved as a companion diagnostic.

The following studies, verifications, validations, and qualifications were performed and submitted to the FDA by Myriad Genetic Laboratories.

39 Non-Clinical Studies

- 4 Comparator Studies (Verification using comparator assay)
- 1 Analytical Bridging Study
- Equipment Qualifications-Qualification of all QSR laboratory equipment
- Software Validations-Validation of software subsystems
- Facilities Validations-Validation of QSR laboratory facility
- Clinical Validation Studies-assessment of safety and effectiveness of Zejula® (conducted by GSK) and the myChoice CDx test

On October 23, 2019, myChoice became commercially available as the first and only FDA-approved companion diagnostic that identifies women with advanced ovarian, fallopian, or primary peritoneal cancer who are candidates for Zejula® (niraparib).

On May 11, 2020, Myriad announced FDA approval of myChoice for use as a companion diagnostic to identify advanced ovarian cancer patients who are eligible, or may become eligible, for treatment with Lynparza® (olaparib) in combination with bevacizumab.

GUIDELINE INCLUSION

ASCO published new recommendations on the use of PARP inhibitors for the treatment and management of certain patients with advanced ovarian cancer. myChoice CDx is the only FDA-approved commercial companion diagnostic listed by name in the Guideline, which states that women with ovarian cancer and germline or somatic mutations in BRCA1 or BRCA2 genes and/or genomic instability – as determined by Myriad myChoice CDx – are recommended by ASCO for PARP inhibitor therapy. The guideline includes myChoice CDx guided management in both newly diagnosed and recurrent ovarian cancer.[6]

SUMMARY

Why myChoice CDx is the right choice for clinicians, patients, and payers:

Only FDA-approved tumor test to determine HRD status with two individual methods: *BRCA 1/2* status and genomic instability status.

Proprietary algorithm is the most accurate of any test on the market: over 2.5x as many patients identified as tumor BRCA testing and 3.5x as many patients as germline BRCA testing alone.

Supports targeted treatment and overall healthcare cost management by identifying which patients may – or may not – preferentially respond to therapy with Zejula® (niraparib) or Lynparza® (olaparib) in combination with bevacizumab.

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6. Tew W, et al. PARP inhibitors in the management of ovarian cancer: ASCO Guideline. J Clin Oncol. 2020 Aug 13. Online ahead of print.

myriad® WHEN DECISIONS MATTER