Myriad myRisk® Hereditary Cancer Test

myRisk Genetic Result

MYRIAD myRisk® Hereditary Cancer | Powered by myVision®

RECEIVING HEALTHCARE PROVIDER

Test HCP, MD
Test Medical Center
123 Main St
Testville, TX 55555

SPECIMEN

Specimen Type:	**Blood**
Draw Date:	**Nov 18, 2019**
Accession Date:	**Nov 18, 2019**
Report Date:	**Nov 18, 2019**

PATIENT

Name:	**Pt Last Name, Pt First Name**
Date of Birth:	**Nov 18, 1961**
Patient ID:	**Patient id**
Gender:	**Female**
Accession #:	**07236814-BLD**
Requisition #:	**90481600**

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.

CLINICAL HISTORY ANALYSIS: BEYOND THE GENETIC RESULT, NO MODIFIED MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

GENE	MUTATION	INTERPRETATION
BRCA2	**c.xxxxx (p.xxxxx)** Heterozygous	**High Cancer Risk** This patient has Hereditary Breast and Ovarian Cancer syndrome (HBOC).

DETAILS ABOUT: *BRCA2* c.xxxxx (p.xxxxx): NM_000059.3

Functional Significance: Deleterious - Abnormal Protein Production and/or Function
The heterozygous germline *BRCA2* mutation c.xxxxx is predicted to result in the premature truncation of the *BRCA2* protein at amino acid position xxxx (p.xxxxx).

Clinical Significance: High Cancer Risk
This mutation is associated with increased cancer risk and should be regarded as clinically significant.

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

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.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers 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 change, that information will automatically be made available to the healthcare provider through an amended report.

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ADDITIONAL INFORMATION

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

APC, *ATM*, *AXIN2*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *EPCAM* (large rearrangement only), *HOXB13* (sequencing only), *GALNT12*, *MLH1*, *MSH2*, *MSH3* (excluding repetitive portions of exon 1), *MSH6*, *MUTYH*, *NBN*, *NTHL1*, *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *RNF43*, *RPS20*, *SMAD4*, *STK11*, *TP53*. Sequencing was performed for select regions of *POLE* and *POLD1*, and large rearrangement analysis was performed for select regions of *GREM1* (see technical specifications).

** Other genes not analyzed with this test may also be associated with cancer.

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Please see the "myRisk 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 based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (https://www.myriadpro.com/documents-and-forms/technical-specifications/) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. Current testing technologies are unable to definitively determine whether a variant is germline or somatic in origin, which may significantly impact risk estimates and medical management; therefore, these results should be correlated with this patient's personal and family history. The interpretation of this test may also be impacted if the patient has a hematologic malignancy or an allogeneic bone marrow transplant.

CLASSIFICATION DISCLAIMER

THE CLASSIFICATION AND INTERPRETATION OF ALL VARIANTS IDENTIFIED IN THIS ASSAY REFLECTS THE CURRENT STATE OF MYRIAD'S SCIENTIFIC UNDERSTANDING AT THE TIME THIS REPORT WAS ISSUED. VARIANT CLASSIFICATION AND INTERPRETATION MAY CHANGE FOR A VARIETY OF REASONS, INCLUDING BUT NOT LIMITED TO, IMPROVEMENTS TO CLASSIFICATION TECHNIQUES, AVAILABILITY OF ADDITIONAL SCIENTIFIC INFORMATION, AND OBSERVATION OF A VARIANT IN MORE PATIENTS.

Please contact Myriad Medical Services at 1-800-469-7423 X 3850 to discuss any questions regarding this result.

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

Benjamin B. Roa, PhD
Diplomate ABMG
Laboratory Director

Johnathan M. Lancaster, MD, PhD
Diplomate ABOG, FACOG, FACS
Chief Medical Officer

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members. The patient's clinical history and test results should not be disclosed to a third party, unless related to treatment or payment for treatment, without the patient's express written authorization. It is strongly recommended that these results be communicated to the patient in a setting that includes appropriate genetic consultation. This test was developed and its performance characteristics determined by Myriad Genetic Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that clearance or approval for laboratory-developed tests is not required.

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Clinical & Cancer Family History Information

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PERSONAL / FAMILY CANCER HISTORY SUMMARY

FAMILY MEMBER	CANCER / CLINICAL DIAGNOSIS	AGE AT DIAGNOSIS
Patient	Breast, Invasive	51

The clinical information displayed here was provided by a qualified healthcare provider on the Test Request Form and other documents, and was not verified by Myriad. Family members listed as "other" are not included in a Tyrer-Cuzick breast cancer risk estimate or other personal/family history assessments. For more information see the Specifications for Personal/Family History Analysis at https://www.myriadpro.com/documents-and-forms/technical-specifications/. The accuracy of the information provided in the Clinical and Cancer Family History Information section of the report may significantly affect the accuracy of breast cancer risk estimates provided based on either Tyrer-Cuzick or riskScore™.

riskScore™ is only calculated for women who meet the eligibility criteria listed below. riskScore™ is not valid, and may significantly over- or under-estimate breast cancer risk for a woman who does not meet these criteria: 1) ancestry is exclusively White/Non-Hispanic (includes Ashkenazi Jewish), 2) age is 18 to 84 years, 3) no personal history of breast cancer, LCIS, hyperplasia (with or without atypia), or a breast biopsy with unknown results, 4) no known mutation or inconclusive result in a breast cancer risk gene has been found in the woman or any of her relatives, and 5) the sample was submitted with a current Test Request Form and the ordering healthcare provider has not determined that riskScore™ is inappropriate for the patient.

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CLINICAL HISTORY ANALYSIS: BEYOND THE GENETIC RESULT, NO MODIFIED MANAGEMENT GUIDELINES IDENTIFIED BASED ON THE CLINICAL HISTORY PROVIDED

Other clinical factors may influence individualized management. This analysis may be incomplete if details about cancer diagnoses, ages, family relationships or other factors were omitted or ambiguous.

GENE	MUTATION	THIS GENETIC TEST RESULT IS ASSOCIATED WITH THE FOLLOWING CANCER RISKS:
BRCA2	**c.xxxxx (p.xxxxx)** Heterozygous	**HIGH RISK: Female Breast, Ovarian, Pancreatic**
		ELEVATED RISK: Melanoma

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

OVERVIEW

Hereditary Breast and Ovarian Cancer syndrome (HBOC):

- This patient has been found to have a mutation in the *BRCA2* gene. Individuals with mutations in *BRCA2* have a condition called 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.
- Women with HBOC also have high risks for ovarian, fallopian tube, and primary peritoneal cancer.
- Men with HBOC due to mutations in *BRCA2* have a high risk for breast cancer and prostate cancer. The increase in prostate cancer risk is most significant at younger ages. Additionally, men with a *BRCA2* mutation have a higher risk for an aggressive prostate cancer.
- Male and female patients with HBOC due to a mutation in *BRCA2* also have a high risk for pancreatic cancer and an elevated risk for melanomas of both the skin and eyes.
- 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 *BRCA2* 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.

WHAT ARE THE PATIENT'S GENE-RELATED CANCER RISKS?

If more than one gene mutation increases a specific cancer risk (e.g., breast), only the highest cancer risk is shown. If this patient has more than one gene mutation, risks may be different, as this analysis does not account for possible interactions between gene mutations.

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION	RELATED TO
FEMALE BREAST			
To age 50	23%-35%	1.9%	*BRCA2*
To age 70	43%-84%	7.1%	*BRCA2*
Second primary within 5 years of first breast cancer diagnosis	8%-12%	2%	*BRCA2*
OVARIAN			
To age 50	0.4%-4%	0.2%	*BRCA2*
To age 70	15%-27%	0.7%	*BRCA2*
Ovarian cancer within 10 years of a breast cancer diagnosis	6.8%	<1.0%	*BRCA2*
PANCREATIC			
To age 80	7%, or higher if there is a family history of pancreatic cancer.	1%	*BRCA2*
MELANOMA			
To age 80	Elevated risk for melanomas of both the skin and eye	1.6%	*BRCA2*

WHAT MANAGEMENT FOR CANCER RISKS SHOULD BE CONSIDERED?

This overview of clinical management guidelines is based on the patient's personal and family history and genetic test results. Medical management guidelines are summarized from established medical societies, primarily the National Comprehensive Cancer Network (NCCN). The reference cited should always be consulted for more details. If management for a specific cancer (e.g. breast) is available due to multiple causes (e.g. a mutation and a Tyrer-Cuzick risk estimate >20%, or multiple mutations in different genes), only the most aggressive management is shown. Only guidelines for the patient's long-term care related to cancer prevention are included.

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.

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.[1]	18 years	NA	*BRCA2*
Clinical breast examination[1]	25 years	Every 6 to 12 months	*BRCA2*
Breast MRI with contrast and/or mammography with consideration of tomosynthesis[1]	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	*BRCA2*
Consider investigational screening studies within clinical trials.[1]	Individualized	NA	*BRCA2*
Consider risk-reducing mastectomy.[1]	Individualized	NA	*BRCA2*
Consider options for breast cancer risk-reduction agents (i.e. tamoxifen).[1]	Individualized	NA	*BRCA2*
OVARIAN			
Bilateral salpingo-oophorectomy[1]	35 to 45 years, upon completion of childbearing	NA	*BRCA2*
Consider transvaginal ultrasound and CA-125 measurement. Consider investigational screening studies within clinical trials.[1]	30 to 35 years	Individualized	*BRCA2*
Consider options for ovarian cancer risk-reduction agents (i.e. oral contraceptives).[1,2]	Individualized	NA	*BRCA2*

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PROCEDURE	AGE TO BEGIN	FREQUENCY Unless otherwise indicated by findings	RELATED TO
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 the screening for pancreatic cancer, preferably within research protocols.[3,4]	Age 50, or 10 years younger than the earliest age of pancreatic cancer diagnosis in the family	Annually	*BRCA2*
Provide education about smoking cessation to reduce pancreatic cancer risk[3]	Individualized	Individualized	*BRCA2*
MELANOMA			
Consider whole-body skin and eye examinations.[1]	Individualized	NA	*BRCA2*
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)[5,6,7,8,9,10]	NA	NA	*BRCA2*

1. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast and Ovarian. V 2.2019. July 30. Available at http://www.nccn.org.
2. Provenzale D, et al. NCCN Clinical Practice Guidelines in Oncology® Genetic/Familial High-Risk Assessment: Colorectal. V 1.2018. July 12. Available at http://www.nccn.org.
3. Syngal S, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015 110:223-62. PMID: 25645574.
4. Canto MI, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 62:339-47. PMID: 23135763.
5. Armstrong DK, et al. NCCN Clinical Practice Guidelines in Oncology®: Ovarian Cancer. V 2.2018. March 9. Available at http://www.nccn.org.
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208558s002lbl.pdf
7. Mohler JL, et al. NCCN Clinical Practice Guidelines in Oncology®: Prostate Cancer. V 4.2018. August 15. Available at http://www.nccn.org.
8. Tempero MA, et al. NCCN Clinical Practice Guidelines in Oncology®: Pancreatic Adenocarcinoma. V 2.2018. July 10. Available at http://www.nccn.org.
9. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf
10. Gradishar WJ et al. NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer. V 1.2018. March 20. Available at http://www.nccn.org.

Notes for Personalized Management: _____

INFORMATION ON HOW CANCER RISKS AND MANAGEMENT ARE DETERMINED

The myRisk Management Tool provides cancer risk levels based on analysis of genetic test results (see myRisk Genetic Result) and a summary of medical society management recommendations based on a combined analysis of the genetic test results and, when possible, personal clinical factors and personal/family cancer history. Here are some important points to understand as you interpret this test report and decide on the best plan for management:

- Comprehensive patient management. The management recommendations presented in this report are a summary of management options recommended by the National Comprehensive Cancer Network (NCCN) and other medical societies and are general in nature. The patient's actual management should be modified based on personal medical history, surgeries and other treatments. A comprehensive risk assessment and management plan may take into account this report and other aspects of the patient's personal/family medical history (e.g., all known clinical diagnoses), as well as lifestyle, environmental and other factors.

- Risk estimates based on provider-supplied information. Some of the risk estimates and management recommendation summaries provided in this report are based on our interpretation of information supplied by the ordering health care provider on the test request form (see Specifications for Personal/Family History analysis at https://myriadpro.com/documents-and-forms/technical-specifications/). The patient's actual risks and appropriate management may be significantly different if details provided for cancer diagnoses, ages, family relationships or other factors were incorrect, omitted, ambiguous or have since changed. Please review the clinical history listed on the Clinical & Family History Information page of this report to make sure that the information used was provided and interpreted correctly.

- Variability in Tyrer-Cuzick risk estimates. Tyrer-Cuzick estimates of breast cancer risk can vary significantly based on the way in which the model is used, and the estimate provided here may be higher or lower than what would be calculated by other users. For complete details of how Myriad calculates Tyrer-Cuzick risk estimates, including how Myriad handles information provided in a format not compatible with the model, please see the Specifications for Personal/Family History analysis at https://myriadpro.com/documents-and-forms/technical-specifications/). These Specifications also include information for recalculating the Tyrer-Cuzick breast cancer risk estimate if desired.

- What is meant by "High Risk" and "Elevated Risk"? In the Genetic Test Result 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 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.

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. Any cancer risks that apply to female and male relatives with 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 of 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. In some cases, it may be recommended that relatives be tested for additional mutations. More resources for family testing are available at MySupport360.com.

- In rare instances, an individual may inherit mutations in both copies of the *BRCA2* gene, leading to the condition Fanconi Anemia, Complementation Group D1 (FANCD1). This condition is rare and includes physical abnormalities, growth retardation, progressive bone marrow failure and a high risk for cancer. The children of this patient are at risk of inheriting FANCD1 only if the other parent is also a carrier of a *BRCA2* mutation. Screening the spouse/partner of this patient for *BRCA2* mutations may be appropriate.

- Parents who are concerned about the possibility of passing on a *BRCA2* 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 *BRCA2* CLINICALLY SIGNIFICANT MUTATION

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION
	FEMALES	
FEMALE BREAST		
To age 50	23%-35%	1.9%
To age 70	43%-84%	7.1%
Second primary within 5 years of first breast cancer diagnosis	8%-12%	2%
OVARIAN		
To age 50	0.4%-4%	0.2%
To age 70	15%-27%	0.7%
Ovarian cancer within 10 years of a breast cancer diagnosis	6.8%	<1.0%
	MALES	

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CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION
	MALES	
MALE BREAST		
To age 70	6.8%	<0.1%
PROSTATE		
To age 70	20%	6.6%
	FEMALES AND MALES	
PANCREATIC		
To age 80	7%, or higher if there is a family history of pancreatic cancer.	1%
MELANOMA		
To age 80	Elevated risk for melanomas of both the skin and eye	1.6%

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END OF MYRISK MANAGEMENT TOOL