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Integrated BRACAnalysis® with Myriad myRisk® Hereditary Cancer
myRisk Genetic Result



RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT
Test HCP, MD Test Medical Center 123 MAIN ST TESTVILLE, TX 55555	Specimen Type: Blood Draw Date: Mar 06, 2020 Accession Date: Mar 06, 2020 Report Date: Mar 06, 2020	Name: Pt Last Name, Pt First Name Date of Birth: Mar 06, 1978 Patient ID: Patient id Gender: Female Accession #: 07000187-BLD Requisition #: 90013517

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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.

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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	INTERPRETATION
CHEK2	c.xxxxx (p.xxxxx) Heterozygous	High Cancer Risk This patient has CHEK2-associated Cancer Risk.

DETAILS ABOUT: CHEK2 c.xxxxx (p.xxxxx): NM_007194.3

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

The heterozygous germline *CHEK2* mutation c.xxxxx is predicted to result in the premature truncation of the *CHEK2* protein at amino acid position 60 (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.





myRisk Genetic Result

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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

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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Integrated BRACAnalysis® with Myriad myRisk® Hereditary Cancer
Clinical & Cancer Family History Information



RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT
Test HCP, MD Test Medical Center 123 MAIN ST TESTVILLE, TX 55555	Specimen Type: Blood Draw Date: Mar 06, 2020 Accession Date: Mar 06, 2020 Report Date: Mar 06, 2020	Name: Pt Last Name, Pt First Name Date of Birth: Mar 06, 1978 Patient ID: Patient id Gender: Female Accession #: 07000187-BLD Requisition #: 90013517

PERSONAL / FAMILY CANCER HISTORY SUMMARY

FAMILY MEMBER	CANCER / CLINICAL DIAGNOSIS	AGE AT DIAGNOSIS
Patient	None	
Aunt Paternal 1	Breast, DCIS	67
Aunt Paternal 2	Breast, DCIS	66
1st Cousin Paternal	Breast, DCIS	42

PATIENT CLINICAL HISTORY SUMMARY

Woman's age	42	Hormone Replacement Therapy (HRT)	No
Ancestry	White/Non-Hispanic	- HRT: Treatment type	N/A
Height	5 ft 7 in	- HRT: Current user	N/A
Weight	175 lbs	- Number of years ago started	N/A
Age of menarche	13	- Additional years of intended use	N/A
Patient's menopausal status	Pre-menopausal	- HRT: Past user	N/A
- Age of onset	N/A	- Number of years ago ended	N/A
Age of first live birth	27	Breast biopsy	N/A

NUMBER OF PATIENT'S FEMALE RELATIVES

Daughters	0	Sisters	2	Maternal Aunts	2	Paternal Aunts	2
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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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myRisk Management Tool

MYRIAD
myRisk®
Hereditary Cancer

Powered by
myVision®

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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	THIS GENETIC TEST RESULT IS ASSOCIATED WITH THE FOLLOWING CANCER RISKS:
<i>CHEK2</i>	c.xxxxx (p.xxxxx) Heterozygous	HIGH RISK: Female Breast
		ELEVATED RISK: Colorectal

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

TYRER-CUZICK BREAST CANCER RISK CALCULATION

REMAINING LIFETIME BREAST CANCER RISK: Not Calculated	5-YEAR BREAST CANCER RISK: Not Calculated
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The Tyrer-Cuzick breast cancer risk estimate is only calculated for women who meet the following criteria: 1) age is younger than 85 years, 2) no known mutation or inconclusive result has been found in the woman or any of her relatives, and 3) the sample was submitted with a current Test Request Form that includes all of the fields required to collect the information used in the calculation, and the provider has not indicated on the Test Request Form that the Tyrer-Cuzick calculation is not appropriate for the patient. Version 7.02 of the Tyrer-Cuzick model was used for this risk estimate. Tyrer-Cuzick model Versions 7.02 and 8.0 are available for download at the EMS-Trials website, <http://www.ems-trials.org/riskevaluator>.





myRisk Management Tool

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OVERVIEW

CHEK2-associated Cancer Risk:

- This patient has been found to have a mutation in the *CHEK2* gene. Women with *CHEK2* mutations have a risk for breast cancer that is significantly increased over the 12.5% lifetime risk for women in the general population of the United States. Men with *CHEK2* mutations also have an increased risk for breast cancer.
- Estimates of cancer risk for men and women with *CHEK2* mutations vary widely and are strongly influenced by family history. In cases where there is no family history of one of these cancers, the risk for a patient with a *CHEK2* mutation may be lower than in cases where that cancer has been diagnosed in one or more close relatives. Therefore, the family history of a patient should be considered when deciding on the most appropriate strategies to manage cancer risk, with more aggressive strategies targeted to patients with significant family histories of related cancers.
- Individuals with *CHEK2* mutations may have an elevated risk for colorectal cancer, and the National Comprehensive Cancer Network (NCCN) has provided screening recommendations to address this possible risk.
- Although many different *CHEK2* mutations have been identified, estimated cancer risks for *CHEK2* are currently based largely on studies of a single mutation (c.1100del) that is common in patients of European ancestry. These estimates may be modified as we learn more about other *CHEK2* mutations in patients of varied ancestries.
- Some studies have described a possible increased risk for a wide range of cancers in patients with *CHEK2* mutations, including prostate, gastric, thyroid, hematological malignancies, testicular germ cell tumors, and other malignancies. However, these studies are not conclusive and there are currently no medical management guidelines to address these possible risks.
- Although there are increased risks for cancer in men and women with mutations in *CHEK2*, there are interventions that may reduce these risks. Guidelines from the National Comprehensive Cancer Network (NCCN) that may apply are listed below. Since information about the cancer risks associated with *CHEK2* mutations is relatively new, and there is still some uncertainty about the best ways to reduce these risks, it may be appropriate to interpret these results in consultation with cancer genetics experts in this emerging area of knowledge.

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

The cancer risks in the table 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.

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 80	23%-48%	10.2%	<i>CHEK2</i>
Second primary within 10 years of first breast cancer diagnosis	Up to 29%	4.0%	<i>CHEK2</i>
COLORECTAL			
To age 80	Possibly elevated risk	3.0%	<i>CHEK2</i>

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.





myRisk Management Tool

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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	Individualized	NA	CHEK2
Clinical encounter, including clinical breast exam, ongoing risk assessment and risk-reduction counseling ²	When genetic risk is identified	Every 6 to 12 months	CHEK2
Mammography with consideration of tomosynthesis and consideration of breast MRI with contrast ¹	Age 40, or modified to a younger age based on the family history of breast cancer	Annually	CHEK2
Consider additional risk-reduction strategies. ^{1,2}	Individualized	NA	CHEK2
COLORECTAL			
Colonoscopy ³	40 years, or 10 years younger than the age of diagnosis for any first-degree relative with colorectal cancer	Every 5 years	CHEK2

1. Daly M et al. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. V 1.2020. Dec 4. Available at <http://www.nccn.org>.

2. Bevers TB, et al. NCCN Clinical Practice Guidelines in Oncology®: Breast Cancer Screening and Diagnosis. V 1.2019. May 17. Available at <http://www.nccn.org>.

3. Provenzale D, et al. NCCN Clinical Practice Guidelines in Oncology® Genetic/Familial High-Risk Assessment: Colorectal. V 3.2019. Dec 13. 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.





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- 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.

CANCER RISK FOR *CHEK2* CLINICALLY SIGNIFICANT MUTATION

CANCER TYPE	CANCER RISK	RISK FOR GENERAL POPULATION
FEMALES		
FEMALE BREAST		
To age 80	23%-48%	10.2%
Second primary within 10 years of first breast cancer diagnosis	Up to 29%	4.0%
MALES		
MALE BREAST		
To age 80	0.4%-1%	0.1%
FEMALES AND MALES		
COLORECTAL		
To age 80	Possibly elevated risk	3.0%

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

END OF MYRISK MANAGEMENT TOOL

