Patient Information:

Patient Name:	Jane Smith
Date Of Birth:	9/19/1972
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Northern European Caucasian

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	02/21/2024
Sample Collected:	02/05/2024
Sample Received:	02/07/2024
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: Empower™ Comprehensive (81 genes)

FINAL RESULTS SUMMARY

Negative

No known pathogenic or likely pathogenic variants were detected.

18.5% **Tyrer-Cuzick Lifetime Breast Cancer Risk**

See Breast Cancer Risk Assessment for details.

Patient Information:

Patient Name:	Jane Smith
Date Of Birth:	9/19/1972
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Northern European Caucasian

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
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Order Selected: Empower™ Comprehensive (81 genes)

FINAL RESULTS SUMMARY

Negative

No known pathogenic or likely pathogenic variants were detected.

Genes analyzed on this panel

AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, CYLD, DDX41, DICER1, EGFR, EPCAM, EXT1, EXT2, FH, FLCN, GATA2, GREM1, HOXB13, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RHBDF2, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WT1

ADDITIONAL FINDINGS: VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Variants of uncertain significance (VUS) are common and the American College of Medical Genetics and Genomics (ACMG) states that a VUS should NOT be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not the change increases the risk of cancer. Many VUS represent normal human variation. Medical management should be based on the patient's personal and/or family history.

Gene	Variant	Zygosity	Classification
RHBDF2	c.2416C>G (p.L806V)	heterozygous	VUS

Interpretation

A heterozygous variant of uncertain significance (VUS) was detected in the RHBDF2 gene as tabulated above. The c.2416C>G (p.L806V) variant in the RHBDF2 gene has been observed at a frequency of 0.0018% in the gnomAD v2.1.1 non-cancer dataset. This variant has not been described in ClinVar.

Gene description(s)

The RHBDF2 gene encodes a product that belongs to a conserved family of inhibitory rhomboid-like pseudoproteases that lack essential catalytic residues and inhibit rhomboid-dependent EGF signaling. Heterozygous pathogenic or likely pathogenic variants in this gene are associated with Tylosis with esophageal cancer [MIM:148500], an autosomal dominant disorder characterized by palmoplantar keratoderma, oral precursor lesions, and a high lifetime risk of esophageal cancer.

Recommendations

Clinical correlation and genetic counseling are recommended for this individual to discuss associated cancer risks as well as cancer screening and prevention/risk reduction options. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle and age.

Individuals who would like to review their Empower test report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090 or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Assessment for a familial VUS may be useful for conditions with high penetrance. The American College of Medical Genetics and Genomics (ACMG) does NOT recommend that a VUS be used in clinical decision making. Patients should remain in contact with their healthcare provider for potential updates on changes for a VUS classification.

Patient Information:

Patient Name:	Jane Smith
Date Of Birth:	9/19/1972
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Northern European Caucasian

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	02/21/2024
Sample Collected:	02/05/2024
Sample Received:	02/07/2024
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: Empower™ Comprehensive (81 genes)

Methodology & Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in coding exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced. Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will not detect variants within noncoding regions (promoter, 5'UTR, 3'UTR, deep intronic regions, unless otherwise specified), small deletions or insertions larger than 25bp, balanced translocations, inversions (unless otherwise specified), low-level mosaicism, uniparental disomy, and imprinting defects. Detection sensitivity of CNV and sequencing analysis may be reduced in complex genomic regions including those with high GC content, high homologous sequences in the genome or repetitive sequence. Single exon duplications, sub-exonic deletions and duplications will not be analyzed or reported unless otherwise specified. Certain variants will not be reported depending on the disease mechanism for the gene in question (i.e. for genes with GoF disease mechanism, LoF variants may not be reported). CNVs of small size may have reduced detection rate. If the patient had a recent blood transfusion, an allogeneic transplant (bone marrow or peripheral stem cell) or has an active hematologic malignancy at the time of Empower testing, the result may be impacted and may not reflect the patient's true germline status. The presence or absence of a reported familial hereditary cancer variant cannot be confirmed without review of the original report. Familial variants in genes outside of the test order will not be commented on. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods may be used to confirm copy number changes involving the genes in this panel.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

SPECIAL NOTES: For the *CDK4* gene, only variants within codon 24 will be analyzed and reported. For the *EPCAM* gene, only cancer-related copy number changes will be analyzed and reported. For the *GREM1* gene, only the 5' untranslated region (UTR) 40 kb duplication will be analyzed and reported. For the *HOXB13* gene, analysis and reporting is limited to the c.251G>A (p.G84E) variant. For the *MITF* gene, analysis and reporting is limited to the c.952G>A (p.E318K) variant. For the *POLD1* and *POLE* genes, variants outside of the exonuclease domains (*POLD1* codons 311-541 and *POLE* codons 269-485) will not be analyzed or reported. For the *EGFR* gene, only c.2369C>T (p.T790M) variant will be reported. For the *MSH3* and *PHOX2B* genes, sequencing analysis is not offered for the polyalanine repeat regions.

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. For splicing related variants in *AIP, APC, ATM, AXIN2, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDKN1B, CHEK2, DICER1, FH, FLCN, GATA2, LZTR1, MAX, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PMS2 EX1-10, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL,* RNA sequencing evidence may be included as supporting evidence to update the classification of the variant. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Sequence analysis is based on the following gene transcripts: *AIP* (NM_003977), *ALK* (NM_004304), *APC* (NM_000038), *ATM* (NM_000051), *AXIN2* (NM_004655), *BAP1* (NM_004656), *BARD1* (NM_000465), *BMPR1A* (NM_004329), *BRCA1* (NM_007294), *BRCA2* (NM_000059), *BRIP1* (NM_032043), *CDC73* (NM_024529), *CDH1* (NM_004360), *CDK4* (NM_000075), *CDKN1B* (NM_004064), *CDKN1C* (NM_000076), *CDKN2A* (NM_000077), *CEBPA* (NM_004364), *CHEK2* (NM_007194), *CYLD* (NM_015247), *DDX41* (NM_016222), *DICER1* (NM_177438), *EGFR* (NM_005228), *EPCAM* (NM_002354), *EXT1* (NM_000127), *EXT2* (NM_207122), *FH* (NM_000143), *FLCN* (NM_144997), *GATA2* (NM_032638), *GREM1* (NM_013372), *HOXB13* (NM_006361), *KIT* (NM_000222), *LZTR1* (NM_006767), *MAX* (NM_002382), *MEN1* (NM_130799), *MET* (NM_001127500), *MITF* (NM_000248), *MLH1* (NM_000249), *MSH2* (NM_000251), *MSH3* (NM_002439), *MSH6* (NM_000179), *MUTYH* (NM_001128425), *NBN* (NM_002485), *NF1* (NM_000267), *NF2* (NM_000268), *NTHL1* (NM_002528.7), *PALB2* (NM_024675), *PDGFRA* (NM_006206), *PHOX2B* (NM_003924), *PMS2* (NM_000535), *POLD1* (NM_002691), *POLE* (NM_006231), *POT1* (NM_015450), *PRKAR1A* (NM_002734), *PTCH1* (NM_000264), *PTEN* (NM_000314), *RAD51C* (NM_058216), *RAD51D* (NM_002878), *RB1* (NM_000321), *RET* (NM_020975), *RHBDF2* (NM_024599), *RUNX1* (NM_001754), *SDHA* (NM_004168), *SDHAF2* (NM_017841), *SDHB* (NM_003000), *SDHC* (NM_003001), *SDHD* (NM_003002), *SMAD4* (NM_005359), *SMARCA4* (NM_003072), *SMARCB1* (NM_003073), *SMARCE1* (NM_003079), *STK11* (NM_000455), *SUFU* (NM_016169), *TERC* (NR_001566), *TERT* (NM_198253), *TMEM127* (NM_017849), *TP53* (NM_000546), *TSC1* (NM_000368), *TSC2* (NM_000548), *VHL* (NM_000551), *WT1* (NM_024426)

Patient Information:

Patient Name:	Jane Smith
Date Of Birth:	9/19/1972
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Northern European Caucasian

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	02/21/2024
Sample Collected:	02/05/2024
Sample Received:	02/07/2024
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

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Order Selected: Empower™ Comprehensive (81 genes)

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with an increased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

Linyan Meng

Linyan Meng Ph.D., FACMGG
Laboratory Director, Baylor Genetics

YOUBAO SHA

Youbao Sha, Ph.D., FACMG
Laboratory Director, Natera

CLIA Laboratory Directors: J. Dianne Keen-Kim, Ph.D, FACMG and Christine M. Eng, MD, FACMG

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

Understanding Your Negative Test Results

Your results show that you do not have any variants that are known to increase cancer risk in the genes tested. You were found to carry at least one variant of uncertain significance (VUS). Variants are changes in genes that are different from what most people have. Pathogenic or likely pathogenic variants are changes that cause genes to work differently and can increase cancer risk. *A **negative result** means that no pathogenic or likely pathogenic variants were found.* Having a VUS means that a change in your gene was found, but there is not enough information to know if the change increases your risk of cancer or not. A VUS should not be used to make clinical decisions. No specific changes to your healthcare are needed based on this test result. Your healthcare provider will use your health and family history information to determine the cancer screening that is best for you.

The information below is provided to help you better understand your results. However, it should not be interpreted as medical advice. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider.

What does a negative test result mean?

A negative test result means that your risk for hereditary cancer has been significantly reduced, but you could still have a variant this test cannot detect or a variant in a gene not on this panel. Your result does not mean you have no risk for cancer. Around 5-10% of cancer is hereditary. Your risk for cancer depends on multiple factors, including your personal medical history, lifestyle, and family history. Your negative result does not mean that your family members will also have negative results. They should discuss genetic testing with their healthcare providers. It is best for the whole family if a family member who had cancer has genetic testing. If you have a family member that previously tested positive on a hereditary cancer test, please discuss this information with your healthcare provider. Knowledge about the genes and variants involved in hereditary cancer changes over time so you and/or family members may need further genetic testing in the future.

What is a variant of uncertain significance?

A variant of uncertain significance (VUS) means that a change in your gene was found, but there is not enough information to know if the change increases your risk of cancer or not. A variant can be called a VUS because there is not enough information about how the *variant* impacts the way the gene works **or** because there is not enough information about whether or not the *gene* is associated with cancer risk. Over time, the lab may learn more about the variant or about the gene's association with cancer risk. This further information could change your VUS result into a negative result, meaning that the variant does not increase your cancer risk, or it could change your VUS result into a pathogenic/likely pathogenic (positive) result. The healthcare provider that ordered your genetic test will be notified if new information becomes available about your VUS. If you change healthcare providers, please have your new healthcare provider contact the lab for more information.

What should I do next?

Discuss your results with your healthcare provider. You and your healthcare providers should consider whether any additional cancer screening would be of benefit for you, as you may have higher risks for cancer based on your personal and family histories. You may also wish to speak with a local genetic counselor. A genetic counselor in the United States or Canada can be located on the National Society of Genetic Counselors website (findageneticcounselor.nsgc.org).

Can I be discriminated against because of this result?

There is a federal law in the United States called the Genetic Information Nondiscrimination Act (GINA) that prohibits medical insurance companies and employers from discriminating against individuals on the basis of genetic information. There are exceptions to this law, and it does not apply to some types of insurance, including life insurance, disability insurance, and long-term care insurance. Some US states may have laws/regulations that cover some of these exceptions. If you live outside the US, please seek legal advice in your area. Laws regarding genetic discrimination can change over time. The above statements do not constitute legal advice.

Where can I go for more information and support?

National Society of Genetic Counselors www.nsgc.org

American Cancer Society www.cancer.org

Genetic Information Nondiscrimination Act (GINA) www.ginahelp.org

Option to Enroll in National Research Registry

The Prospective Registry of Multiplex Testing (PROMPT) is an online research registry created by cancer researchers at the Dana Farber Cancer Institute, Mayo Clinic, Memorial Sloan Kettering Cancer Center, and the University of Pennsylvania. People who have a VUS in a cancer predisposition gene can enroll themselves in this registry. By taking part in PROMPT, participants can help researchers better understand how variants in cancer predisposition genes may affect cancer risk. For more information, please visit PROMPT's website www.promptstudy.info.

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natera™ | Empower™ Hereditary cancer test

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TYRER-CUZICK BREAST CANCER RISK ASSESSMENT

General Population Risk	Your Lifetime Risk
11.6%	18.5%

General population 5-year risk for breast cancer:	1.3%
Your 5-year risk for breast cancer:	2%
Your risk was calculated on:	02/08/2024

Recommendations

Based on your personalized risk calculation, your lifetime breast cancer risk is estimated to be ***less than 20%***.

Females with a lifetime breast cancer risk of less than 20% are considered to be at average risk for breast cancer. Females at average risk should have annual mammogram starting age 40-45. Your healthcare provider may recommend additional screening based on your personal history, such as if you have had radiation therapy to the chest or have dense breast tissue.

Mode of Screening	Age to Begin	How Often
Mammogram	Option to start at 40 years old with recommendation to start by age 45[1]	Every 12 months

*If you would like to review this report with a Natera genetic counselor, you can schedule a free genetic information session at **naterasession.com**, by calling **844.706.9530**, or by texting **SESSION** to **636363**.*

More information about your risk assessment

Tyrer-Cuzick is a breast cancer risk assessment model used to estimate a female's risk of developing breast cancer.[2] It uses your health and family history to determine the chance you will get breast cancer in the next five years and in your lifetime (up to age 85). It can be used alongside genetic testing as another tool to help provide a more personalized approach to breast cancer screening and risk reduction.

Tyrer-Cuzick risk model version 8.0 was used to provide breast cancer risk estimates for females with no personal history of breast cancer. Please note, the calculation may not include mammographic breast density if that information was not available. Personal and family health history information utilized in the calculation was obtained from the ordering provider and/or patient; this information was not independently verified by Natera. The Tyrer-Cuzick risk model only accounts for the following relatives: the patient's children, siblings (including half-siblings), parents, aunts, uncles, first cousins, and grandparents in their maternal and paternal lineages. The model only accounts for the following types of cancers in its risk calculations: female breast and ovarian cancer, as well as male breast cancer in a father and/or brother(s). The Tyrer-Cuzick risk model assumes BRCA1/2 negative status for the patient and does not select for competing mortality. Tyrer-Cuzick risk assessment will not be performed for females over age 84, females known to carry a mutation in a breast cancer predisposition gene, or when there is missing information necessary to perform the calculation. This risk assessment may not be valid if the patient has a pathogenic variant in a breast cancer predisposition gene. Of note, this risk assessment is specific to the patient and does not inform the risk for other relatives to develop breast cancer. The patient's female relatives may wish to speak with their healthcare providers to undergo a personalized risk assessment. The Tyrer-Cuzick model is available for download at the EMS-Trial website: ems-trials.org/riskevaluator.

1 Oeffinger et al. *Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society.* JAMA. 2015;314(15):1599–1614.
2 Tyrer et al. *Statist. Med.* 2004; 23:1111–1130.

Your reported information used to calculate the Tyrer-Cuzick risk score

Clinical History Summary			
Age	51	Hormone replacement therapy (HRT)	Not provided
Ashkenazi Jewish ancestry	No	Treatment type	N/A
Height / Weight	67 in 241 lb	Current user	Not provided
Age of menarche	13	Number of years ago started	N/A
Menopausal status / Age of onset	Post-menopausal 47	Additional years of intended use	N/A
Age of first live birth	N/A	Past user	Not provided
Breast biopsy	No	Number of years ago stopped	N/A
Mammographic density (method)		Length of use	N/A

Family history of cancer

	First-Degree Relatives		
Cancer Type	**Relationship**	**Number**	**Age at diagnosis**
Breast	Mother	0	
	Daughter(s)	0	
	Sister(s)	0	
	Niece(s)	0	
Male breast	Father	0	
	Brother(s)	0	
Ovarian	Mother	0	
	Daughter(s)	0	
	Sister(s)	0	
	Maternal Relatives		
Breast	Half-sister(s)	0	
	Grandmother	0	
	Aunt(s)	0	
	Female cousin(s)	0	
Ovarian	Grandmother	0	
	Aunt(s)	0	
	Paternal Relatives		
Breast	Half-sister(s)	0	
	Grandmother	1	75
	Aunt(s)	0	
	Female cousin(s)	0	
Ovarian	Grandmother	0	
	Aunt(s)	0	

Total Number of Female Relatives					
Daughter(s)	0	Maternal aunt(s)	1	Paternal aunt(s)	1
Sister(s)	1	Maternal half-sister(s)	0	Paternal half-sister(s)	0

Relatives with *BRCA* Mutations		
	BRCA1 Positive	*BRCA2* Positive
Relative(s)		

Patient Information:

Patient Name:	John Smith
Date Of Birth:	11/13/1954
Gender:	Male
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	9125284
Ethnicity:	Caucasian/Non-Hispanic White

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	06/15/2023
Sample Collected:	05/04/2023
Sample Received:	05/06/2023
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

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Order Selected: Empower™ Comprehensive (81 genes)

UPDATED FINAL RESULTS SUMMARY

Positive

A likely pathogenic variant in the BARD1 gene was detected.

Updated Report [06/15/2023]: This is an update to the report issued on [05/18/2023]. See next page for details.

Patient Information:

Patient Name:	John Smith
Date Of Birth:	11/13/1954
Gender:	Male
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	9125284
Ethnicity:	Caucasian/Non-Hispanic White

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	06/15/2023
Sample Collected:	05/04/2023
Sample Received:	05/06/2023
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: Empower™ Comprehensive (81 genes)

UPDATED FINAL RESULTS SUMMARY

Positive

A likely pathogenic variant in the BARD1 gene was detected.

Updated Report [06/15/2023]: This updates previous report dated 05/18/2023 due to variant reclassification of BARD1 c.1568+5G>A variant. The previous classification was VUS. RNA sequencing has shown a significant change in splicing leading to a reclassification of this variant to likely pathogenic.

FINDINGS: POSITIVE VARIANT(S)

Gene	Associated Disease(s)	Variant	Zygosity	Classification
BARD1	Hereditary breast cancer, BARD1-related	c.1568+5G>A	heterozygous	likely pathogenic

Interpretation

A heterozygous likely pathogenic variant, c.1568+5G>A in the BARD1 gene, was detected. The c.1568+5G>A variant in the BARD1 gene has not been observed in the gnomAD v2.1.1 non-cancer dataset. Internal RNA study showed the variant results in abnormal splicing and introduces an out-of-frame deletion with premature stop codon. This variant has been described in ClinVar [ID: 2135622].

No copy number abnormalities were detected by the methods described in the Methodology & Limitations section below.

Gene description(s)

The BARD1 gene encodes a protein that interacts with the N-terminal region of BRCA1 forming a stable protein complex which may be an essential aspect of BRCA1 tumor suppression (OMIM: 601593). Heterozygous pathogenic or likely pathogenic variants in the BARD1 gene are associated with an increased risk of breast cancer in females.

Genes analyzed on this panel

AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN1C, CDKN2A, CEBPA, CHEK2, CYLD, DDX41, DICER1, EGFR, EPCAM, EXT1, EXT2, FH, FLCN, GATA2, GREM1, HOXB13, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RHBDF2, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WT1

Recommendations

Clinical correlation and genetic counseling are recommended for this individual to discuss associated cancer risks as well as cancer screening and prevention/risk reduction options. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle and age.

Individuals who would like to review their Empower test report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090 or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Methodology & Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced. Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will

not detect variants within promoter or deep intronic regions (unless otherwise specified), balanced translocations, inversions (unless otherwise specified), low-level mosaicism, uniparental disomy, and imprinting defects. Single exon duplications will not be analyzed or reported unless otherwise specified. The presence or absence of a reported familial hereditary cancer variant cannot be confirmed without review of the original report. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods may be used to confirm copy number changes involving the genes in this panel. Detection sensitivity of CNV and SNV analysis may be reduced in complex genomic regions such as those with high homologous sequences in the genome and long stretch of repetitive sequence.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

SPECIAL NOTES: For the CDK4 gene, only variants within codon 24 will be analyzed and reported. For the EPCAM gene, only cancer-related copy number changes will be analyzed and reported. For the GREM1 gene, only the 5' untranslated region (UTR) 40 kb duplication will be analyzed and reported. For the HOXB13 gene, analysis and reporting is limited to the c.251G>A (p.G84E) variant. For the MITF gene, analysis and reporting is limited to the c.952G>A (p.E318K) variant. For the POLD1 and POLE genes, variants outside of the exonuclease domains (POLD1 codons 311-541 and POLE codons 269-485) will not be analyzed or reported. For the EGFR gene, only c.2369C>T (p.T790M) variant will be reported.

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. For splicing related variants in *AIP, APC, ATM, AXIN2, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDKN1B, CHEK2, DICER1, FH, FLCN, GATA2, LZTR1, MAX, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PMS2 EX1-10, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL,* RNA sequencing evidence may be included as supporting evidence to update the classification of the variant. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Sequence analysis is based on the following gene transcripts: *AIP* (NM_003977), *ALK* (NM_004304), *APC* (NM_000038), *ATM* (NM_000051), *AXIN2* (NM_004655), *BAP1* (NM_004656), *BARD1* (NM_000465), *BMPR1A* (NM_004329), *BRCA1* (NM_007294), *BRCA2* (NM_000059), *BRIP1* (NM_032043), *CDC73* (NM_024529), *CDH1* (NM_004360), *CDK4* (NM_000075), *CDKN1B* (NM_004064), *CDKN1C* (NM_000076), *CDKN2A* (NM_000077), *CEBPA* (NM_004364), *CHEK2* (NM_007194), *CYLD* (NM_015247), *DDX41* (NM_016222), *DICER1* (NM_177438), *EGFR* (NM_005228), *EPCAM* (NM_002354), *EXT1* (NM_000127), *EXT2* (NM_207122), *FH* (NM_000143), *FLCN* (NM_144997), *GATA2* (NM_032638), *GREM1* (NM_013372), *HOXB13* (NM_006361), *KIT* (NM_000222), *LZTR1* (NM_006767), *MAX* (NM_002382), *MEN1* (NM_130799), *MET* (NM_001127500), *MITF* (NM_000248), *MLH1* (NM_000249), *MSH2* (NM_000251), *MSH3* (NM_002439), *MSH6* (NM_000179), *MUTYH* (NM_001128425), *NBN* (NM_002485), *NF1* (NM_000267), *NF2* (NM_000268), *NTHL1* (NM_002528.7), *PALB2* (NM_024675), *PDGFRA* (NM_006206), *PHOX2B* (NM_003924), *PMS2* (NM_000535), *POLD1* (NM_002691), *POLE* (NM_006231), *POT1* (NM_015450), *PRKAR1A* (NM_002734), *PTCH1* (NM_000264), *PTEN* (NM_000314), *RAD51C* (NM_058216), *RAD51D* (NM_002878), *RB1* (NM_000321), *RET* (NM_020975), *RHBDF2* (NM_024599), *RUNX1* (NM_001754), *SDHA* (NM_004168), *SDHAF2* (NM_017841), *SDHB* (NM_003000), *SDHC* (NM_003001), *SDHD* (NM_003002), *SMAD4* (NM_005359), *SMARCA4* (NM_003072), *SMARCB1* (NM_003073), *SMARCE1* (NM_003079), *STK11* (NM_000455), *SUFU* (NM_016169), *TERC* (NR_001566), *TERT* (NM_198253), *TMEM127* (NM_017849), *TP53* (NM_000546), *TSC1* (NM_000368), *TSC2* (NM_000548), *VHL* (NM_000551), *WT1* (NM_024426)

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with an increased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

Patient Information:

Patient Name:	John Smith
Date Of Birth:	11/13/1954
Gender:	Male
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	9125284
Ethnicity:	Caucasian/Non-Hispanic White

Test Information:

Ordering Physician:	Dr. Davis
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	06/15/2023
Sample Collected:	05/04/2023
Sample Received:	05/06/2023
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: Empower™ Comprehensive (81 genes)

Xiaonan Zhao, Ph.D.
Assistant Laboratory Director, Baylor Genetics

YOUBAO SHA

Youbao Sha, Ph.D., FACMG
Associate Laboratory Director, Natera

CLIA Laboratory Directors: J. Dianne Keen-Kim, Ph.D, FACMG and Christine M. Eng, MD, FACMG

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

Understanding Your Positive Hereditary Cancer Test Result

A positive result means that a variant in a gene was found which is known to, or is likely to, change the way this gene works. Such variants are sometimes referred to as "pathogenic" or "likely pathogenic." Your test result shows that a positive variant was found in your *BARD1* gene. This result means that you may have an increased chance of developing female breast cancer over your lifetime compared to the average female.

A positive result on Empower cannot predict whether individuals will get cancer in their lifetime, only that the risk for developing certain cancers may be increased compared to the general population. Risk for cancer depends on multiple factors in addition to genetic test results, including personal medical history, lifestyle, and family history. The information below is provided to help you better understand what this means for you and your family. However, it should not be interpreted as medical advice. Knowledge about this gene is evolving, so information may change over time. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider. Management guidelines may vary depending on your personal and family history.

If you are being treated for certain cancers related to the *BARD1* gene, you may have treatment options that are targeted to your specific type of cancer. These treatments are designed specifically to treat some of the cancers that develop in people with pathogenic or likely pathogenic *BARD1* variants. Possible options for cancer treatment based on this result should be discussed with an oncologist.

Cancer Risk Estimates for *BARD1*

Cancer risk estimates for a positive result are typically based on individuals with a family or personal history of cancer. Your risk may be different if you do not have a personal or family history of cancer.

Cancer Type	General Population – Estimated Lifetime Cancer Risk[1]	Positive Result – Estimated Lifetime Cancer Risk[2]
Female breast	12.9%	20-40%

Risk Management and Screening Guidelines for *BARD1*[2]

The following information is a summary of current US guidelines. Please discuss with your healthcare provider as screening recommendations may vary by country and can change often.

Cancer Type	Mode of Screening or Risk Reduction	Typical Age to Begin	How Often
Female breast	Mammogram	40 years (or 5-10 years before the youngest known breast cancer in the family)	Every 12 months
	Consider breast MRI with contrast	40 years (or 5-10 years before the youngest known breast cancer in the family)	Every 12 months
	Risk-reducing mastectomy (breast surgery) is not recommended but may be considered based on family history of breast cancer	Discuss with your healthcare provider	N/A

Frequently Asked Questions

What is a pathogenic or likely pathogenic variant?

A pathogenic variant is a change in a gene that causes that gene to not work properly. A likely pathogenic variant is a change in a gene that *most likely* causes that gene to not work properly. Pathogenic and likely pathogenic variants are commonly called mutations and are both considered positive results, meaning that they may be associated with an increased risk for developing certain cancers.

Could other people in my family have this same mutation?

Yes. In most cases, mutations are inherited from a biological parent. This means that the mutation likely came from one of your biological parents. Each of your children (or future children) has a 1 in 2 (50%) chance of having this mutation. Your relatives, including your siblings, aunts, uncles, and cousins, may also carry this mutation. We encourage you to share these results with your relatives so they can discuss with their healthcare providers and consider being tested themselves. Family members can be tested for the specific mutation that was found in you. If you or your partner are pregnant or considering pregnancy, you may wish to discuss your reproductive testing options with your healthcare provider or ask to speak with a genetic counselor. It is possible to find out during pregnancy if a baby inherited a gene variant and, for some variants, there may be the option to use assisted reproductive technology to avoid passing on a variant.

Does this result mean I have cancer or that I will get cancer?

No. This result does not mean that you have cancer or that you will develop cancer. People with these mutations may have a higher risk for certain cancers than the average person. Awareness of these risks, and following screening and management options recommended by your healthcare providers, may help catch cancers early. Please review the information provided in your test report and discuss it with your healthcare provider to come up with the best plan for you.

If I have already been diagnosed with cancer, what does this result mean for me?

It is important to continue to follow the recommendations of your healthcare providers and to discuss these specific test results with them. In some cases, there may be cancer treatment options available based on a particular positive result. A positive result may also mean there is an increased risk for other cancer types.

Can I be discriminated against because of this result?

There is a federal law in the United States called the Genetic Information Nondiscrimination Act (GINA) that prohibits medical insurance companies and employers from discriminating against individuals on the basis of genetic information. There are exceptions to this law, and it does not apply to some types of insurance, including life insurance, disability insurance, and long-term care insurance. Some US states may have laws/regulations that cover some of these exceptions. If you live outside the US, please seek legal advice in your area. Laws regarding genetic discrimination can change over time. The above statements do not constitute legal advice.

What should I do next?

Discuss your results with your healthcare providers to consider whether any additional cancer screening would be of benefit in the context of your personal and family health history. You may also wish to speak with a local genetic counselor. A genetic counselor in your area can be located on the National Society of Genetic Counselors website (findageneticcounselor.nsgc.org).

Where can I go for more information and support?

Facing Hereditary Cancer EMPOWERED (FORCE) www.facingourrisk.org

National Society of Genetic Counselors www.nsgc.org

American Cancer Society www.cancer.org

Genetic Information Nondiscrimination Act (GINA) www.ginahelp.org

1. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program, National Cancer Institute. [Cited 2022 August 2]. Available from https://seer.cancer.gov/statistics-network/explorer/.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High Risk Assessment: Breast, Ovarian, and Pancreatic V.1.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed September 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

13011 McCallen Pass, Building A Suite 100 | Austin, TX 78753 | natera.com

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Patient Information:

Patient Name:	Grace Goe
Date Of Birth:	03/03/1975
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Ashkenazi Jewish

Test Information:

Ordering Physician:	Dr. Smith
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	11/14/2022
Sample Collected:	10/05/2022
Sample Received:	10/05/2022
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: The Empower™ BRCA1 and BRCA2 panel (2 genes)

FINAL RESULTS SUMMARY

Negative

No known pathogenic or likely pathogenic variants were detected.

32.6% **Tyrer-Cuzick Lifetime Breast Cancer Risk**

See Breast Cancer Risk Assessment for details.

Patient Information:

Patient Name:	Grace Goe
Date Of Birth:	03/03/1975
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Ashkenazi Jewish

Test Information:

Ordering Physician:	Dr. Smith
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Order Selected: The Empower™ BRCA1 and BRCA2 panel (2 genes)

FINAL RESULTS SUMMARY

Negative

No known pathogenic or likely pathogenic variants were detected.

Interpretation

No known or potential disease-causing pathogenic variants or variants of uncertain significance were detected by the methods described in the Methodology & Limitations section below.

Genes analyzed on this panel

BRCA1, BRCA2

Recommendations

Clinical correlation and genetic counseling are recommended for this individual to discuss associated cancer risks as well as cancer screening and prevention/risk reduction options. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle and age.

Individuals who would like to review their Empower test report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090 or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Methodology & Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced. Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will not detect variants within promoter or deep intronic regions (unless otherwise specified), balanced translocations, inversions (unless otherwise specified), low-level mosaicism, uniparental disomy, and imprinting defects. Single exon duplications will not be analyzed or reported unless otherwise specified. The presence or absence of a reported familial hereditary cancer variant cannot be confirmed without review of the original report. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods may be used to confirm copy number changes involving the genes in this panel. Detection sensitivity of CNV and SNV analysis may be reduced in complex genomic regions such as those with high homologous sequences in the genome and long stretch of repetitive sequence.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. For splicing related variants in *BRCA1, BRCA2,* RNA sequencing evidence may be included as supporting evidence to update the classification of the variant. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Sequence analysis is based on the following gene transcripts: *BRCA1* (NM_007294), *BRCA2* (NM_000059)

Patient Information:

Patient Name:	Grace Goe
Date Of Birth:	03/03/1975
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	N/A
Accession ID:	N/A
Case File ID:	N/A
Ethnicity:	Ashkenazi Jewish

Test Information:

Ordering Physician:	Dr. Smith
Clinic Information:	Natera, Inc.
Phone:	555-555-5555
Report Date:	11/14/2022
Sample Collected:	10/05/2022
Sample Received:	10/05/2022
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: The Empower™ BRCA1 and BRCA2 panel (2 genes)

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with an increased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

QA/UAT

Chonghua Li
Software Engineer, Baylor Genetics

YOUBAO SHA

Youbao Sha, Ph.D., FACMG
Associate Laboratory Director, Natera

CLIA Laboratory Directors: J. Dianne Keen-Kim, Ph.D, FACMG and Christine M. Eng, MD, FACMG

natera | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

Understanding Your Negative Hereditary Cancer Test Result

You tested negative for known disease-causing variants in the genes analyzed. The information below is provided to help you better understand your results. However, it should not be interpreted as medical advice. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider.

What does a negative result mean?

A negative test result means that your risk for hereditary cancer has been significantly reduced; however, there could still be a variant that was not detected by this test or in a gene not on this panel. It does not mean you have no risk for cancer. Around 5-10% of cancer is hereditary. Your risk for cancer depends on multiple factors, including your personal medical history, lifestyle and family history. Your negative result does not rule out a positive result for your family members; they should discuss genetic testing with their healthcare providers. It can be especially informative if a family member who has had cancer undergoes genetic testing. If you have a family member that previously tested positive on a hereditary cancer test, please discuss this information with your healthcare provider as you may need specific testing that might not be covered by this test. Knowledge about the genes and variants involved in hereditary cancer changes over time so future genetic testing may still be considered.

What should I do next?

Discuss your results with your healthcare provider. If you have a family history of cancer or other risk factors, you may be eligible for additional cancer screening above what is recommended for the general population. You may also wish to speak with a local genetic counselor. A genetic counselor in your area can be located on the National Society of Genetic Counselors website (www.ngsc.org) by using the “Find a Counselor” feature. Please keep your healthcare provider informed of any changes in your personal or family history.

Can I be discriminated against because of this result?

There is a US federal law called the Genetic Information Nondiscrimination Act (GINA) that prohibits medical insurance companies and employers from discriminating against individuals on the basis of genetic information. Laws regarding genetic discrimination can change over time. The above statements do not constitute legal advice. For more information about GINA, please visit the links provided below.

Where can I go for more information and support?

National Society of Genetic Counselors www.nsgc.org
American Cancer Society www.cancer.org
Bright Pink (prevention and early detection of breast and ovarian cancers) www.brightpink.org
Genetic Information Nondiscrimination Act (GINA) www.ginahelp.org
GINA: https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination

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MLB-10177_NAT Negative Supplement_20210311 rev02

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natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

TYRER-CUZICK BREAST CANCER RISK ASSESSMENT

General Population Risk	Your Lifetime Risk
12.3%	32.6%

General population 5-year risk for breast cancer:	1%
Your 5-year risk for breast cancer:	2.8%
Your risk was calculated on:	10/05/2022

Recommendations

Based on your personalized risk calculation, your lifetime breast cancer risk is estimated to be ***equal to or greater than 20%***.

Females with an estimated lifetime breast cancer risk of 20% or higher should speak with their healthcare provider about American Cancer Society (ACS) guidelines for increased breast cancer surveillance, as well as published recommendations for risk-reducing agents and comprehensive risk assessment. ACS suggests consideration of yearly breast MRI in addition to yearly mammogram for females with an elevated lifetime breast cancer risk, as outlined below.[1]

Mode of Screening	Age to Begin	How Often
Mammogram	40 years (or 10 years younger than the earliest breast cancer diagnosis in the family, whichever is earlier, but not earlier than age 30)	Every 12 months
Breast MRI	40 years (or 10 years younger than the earliest breast cancer diagnosis in the family, whichever is earlier, but not earlier than age 25)	Every 12 months

*If you would like to review this report with a Natera genetic counselor, you can schedule a free genetic information session at **naterasession.com**, by calling **844.706.9530**, or by texting **SESSION** to **636363**.*

More information about your risk assessment

Tyrer-Cuzick is a breast cancer risk assessment model used to estimate a female's risk of developing breast cancer.[2] It uses your health and family history to determine the chance you will get breast cancer in the next five years and in your lifetime (up to age 85). It can be used alongside genetic testing as another tool to help provide a more personalized approach to breast cancer screening and risk reduction.

Tyrer-Cuzick risk model version 8.0 was used to provide breast cancer risk estimates for females with no personal history of breast cancer. Please note, the calculation may not include mammographic breast density if that information was not available. Personal and family health history information utilized in the calculation was obtained from the ordering provider and/or patient; this information was not independently verified by Natera. The Tyrer-Cuzick risk model only accounts for the following relatives: the patient's children, siblings (including half-siblings), parents, aunts, uncles, first cousins, and grandparents in their maternal and paternal lineages. The model only accounts for the following types of cancers in its risk calculations: female breast and ovarian cancer, as well as male breast cancer in a father and/or brother(s). The Tyrer-Cuzick risk model assumes BRCA1/2 negative status for the patient and does not select for competing mortality. Tyrer-Cuzick risk assessment will not be performed for females over age 84, females known to carry a mutation in a breast cancer predisposition gene, or when there is missing information necessary to perform the calculation. This risk assessment may not be valid if the patient has a pathogenic variant in a breast cancer predisposition gene. Of note, this risk assessment is specific to the patient and does not inform the risk for other relatives to develop breast cancer. The patient's female relatives may wish to speak with their healthcare providers to undergo a personalized risk assessment. The Tyrer-Cuzick model is available for download at the EMS-Trial website: ems-trials.org/riskevaluator.

1 Saslow et al. *CA Cancer J Clin* 2007;57:75–89.
2 Tyrer et al. *Statist. Med.* 2004; 23:1111–1130.

Your reported information used to calculate the Tyrer-Cuzick risk score

Clinical History Summary			
Age	47	Hormone replacement therapy (HRT)	Not provided
Ashkenazi Jewish ancestry	No	Treatment type	N/A
Height / Weight	5 ft 140 lb	Current user	Not provided
Age of menarche	13	Number of years ago started	N/A
Menopausal status / Age of onset	Not provided N/A	Additional years of intended use	N/A
Age of first live birth	29	Past user	Not provided
Breast biopsy	Not provided	Number of years ago stopped	N/A
Mammographic density (method)		Length of use	N/A

Family history of cancer

	First-Degree Relatives		
Cancer Type	**Relationship**	**Number**	**Age at diagnosis**
Breast	Mother	0	
	Daughter(s)	0	
	Sister(s)	1	40 to 49 years
	Niece(s)	0	
Male breast	Father	0	
	Brother(s)	0	
Ovarian	Mother	0	
	Daughter(s)	0	
	Sister(s)	0	
	Maternal Relatives		
Breast	Half-sister(s)	0	
	Grandmother	0	
	Aunt(s)	0	
	Female cousin(s)	0	
Ovarian	Grandmother	0	
	Aunt(s)	0	
	Paternal Relatives		
Breast	Half-sister(s)	0	
	Grandmother	1	Over 60 years
	Aunt(s)	0	
	Female cousin(s)	0	
Ovarian	Grandmother	0	
	Aunt(s)	0	

Total Number of Female Relatives					
Daughter(s)	2	Maternal aunt(s)	1	Paternal aunt(s)	2
Sister(s)	1	Maternal half-sister(s)	0	Paternal half-sister(s)	0

Relatives with *BRCA* Mutations		
	***BRCA1* Positive**	***BRCA2* Positive**
Relative(s)		

Patient Information:

Patient Name: Gloria Howells

Date Of Birth: 04/18/1960
Gender: Female
Patient ID: N/A
Medical Record #: N/A
Collection Kit:
Accession ID: N/A
Case File ID:
Ethnicity: Caucasian, Non-Hispanic White

Test Information:

Ordering Physician: Jelsema

Clinic Information: Natera Inc.

Phone: 555-555-5555
Report Date: 12/08/2021
Sample Collected: 06/22/2021
Sample Received: 06/24/2021
Sample Type: Blood

natera | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: The Empower™ Multi-Cancer Expanded panel (53 genes)

FINAL RESULTS SUMMARY

Positive

A pathogenic variant in the BRCA1 gene was detected.

FINDINGS: POSITIVE VARIANT(S)

Gene	Associated Disease(s)	Variant	Zygosity	Classification
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome	c.2197_2201del (p.E733Tfs*5)	heterozygous	pathogenic

Interpretation

A heterozygous pathogenic variant, c.2197_2201del (p.E733Tfs*5) in the BRCA1 gene, was detected. The c.2197_2201del (p.E733Tfs*5) variant in the BRCA1 gene has not been observed in the gnomAD v2.1.1 non-cancer dataset. This variant has been previously reported (PMIDs: 7663517, 9145677, 21553119, 27767231, and 29446198). This variant has been classified as pathogenic by an expert panel in ClinVar [ID: 54495].

Gene description(s)

The BRCA1 gene encodes a tumor suppressor that is involved in maintaining genome stability through coordination of various aspects of DNA double strand break repair. Heterozygous pathogenic variants in the BRCA1 gene are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer (OMIM: 604370; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/). Biallelic germline pathogenic variants in the BRCA1 gene are associated with Fanconi anemia, complementation group S (OMIM: 617883).

Genes analyzed on this panel

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, DICER1, EPCAM, GALNT12, GREM1, HOXB13, KIT, MEN1, MITF, MLH1, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, RNF43, RPS20, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL

ADDITIONAL FINDINGS: VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Variants of uncertain significance (VUS) are common and the American College of Medical Genetics and Genomics (ACMG) states that a VUS should NOT be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not the change increases the risk of cancer. Many VUS represent normal human variation. Medical management should be based on the patient's personal and/or family history.

Gene	Variant	Zygosity	Classification
BRCA2	c.9699_9702del (p.C3233Wfs*15)	heterozygous	VUS
TP53	c.847C>T (p.R283C)	heterozygous	VUS

Interpretation

Multiple variants of uncertain significance (VUS) were detected as tabulated above. The c.9699_9702del (p.C3233Wfs*15) variant in the BRCA2 gene has been observed at a frequency of 0.006364% in the gnomAD v2.1.1 non-cancer dataset. This variant has been reported in individuals with breast cancer (PMIDs: 16683254, 10923033, 25863477, and 25639900). This variant has been described in ClinVar [ID: 38260].

Patient Information:

Patient Name:	Gloria Howells
Date Of Birth:	04/18/1960
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	
Accession ID:	N/A
Case File ID:	
Ethnicity:	Caucasian, Non-Hispanic White

Test Information:

Ordering Physician:	Jelsema
Clinic Information:	Natera Inc.
Phone:	555-555-5555
Report Date:	12/08/2021
Sample Collected:	06/22/2021
Sample Received:	06/24/2021
Sample Type:	Blood

natera™ | Empower™ Hereditary cancer test

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Order Selected: The Empower™ Multi-Cancer Expanded panel (53 genes)

The c.847C>T (p.R283C) variant in the TP53 gene has been observed at a frequency of 0.005964% in the gnomAD v2.1.1 non-cancer dataset. This variant has been reported in individuals with breast cancer and leiomyosarcoma, gastric cancer, colorectal cancer, sarcoma or leukemia (PMIDs: 15173255, 17224268, 21761402, 23894400, 25527155, and 26086041). This variant has been described in ClinVar [ID: 127824].

Gene description(s)

The BRCA2 gene encodes a tumor suppressor that is involved in repairing double strand breaks in DNA. Heterozygous pathogenic variants in the BRCA2 gene are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer as well as melanoma cancer (OMIM: 612555; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/). Biallelic germline pathogenic variants in the BRCA2 gene are associated with Fanconi anemia, complementation group D1 (OMIM: 605724).

The TP53 gene encodes a multifunctional tumor suppressor that plays a critical role in maintaining genome integrity. It facilitates the cellular response to DNA damage by regulating if a cell will be repaired, arrested, or undergo apoptosis (OMIM: 191170). Heterozygous pathogenic variants in the TP53 gene are associated with Li-Fraumeni syndrome and an increased risk for sarcoma, breast, brain, and adrenocortical cancers, and leukemias (OMIM: 151623; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1311/).

Recommendations

Clinical correlation and genetic counseling are recommended for this individual to discuss associated cancer risks as well as cancer screening and prevention/risk reduction options. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle and age.

Individuals who would like to review their Empower test report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090 or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Assessment for a familial VUS may be useful for conditions with high penetrance. The American College of Medical Genetics and Genomics (ACMG) does NOT recommend that a VUS be used in clinical decision making. Patients should remain in contact with their healthcare provider for potential updates on changes for a VUS classification.

Methodology & Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced. Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will not detect variants within promoter or deep intronic regions (unless otherwise specified), balanced translocations, inversions (unless otherwise specified), low-level mosaicism, uniparental disomy, and imprinting defects. Single exon duplications will not be analyzed or reported unless otherwise specified. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods, and/or array comparative genomic hybridization (aCGH) may be used to confirm copy number changes involving the genes in this panel. Certain genes or regions with highly homologous sequences in the genome will be evaluated, but 100% coverage by the above analyses are not guaranteed due to genetic complexity.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

SPECIAL NOTES: For the CDK4 gene, only variants within codon 24 will be analyzed and reported. For the EPCAM gene, only cancer-related copy number changes will be analyzed and reported. For the GREM1 gene, only the 5' untranslated region (UTR) 40 kb duplication will be analyzed and reported. For the HOXB13 gene, analysis and reporting is limited to the c.251G>A (p.G84E) variant. For the MITF gene, analysis and reporting is limited to the c.952G>A (p.E318K) variant. For the POLD1 and POLE genes, variants outside of the exonuclease domains (POLD1 codons 311-541 and POLE codons 269-485) will not be analyzed or reported. For the RNF43, RPS20, and SDHA genes, copy number changes will not be analyzed or reported.

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Patient Information:

Patient Name:	Gloria Howells
Date Of Birth:	04/18/1960
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	
Accession ID:	N/A
Case File ID:	
Ethnicity:	Caucasian, Non-Hispanic White

Test Information:

Ordering Physician:	Jelsema
Clinic Information:	Natera Inc.
Phone:	555-555-5555
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natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: The Empower™ Multi-Cancer Expanded panel (53 genes)

Sequence analysis is based on the following gene transcripts: *APC* (NM_000038), *ATM* (NM_000051), *AXIN2* (NM_004655), *BAP1* (NM_004656), *BARD1* (NM_000465), *BMPR1A* (NM_004329), *BRCA1* (NM_007294), *BRCA2* (NM_000059), *BRIP1* (NM_032043), *CDH1* (NM_004360), *CDK4* (NM_000075), *CDKN2A* (NM_000077), *CHEK2* (NM_007194), *CTNNA1* (NM_001903), *DICER1* (NM_177438), *EPCAM* (NM_002354), *GALNT12* (NM_024642), *GREM1* (NM_013372), *HOXB13* (NM_006361), *KIT* (NM_000222), *MEN1* (NM_130799), *MITF* (NM_000248), *MLH1* (NM_000249), *MRE11* (NM_005591), *MSH2* (NM_000251), *MSH3* (NM_002439), *MSH6* (NM_000179), *MUTYH* (NM_001128425), *NBN* (NM_002485), *NF1* (NM_000267), *NTHL1* (NM_002528), *PALB2* (NM_024675), *PDGFRA* (NM_006206), *PMS2* (NM_000535), *POLD1* (NM_002691), *POLE* (NM_006231), *PTEN* (NM_000314), *RAD50* (NM_005732), *RAD51C* (NM_058216), *RAD51D* (NM_002878), *RNF43* (NM_017763), *RPS20* (NM_001023), *SDHA* (NM_004168), *SDHB* (NM_003000), *SDHC* (NM_003001), *SDHD* (NM_003002), *SMAD4* (NM_005359), *SMARCA4* (NM_001128849), *STK11* (NM_000455), *TP53* (NM_000546), *TSC1* (NM_000368), *TSC2* (NM_000548), *VHL* (NM_000551)

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with an increased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

Jennifer Scull, Ph.D.
Laboratory Co-Director, Baylor Genetics

YOUBAO SHA

Youbao Sha, Ph.D., FACMG
Associate Laboratory Director, Natera

CLIA Laboratory Directors: J. Dianne Keen-Kim, Ph.D, FACMG and Christine M. Eng, MD, FACMG

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

Understanding Your Positive Hereditary Cancer Test Result

A positive result means that a variant in a gene was found which is known to, or is likely to, change the way this gene works. Such variants are sometimes referred to as "pathogenic" or "likely pathogenic." Your test result shows that a positive variant was found in your *BRCA1* gene. Individuals with pathogenic or likely pathogenic *BRCA1* variants have Hereditary Breast and Ovarian Cancer (HBOC) syndrome. HBOC syndrome is associated with an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. There may also be a slightly increased risk of uterine cancer although there is currently limited evidence. This result means that you have an increased chance of developing certain cancers over your lifetime compared to the average person.

A positive result on Empower cannot predict whether individuals will get cancer in their lifetime, only that the risk for developing certain cancers may be increased compared to the general population. Risk for cancer depends on multiple factors in addition to genetic test results, including personal medical history, lifestyle and family history. The information below is provided to help you better understand what this means for you and your family. However, it should not be interpreted as medical advice. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider. Management guidelines may vary depending on your personal and family history.

Cancer Risk Estimates for *BRCA1*

Cancer risk estimates for a positive result are typically based on individuals with a family or personal history of cancer. Your risk may be different if you do not have a personal or family history of cancer.

	Female		Male	
Cancer Type	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**
Breast	12.9%	Up to 87% risk	<1%	1.2%
Ovarian	1.2%	Up to 62% risk	N/A	N/A
Prostate	N/A	N/A	12.1%	Increased
Pancreatic	1.6%	1-3%	1.7%	1-3%
Uterine	3.1%	Possibly increased	N/A	N/A

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic V.1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed Sep 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
3. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic V.1.2021. © 2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.
4. Petrucelli N, Daly MB, Pal T.BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Dec 2016; Accessed: Jul 2020].

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Risk Management and Screening Guidelines for BRCA-Related Breast and Ovarian Cancer Syndrome[2,3]

The following information is a summary of current US guidelines. Please discuss with your healthcare provider as screening recommendations may vary by country and can change often.

Cancer Type	Mode of Screening or Risk Reduction	Typical Age to Begin	How often
Female Breast	Breast self-exam	18y	Monthly
	Breast exam with clinician	25y	Every 6-12 months
	Breast MRI with contrast	25-29y (or individualized if family history of breast cancer before age 30)	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Mammogram with consideration of tomosynthesis (3-D Mammogram)	30y	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Risk-reducing medication	Individualized	Discuss with your healthcare provider
	Risk-reducing mastectomy (breast surgery); discuss with your healthcare provider	Individualized	N/A
Male Breast	Breast self-exam	35y	Monthly
	Breast exam with clinician	35y	Annually
	Consider mammogram in men with gynecomastia (enlargement of breast tissue)	50y (or 10 years younger than earliest known male breast cancer in the family)	Annually
Ovarian	Risk-reducing salpingo-oophorectomy (RRSO) (surgical removal of ovaries and fallopian tubes); discuss with your healthcare provider	Typically between 35 and 40y, after completion of childbearing	N/A
	For those who have not had RRSO, consider screening with CA-125 blood test and transvaginal ultrasound of the ovaries; discuss with your healthcare provider	30-35y	Individualized
Prostate	Consider screening with PSA blood test and rectal exams with clinician (digital rectal exam)	40y	Individualized; discuss with your healthcare provider
Pancreatic	Endoscopic ultrasound and/or MRI of pancreas when there is a family history of pancreatic cancer; screening not recommended in absence of family history of pancreatic cancer	50y (or 10 years younger than the earliest known pancreatic cancer in the family)	Every 12 months
Uterine	Evidence currently limited, discuss risks and benefits of hysterectomy at time of risk reducing salpingo-oophrectomy	Individualized	N/A

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Other Medical Implications

Individuals who have mutations in both copies of their *BRCA1* gene may have the condition Fanconi Anemia Complementation Group S. This condition is very rare and can cause features such as abnormal skin pigmentation, thumb abnormalities, malformations of the skeletal and central nervous systems, short stature, bone marrow failure and an increased risk for certain cancers. If you have a single *BRCA1* mutation and your partner also carries a mutation in *BRCA1*, there is a 1 in 4 (25%) chance for your children to two *BRCA1* mutations. Genetic counseling is suggested. Please discuss with your healthcare provider and/or to find a genetic counselor in the US and Canada, please use this link: https://www.nsgc.org/page/find-a-genetic-counselor.

FREQUENTLY ASKED QUESTIONS

What is a pathogenic or likely pathogenic variant?

A pathogenic variant is a change in a gene that causes that gene to not work properly. A likely pathogenic variant is a change in a gene that most likely causes that gene to not work properly. Pathogenic and likely pathogenic variants are commonly called mutations and are both considered a positive result, meaning that they may be associated with an increased risk for developing certain cancers.

Could other people in my family have this same mutation?

Yes. In most cases, mutations are inherited from a biological parent. This means that the mutation likely came from either your father or your mother. Your children (or future children) have a 1 in 2 (50%) chance of inheriting this mutation. It also means that relatives such as your siblings, aunts, uncles and cousins could be at-risk to carry this mutation as well. We encourage you to share these results with your relatives so they can discuss with their healthcare providers and consider being tested themselves. Family members can be tested for the specific mutation that was found in you. If you are pregnant or considering pregnancy, you may wish to discuss your reproductive testing options with your healthcare provider or request a referral to a genetic counselor. It is possible to find out during pregnancy whether a future child will have this gene mutation, and for some gene mutations there may be the option to use assisted reproductive techniques to avoid this risk.

Does this result mean I have cancer or that I will get cancer?

No. This result does not mean that you have cancer or that you will develop cancer. People with these mutations have or may have a higher risk for certain cancers than the average population. There may be management options available now or in the future that could lower the risk and help catch cancer early. Please discuss the information provided in your report with your healthcare provider to come up with the best plan for you.

If I have already been diagnosed with cancer, what does this result mean for me?

It is important to continue to follow the recommendations of your healthcare providers and discuss these results with them. In some cases, there can be implications for cancer treatment based on a positive result. A positive result may also mean there is an increased risk for other cancer types.

Can I be discriminated against because of this result?

There is a federal law in the US called the Genetic Information Nondiscrimination Act (GINA) that prohibits medical insurance companies and employers from discriminating against individuals on the basis of genetic information. There are exceptions to this law, and it does not apply to some types of insurance such as life insurance, disability insurance, or long-term care insurance. Some US states may have laws/regulations that cover some of these exceptions. If you live outside the US, please consult legal advice in your area. Laws regarding genetic discrimination can change over time. The above statements do not constitute legal advice.

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What should I do next?

Discuss your results with your healthcare providers and work with them to come up with a plan for ongoing management. You may also wish to speak with a local genetic counselor. A genetic counselor in your area can be located on the National Society of Genetic Counselors website (www.ngsc.org) by using the “Find a Counselor” feature.

Where can I go for more information and support?

National Society of Genetic Counselors: www.nsgc.org
Facing Our Risk of Cancer Empowered (FORCE): www.facingourrisk.org
Bright Pink (prevention and early detection of breast and ovarian cancers): www.brightpink.org
American Cancer Society: www.cancer.org
Genetic Information Nondiscrimination Act (GINA): www.ginahelp.org

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Patient Information:

Patient Name:	Gloria Howells
Date Of Birth:	04/18/1960
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	
Accession ID:	N/A
Case File ID:	
Ethnicity:	Caucasian, Non-Hispanic White

Test Information:

Ordering Physician:	Jelsema
Clinic Information:	Natera Inc.
Phone:	555-555-5555
Report Date:	12/08/2021
Sample Collected:	06/22/2021
Sample Received:	06/24/2021
Sample Type:	Blood

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Order Selected: The Empower™ Multi-Cancer Expanded panel (53 genes)

UPDATED FINAL RESULTS SUMMARY

Positive

A pathogenic variant in the BRCA1 gene and a likely pathogenic variant in the BRCA2 gene were detected.

Updated Report [12/06/2021]: This is an update to the original report from 7/6/2021 due to a classification change of the BRCA2 variants. The BRCA2 c.9699_9702del (p.C3233Wfs*15) variant classification has been reclassified as likely pathogenic.

FINDINGS: POSITIVE VARIANT(S)

Gene	Associated Disease(s)	Variant	Zygosity	Classification
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome / Fanconi anemia, complementation group S	c.2197_2201del (p.E733Tfs*5)	heterozygous	pathogenic
BRCA2	Hereditary Breast and Ovarian Cancer Syndrome / Fanconi anemia, complementation group D1	c.9699_9702del (p.C3233Wfs*15)	heterozygous	likely pathogenic

Interpretation

A heterozygous pathogenic variant, c.2197_2201del (p.E733Tfs*5) in the BRCA1 gene, was detected. The c.2197_2201del (p.E733Tfs*5) variant in the BRCA1 gene has not been observed in the gnomAD v2.1.1 non-cancer dataset. This variant has been previously reported (PMIDs: 7663517, 9145677, 21553119, 27767231, and 29446198). This variant has been classified as pathogenic by an expert panel in ClinVar [ID: 54495].

A heterozygous likely pathogenic variant, c.9699_9702del (p.C3233Wfs*15) in the BRCA2 gene, was detected. The c.9699_9702del (p.C3233Wfs*15) variant in the BRCA2 gene has been observed at a frequency of 0.006364% in the gnomAD v2.1.1 non-cancer dataset. This variant has been reported in individuals with autosomal recessive atypical Fanconi anemia (PMID 25639900, ClinVar) and breast cancer (PMID: 16683254, 10923033, 25863477, 25639900). The variant may be hypomorphic and associated with reduced risk. The risk estimation for cancer is unknown at this time. This variant has been described in ClinVar [ID: 38260].

Gene description(s)

The BRCA1 gene encodes a tumor suppressor that is involved in maintaining genome stability through coordination of various aspects of DNA double strand break repair. Heterozygous pathogenic or likely pathogenic variants in the BRCA1 gene are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer (OMIM: 604370; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/). Biallelic germline pathogenic variants in the BRCA1 gene are associated with Fanconi anemia, complementation group S (OMIM: 617883).

The BRCA2 gene encodes a tumor suppressor that is involved in repairing double strand breaks in DNA. Heterozygous pathogenic or likely pathogenic variants in the BRCA2 gene are associated with increased risks of breast, ovarian, prostate, and pancreatic cancer as well as melanoma cancer (OMIM: 612555; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1247/). Biallelic germline pathogenic variants in the BRCA2 gene are associated with Fanconi anemia, complementation group D1 (OMIM: 605724).

Genes analyzed on this panel

APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, CTNNA1, DICER1, EPCAM, GALNT12, GREM1, HOXB13, KIT, MEN1, MITF, MLH1, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, RNF43, RPS20, SDHA, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL

ADDITIONAL FINDINGS: VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Patient Information:

Patient Name:	Gloria Howells
Date Of Birth:	04/18/1960
Gender:	Female
Patient ID:	N/A
Medical Record #:	N/A
Collection Kit:	
Accession ID:	N/A
Case File ID:	
Ethnicity:	Caucasian, Non-Hispanic White

Test Information:

Ordering Physician:	Jelsema
Clinic Information:	Natera Inc.
Phone:	555-555-5555
Report Date:	12/08/2021
Sample Collected:	06/22/2021
Sample Received:	06/24/2021
Sample Type:	Blood

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Variants of uncertain significance (VUS) are common and the American College of Medical Genetics and Genomics (ACMG) states that a VUS should NOT be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not the change increases the risk of cancer. Many VUS represent normal human variation. Medical management should be based on the patient's personal and/or family history.

Gene	Variant	Zygosity	Classiÿcation
TP53	c.847C>T (p.R283C)	heterozygous	VUS

Interpretation

A heterozygous variant of uncertain significance (VUS) was detected in the TP53 gene as tabulated above. The c.847C>T (p.R283C) variant in the TP53 gene has been observed at a frequency of 0.005964% in the gnomAD v2.1.1 non-cancer dataset. This variant has been reported in individuals with breast cancer and leiomyosarcoma, gastric cancer, colorectal cancer, sarcoma or leukemia (PMIDs: 15173255, 17224268, 21761402, 23894400, 25527155, and 26086041). This variant has been described in ClinVar [ID: 127824].

Gene description(s)

The TP53 gene encodes a multifunctional tumor suppressor that plays a critical role in maintaining genome integrity. It facilitates the cellular response to DNA damage by regulating if a cell will be repaired, arrested, or undergo apoptosis (OMIM: 191170). Heterozygous pathogenic or likely pathogenic variants in the TP53 gene are associated with Li-Fraumeni syndrome and an increased risk for sarcoma, breast, brain, and adrenocortical cancers, and leukemias (OMIM: 151623; GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1311/).

Recommendations

Clinical correlation and genetic counseling are recommended for this individual to discuss associated cancer risks as well as cancer screening and prevention/risk reduction options. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle and age.

Individuals who would like to review their Empower test report with a Natera Laboratory Genetic Counselor may schedule a telephone genetic information session by calling 650-249-9090 or visiting naterasession.com. Clinicians with questions may contact Natera at 650-249-9090 or email support@natera.com. Individuals with positive results may wish to discuss these results with family members to allow them the option to be screened. Comprehensive genetic counseling to discuss the implications of these test results and possible associated reproductive risk is recommended.

Assessment for a familial VUS may be useful for conditions with high penetrance. The American College of Medical Genetics and Genomics (ACMG) does NOT recommend that a VUS be used in clinical decision making. Patients should remain in contact with their healthcare provider for potential updates on changes for a VUS classification.

Methodology & Limitations

The targeted regions in this panel are enriched using a capture-based method and sequenced using the Illumina platform. Nucleotide 1 corresponds to the A of the start codon ATG. Variants detected in exons and within 20 bp of the exon/intron boundary are reported, unless otherwise specified. Overall, more than 99% of targeted regions are sequenced (certain regions with high homologous sequences in the genome are excluded). Read depth analysis is used to detect copy number variation (CNV) for genes in this panel. This analysis will not detect variants within promoter or deep intronic regions (unless otherwise specified), balanced translocations, inversions (unless otherwise specified), low-level mosaicism, uniparental disomy, and imprinting defects. Single exon duplications will not be analyzed or reported unless otherwise specified. Positive sequencing results from certain genes or regions with highly homologous sequences in the genome will be confirmed by gene-specific long-range PCR and Sanger sequencing of the amplification products. Multiplex ligation-dependent probe amplification (MLPA), PCR-based methods, may be used to confirm copy number changes involving the genes in this panel. Detection sensitivity of CNV and SNV analysis may be reduced in complex genomic regions such as those with high homologous sequences in the genome and long stretch of repetitive sequence.

Note that next-generation sequencing-based CNV analysis can be impacted by sample quality, DNA input, characteristics of targeted regions (GC content, presence of homologous sequences, etc.), and other technical variations. Read depth analyses that are either uninformative or unsupportive of a copy number change may not exclude large deletions or duplications. Findings are reported according to the human genome build hg19.

SPECIAL NOTES: For the CDK4 gene, only variants within codon 24 will be analyzed and reported. For the EPCAM gene, only cancer-related copy number changes will be analyzed and reported. For the GREM1 gene, only the 5' untranslated region (UTR) 40 kb duplication will be analyzed and reported. For the HOXB13 gene, analysis and reporting is limited to the c.251G>A (p.G84E) variant. For the MITF gene, analysis and reporting is limited to the c.952G>A (p.E318K) variant. For the POLD1 and POLE genes, variants outside of the exonuclease domains (POLD1 codons 311-541 and POLE codons 269-485) will not be analyzed or reported. For the RNF43, RPS20, and SDHA genes, copy number changes will not be analyzed or reported.

Patient Information:

Patient Name: Gloria Howells

Date Of Birth: 04/18/1960
Gender: Female
Patient ID: N/A
Medical Record #: N/A
Collection Kit:
Accession ID: N/A
Case File ID:
Ethnicity: Caucasian, Non-Hispanic White

Test Information:

Ordering Physician: Jelsema

Clinic Information: Natera Inc.

Phone: 555-555-5555
Report Date: 12/08/2021
Sample Collected: 06/22/2021
Sample Received: 06/24/2021
Sample Type: Blood

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk for common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime

Order Selected: The Empower™ Multi-Cancer Expanded panel (53 genes)

Variants that have been classified as pathogenic, likely pathogenic and of uncertain significance are reported per our internal classification methods. Our laboratory's variant classification criteria are based on the American College of Medical Genetics and Genomics (ACMG), internal guidelines, and our current understanding of the specific genes. If the majority of available information suggests the variant has no clinical significance it is not reported. This interpretation may change over time as more information about a gene and/or variant becomes available. For splicing related variants in *APC, ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, PMS2 EX1-10, MUTYH, NF1, PTEN, PALB2, RAD51C, RAD51D, TP53,* RNA sequencing evidence may be included as supporting evidence to update the classification of the variant. Most silent variants or known polymorphisms are likely benign; however, we cannot exclude the possibility of their interference with precursor RNA processing. Missense polymorphisms may also have effects on disease predisposition or may be synergistic for disease expression. Possible diagnostic errors include sample mix-ups, interfering substances, genetic variants that interfere with analysis, incorrect assignment of biological parentage, history of bone marrow transplant, and other sources. Please contact Natera if there is reason to suspect one of these sources of error.

Sequence analysis is based on the following gene transcripts: *APC* (NM_000038), *ATM* (NM_000051), *AXIN2* (NM_004655), *BAP1* (NM_004656), *BARD1* (NM_000465), *BMPR1A* (NM_004329), *BRCA1* (NM_007294), *BRCA2* (NM_000059), *BRIP1* (NM_032043), *CDH1* (NM_004360), *CDK4* (NM_000075), *CDKN2A* (NM_000077), *CHEK2* (NM_007194), *CTNNA1* (NM_001903), *DICER1* (NM_177438), *EPCAM* (NM_002354), *GALNT12* (NM_024642), *GREM1* (NM_013372), *HOXB13* (NM_006361), *KIT* (NM_000222), *MEN1* (NM_130799), *MITF* (NM_000248), *MLH1* (NM_000249), *MRE11* (NM_005591), *MSH2* (NM_000251), *MSH3* (NM_002439), *MSH6* (NM_000179), *MUTYH* (NM_001128425), *NBN* (NM_002485), *NF1* (NM_000267), *NTHL1* (NM_002528), *PALB2* (NM_024675), *PDGFRA* (NM_006206), *PMS2* (NM_000535), *POLD1* (NM_002691), *POLE* (NM_006231), *PTEN* (NM_000314), *RAD50* (NM_005732), *RAD51C* (NM_058216), *RAD51D* (NM_002878), *RNF43* (NM_017763), *RPS20* (NM_001023), *SDHA* (NM_004168), *SDHB* (NM_003000), *SDHC* (NM_003001), *SDHD* (NM_003002), *SMAD4* (NM_005359), *SMARCA4* (NM_001128849), *STK11* (NM_000455), *TP53* (NM_000546), *TSC1* (NM_000368), *TSC2* (NM_000548), *VHL* (NM_000551)

Glossary

Pathogenic variant: A change in DNA that is considered by this laboratory to be associated with an increased risk for disease.

Likely pathogenic variant: A change in DNA that is considered by this laboratory to have high, although not complete, certainty to be associated with an increased risk for disease.

Variant of uncertain significance (VUS): There is insufficient data available for these variants to classify them as either pathogenic or benign, as clinical significance remains unknown.

Linyan Meng

Linyan Meng Ph.D., FACMGG
Laboratory Director, Baylor Genetics

YOUBAO SHA

Youbao Sha, Ph.D., FACMG
Associate Laboratory Director, Natera

CLIA Laboratory Directors: J. Dianne Keen-Kim, Ph.D, FACMG and Christine M. Eng, MD, FACMG

natera™ | Empower™ Hereditary cancer test

About this test: Empower™ is a test to identify risk from common hereditary cancer syndromes. This information can help individuals learn if they have an elevated risk for developing certain cancers over their lifetime.

Understanding Your Positive Hereditary Cancer Test Result

A positive result means that a variant in a gene was found which is known to, or is likely to, change the way this gene works. Such variants are sometimes referred to as "pathogenic" or "likely pathogenic." Your test result shows that a positive variant was found in your *BRCA1* gene. Individuals with pathogenic or likely pathogenic *BRCA1* variants have Hereditary Breast and Ovarian Cancer (HBOC) syndrome. HBOC syndrome is associated with an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. There may also be a slightly increased risk of uterine cancer although there is currently limited evidence. This result means that you have an increased chance of developing certain cancers over your lifetime compared to the average person.

A positive result on Empower cannot predict whether individuals will get cancer in their lifetime, only that the risk for developing certain cancers may be increased compared to the general population. Risk for cancer depends on multiple factors in addition to genetic test results, including personal medical history, lifestyle and family history. The information below is provided to help you better understand what this means for you and your family. However, it should not be interpreted as medical advice. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider. Management guidelines may vary depending on your personal and family history.

Cancer Risk Estimates for *BRCA1*

Cancer risk estimates for a positive result are typically based on individuals with a family or personal history of cancer. Your risk may be different if you do not have a personal or family history of cancer.

	Female		Male	
Cancer Type	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**
Breast	12.9%	Up to 87% risk	<1%	1.2%
Ovarian	1.2%	Up to 62% risk	N/A	N/A
Prostate	N/A	N/A	12.1%	Increased
Pancreatic	1.6%	1-3%	1.7%	1-3%
Uterine	3.1%	Possibly increased	N/A	N/A

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic V.1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed Sep 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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4. Petrucelli N, Daly MB, Pal T.BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Dec 2016; Accessed: Jul 2020].

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Risk Management and Screening Guidelines for BRCA-Related Breast and Ovarian Cancer Syndrome[2,3]

The following information is a summary of current US guidelines. Please discuss with your healthcare provider as screening recommendations may vary by country and can change often.

Cancer Type	Mode of Screening or Risk Reduction	Typical Age to Begin	How often
Female Breast	Breast self-exam	18y	Monthly
	Breast exam with clinician	25y	Every 6-12 months
	Breast MRI with contrast	25-29y (or individualized if family history of breast cancer before age 30)	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Mammogram with consideration of tomosynthesis (3-D Mammogram)	30y	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Risk-reducing medication	Individualized	Discuss with your healthcare provider
	Risk-reducing mastectomy (breast surgery); discuss with your healthcare provider	Individualized	N/A
Male Breast	Breast self-exam	35y	Monthly
	Breast exam with clinician	35y	Annually
	Consider mammogram in men with gynecomastia (enlargement of breast tissue)	50y (or 10 years younger than earliest known male breast cancer in the family)	Annually
Ovarian	Risk-reducing salpingo-oophorectomy (RRSO) (surgical removal of ovaries and fallopian tubes); discuss with your healthcare provider	Typically between 35 and 40y, after completion of childbearing	N/A
	For those who have not had RRSO, consider screening with CA-125 blood test and transvaginal ultrasound of the ovaries; discuss with your healthcare provider	30-35y	Individualized
Prostate	Consider screening with PSA blood test and rectal exams with clinician (digital rectal exam)	40y	Individualized; discuss with your healthcare provider
Pancreatic	Endoscopic ultrasound and/or MRI of pancreas when there is a family history of pancreatic cancer; screening not recommended in absence of family history of pancreatic cancer	50y (or 10 years younger than the earliest known pancreatic cancer in the family)	Every 12 months
Uterine	Evidence currently limited, discuss risks and benefits of hysterectomy at time of risk reducing salpingo-oophrectomy	Individualized	N/A

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Other Medical Implications

Individuals who have mutations in both copies of their *BRCA1* gene may have the condition Fanconi Anemia Complementation Group S. This condition is very rare and can cause features such as abnormal skin pigmentation, thumb abnormalities, malformations of the skeletal and central nervous systems, short stature, bone marrow failure and an increased risk for certain cancers. If you have a single *BRCA1* mutation and your partner also carries a mutation in *BRCA1*, there is a 1 in 4 (25%) chance for your children to two *BRCA1* mutations. Genetic counseling is suggested. Please discuss with your healthcare provider and/or to find a genetic counselor in the US and Canada, please use this link: https://www.nsgc.org/page/find-a-genetic-counselor.

FREQUENTLY ASKED QUESTIONS

What is a pathogenic or likely pathogenic variant?

A pathogenic variant is a change in a gene that causes that gene to not work properly. A likely pathogenic variant is a change in a gene that most likely causes that gene to not work properly. Pathogenic and likely pathogenic variants are commonly called mutations and are both considered a positive result, meaning that they may be associated with an increased risk for developing certain cancers.

Could other people in my family have this same mutation?

Yes. In most cases, mutations are inherited from a biological parent. This means that the mutation likely came from either your father or your mother. Your children (or future children) have a 1 in 2 (50%) chance of inheriting this mutation. It also means that relatives such as your siblings, aunts, uncles and cousins could be at-risk to carry this mutation as well. We encourage you to share these results with your relatives so they can discuss with their healthcare providers and consider being tested themselves. Family members can be tested for the specific mutation that was found in you. If you are pregnant or considering pregnancy, you may wish to discuss your reproductive testing options with your healthcare provider or request a referral to a genetic counselor. It is possible to find out during pregnancy whether a future child will have this gene mutation, and for some gene mutations there may be the option to use assisted reproductive techniques to avoid this risk.

Does this result mean I have cancer or that I will get cancer?

No. This result does not mean that you have cancer or that you will develop cancer. People with these mutations have or may have a higher risk for certain cancers than the average population. There may be management options available now or in the future that could lower the risk and help catch cancer early. Please discuss the information provided in your report with your healthcare provider to come up with the best plan for you.

If I have already been diagnosed with cancer, what does this result mean for me?

It is important to continue to follow the recommendations of your healthcare providers and discuss these results with them. In some cases, there can be implications for cancer treatment based on a positive result. A positive result may also mean there is an increased risk for other cancer types.

Can I be discriminated against because of this result?

There is a federal law in the US called the Genetic Information Nondiscrimination Act (GINA) that prohibits medical insurance companies and employers from discriminating against individuals on the basis of genetic information. There are exceptions to this law, and it does not apply to some types of insurance such as life insurance, disability insurance, or long-term care insurance. Some US states may have laws/regulations that cover some of these exceptions. If you live outside the US, please consult legal advice in your area. Laws regarding genetic discrimination can change over time. The above statements do not constitute legal advice.

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What should I do next?

Discuss your results with your healthcare providers and work with them to come up with a plan for ongoing management. You may also wish to speak with a local genetic counselor. A genetic counselor in your area can be located on the National Society of Genetic Counselors website (www.ngsc.org) by using the “Find a Counselor” feature.

Where can I go for more information and support?

National Society of Genetic Counselors: www.nsgc.org
Facing Our Risk of Cancer Empowered (FORCE): www.facingourrisk.org
Bright Pink (prevention and early detection of breast and ovarian cancers): www.brightpink.org
American Cancer Society: www.cancer.org
Genetic Information Nondiscrimination Act (GINA): www.ginahelp.org

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natera | Empower™ Hereditary cancer test

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Understanding Your Positive Hereditary Cancer Test Result

A positive result means that a variant in a gene was found which is known to, or is likely to, change the way this gene works. Such variants are sometimes referred to as "pathogenic" or "likely pathogenic." Your test result shows that a positive variant was found in your *BRCA2* gene. Individuals with pathogenic or likely pathogenic *BRCA2* variants have Hereditary Breast and Ovarian Cancer (HBOC) syndrome. HBOC syndrome is associated with an increased risk to develop breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, and melanoma. This result means that you have an increased chance of developing certain cancers over your lifetime compared to the average person.

A positive result on Empower cannot predict whether individuals will get cancer in their lifetime, only that the risk for developing certain cancers may be increased compared to the general population. Risk for cancer depends on multiple factors in addition to genetic test results, including personal medical history, lifestyle and family history. The information below is provided to help you better understand what this means for you and your family. However, it should not be interpreted as medical advice. Please discuss your results, risk(s) for cancer, and management/screening options with your healthcare provider. Management guidelines may vary depending on your personal and family history.

Cancer Risk Estimates for *BRCA2*

Cancer risk estimates for a positive result are typically based on individuals with a family or personal history of cancer. Your risk may be different if you do not have a personal or family history of cancer.

	♀ Female		♂ Male	
Cancer Type	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**	**General Population - Estimated Lifetime Cancer Risk[1]**	**Positive Result - Estimated Lifetime Cancer Risk[2,3,4]**
Breast	12.9%	Up to 84% risk	<1%	Up to 9%
Ovarian	1.2%	Up to 27% risk	N/A	N/A
Prostate	N/A	N/A	12.1%	20%
Pancreatic	1.6%	2-7%	1.7%	2-7%
Melanoma	1.8%	Increased	2.8%	Increased

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic V.1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed Sep 2020. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
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4. Petrucelli N, Daly MB, Pal T.BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. In: Adam MP, Ardinger HH, Pagon RA, *et al*, editors. GeneReviews, University of Washington; 1993-2020. [Last Update: Dec 2016; Accessed: Jul 2020].

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Cancer Type	Mode of Screening or Risk Reduction	Typical Age to Begin	How often
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	Breast exam with clinician	25y	Every 6-12 months
	Breast MRI with contrast	25-29y (or individualized if family history of breast cancer before age 30)	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Mammogram with consideration of tomosynthesis (3-D mammogram)	30y	Annually until age 75y (screening after 75 should be considered on an individual basis)
	Risk-reducing medication	Individualized	Discuss with your healthcare provider
	Risk-reducing mastectomy (breast surgery); discuss with your healthcare provider	Individualized	N/A
Male Breast	Breast self-exam	35y	Monthly
	Breast exam with clinician	35y	Annually
	Consider mammogram in men with gynecomastia (enlargement of breast tissue)	50y (or 10 years younger than earliest known male breast cancer in the family)	Annually
Ovarian	Risk-reducing salpingo-oophorectomy (RRSO) (surgical removal of ovaries and fallopian tubes); discuss with your healthcare provider	Typically between 35 and 40y but may be delayed until 40-45y, after completion of childbearing	N/A
	For those who have not had RRSO, consider screening with CA-125 blood test and transvaginal ultrasound of the ovaries; discuss with your healthcare provider	30-35y	Individualized
Prostate	Screening with PSA blood test and consideration of rectal exams with clinician (digital rectal exam)	40y	Individualized; discuss with your healthcare provider
Pancreatic	Endoscopic ultrasound and/or MRI of pancreas when there is a family history of pancreatic cancer; screening not recommended in absence of family history of pancreatic cancer	50y (or 10 years younger than the earliest known pancreatic cancer in the family)	Every 12 months
Melanoma	Full body skin exam	Discuss with healthcare provider	Annually
	Limit UV ray exposure	Infancy and continue throughout life for all individuals	Daily

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Other Medical Implications

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Could other people in my family have this same mutation?

Yes. In most cases, mutations are inherited from a biological parent. This means that the mutation likely came from either your father or your mother. Your children (or future children) have a 1 in 2 (50%) chance of inheriting this mutation. It also means that relatives such as your siblings, aunts, uncles and cousins could be at-risk to carry this mutation as well. We encourage you to share these results with your relatives so they can discuss with their healthcare providers and consider being tested themselves. Family members can be tested for the specific mutation that was found in you. If you are pregnant or considering pregnancy, you may wish to discuss your reproductive testing options with your healthcare provider or request a referral to a genetic counselor. It is possible to find out during pregnancy whether a future child will have this gene mutation, and for some gene mutations there may be the option to use assisted reproductive techniques to avoid this risk.

Does this result mean I have cancer or that I will get cancer?

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If I have already been diagnosed with cancer, what does this result mean for me?

It is important to continue to follow the recommendations of your healthcare providers and discuss these results with them. In some cases, there can be implications for cancer treatment based on a positive result. A positive result may also mean there is an increased risk for other cancer types.

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Facing Our Risk of Cancer Empowered (FORCE): www.facingourrisk.org
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