Myriad MyRisk® Plus Technical Specifications

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CE IVD

TEST RESULTS SHOULD BE USED ONLY AFTER REVIEW OF THE FOLLOWING SPECIFICATIONS

NOTE: Test results should be communicated to the patient in a setting that includes appropriate counseling.

Intended Use Statement:

Myriad Genetics MyRisk® Plus is a next generation sequencing based in vitro diagnostic device that provides sequencing and large rearrangement analyses for the qualitative detection and classification of variants on a panel of genes related to hereditary cancer using genomic DNA extracted from peripheral blood, saliva, and fibroblast specimens. MyRisk Plus may be used as a companion diagnostic to identify patients who are or may become eligible for treatment with specific therapies in accordance with the approved therapeutic product labeling. In addition, polygenic risk score analysis is also performed and reported for eligible patients. Results of these analyses are to be used by qualified health care professionals in accordance with professional society guidelines.

NOTE: *Analytical concordance studies have been performed with BRACAnalysis CDx test for BRCA1 and BRCA2.*

Contraindication

- Patients who have undergone a previous allogeneic bone marrow transplant or who have been diagnosed with certain hematologic malignancies (e.g., CLL) should not be tested with the MyRisk Plus test.
- Patients who have had an allogeneic bone marrow transplant cannot submit a blood or saliva specimen but may be able to submit a fibroblast sample.

Warnings and Precautions

- When drawing blood for the MyRisk Plus test, universal precautions for bloodborne pathogens should be observed.
- Genetic testing results on blood or saliva samples from patients with a hematologic malignancy, or patients who underwent allogeneic bone marrow transplants may not reflect their germline genetic status.
- Patients under consideration for testing who have been diagnosed with a hematologic malignancy, such as leukemia, could generate a positive (deleterious or suspected deleterious) result that is somatic, and not germline, due to chromosome instability.
- This test is designed to detect germline mutations, however:
  - in rare cases, testing blood or saliva derived DNA may identify somatic sequence variants that display allele frequencies within the expected range for heterozygous germline variants (e.g., in the *TP53* gene).
  - A negative test result on a blood or saliva specimen does not rule out the possibility of a somatic mutation in tumor tissue from patients affected with cancer.
- The classification and interpretation of all variants identified reflects the current state of scientific understanding at the time the result report is issued. In some instances, the classification and interpretation of variants may change as scientific information becomes available.

Limitations:

- For *in vitro* diagnostic use
- For professional use only
- Unequal allele frequencies in germline testing may result from certain DNA sequence contexts, including repetitive or low complexity sequences.
- The presence of pseudogenes, non-reference paralogous sequences, or gene conversion may complicate the detection of sequencing and large rearrangement (LR) mutations, potentially leading to decreased sensitivity and specificity, in certain genes such as *PMS2* and *SDHA*.
- There may be uncommon genetic abnormalities such as specific insertions, inversions, deep intronic and certain regulatory mutations that will not be detected by MyRisk Plus. Due to the potential location and complexity of retrotransposon insertions, not all events may be detected. This analysis, however, is believed to rule out the majority of abnormalities in the genes analyzed.

Description of Analysis:

The Myriad MyRisk® Plus assay includes germline DNA-based next generation sequencing (NGS) for sequence and large rearrangement (LR) analyses on a panel of genes related to Hereditary Cancer[i] using DNA extracted from peripheral blood, saliva, and fibroblast. Sequence and/or LR analysis can be performed for the following genes: *APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A* (*p16* and *p14ARF*), *CHEK2, CTNNA1, EGFR, EPCAM, FH, FLCN, GREM1, HOXB13, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RET, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TERT, TP53, TSC1, TSC2, VHL*, see Table 1 for details.

Unless otherwise specified, all coding regions and flanking non-coding regions are analyzed for sequence variation. Analysis of flanking intronic regions typically does not extend more than 20 bp before and 10 bp after each exon, though the exact region may be adjusted based on the presence of either potentially significant variants or highly repetitive sequences. Coding regions and proximal promoter regions near the transcription start sites are analyzed for large deletions or duplications. For specific genes, sequence and/or LR analysis is performed within limited clinically relevant regions (Table 1).

In addition to this panel of genes, the comprehensive MyRisk test also produces a combined RiskScore® result for breast cancer risk assessment in women of all ancestries who meet eligibility criteria. The RiskScore® result is generated by taking clinical and family history data, in the form of a Tyrer-Cuzick score, together with data generated from up to 149 weighted genetic markers throughout the genome to assess breast cancer risk and global ancestry. In some cases, RiskScore® results may not be included with the test per healthcare provider or payer request.

Description of Method:

DNA sequence analysis by NGS

The samples are prepared through a hybridization capture-based target-enrichment strategy for subsequent next generation sequencing. Aliquots of patient genomic DNA are fragmented. The fragmented DNA is built into a library by ligation of sequencing adaptors containing unique patient indices. This library is purified and then enriched for targets of interest through hybridization to a set of biotinylated probes, which are then captured on streptavidin coated beads. Indexed samples are then pooled and loaded onto massively parallel next generation sequencers for paired-end sequencing. Probe design and NGS data analysis were optimized for the analysis of genes with known pseudogene regions.

A combination of open source and laboratory-developed software is used for NGS data processing, which includes base-calling, alignment, variant identification, annotation, and generation of quality metrics. Genetic variants are reviewed by computer software and human reviewers. Regions that do not meet required NGS quality and coverage metrics are independently confirmed, generally with repeat NGS. Germline heterozygous sequence variants identified by NGS have allele frequencies between approximately 30% and 70%; homozygous sequence variants have allele frequencies above approximately 90%. NGS variants with intermediate frequencies may be tested with repeat NGS, and putative NGS variants below

approximately 10% allele frequencies are not called. Where necessary due to *PMS2* gene conversion, non-specific NGS is performed with modified thresholds and any potentially actionable variants are confirmed by site-specific Sanger sequencing nested from long-range PCR products.

Large Rearrangement Analysis

Patient samples undergo NGS dosage analysis to assess changes in dosage indicative of deletion or duplication mutations. NGS dosage analysis uses normalized read counts to determine gene copy number. Pseudogenes are avoided through assay design and alignment quality filters for NGS data analysis. Promoter regions of all genes undergoing full-gene sequence analysis are also analyzed for gross copy number variation (deletions or duplications). For NGS dosage analysis, the normalized ratio of each region of interest is compared across patients to identify regions of altered copy number. Limited analysis is also performed for additional structural variants (SV) and is included concurrently with the comprehensive large rearrangement (LR) analysis for deletions and duplications. Samples are evaluated for an Alu insertion in *BRCA2* exon 3 (c.156_157insAlu), which is a Portuguese founder mutation, and a 10 Mb inversion mutation involving *MSH2* exons 1-7. Additional retrotransposon insertion detection is accomplished by a combination of direct analysis of NGS reads for inserted transposon sequence and by monitoring for the impacts of read misalignment due to large foreign sequence insertion. Patient samples positive for LRs or SVs are confirmed by repeat testing using one or more methods, which can include NGS dosage analysis, Multiplex Ligation-dependent Probe Amplification (MLPA), or PCR analysis.

RiskScore® Analysis

Allele status at up to 149 genome-wide markers is collected during NGS sequencing by automated variant analysis, including 56 ancestry-informative markers, and 93 markers that are associated with risk of breast cancer.[ii] RiskScore® is not reported if 6 or more ancestry-informative markers, or 3 or more breast cancer markers, fail analysis. These data are weighted and combined with a Tyrer-Cuzick risk score based on personal and family history data.[iii] This RiskScore® result has been validated in patients of all ancestries. RiskScore® results are calculated for eligible women ages 18-84 years and without a personal history of breast cancer, LCIS, hyperplasia, atypical hyperplasia, or a breast biopsy of unknown results. RiskScore® results are also calculated to modify breast cancer risk in mono-allelic *CHEK2* mutation carrier women only of European ancestry. Otherwise, RiskScore® results are not calculated if a woman has a mutation, or has a blood relative with a known mutation, in a high-penetrance breast cancer risk gene (*BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *PALB2*, *ATM* c.7271T>G, or bi-allelic *CHEK2*). RiskScore® eligible patients will also receive breast cancer risk estimates based solely on the Tyrer-Cuzick model, except for those who carry mono-allelic *CHEK2* mutations.

Performance Characteristics:

Analytical specificity

The incidence of a false report of a genetic variant or mutation resulting from technical error is considered negligible. The incidence of a false report of a clinically significant genetic variant or mutation resulting from errors in specimen handling and tracking was assessed by performing a comparison of all eligible variants in 6,882 samples that underwent at least two independent DNA extractions and cycles of NGS testing. No evidence of sample switches was found during this comparison; therefore, the incidence of a false report of a clinically significant genetic variant or mutation is estimated to be <0.00003% (upper bound of the 95% CI).

Analytical sensitivity

Failure to detect a genetic variant in the analyzed DNA regions may result from errors in specimen handling and tracking, amplification and sequencing reactions, or computer-assisted analysis and data review. The rate of such errors is estimated from validation studies to be less than one percent (<1%). The analytical sensitivity of next-generation sequencing for genes in the MyRisk test was 100% (>99.99%-100%, 95% C.I.) and the analytical specificity was 100% (>99.99%-100%, 95% C.I.) based on complete concordance of heterozygous and homozygous germline variant detection in comparative studies to validated reference methods. These studies were performed on 7,174 samples originating either from de-identified samples extracted from blood, saliva, or fibroblast, or well-characterized external reference samples (6 NIST Genome in a

Bottle Consortium (GIAB), 2 Illumina platinum genomes (with one sample in common to GIAB samples), and 24 Broad Institute 1000 Genomes). A total of 339,810 heterozygous or homozygous sequence variants were successfully identified for genes in the MyRisk test in these validation studies.

Large Rearrangement Validation

Validation studies for large rearrangement (LR) detection using NGS dosage analysis were performed using DNA samples extracted from blood, saliva, and fibroblast samples. These samples included 564 that had previously tested positive for LR mutations, which were all successfully detected by NGS dosage analysis for the genes in the MyRisk panel. All reviewable results for LRs were 100% concordant with the expected mutations.

Concurrent with comprehensive LR validation, samples positive for a variety of previously identified transposon element insertions were also tested using NGS analysis. All 90/90 samples reviewed were concordant with the expected transposon insertion mutations.

Test reproducibility

Reproducibility and accuracy were assessed using a set of 4 well-characterized references samples from NIST Genome in a Bottle Consortium or Illumina platinum genomes as well as de-identified previously tested samples. These samples were processed by NGS in triplicate within a batch and then repeated across three independent batches, to assess intra-batch and inter-batch assay reproducibility. All reviewable sequence results were 100% concordant.

Description of Nomenclature:

All sequencing mutations and genetic variants are referenced to cDNA positions on their respective primary transcripts and named according to the HGVS convention (J Mol Diagn. 2007 Feb;9(1):1-6). The reference sequence used for variant naming is hg19/GRCh37. Transcript IDs are indicated on patient-reports with their associated variants (Table 1). Allele differences have been documented at a limited number of nucleotide locations, based on the major/minor alleles observed upon testing and reference sequences used historically at Myriad Genetic Laboratories. LR variants are named according to the convention of Beaudet and Tsui. (*Hum Mut* 1993; 2:245-248).

Interpretive Criteria:

Functional Variant Interpretations

A functional interpretation is assigned to each variant identified. This interpretation reflects whether or not the variant is predicted to result in a significant change to normal protein production and/or function. It may not necessarily reflect cancer risk (see Clinical Variant Interpretations).

"Deleterious mutation": Includes most nonsense and frameshift mutations that occur at/or before the last known deleterious amino acid position of the affected gene. In addition, specific missense mutations and non-coding intervening sequence (IVS) mutations are recognized as deleterious on the basis of data derived from linkage analysis of high-risk families, functional assays, biochemical evidence, statistical evidence, and/or demonstration of abnormal mRNA transcript processing.

"Genetic variant, suspected deleterious": Includes genetic variants for which the available evidence indicates a high likelihood, but not definitive proof, that the mutation is deleterious. The specific evidence supporting an interpretation will be summarized for individual variants on the Genetic Test Result.

"Genetic variant of uncertain significance": Includes missense variants and variants that occur in analyzed intronic regions whose functional significance has not yet been determined, as well as nonsense and frameshift mutations that occur distal to the last known deleterious amino acid positions of the affected genes.

"Genetic variant, favor polymorphism"* and *"Genetic variant, polymorphism": Includes genetic variants for which available evidence indicates that the variant is highly unlikely to alter protein production and/or function or contribute substantially to cancer risk. Variants of this type are not reported.

In the case of genes with recessive risk transmission (*MSH3, MUTYH,* and *NTHL1*), these interpretations may be modified depending on the ability to determine whether the mutations are on opposite alleles. Two mutations detected may be labelled "Positive for two mutations" or "Positive for two mutations, clinical significance uncertain" depending on whether test data can or cannot confirm that the mutations are on opposite alleles, respectively. If a single mutation is detected in one of these genes, an interpretation of "Carrier for a clinically significant mutation of a recessive condition" may be applied.

Clinical Variant Interpretations

A clinical interpretation is assigned to each variant identified. This interpretation reflects whether or not the variant is predicted to be associated with significantly increased risk for one or more cancer types.

"High Cancer Risk": Includes genetic variants for which absolute cancer risk is predicted to be higher than ~5% with a ~3-fold or higher increased relative risk over that of the general population. Strong data is available to support gene-specific risk estimates, although actual variant-specific risks may differ.

"Elevated Cancer Risk": Includes genetic variants for which there is sufficient data to indicate that the specific variant increases risk for one or more cancers over that of the general population. These risks may be lower than those conveyed by "High Cancer Risk" variants or may be supported by less solid, but still significant, data.

"Clinical Significance Unknown": Includes genetic variants for which there is insufficient data to determine whether or not the variant is associated with increased cancer risk.

"Clinically Insignificant": Includes genetic variants for which available evidence indicates that the variant is highly unlikely to significantly contribute to cancer risk. Variants of this type are not reported.

"Special Interpretation": Includes genetic variants with more complex clinical interpretations. Specific interpretations will be provided for each variant on the Genetic Test Result.

"Carrier Interpretation": Includes functionally deleterious or suspected deleterious genetic variants in autosomal recessive genes, for which there is no known cancer risk when found in the heterozygous state. However, the biological children of patients provided with a 'carrier' classification are at risk for an autosomal recessive condition if the other parent is also a carrier of a pathogenic variant in the same gene. Screening the other biological parent of any children for variants within the same gene and genetic counseling to discuss reproductive risks may be appropriate.

Summary Interpretations

"Clinically significant mutation identified": Includes Genetic Test Results in which one or more genetic variants, which are associated with the potential to alter medical intervention, were identified."

"No clinically significant mutation identified": Includes Genetic Test Results in which either no genetic variants were identified, or all identified variants were classified as "Clinical Significance Unknown" or "Clinically Insignificant."

"Carrier for a clinically significant mutation of a recessive condition": Includes Genetic Test Results in which one or more genetic mutations were identified in the heterozygous state in a gene for which two mutations are required to manifest a cancer or non-cancer phenotype. There are no known cancer risks associated with carrying a single gene mutation.

"Mutation identified with special interpretation": Includes Genetic Test Results in which one or more genetic mutations have complex clinical interpretations that may or may not be related to cancer.

Change of interpretation and issuance of amended reports

The classification and interpretation of all variants identified in the assay reflect the current state of scientific understanding at the time the report is issued. In some instances, the classification and interpretation of such variants may change as new

scientific information becomes available. Whenever there is a clinically significant change in the classification of a variant an amended report will be provided by Myriad Genetic Laboratories. Amended reports may not be issued for RiskScore changes resulting from changes in personal and/or family clinical history. Reports that are amended for reasons outside of RiskScore and issued more than 30 days after the original report date, may not include RiskScore or Tyrer-Cuzick breast cancer risk estimates since clinical variables that affect these estimates may change over time.

Summary of Clinical Studies

NOTE: *Analytical concordance studies have been performed with the BRACAnalysis CDx test for BRCA1 and BRCA2.*

1. Summary of Clinical Study – Olaparib D0819C00003 (OlympiAD)

   The olaparib clinical study D0819C00003 (OlympiAD) was a Phase III randomized, open label, controlled, multi-center study of olaparib monotherapy versus healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard dose) in the treatment of metastatic HER2-negative breast cancer patients with germline *BRCA1/2* mutations. A total of 302 patients were enrolled from 125 centers in 19 countries, including the United States. Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either *BRCA1* or *BRCA2* to be enrolled into the study. Evidence of a qualifying *BRCA* mutation could be from either an existing *BRCA* mutation result from local testing or from prospective testing performed by Myriad (Salt Lake City, UT) using either the Myriad Integrated BRAC*Analysis*® or BRACAnalysis CDx® test, or by BGI Clinical Laboratories (Shenzhen, China) for Chinese patients. Samples from 29 patients were tested prospectively using the BRACAnalysis CDx® test, and samples from 270 patients who were randomized based on local, BGI or Myriad Integrated BRAC*Analysis*® testing were retrospectively evaluated using the BRACAnalysis CDx® test. The clinical performance of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline *BRCA* status upon prospective or retrospective testing with the BRACAnalysis CDx® test.
   Lynparza® (olaparib) demonstrated a clinically relevant improvement in progression- free survival (PFS) for olaparib-treated patients compared to chemotherapy-treated patients in metastatic HER2-negative breast cancer patients with germline *BRCA1/2* mutations. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the overall population.

   a. Accountability of PMA Cohort
      Of the 302 patients randomized in OlympiAD, 29 patients were randomized on the basis of the BRACAnalysis CDx® test. The remaining 273 cases were randomized on the basis of an Integrated BRAC*Analysis*® test result (n=65), an alternative test performed in China (n=41), or local test results (n=167).
      Retrospective testing using the BRACAnalysis CDx® test was performed for 270 of the 273 cases randomized on the basis of results from tests other than the BRACAnalysis CDx® test.

      Overall, of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® test and 297 patients were confirmed to carry a deleterious or suspected deleterious germline *BRCA* mutation. The PMA cohort represented 98% of the full analysis set in OlympiAD.

b. Effectiveness Results

The primary efficacy endpoint of the therapeutic study was progression-free survival (PFS) determined by blinded independent central review assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). The study population consisted of 302 metastatic breast cancer patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by the Myriad Integrated BRAC*Analysis*® test, BRACAnalysis CDx® test, or local test results. In this study, the PFS improvement was statistically significant and clinically meaningful, as evidenced by a 42% reduction in the risk of progression or death, and a median PFS of 2.8 months longer for olaparib-treated patients (7.0 months) compared with chemotherapy-treated patients (4.2 months). These results are shown in the table below.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 297 confirmed metastatic breast cancer patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective or retrospective testing was performed with the BRACAnalysis CDx® test. Five cases among the 302 randomized patients were not confirmed to have a germline *BRCA* mutation using the BRACAnalysis CDx® test. In 3 cases no BRACAnalysis CDx® result was available, and in 2 cases the BRACAnalysis CDx® result reported a variant that was not deleterious or suspected deleterious.

The clinical outcome data for the 297 patients with a confirmed germline BRCA1/2 mutation was as follows: a 43% reduction in the risk of progression or death, and a median PFS of 3.2 months longer for olaparib-treated patients compared with chemotherapy-treated patients. Taken together, these results are very similar to those observed in the 302 patients in the OlympiAD study, which supports the effectiveness of the device.

The clinical outcome results for cases classified as having a deleterious or suspected deleterious germline *BRCA* mutation by the BRACAnalysis CDx® test are shown in the table below.

	OlympiAD		**BRACAnalysis CDx® test**	
	Olaparib 300 mg bd[a]	**Comparator[b]**	**Olaparib 300 mg bd[a]**	**Comparator[b]**
PFS				
Number of events: total number of patients (%)	163:205 (80)	71:97 (73)	160:202 (79)	71:95 (75)
Median PFS (months)	7.0	4.2	7.4	4.2
HR (95% CI)	0.58 (0.43-0.80)		0.57 (0.41-0.78)	
P-value (2-sided)	p=0.0009		p=0.0005	

a- tablet formulation, b - Comparator consisting of either capecitabine, eribulin or vinorelbine

2. Summary of Clinical Study – Olaparib D0818C00001 (SOLO1)

The olaparib clinical study D0818C00001 (SOLO1) was a Phase III, randomised, double blind, placebo controlled, multicentre study to assess the efficacy of olaparib maintenance monotherapy in newly diagnosed advanced ovarian cancer patients (including patients with primary peritoneal and/or fallopian tube cancer) with BRCA mutations (documented mutation in *BRCA1* or *BRCA2*) that were predicted to be deleterious or suspected deleterious

(known or predicted to be detrimental/lead to loss of function) who had responded following first-line platinum based chemotherapy. A total of 391 patients were randomized from 118 centers in 15 countries, including the United States. Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either *BRCA1* or *BRCA2* to be enrolled into the study. Evidence of a qualifying BRCA mutation could be from either an existing BRCA mutation result from local testing (n=210) or from prospective testing (n=181) performed by Myriad (Salt Lake City, UT) using the Myriad Integrated BRACAnalysis® or by BGI Clinical Laboratories (Shenzhen, China).

Out of 181 samples enrolled, 178 patients were tested prospectively using the Myriad Integrated BRACAnalysis® test and 3 patients were tested prospectively using the BGI test. Out of 210 enrolled by local testing, 208 patients were retrospectively evaluated using the Myriad Integrated BRACAnalysis® (n=205) or the BRACAnalysis CDx® (n=3) test. Samples from 2 patients who were randomized based on local testing in China could not be exported for testing at Myriad. A total of 383 patients were tested with the Myriad Integrated BRACAnalysis® and 3 patients were tested with the BRACAnalysis CDx®. Concordance studies between the Integrated BRACAnalysis® and BRACAnalysis CDx® have demonstrated a 100% agreement between the two tests. Thus, for simplification, the terminology Myriad BRACAnalysis test will be used if either the Integrated BRACAnalysis® or BRACAnalysis CDx® was used.

The clinical performance of the Myriad BRACAnalysis test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline BRCA status upon prospective or retrospective testing with a Myriad BRACAnalysis test. The data from SOLO1 demonstrated a substantial improvement in investigator- assessed progression-free survival (PFS) that was statistically significant and clinically relevant for olaparib compared with placebo treated patients with newly diagnosed BRCA-mutated advanced ovarian cancer. The magnitude of response in the population tested with a Myriad BRACAnalysis test was comparable to that in the overall population.

a. Accountability of PMA Cohort
   Of the 391 patients randomized in the global SOLO1 cohort, 178 patients were randomized on the basis of the Integrated BRACAnalysis® test and 3 on the basis of the BGI test. The remaining 210 cases were randomized on the basis of local test results; 208 out of the 210 cases with a local result were retrospectively tested using either the Integrated BRACAnalysis® test (n=205) or the BRACAnalysis CDx® (n=3).

   Overall, of the 391 patients randomized in the global SOLO1 cohort, 386 were tested with either the Integrated BRACAnalysis® test or the BRACAnalysis CDx® test and 383 patients were confirmed to carry a deleterious or suspected deleterious germline BRCA mutation. The PMA cohort represented 98% of the full analysis set in the global SOLO1 cohort.

b. Effectiveness Results
   The primary objective of this study was to determine the efficacy by PFS (using investigator assessment of scans according to modified Response Evaluation Criteria in Solid Tumours [RECIST] 1.1) of olaparib maintenance monotherapy compared with placebo in newly diagnosed BRCA mutated advanced ovarian cancer patients who were in clinical CR or PR following first line platinum- based chemotherapy. The study

population consisted of 391 ovarian cancer patients with a deleterious or suspected deleterious germline BRCA mutation as detected by the Myriad Integrated BRACAnalysis® test, BRACAnalysis CDx® test, BGI test or local test results (Full Analysis Set – FAS). A statistically significant and clinically relevant improvement in investigator-assessed PFS was observed, as evidenced by the magnitude of effect: a 70% reduction in the risk of disease progression or death at any point in time for olaparib vs placebo treated patients (Hazard Ratio [HR] 0.30; 95% CI 0.23-0.41; p<0.0001; see table below). After a median follow-up of 41 months, median PFS was not reached on the olaparib arm vs 13.8 months for placebo.

The effectiveness of the Myriad BRACAnalysis test was based on a subset of 383 confirmed ovarian cancer patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutations for whom prospective or retrospective testing was performed with either the Myriad Integrated BRACAnalysis® test or the BRACAnalysis CDx® test. Three cases among the 386 randomized patients were not confirmed to have a germline BRCA mutation using the Myriad test. In 1 case, the Myriad BRACAnalysis test result reported a variant that was not deleterious or suspected deleterious and in the other 2 cases, the Myriad BRACAnalysis test result did not report any variant.

The clinical outcome data for the 383 patients with a confirmed germline *BRCA1* or *BRCA2* mutation was as follows: a 70% reduction in the risk of disease progression or death at any point in time for olaparib vs placebo treated patients (HR 0.30; 95% CI 0.22-0.40; p<0.0001; see table below). After a median follow-up of 41 months, median PFS was not reached on the olaparib arm vs 13.8 months for placebo. Taken together, these results are very similar to those observed in the 391 patients in the SOLO1 study, which supports the effectiveness of the Myriad BRACAnalysis device.

The clinical outcome results for cases classified as having a deleterious or suspected deleterious germline BRCA mutation by the Myriad BRACAnalysis test (Myriad gBRCAm subset) are shown in the following table.

SOLO1	**FAS**		**Myriad *gBRACAm* subset**	
	Olaparib 300 mg bd[a]	**Placebo**	**Olaparib 300 mg bd[a]**	**Placebo**
	PFS			
Number of events: total number of patients (%)	102:260 (39)	96:131 (73)	99:253 (39)	95:130 (73)
Median PFS (months)	Not reached	13.8	Not reached	13.8
HR (95% CI)	0.30 (0.23-0.41)		0.30 (0.22-0.40)	
P-value (2-sided)	<0.0001		<0.0001	

a- tablet formulation

3. Summary of Clinical Study – Olaparib D081FC00001 (POLO)

The olaparib clinical study D081FC00001 (POLO) was a Phase III, randomized, double-blind, placebo-controlled, multicenter trial to assess the efficacy of Lynparza maintenance treatment in patients with metastatic adenocarcinoma of the pancreas who have a deleterious or suspected deleterious germline *BRCA* mutation (*gBRCAm*) and whose disease had not progressed after at least 16 weeks of first-line platinum-based chemotherapy. The study randomized 154 patients (3:2 randomization: 92

olaparib and 62 placebo). Patients were enrolled from 59 centers in twelve countries, including the United States. Patients with germline *BRCA* mutations were identified from prior local testing results or by central testing using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test. The g*BRCAm* status of all patients identified using prior local testing results was confirmed, if a sample was available, using the Myriad BRAC*Analysis*® or Myriad BRACAnalysis CDx® test at one laboratory, Myriad Genetic Laboratories (Salt Lake City, UT). The clinical performance of the Myriad BRACAnalysis test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to those for the subset of patients with confirmed germline *BRCA* status upon prospective or retrospective testing with a Myriad BRACAnalysis test. Lynparza® (olaparib) demonstrated an improvement in progression free survival for olaparib compared to placebo.

a. Accountability of PMA Cohort

Of the 154 patients randomised in the global POLO cohort, 106 patients were randomized on the basis of a Myriad *gBRCAm* result using either the Myriad BRAC*Analysis*® (n=6) or Myriad BRACAnalysis CDx® test (n=100). The remaining 48 cases were randomized on the basis of local test results; 44 out of the 48 cases with a local result were retrospectively tested using either the Myriad BRAC*Analysis*® test (n=3) or the Myriad BRACAnalysis CDx® (n=41).

Overall, of the 154 patients randomized in the global POLO cohort, 150 were tested with either the Myriad BRAC*Analysis*® test (n=9) or the Myriad BRACAnalysis CDx® test (n=141) and 150 patients were confirmed to carry a deleterious or suspected deleterious germline *BRCA* mutation. The PMA cohort represented 97.4% of the full analysis set in the global POLO cohort.

b. Effectiveness Results

The primary endpoint of POLO was Progression-Free Survival (PFS), defined as time from randomisation to progression determined by Blinded Independent Central Review (BICR) using modified Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), or death. The study population consisted of 154 pancreatic cancer patients with a deleterious or suspected deleterious germline *BRCA* mutation as detected by the Myriad BRAC*Analysis*® test, Myriad BRACAnalysis CDx® test or local test results (Full Analysis Set – FAS). The study demonstrated a clinically meaningful and statistically significant improvement in PFS for olaparib compared to placebo, with a HR of 0.53 (95% CI 0.35 – 0.81; p=0.0035; the median was 7.4 months for olaparib vs 3.8 months for placebo). The results are shown in the table below.

The PFS data for the 150 patients in the confirmed Myriad *gBRCAm* subset was as follows: HR of 0.55 (95% CI 0.36-0.84; p=0.0060; the median was 7.4 months for olaparib vs 3.8 months for placebo).

These results are consistent to those observed in the 154 patients in the POLO study, which supports the effectiveness of the Myriad BRACAnalysis device.
The POLO PFS results for the FAS and the confirmed Myriad *gBRCAm* subset of patients are shown in the table below.

Clinical Study Results

POLO	FAS		Myriad *gBRCAm* subset	
	Olaparib 300 mg bd[a]	**Placebo**	**Olaparib 300 mg bd[a]**	**Placebo**
PFS				
Number of events: total number of patients (%)	60:92 (65)	44:62 (71)	59:89 (66)	44:61 (72)
Median PFS (months)	7.4	3.8	7.4	3.8
HR (95% CI)	0.53 (0.35-0.81)		0.55 (0.36-0.84)	
P-value (2-sided)	p=0.0035		p=0.0060	

a- tablet formulation.

The effectiveness analysis for the Myriad BRACAnalysis test was based on a subset of 150/154 metastatic pancreatic adenocarcinoma patients who were confirmed with a deleterious or suspected deleterious germline *BRCA1/2* mutation by either the Myriad BRAC*Analysis*® test or the Myriad BRACAnalysis CDx® test. Four patients were not confirmed to have a germline *BRCA* mutation by the Myriad test as no sample was submitted for testing. The data demonstrated that the Myriad test supports the efficacy conclusions obtained with the ITT population.

4. Summary of Clinical Study-Olaparib D081DC00007 (PROfound)

The clinical benefit of BRACAnalysis CDx® test was demonstrated in a retrospective analysis of efficacy and safety data obtained from the Phase III randomized, open label, randomized study to assess the efficacy and safety of olaparib (Lynparza™) versus enzalutamide or abiraterone acetate (physician's choice of new hormonal agent [NHA]) in men with metastatic castration-resistant prostate cancer who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations.

Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in one of 15 genes with a direct or indirect role in homologous recombination repair (HRR) to be enrolled into the study. The 15 gene panel included *BRCA1* and *BRCA2*. HRR gene mutation status was prospectively determined using a tumour tissue test. Patients were enrolled from 206 study centers in 20 countries (of these, 139 centers randomized patients) including the United States. Patients were randomized into 2 cohorts: Cohort A included 245 patients with *BRCA1*, *BRCA2* and *ATM* mutations (162 patients received olaparib, 83 patients received physician's choice of NHA), Cohort B included 142 patients with mutations in the remaining 12 HRR genes (94 patients received olaparib, 47 patients received physician's choice of NHA).
Determination of the germline *BRCA* mutation status was performed by testing blood samples from patients randomized onto the PROfound study retrospectively using the BRACAnalysis CDx® test performed by Myriad (Salt Lake City, UT).

The clinical utility of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the Cohort A PROfound population to those for the subset of patients with confirmed *gBRCAm* status by retrospective testing with

the BRACAnalysis CDx® test. Lynparza™ (olaparib) demonstrated a clinically relevant improvement in Progression Free Survival for olaparib treated patients compared to physician's choice NHA treated patients in HRRm metastatic castration resistant prostate cancer patients. The PFS improvement in Cohort A patients was statistically significant and clinically relevant. The magnitude of response in the population tested with the BRACAnalysis CDx® test was comparable to that in the overall population. Data from this bridging study were used to support PMA approval.

a. Accountability of PMA Cohort
Of the 387 patients randomised in PROfound, 288 patients reported a successfully *gBRCAm* status using the BRACAnalysis CDx® test. For 98 patients, no retrospective BRACAnalysis CDx® test result was obtained due to no sample being provided for retrospective testing (n=39), consent not being granted for diagnostic development (n=55), samples being unsuitable for testing (n=4). In addition, in one patient also reported an inconclusive result.

Of the 288 patients with a *gBRCA* status reported by the BRACAnalysis CDx® test, 114 carried a tumor *BRCA1*/2 mutation and 174 patients were tumor non-*BRCA* mutation positive. In total, 62 patients were reported as germline *BRCA* mutation positive by the BRACAnalysis CDx® test. The PMA cohort represented 25.3% (62/245) of Cohort A and 16.0% (62/387) of Cohort A+B in PROfound. Germline *BRCA* mutations were seen in 53.5% (61/114) of tumor *BRCA* mutation positive patients. Additionally, one patient who was tumor non-*BRCA* mutation positive reported a germline *BRCA* mutation.

b. Effectiveness results

The analysis of efficacy was based on the primary endpoint of the study of radiological progression free survival determined by blinded independent central review observed in the 245 metastatic castration resistant prostate cancer cases with *BRCA1/2* or *ATM* mutations (Cohort A). In this study the PFS improvement was statistically significant and clinically relevant, as evidenced by the magnitude of effect: a 66% reduction in the risk of progression or death, and a median PFS of 3.84 months longer for olaparib-treated patients (7.39 months) compared with NHA-treated patients (3.55 months). A key secondary endpoint of radiological progression free survival determined by blinded independent central review in the overall HRRm treated population (Cohort A+B) also demonstrated a statistically significant and clinically relevant improvement in olaparib treated patients compared with NHA-treated patients (rPFS HR=0.49, median PFS: 5.82mo [olaparib], 3.52mo [NHA]). These results are shown in the table below.

Within the PROfound study, there were 160 patients who carried a *BRCA1/2* mutation according to the tissue test, 15 patients carried a t*BRCA1* mutation and 145 patients carried a t*BRCA2* mutation. No patients carried both t*BRCA1* and t*BRCA2* mutations. Of the 160 t*BRCAm* patients in PROfound, 114 patients had a valid result reported by BRACAnalysis CDx® test and 46 patients were not tested/did not have a valid result. One (1) patient excluded as they were tested using the tissue test that did not meet inclusion criteria. Of these, 113 patients had a valid result reported by BRACAnalysis CDx® test, and 61 germline *BRCA1/2* mutations were identified in these cases. Additionally, 1 patient was reported as germline *BRCA1/2* mutation positive which did not report a *BRCA1/2* mutation in the tissue test. Overall therefore, 62 patients randomised in PROfound were

germline *BRCA1/2* mutation positive. These 62 patients were used to generate the efficacy estimates for patients with *BRCAm* status defined by BRACAnalysis CDx®.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 62 confirmed *gBRCAm* metastatic castration resistant prostate cancer cases for whom retrospective testing was performed with the BRACAnalysis CDx® test and a *gBRCAm* result identified (43 patients received olaparib, 19 patients received physician's choice of NHA).

The clinical outcome data for the 62 patients with confirmed *gBRCAm* status was as follows: a 92% reduction in the risk of progression or death, and a median PFS of 8.25 months longer for *gBRCAm* olaparib-treated patients (10.12 months) compared with NHA-treated patients (1.87 months). Taken together, the results in the subset of *gBRCAm* patients tested with the BRACAnalysis CDx® test were comparable to those observed in the 245 Cohort A patients and 387 Cohort A+B patients in the overall PROfound study, which supports the effectiveness of the device.

The clinical outcome data for cases classified as *gBRCAm* by the BRACAnalysis CDx® test is shown in the table below.

	PROfound Cohort A (n=245)		**PROfound Cohort A+B (n=387)**		**BRACAnalysis CDx® test *gBRCAm* confirmed (n=62)**	
	Olaparib 300 mg bd[a]	**Physicians choice NHA[b]**	**Olaparib 300 mg bd[a]**	**Physicians choice NHA[b]**	**Olaparib 300 mg bd[a]**	**Physicians choice NHA[b]**
Number of events: total number of patients (%)	106:162 (65.4)	68:83 (81.9)	180:256 (70.3)	99:131 (75.6)	25:43 (58.1)	17:19 (89.5)
Median PFS (months)	7.39	3.55	5.82	3.52	10.12	1.87
HR (95% CI)	0.34 (0.25, 0.47)		0.49 (0.38, 0.63)		0.08 (0.03, 0.18)	
P-value (2-sided)	<0.0001		<0.0001		<0.0001	

a- tablet formulation, b - Physician's choice of NHA consisting of either enzalutamide or abiraterone acetate

5. Summary of Clinical Study – Olaparib D081CC00006 (OlympiA)

The olaparib clinical study D081CC00006 (OlympiA) was a randomized, double-blind, parallel group, placebo-controlled multi-center Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA* mutations and high risk HER2 negative early breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.

A total of 1836 patients were enrolled from 546 centers in 23 countries, including the United States. Patients were required to have documented evidence of a deleterious or suspected deleterious mutation in either *BRCA1* or *BRCA2* to be enrolled into the study. Evidence of a qualifying *BRCA* mutation could be from either an existing *BRCA* mutation result from local testing (n=1114) or from prospective testing (n=474; plus 1 patient tested under a different study ID code) performed by Myriad with BRACAnalysis CDx® assay (Salt Lake City, UT), or by BGI Clinical Laboratories (Shenzhen, China) for Chinese patients (n=247). For patients enrolled outside China, 474 samples were tested prospectively, and 1091 samples were tested retrospectively at Myriad. Out of 247 patients randomized in China, 85 were tested retrospectively with the Myriad test at Myriad Genetic Laboratories in Salt Lake City, UT. In total 1650 patients were tested at Myriad, out of which 164 patients were tested with Myriad Integrated BRAC*Analysis*® and 1486 patients were tested with BRACAnalysis CDx® assay.

The clinical performance of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall study population to the subset of patients with confirmed germline *BRCA* status upon prospective or retrospective testing with BRACAnalysis CDx®. Lynparza® (olaparib) demonstrated a statistically significant and clinically meaningful improvement in invasive-disease-free-survival (IDFS) compared to placebo-treated patients, reducing the risk of recurrence of disease in patients with germline *BRCA* mutation, high risk early-stage breast cancer after standard of care neo/adjuvant chemotherapy and surgery. The magnitude of response in the population confirmed as germline *BRCA* mutated by BRACAnalysis CDx® test was comparable to that in the overall population.

a. Accountability of PMA Cohort
Of the 1836 patients randomized in OlympiA, 1114 patients were enrolled based on a local test, 474 patients were enrolled with prospective BRACAnalysis CDx® test, 1 patient tested prospectively at Myriad under a different study code, and 247 patients were enrolled in China using BGI test. Out of 1114 patients enrolled with a local test, 1069 were retrospectively determined as *BRCA* mutation carriers by Myriad. Of 247 patients enrolled in China no patients were tested with Integrated BRAC*Analysis*® and 85 patients were tested with BRACAnalysis CDx®. Out of 474 patients enrolled with prospective Myriad test, 74 patients were tested with Integrated BRAC*Analysis*® and 400 patients tested with BRACAnalysis CDx® test, and 470 confirmed as germline *BRCA* mutated.

Overall, of the 1836 patients randomized onto OlympiA, 1650 were tested with the BRACAnalysis CDx® test and 1623 patients were confirmed to carry a deleterious or suspected deleterious germline *BRCA* mutation. Therefore, the PMA cohort represented 88.4% of the full analysis population in OlympiA.

b. Effectiveness Results
The primary efficacy endpoint of the therapeutic study was invasive disease-free survival (IDFS) according to the Standardized Definitions for Efficacy End Points (STEEP). The study population consisted of 1836 early breast cancer patients with a deleterious or suspected deleterious germline BRCA mutation as detected by the Myriad Integrated BRACAnalysis® test, BRACAnalysis CDx® test, or local test results.

In this study, the IDFS improvement was statistically significant and clinically meaningful, as evidenced by a 42% reduction in the risk of invasive disease recurrence or death for olaparib compared to the placebo arm (IDFS HR 0.58, 95% CI 0.46 - 0.73; $p<0.0001$).
The effectiveness of the BRACAnalysis CDx® test was based on a subset of 1623 confirmed early breast cancer patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective or retrospective testing was performed with BRACAnalysis CDx® test (IDFS HR 0.53, 95% CI 0.41 - 0.68).

For 213 cases out of 1836 randomized patients a germline *BRCA* mutation status using the BRACAnalysis CDx® was not confirmed, including 185 patients not tested, 27 patients reported variants that was not deleterious or suspected deleterious and 1 patient tested under incorrect study ID.
The clinical outcome data for the 1623 patients with a confirmed germline *BRCA1/2* mutation was as follows: a 47% reduction in the risk of invasive disease recurrence or death. Taken together, these results are very similar to those observed in the overall OlympiA study population, which supports the effectiveness of the device.

The clinical outcome results for cases classified as with deleterious or suspected deleterious germline *BRCA* mutation by BRACAnalysis CDx® test are summarized in the table below.

	FAS (1836)		**Confirmed Myriad *gBRCAm* (1623)**	
	Olaparib 300 mg bd	Placebo	Olaparib 300 mg bd	Placebo
n	921	915	816	807
Events (%)	106 (12)	178 (20)	94 (12)	168 (21)
HR (95% CI)	0.58 (0.46 - 0.74)		0.53 (0.41 - 0.68)	
p-value (2-sided)	<0.0001		NA*	

* not formally tested

6. Summary of Clinical Study - Niraparib PR-30-5011-C (NOVA)

The niraparib clinical study PR-30-5011-C (NOVA) was a double-blind, 2:1 (niraparib: placebo) randomized, placebo-controlled, multicenter, global clinical trial designed to evaluate the efficacy and safety of niraparib in patients with ovarian cancer who had received at least two platinum-based regimens and were in response to their last platinum-based chemotherapy. Patients were required to have received a minimum of four cycles of treatment and, following treatment, have an investigator- defined complete or partial response to their last platinum regimen with no observable residual disease of <2 cm and cancer antigen 125 (CA-125) values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least 7 days.

a. Accountability of PMA Cohort
Enrollment into cohorts was determined by the results of Myriad's BRACAnalysis CDx® test. Randomization was stratified by time to progression after the penultimate platinum therapy before study enrollment (6 to <12 months or ≥12 months); use of bevacizumab in conjunction with the penultimate or last platinum regimen (yes/no); and best response during the last platinum regimen (complete response [CR] or partial response [PR]).
Patients were enrolled from 128 centers in 15 countries, including the United States. All testing for germline BRCA was conducted centrally using the BRACAnalysis CDx® test. Overall, 553 patients were randomized. A total of 203 patients were assigned to the BRACAnalysis CDx positive cohort and 350 patients were assigned to the BRACAnalysis CDx negative cohort.

b. Effectiveness Results
The evaluation of efficacy was based on serial assessments of disease using radiographs of the abdomen/pelvis and other clinically indicated areas, physical examinations, and CA-125 testing; PRO questionnaires; and post- treatment information on follow-up anti-cancer therapy (including progression on that therapy), and survival status.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time from the date of treatment randomization to the date of first documentation of progression (by blinded IRC review according to RECIST 1.1) or death by any cause in the absence of documented progression, whichever occurred first. There were several secondary and exploratory endpoints.

Patients receiving niraparib exhibited significantly longer PFS than those receiving placebo. Within the BRACAnalysis CDx positive cohort, the median PFS was 21.0 months versus 5.5 months with placebo (HR: 0.27; 95% CI: 0.173 to 0.410) (p<0.0001). PFS was statistically significantly longer with niraparib than with placebo in the overall BRACAnalysis CDx negative cohort (median, 9.3 months versus 3.9 months; HR: 0.45; 95% CI: 0.338 to 0.607) (p<0.0001). Progression-Free Survival in the Primary Efficacy Cohorts (ITT Population, N=553)

Treatment	Median PFS[a] (95% CI) (Months)	Hazard Ratio[b] (95% CI) p-value[c]
BRACAnalysis CDx Positive Cohort		
Niraparib (N=138)	21.0 (12.9, NR)	0.26 (0.17, 0.41) p<0.0001
Placebo (N=65)	5.5 (3.8, 7.2)	
BRACAnalysis CDx Negative Cohort		
Niraparib (N=234)	9.3 (7.2, 11.2)	0.45 (0.34, 0.61) p<0.0001
Placebo (N=116)	3.9 (3.7, 5.5)	

Abbreviations: BRCA=breast cancer susceptibility gene; CI=confidence interval; BRACAnalysis CDx positive=germline BRCA mutation; ITT=intent-to-treat; BRACAnalysis CDx negative=without a germline BRCA mutation; PFS=progression-free survival; NR=not reached.
[a] Progression-free survival is defined as the time in months from the date of randomization to progression or death.
[b] Niraparib:Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.
[c] Based on stratified log-rank test using randomization stratification factors.

7. Summary of Clinical Study – EMBRACA (NCT01945775)

The talazoparib clinical study EMBRACA was a Phase III randomized, open label, study of talazoparib versus protocol specified healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) and was designed to assess the safety and efficacy of talazoparib in patients with deleterious or suspected deleterious germline *BRCA1/2*-mutated HER2-negative locally advanced or metastatic breast cancer who received no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic breast cancer. A total of 431 patients were enrolled from 145 study sites across 16 countries, including the United States.

Patients were required to have documentation of a deleterious, suspected deleterious, or pathogenic germline *BRCA1* or *BRCA2* mutation from Myriad Genetics (Myriad; Salt Lake City, UT) or another laboratory approved by the Sponsor. Myriad used a combination of Integrated BRAC*Analysis*® and BRACAnalysis CDx® test results for study enrollment. The concordance studies between the Integrated BRACAnalysis® and BRACAnalysis CDx® for the OlympiAD and NOVA trials demonstrated a 100% agreement between the two tests. For data obtained regarding a BRCA1/2 mutation from a non Myriad laboratory, the pathology report was submitted to and approved by the Sponsor and a blood sample was

sent to Myriad for analysis before randomization.

The clinical performance of the BRACAnalysis CDx® test was established by comparing the mutation results and the associated clinical outcomes for the overall (Intent-to-Treat) study population to those for the subset of patients with confirmed deleterious or suspected deleterious germline *BRCA1/2* status by the BRACAnalysis CDx® test.

Talazoparib treatment demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of progression-free survival (PFS) over healthcare provider's choice of chemotherapy patients with deleterious or suspected deleterious germline *BRCA1/2* -mutated HER2-negative locally advanced or metastatic breast cancer. The magnitude of benefit in the population tested with the BRACAnalysis test was comparable to that in the overall population.

a. Accountability of PMA Cohort
Based on central testing conducted by Myriad and on local testing, a total of 431 patients were randomized into the EMBRACA study. Of the 431 patients randomized into the clinical study, 408 (95%) patients were tested centrally (114 were tested with the Integrated BRAC*Analysis*® test and 294 with the BRACAnalysis CDx). Of the 114 samples tested with the Integrated BRAC*Analysis*® test, 60 were retested with the BRACAnalysis CDx® test and shown to have 100 % agreement. The remaining 23 patients (5.3%) were enrolled using a non-Myriad laboratory test.

b. Effectiveness Results
The primary efficacy endpoint was PFS evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and assessed by blinded independent central review (BICR). The study population consisted of 431 patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* -mutated (as detected by central testing conducted by Myriad or local test results) HER2-negative locally advanced or metastatic breast cancer.
In the EMBRACA study, talazoparib treatment demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS over chemotherapy in patients with deleterious or suspected deleterious germline *BRCA1* or *BRCA2*-mutated HER2-negative locally advanced or metastatic breast cancer, with a 46% relative risk reduction of disease progression or death (hazard ratio [HR]: 0.54 [95% confidence interval {CI}: 0.41, 0.71]; p<0.0001). The median PFS by BICR assessment was 8.6 months (95% CI: 7.2, 9.3) in the talazoparib arm and 5.6 months (95% CI: 4.2, 6.7) in the chemotherapy arm. These results are shown in the table below.

The effectiveness of the BRACAnalysis CDx® test was based on a subset of 354 (82%) patients with deleterious or suspected deleterious germline *BRCA1/2* mutations for whom prospective and retrospective testing was performed with the BRACAnalysis CDx® test. For the remaining 77 patients (18%) whose samples were not available for testing with the BRACAnalysis CDx® test, *BRCA1* or *BRCA2* status was determined with the Integrated BRAC*Analysis*® test for 54 patients (18%) or by local assessment for 23 patients (5.3%). As shown in the table below, the clinical outcome data for the 354 patients with confirmed deleterious or suspected deleterious *BRCA1/2* mutation by the BRACAnalysis CDx® test was as follows: a 47% reduction in the risk of progression or death, and a median PFS of 8.5 months for talazoparib-treated patients compared with 5.6 months for chemotherapy treated patients. These PFS results are comparable to those observed in the

431 patients in the EMBRACA study, which supports the effectiveness of the device.

PFS by BICR (Intent-to-Treat Population) in the EMBRACA Study		
	Talazoparib	Chemotherapy[a]
Number of patients analyzed, N	N=287	N=144
Events, n (%)	186 (65%)	83 (58%)
Median (95% CI), months	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI); 2-sided P-value	**0.54 (0.41, 0.71); <0.0001**	
PFS by BICR in BRACAnalysis CDx® Test Population		
Number of patients analyzed, N	N=238	N=116
Events, n (%)	144 (61%)	67 (58%)
Median (95% CI)	8.5 (7.0, 9.3)	5.6 (3.9, 6.7)
Hazard Ratio (95% CI); p-value	**0.53 (0.39, 0.72); <0.0001**	
a - comparator consisting of healthcare provider's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine).		

8. Summary of Clinical Studies- Maintenance Indication for rucaparib

The rucaparib maintenance indication is supported by data from Study CO-338-014 (ARIEL3; NCT01968213).
Study CO-338-014 is an ongoing, double-blind, placebo-controlled, randomized study of rucaparib as switch maintenance treatment in patients with relapsed platinum-sensitive, highgrade EOC, FTC, or PPC who achieve a response to platinum-based chemotherapy. The primary efficacy population included 564 patients who were enrolled at sites in North America (including the United States), Europe Australia, and Israel.

The primary endpoint for this study is to evaluate PFS, as assessed by the investigator (invPFS), in molecularly-defined HRD subgroups. Patients were assigned to molecularly-defined HRD subgroups for the final analysis of invPFS. The nested populations are ITT, HRD, and tBRCA.

Patient blood samples from a subset of the primary efficacy population were retrospectively evaluated at one laboratory, Myriad (Salt Lake City, UT) using the BRACAnalysis CDx® test. The clinical utility of the BRACAnalysis CDx® test was established by comparing the test results and associated clinical outcomes tBRCA group (inclusive of both germline and somatic deleterious BRCA mutations) with the subset of patients with confirmed *g*BRCA status upon retrospective testing with the BRACAnalysis CDx® test. Rubraca® (rucaparib) demonstrated a robust overall invPFS in gBRCA positive patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in a complete or partial response to platinum- based chemotherapy.

a. Accountability of PMA Cohort
Of the patients randomized, samples from 535/564 patients were available for testing using the BRACAnalysis test. Six patients did not have a sufficient amount of DNA for analysis; therefore, results from BRACAnalysis are available for 529/564 of the randomized patients.

b. Effectiveness Results
The primary efficacy analysis was based on invPFS in 196 patients in the tBRCA population. The primary efficacy endpoint showed a statistical significant benefit

with rucaparib in the tBRCA population An analysis of the 146 patients classified as gBRCA positive by the BRACAnalysis CDx® test showed that the statistically significant benefit of rucaparib in this subgroup, as measured by the hazard ratios, was similar to that in the tBRCA primary efficacy population, as shown in table below.

Analysis Population	**PFS by Investigator Assessment (Primary Endpoint)**	
Group	**Hazard Ratio**	**Median PFS (months) Rucaparib vs. Placebo**
gBRCA positive (n=146)	0.25 (95% CI 0.16-0.39) p<0.001	15.7 vs 5.4
tBRCA (n=196)	0.23 (95% CI: 0.16-0.34) p<0.0001	16.6 vs. 5.4

In addition, invPFS showed a statistically significant benefit with rucaparib in patients classified as gBRCA negative by the BRACAnalysis CDx test compared to placebo (median, 9.1 months versus 5.4 months; HR: 0.393; 95% CI: 0.303 to 0.510) (p<0.0001

Summary of Clinical Validations

Judkins T, *et al*. BMC Cancer (2015) 15:215. DOI 10.1186/s12885-015-1224-y

Hughes, Elisha, et al. "Ancestrally unbiased polygenic breast cancer (BC) risk assessment." (2021): 10502-10502.

Tyrer J, et al. Stat Med. 2004:1111-30. PMID: 15057881

Table 1: MyRisk Plus genes, transcript IDs, and analysis summary

Gene Name	Transcript ID	Analysis Description
APC	NM_000038.5	Full gene, sequence and LR analysis, Promoter 1B LR and sequence of c.-195 to c.-190 and c.-125 (NM_001127511.3)
ATM	NM_000051.3	Full gene, sequence and LR analysis
AXIN2	NM_004655.3	Full gene, sequence and LR analysis
BAP1	NM_004656.4	Full gene, sequence and LR analysis
BARD1	NM_000465.3	Full gene, sequence and LR analysis
BMPR1A	NM_004329.2	Full gene, sequence and LR analysis
BRCA1	NM_007294.3	Full gene, sequence and LR analysis
BRCA2	NM_000059.3	Full gene, sequence and LR analysis
BRIP1	NM_032043.2	Full gene, sequence and LR analysis
CDH1	NM_004360.3	Full gene, sequence and LR analysis
CDK4	NM_000075.3	Full gene, sequence and LR analysis
CHEK2	NM_007194.3	Full gene, sequence and LR analysis
CTNNA1	NM_001903.5	Full gene, sequence and LR analysis
EGFR	NM_005228.5	Exons 18-21, sequence and LR analysis
EPCAM	NM_002354.2	Exons 8-9, LR analysis
FH	NM_000143.3	Full gene, sequence and LR analysis
FLCN	NM_144997.7	Full gene, sequence and LR analysis
GREM1	NM_013372.6	Full gene, including expanded upstream region overlapping *SCG5*, LR analysis
HOXB13	NM_006361.5	Full gene, sequence
MEN1	NM_130799.2	Full gene, sequence and LR analysis
MET	NM_000245.3	Full gene, sequence and LR analysis
MITF	NM_000248.3	Evaluated for c.952 only, sequence
MLH1	NM_000249.3	Full gene, sequence and LR analysis
MSH2	NM_000251.2	Full gene, sequence and LR analysis
MSH3	NM_002439.4	Full gene excluding c.121 to c.237, sequence and LR analysis
MSH6	NM_000179.2	Full gene, sequence and LR analysis
MUTYH (alpha3)	NM_001048171.1	Full gene, sequence and LR analysis
MUTYH (alpha5)	NM_001128425.1	Full gene, sequence and LR analysis
NTHL1	NM_002528.6	Full gene, sequence and LR analysis
p14ARF	NM_058195.3	Full gene, sequence and LR analysis
p16	NM_000077.4	Full gene, sequence and LR analysis
PALB2	NM_024675.3	Full gene, sequence and LR analysis
PMS2	NM_000535.5	Full gene, sequence and LR analysis
POLD1	NM_002691.3	Exonuclease region only (c.841 to c.1686), sequence
POLE	NM_006231.3	Exonuclease region only (c.802 to c.1473), sequence
PTEN	NM_000314.4	Full gene, sequence and LR analysis
RAD51C	NM_058216.2	Full gene, sequence and LR analysis
RAD51D	NM_002878.3	Full gene, sequence and LR analysis
RET	NM_020975.6	Exons 5, 8, 10, 11, and 13-16, sequence and LR analysis
SDHA	NM_004168.4	Full gene, sequence and LR analysis
SDHB	NM_003000.2	Full gene, sequence and LR analysis
SDHC	NM_003001.3	Full gene, sequence and LR analysis
SDHD	NM_003002.4	Full gene, sequence and LR analysis
SMAD4	NM_005359.5	Full gene, sequence and LR analysis
STK11	NM_000455.4	Full gene, sequence and LR analysis
TERT	NM_198253.2	Promoter region only (c.1-71 to c.1-1), sequence
TP53	NM_000546.5	Full gene, sequence and LR analysis
TSC1	NM_000368.4	Full gene, sequence and LR analysis
TSC2	NM_000548.5	Full gene, sequence and LR analysis
VHL	NM_000551.3	Full gene, sequence and LR analysis, including a portion of intron 1 (c.340+556 to c.340+827)

http://www.ncbi.nlm.nih.gov/refseq/

[i] Judkins T, *et al.* BMC Cancer (2015) 15:215. DOI 10.1186/s12885-015-1224-y

[ii] Hughes, Elisha, et al. "Ancestrally unbiased polygenic breast cancer (BC) risk assessment." (2021): 10502-10502.

[iii] Tyrer J, *et al.* Stat Med. 2004 23:1111-30. PMID: 15057881

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The Myriad MyRisk® Plus test was developed and performance characteristics were determined by Myriad Genetic Laboratories, Inc. and in compliance to In-Vitro Diagnostic Device Directive (98/79/EC) and is CE marked. Myriad is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing. Myriad is compliant with multiple international standards including, ISO 13485:2016 and ISO 15189: 2022 as applicable.