BRACAnalysis CDx® Genetic Test Result

FDA Approved *BRCA1* and *BRCA2* Analysis Result

BRACAnalysis CDx®
Germline Companion Diagnostic Test

RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT
	Specimen Type: Blood Draw	Name:
	Date:	Date of Birth:
	Accession Date:	Patient ID:
	Report Date:	Gender:
		Accession #:
		Requisition #:

GENETIC RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

NOTE: MYRIAD GENETIC LABORATORIES WAS UNABLE TO COMPLETE THE LARGE REARRANGEMENT ANALYSIS FOR ALL GENES OF THE PANEL ON THE SAMPLE SUBMITTED DUE TO INSUFFICIENT QUALITY OR QUANTITY OF DNA.

GENE	MUTATION	INTERPRETATION
BRCA1	c.181T>G (p.Cys61Gly) Heterozygous	DELETERIOUS

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

ADDITIONAL INFORMATION

Genes Analyzed: Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:

BRCA1, *BRCA2*

Intended Use: BRACAnalysis CDx® is an *in vitro* diagnostic device intended for the qualitative detection and classification of variants in the protein-coding regions and intron/exon boundaries of the *BRCA1* and *BRCA2* genes using genomic DNA obtained from whole blood specimens collected in EDTA. Single nucleotide variants and small insertions and deletions (indels) are identified by polymerase chain reaction (PCR) and Sanger sequencing. Large deletions and duplications in *BRCA1* and *BRCA2* are detected using multiplex PCR.

Results of the test are used as an aid in identifying patients who are or may become eligible for treatment with the targeted therapies listed in Table 1 in accordance with the most recently approved therapeutic product labeling.

Table 1. Companion Diagnostic Indications

Tumor Type	Biomarker	Therapy
Breast Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)
		Talzenna® (talazoparib)
Ovarian Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)
Pancreatic Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)
Prostate Cancer	Deleterious or suspected deleterious mutations in *BRCA1* and *BRCA2* genes	Lynparza® (olaparib)

Myriad genetics

BRACAnalysis CDx® Genetic Test Result

Name: DOB: Accession #: Report Date:

Detection of deleterious or suspected deleterious germline *BRCA1* and *BRCA2* mutations by the BRACAnalysis CDx test in ovarian cancer patients is also associated with enhanced progression-free survival (PFS) from Zejula® (niraparib) or Rubraca® (rucaparib) maintenance therapy in accordance with the most recently approved therapeutic product labeling.

This assay is for professional use only and is to be performed only at Myriad Genetic Laboratories, a single laboratory site located at 320 Wakara Way, Salt Lake City, UT 84108.

Limitations:

- In Ovarian Cancer, ~70% of tumor *BRCA1* or *BRCA2* mutation positive patients are estimated to have a germline mutation while ~30% of patients are estimated to have a somatic mutation. The BRACAnalysis CDx test detects germline mutations only, not somatic mutations from a patient's blood sample. A negative result using the BRACAnalysis CDx blood test in ovarian cancer patients does not rule out the possibility of a somatic *BRCA1* or *BRCA2* mutation in tumor tissue from these patients.
- In Prostate Cancer, ~50% of tumor *BRCA1* or *BRCA2* mutation positive patients are estimated to have a germline mutation while ~50% of patients are estimated to have a somatic mutation. The BRACAnalysis CDx test detects germline mutations only, not somatic mutations from a patient's blood sample. A negative result using the BRACAnalysis CDx blood test in prostate cancer patients does not rule out the possibility of a somatic *BRCA1* or *BRCA2* mutation in tumor tissue from these patients.
- The test has been designed to detect genomic rearrangements (i.e., deletions or duplications) involving the promoter and coding exons of *BRCA1* and *BRCA2*, but the test will not detect some types of errors in RNA transcript processing. Insertions that do not result in duplications will generally not be detected. Also, the test may not accurately differentiate between duplications and triplications.
- Unequal allele amplification may result from rare polymorphisms under primer sites and lead to false negative results.
- There are limited portions of either *BRCA1* or *BRCA2* for which sequence determination can be performed only in the forward or reverse direction. Approximately 0.25% of interrogated sequences are analyzed in multiple runs in either the forward or reverse direction.

The majority of deleterious or suspected deleterious mutations identified by Myriad in *BRCA1* and *BRCA2* are classified using objective criteria based on the type and genomic position of the mutations. Other deleterious or suspected deleterious mutations may be classified by other criteria that are based on available evidence. Myriad's myVision® Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, the healthcare provider may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management changes, that information will automatically be made available to the healthcare provider through an amended report. If you have any questions or concerns about how the variant(s) in this result were classified, please contact Myriad.

Please contact Myriad at 1-800-469-7423 with any questions or feedback regarding services provided.

This **Authorized Signature** pertains to this laboratory report:

Benjamin B. Roa, PhD
Diplomate ABMGG
Laboratory Director

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. This test was developed and its performance characteristics determined by Myriad Genetic Laboratories. Myriad is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.

Myriad genetics

BRACAnalysis CDx® Genetic Test Result

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The following information has not been reviewed and approved by the FDA. This assay identifies patients at risk for Hereditary Breast and Ovarian Cancer (HBOC) syndrome associated with deleterious or suspected deleterious BRCA1 or BRCA2 variants. Additional information is provided for hereditary cancer management purposes.

DETAILS ABOUT: *BRCA1* c.181T>G (p.Cys61Gly): NM_007294.3; (aka: C61G (300T>G))

Functional Significance: Deleterious - Abnormal Protein Production and/or Function

The heterozygous germline *BRCA1* mutation c.181T>G is predicted to result in the substitution of glycine for cysteine at amino acid position 61 of the *BRCA1* protein (p.Cys61Gly). This mutation occurs in a region of the *BRCA1* protein that is functionally significant.

Clinical Significance: High Risk

Linkage analysis in high-risk families has shown this mutation to segregate with cancer (Friedman LS et al. Nature Genetics 8:399-404,1994). This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL TREATMENT INFORMATION

This assay is intended to be used as an aid in treatment decision making for the PARP inhibitors Lynparza® (olaparib), Zejula® (niraparib), Talzenna® (talazoparib) and Rubraca® (rucaparib). Full prescription information for Lynparza® (olaparib) is available at: http://www.azpicentral.com/Lynparza/pi_lynparza.pdf. Full prescription information for Zejula® (niraparib) is available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Zejula_Capsules/pdf/ZEJULA-CAPSULES-PI-PIL.PDF. Full prescription information for Talzenna® (talazoparib) is available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=11046. Full prescription information for Rubraca® (rucaparib) is available at: https://clovisoncology.com/media/1094/rubraca-prescribing-info.pdf. For more detailed information including Performance Characteristics, please find the complete Technical Information at: myriad.com/technical-specifications.

ASSOCIATED CANCER RISKS AND CLINICAL MANAGEMENT

If a clinically significant mutation is identified, please see the management tool associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient. Testing of other family members may assist in the interpretation of this patient's test result.

DETAILS ABOUT NON-CLINICALLY SIGNIFICANT VARIANTS

All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

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CE IVD

The Myriad Genetics BRACAnalysis CDx® 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, ISO13485:2016 and ISO 15189: 2012 as applicable.

Management Tool - BRACAnalysis CDx®

BRCA1 and *BRCA2* Analysis

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GENETIC RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

GENE	MUTATION	THIS GENETIC TEST RESULT IS ASSOCIATED WITH THE FOLLOWING CANCER RISKS:
BRCA1	c.181T>G (p.Cys61Gly) Heterozygous	HIGH RISK: Breast, Ovarian
		ELEVATED RISK: Pancreatic

Please see the Genetic Test Result for more details on any variant(s) detected in this patient, including variant classification information.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

CLINICAL OVERVIEW OF GENETIC FINDINGS

Hereditary Breast and Ovarian Cancer syndrome (HBOC)

- This patient has been found to have a mutation in the *BRCA1* gene. Individuals with mutations in *BRCA1* have Hereditary Breast and Ovarian Cancer syndrome (HBOC).
- Women with HBOC have a risk for breast cancer that is greatly increased over the 12.5% lifetime risk for women in the general population of the United States. Most breast cancers in women with *BRCA1* mutations are Triple Negative Breast Cancer (TNBC), a type of breast cancer lacking estrogen and progesterone receptors, and not expressing Her2.
- Women with HBOC also have high risks for ovarian, fallopian tube, and primary peritoneal cancer.
- Men with HBOC due to mutations in *BRCA1* have an elevated risk for breast and prostate cancer. The increased risk for prostate cancer may be most significant at younger ages. Additionally, men with a *BRCA1* mutation have a higher risk for an aggressive prostate cancer.
- Male and female patients with HBOC due to mutations in *BRCA1* have an elevated risk for exocrine pancreatic cancer. These are cancers developing in the enzyme-secreting cells of the pancreas.
- Some studies have found that women with *BRCA1* mutations have an increased risk for uterine cancer, but other studies have found no increased risk. There are currently no medical management recommendations for uterine cancer risk in women with mutations in *BRCA1*. If hysterectomy is considered, there is the option for hormone replacement therapy (HRT) with estrogen alone, which is associated with a lower risk of breast cancer than HRT with estrogen and progesterone.
- Although there are high cancer risks for patients with HBOC, there are interventions that have been shown to be effective at reducing many of these risks. Guidelines from the National Comprehensive Cancer Network (NCCN) for the medical management of patients with HBOC are listed below. It is recommended that patients with *BRCA1* mutations and a diagnosis of HBOC be managed by a multidisciplinary team with experience in the prevention and treatment of the cancers associated with HBOC.

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WHAT ARE THE PATIENT'S CANCER RISKS?

The risk table or tables that follow show the clinically significant cancer risks identified as part of this patient's testing. The risk for each gene result is provided separately. If the risk for any individual cancer is affected by more than one of these results, the risk associated with each finding is listed in a separate table. At this time, there is not enough information to estimate risks for cancers affected by more than one gene mutation, or risks based on both gene mutations and personal/family history.

The cancer risks in the table(s) below are estimates based on the best data currently available in the published literature. Risks for individual patients may be significantly higher or lower depending on personal and family history and the presence or absence of other risk factors.

Risks Due to Hereditary Breast and Ovarian Cancer syndrome (HBOC)

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION	RELATED TO
FEMALE BREAST			
To age 50	28%-51%	2.0%	*BRCA1*
To age 70	46%-87%	7.4%	*BRCA1*
Second primary within 5 years of first breast cancer diagnosis	8.9%-20%	2%	*BRCA1*
OVARIAN			
To age 50	8%-23%	0.2%	*BRCA1*
To age 70	39%-63%	0.6%	*BRCA1*
Ovarian cancer within 10 years of a breast cancer diagnosis	12.7%	<1.0%	*BRCA1*
PANCREATIC			
To age 80	Elevated risk	1.1%	*BRCA1*

WHAT MANAGEMENT FOR CANCER RISKS SHOULD BE CONSIDERED?

This overview of clinical management guidelines is based on the patient's genetic test results. Medical management guidelines are summarized from established medical societies, primarily the National Comprehensive Cancer Network (NCCN). If there are overlapping management guidelines for any individual cancer due to more than one gene result, the guidelines associated with each finding are listed in separate tables, even if they are the same. At this time, there are no medical society guidelines for how to adjust management when there are multiple sources of risk, such as from more than one gene mutation. In these cases, it may be appropriate to use the most aggressive management option provided.

The overview provided below should not be used as the sole source of information to determine medical management. The references cited should always be consulted for more details and updates to the recommendations.

No information is provided related to treatment of a previous or existing cancer or polyps. The recommendation summaries below may require modification due to the patient's personal medical history, past surgeries and other treatments. Patients with a past history of cancer, benign tumors, or pre-cancerous findings may be candidates for long term surveillance and risk-reduction strategies beyond what is necessary for the treatment of their initial diagnosis. Any discussion of medical management options is for general information purposes only and does not constitute a recommendation. While genetic testing and medical society recommendations provide important and useful information, medical management decisions should be made in consultation between each patient and his or her healthcare provider.

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Management Options for Hereditary Breast and Ovarian Cancer syndrome (HBOC)

PROCEDURE	AGE TO BEGIN	FREQUENCY Unless otherwise indicated by findings	RELATED TO
FEMALE BREAST			
Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Periodic, consistent breast self-examination (BSE) may facilitate breast awareness. [2]	18 years	NA	*BRCA1*
Clinical breast examination [2]	25 years	Every 6 to 12 months	*BRCA1*
Breast MRI with contrast and/or mammography with consideration of tomosynthesis [2]	Age 25 for MRI, or if MRI is unavailable, mammography with consideration of tomosynthesis. Age 30 for both MRI and mammography. Individualize to a younger age if a relative has been diagnosed younger than age 30.	Annually	*BRCA1*
Consider investigational screening studies within clinical trials. [2]	Individualized	NA	*BRCA1*
Consider risk-reducing mastectomy. [2]	Individualized	NA	*BRCA1*
Consider options for breast cancer risk-reduction agents (i.e. tamoxifen). [2]	Individualized	NA	*BRCA1*
OVARIAN			
Bilateral salpingo-oophorectomy [2]	35 to 40 years, upon completion of childbearing	NA	*BRCA1*
Consider transvaginal ultrasound and CA-125 measurement. Consider investigational screening studies within clinical trials. [2]	30 to 35 years	Individualized	*BRCA1*
Consider options for ovarian cancer risk-reduction agents (i.e. oral contraceptives). [2,5]	Individualized	NA	*BRCA1*
PANCREATIC			
For patients with a family history of pancreatic cancer, consider available options for pancreatic cancer screening, including the possibility of endoscopic ultrasonography (EUS) and MRI/magnetic resonance cholangiopancreatography (MRCP). It is recommended that patients who are candidates for pancreatic cancer screening be managed by a multidisciplinary team with experience in screening for pancreatic cancer, preferably within research protocols. [3]	Age 50, or 10 years younger than the earliest age of pancreatic cancer diagnosis in the family	Annually	*BRCA1*
Provide education about ways to reduce pancreatic cancer risk, such as not smoking and losing weight. [6]	Individualized	Individualized	*BRCA1*

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Management Options for Hereditary Breast and Ovarian Cancer syndrome (HBOC)

PROCEDURE	AGE TO BEGIN	FREQUENCY Unless otherwise indicated by findings	RELATED TO
FOR PATIENTS WITH A CANCER DIAGNOSIS			
For patients with a gene mutation and a diagnosis of cancer, targeted therapies may be available as a treatment option for certain tumor types (e.g., platinum chemotherapy, PARP-inhibitors) [1,4,6,7,8]	NA	NA	*BRCA1*

1. Armstrong DK, et al. NCCN Clinical Practice Guidelines in Oncology®: Ovarian Cancer. V 1.2021. Feb 26. Available at https://www.nccn.org.
2. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. V 1.2022. Aug 11. Available at https://www.nccn.org.
3. Goggins M, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020 69:7-17. PMID: 31672839.
4. Gradishar WJ et al. NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer. V 5.2021. June 28. Available at https://www.nccn.org.
5. Gupta S, et al. NCCN Clinical Practice Guidelines in Oncology® Genetic/Familial High-Risk Assessment: Colorectal. V 1.2021. May 11. Available at https://www.nccn.org.
6. Tempero MA, et al. NCCN Clinical Practice Guidelines in Oncology®: Pancreatic Adenocarcinoma. V 2.2021. Feb 25. Available at https://www.nccn.org.
7. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf
8. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s002lbl.pdf

Notes for Personalized Management:

INFORMATION ON HOW CANCER RISKS AND MANAGEMENT ARE DETERMINED

The Management Tool provides cancer risk levels and management recommendations based on analysis of the genetic results (see Genetic Result). Additional details and references for cancer risks and management recommendations can be found on myriadmyrisk.com/gene-table/.

- A comprehensive risk assessment may include other aspects of the patient's personal/family medical history, as well as lifestyle, environment and other factors.
- No management recommendations are provided related to treatment of a previous or existing cancer or polyps. The recommendations provided may require modification based on the patient's personal medical history, surgeries and other treatments. Patients with a personal history of cancer, benign tumors or pre-cancerous findings may be candidates for long term surveillance and risk-reduction strategies beyond what is necessary for the treatment of their initial diagnosis.
- Patients who have a clinical diagnosis of a genetic cancer syndrome (e.g., Lynch syndrome) may have different management recommendations than provided. Management should be personalized based on all known clinical diagnoses.
- The Genetic Test Result Summary includes: female breast, male breast, colorectal, endometrial, gastric, ovarian, pancreatic and prostate cancers, and melanoma. In this summary a gene associated cancer risk is described as "High Risk" for a cancer type if all of the following conditions are met: the absolute risk of cancer is approximately 5% or higher, the increase in risk over the general population is approximately 2 to 3-fold or higher, and there is significant data from multiple studies supporting the cancer risk estimate. A gene is described as "Elevated Risk" for a cancer type if there is sufficient data to support an increase in cancer risk over the general population risk, but not all criteria for "High Risk" are met.

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INFORMATION FOR FAMILY MEMBERS

Family members should talk to their healthcare providers about hereditary cancer testing to help define their own risk and assist in the interpretation of this patient's genetic test result.

- This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.
- **Family members should talk to a healthcare provider about genetic testing.** Close relatives such as parents, children, brothers, and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance for carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention. More resources for family testing are available at MySupport360.com.

Additional Information for Hereditary Breast and Ovarian Cancer syndrome (HBOC)

- In rare instances, an individual may inherit mutations in both copies of the *BRCA1* gene, leading to the condition Fanconi Anemia, Complementation Group S (FANCS). This condition is rare and may include physical abnormalities, developmental delay, and a high risk for cancer. The children of this patient are at risk of inheriting FANCS only if the other parent is also a carrier of a *BRCA1* mutation. Screening the other biological parent of any children for *BRCA1* mutations may be appropriate.
- Parents who are concerned about the possibility of passing on a *BRCA1* mutation to a future child may want to discuss options for prenatal testing and assisted reproduction techniques, such as pre-implantation genetic diagnosis (PGD).

CANCER RISK FOR *BRCA1* CLINICALLY SIGNIFICANT MUTATION

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION
	FEMALES	
FEMALE BREAST		
To age 50	28%-51%	2.0%
To age 70	46%-87%	7.4%
Second primary within 5 years of first breast cancer diagnosis	8.9%-20%	2%
OVARIAN		
To age 50	8%-23%	0.2%
To age 70	39%-63%	0.6%
Ovarian cancer within 10 years of a breast cancer diagnosis	12.7%	<1.0%
	MALES	
PROSTATE		
To age 70	Up to 16%	6.1%
MALE BREAST		
To age 70	1.2%	<0.1%
	FEMALES AND MALES	
PANCREATIC		
To age 80	Elevated risk	1.1%

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END OF MANAGEMENT TOOL