Ambry Genetics®

SAMPLE REPORT

Ordered By	Contact ID:1384632	Org ID:1	
Medical Professional:	Unknown, Unknown, MD		
Client:	Ambry		
Additional Authorized Recipient:			
Sample Genetic Counselor, MS			

Patient Name:	**Unknown, Unknown**		
Accession #:	**00-060386**	Specimen #:	
AP2 Order #:	638361	Specimen:	Blood EDTA (Purple top)
Birthdate:	01/01/1976	Sex at Birth:	F
MRN #:	N/A	Collected:	N/A
Indication:	Family history	Received:	02/04/2019
		Test Started:	02/27/2024

CancerNext® +RNAinsight®: Analyses of 34 genes Associated with Hereditary Cancer

RESULTS

BRCA1 **Pathogenic Mutation: c.68_69delAG**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **c.68_69delAG (p.E23Vfs*17)** pathogenic mutation in the *BRCA1* gene.
- This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
- **Risk estimate**: increased lifetime risks for female breast cancer (57-72%), ovarian cancer (39-58%), male breast cancer (0.2-1.2%), prostate cancer (7-26%), and pancreatic cancer (3-5%).
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (34 total): ***APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, MLH1, MSH2, MSH6, MUTYH, NF1, NTHL1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, SMARCA4, STK11*** **and** ***TP53*** **(sequencing and deletion/duplication);** ***AXIN2, HOXB13, MSH3, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only)**. RNA data is routinely analyzed for use in variant interpretation for all genes.

BRCA1 **Additional Information**

The **c.68_69delAG** pathogenic mutation, located in coding exon 1 of the *BRCA1* gene, results from a deletion of two nucleotides at nucleotide positions 68 to 69, causing a translational frameshift with a predicted alternate stop codon (p.E23Vfs*17). This alteration is one of three well-characterized Ashkenazi Jewish founder mutations, with an overall carrier frequency of nearly 1% in this population (Struewing JP et al. *Nat. Genet.* 1995 Oct;11:198-200; Schubert EL et al. *Genet Test*, 1997;1:41-6; Hartge P et al. *Am. J. Hum. Genet.* 1999 Apr;64:963-70). This germline mutation has been reported in individuals of Ashkenazi Jewish descent, as well as in cohorts of other ethnicities, with hereditary breast and ovarian cancer (HBOC) syndrome, including individuals with male breast cancer, pancreatic cancer, and prostate cancer (Antoniou AC et al. *J. Med. Genet.* 2005 Jul;42:602-3; Lucas AL et al. *Clin. Cancer Res.* 2013 Jul;19:3396-403; Lucas AL et al. *Cancer.* 2014 Jul;120:1960-7; Bernards SS et al. *Gynecol Oncol*, 2016 Feb;140:221-5; Azzollini J et al. *Eur J Intern Med*, 2016 Jul;32:65-71; Na R et al. *Eur Urol*, 2017 05;71:740-747; Gabaldó Barrios X et al. *Fam. Cancer.* 2017 Oct;16:477-489; Alemar B et al. *PLoS One*, 2017 Nov;12:e0187630; Chan GHJ et al. *Oncotarget*, 2018 Jul;9:30649-30660; Schayek H et al. *Breast Cancer Res Treat*, 2018 Jul;170:399-404; Brand R et al. *Cancer*, 2018 09;124:3520-3527; Singh J et al. *Breast Cancer Res Treat*, 2018 Jul;170:189-196; Wen WX et al. *J Med Genet*, 2018 02;55:97-103; Cock-Rada AM et al. *Fam Cancer*, 2018 01;17:23-30; Mehta A et al. *Cancer Manag Res*, 2018 Nov;10:6505-6516; Li JY et al. *Int J Cancer*, 2019 01;144:281-289; Abe T et al. *J Clin Oncol*, 2019 05;37:1070-1080; Ashour M et al. *Cancer Manag Res*, 2019 Jul;11:6275-6284). In a large case control-study, this variant was reported in 30/60,466 breast cancer cases and in 8/53,461 controls (Dorling et al. *N Engl J Med.* 2021 02;384:428-439). Of note, this alteration is also designated as 185delAG, 187delAG, and 189delAG in published literature. In addition to the clinical data presented in the literature, this alteration is expected to result in loss of function by premature protein truncation or nonsense-

mediated mRNA decay. As such, this alteration is interpreted as a disease-causing mutation.

The *BRCA1* gene (NM_007294.3) is located on chromosome 17q21.31, encodes the breast cancer type 1 susceptibility protein, and contains 22 coding exons. Pathogenic variants in this gene are known to cause hereditary breast and ovarian cancer syndrome (HBOC), which is inherited in an autosomal dominant fashion. Additionally, biallelic pathogenic variants in this gene have been identified in individuals with Fanconi anemia type S (FA-S), which is inherited in an autosomal recessive fashion. Pathogenic variants in *BRCA1* confer a significantly increased cumulative lifetime risk for female breast cancer (57-72%), male breast cancer (up to 1.2%), epithelial ovarian cancer (39-58%), pancreatic cancer (3-5%), and prostate cancer (7-26%). Pathogenic variants in *BRCA1* are also associated with a contralateral female breast cancer risk of up to 40% within 20 years of initial breast cancer diagnosis with no intervention; however, this risk is age-dependent and more significant with earlier age (prior to age 40) of first breast cancer diagnosis (Kuchenbaecker K et al. *JAMA*. 2017 Jun 20;317(23):2402-2416; Hu C et al. *J Natl Cancer Inst.* 2020 Dec 14;112(12):1231-124; Breast Cancer Association Consortium. *N Engl J Med*. 2021;384:428-439; Hu C et al. *N Engl J Med*. 2021 Feb 4; 384(5): 440–451; Tai Y et al. *J Natl Cancer Inst.* 2007 Dec 5;99(23):1811-4; Chen J et al. *JNCI Cancer Spectr.* 2020 Apr 23;4(4):pkaa029; Chaffee K et al. *Genet Med.* 2018 Jan;20(1):119-127; Hu C et al. *JAMA*. 2018 Jun 19;319(23):2401-2409). Penetrance in individuals with pathogenic variants in *BRCA1* is incomplete and variable expressivity is observed; therefore, cancer risks will differ based on individual and family history. Published evidence suggests that both germline and somatic alterations in the *BRCA1* gene may predict sensitivity to chemotherapy agents that induce DNA damage as well as to poly(ADP-ribose) polymerase (PARP) inhibitors (Kim G et al. *Clin Cancer Res.* 2015 Oct 1;21(19):4257-61; Balasubramaniam S et al. *Clin. Cancer Res*., 2017 Dec;23:7165-7170). Fanconi anemia is characterized by progressive bone marrow failure, adult onset aplastic anemia, pre- and postnatal growth deficiency, abnormal skin pigmentation, characteristic skeletal malformations, and impaired endocrine functioning. Fanconi anemia can be established in a patient following cytogenic testing of patient lymphocytes that demonstrate increased chromosomal breakage and radial forms following diepoxybutane and mitomycin C exposure (Mehta P et al. *Fanconi Anemia.* 2002 Feb 14 [updated 2021 Jun 3]. In: GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022). Individuals with Fanconi anemia are at an increased risk of malignancies with highest risk of acute myelogenous leukemia, early-onset solid tumors including head and neck squamous cell carcinoma, and non-melanoma skin cancer (García-de-Teresa B et al. *Genes (Basel).* 2020 Dec 21;11(12):1528., 2020). Individuals of reproductive age are at 25% risk of having a child with Fanconi anemia with each pregnancy when both biological parents have a pathogenic variant in *BRCA1*. Loss of function has been reported as the mechanism of disease for HBOC and Fanconi anemia.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- CancerNext® +RNAinsight® (Product Code 8824-R)

ASSAY INFORMATION

Methodology: The **CancerNext® +RNAinsight®** test is a comprehensive screen of 34 genes associated with hereditary cancer predisposition. Genomic deoxyribonucleic acid (gDNA) and ribonucleic acid (RNA) are isolated from the patient's specimen using standardized methodology and quantified. RNA is converted to complementary DNA (cDNA) by reverse transcriptase polymerase chain reaction (RT-PCR). Sequence enrichment of the targeted coding exons and adjacent intronic nucleotides is carried out by a bait-capture methodology using long biotinylated oligonucleotide probes followed by polymerase chain reaction (PCR) and Next-Generation sequencing (NGS). Additional DNA analyses include Sanger sequencing for any regions missing or with insufficient read depth coverage for reliable heterozygous variant detection. Variants in regions complicated by pseudogene interference, variant calls not satisfying depth of coverage and variant allele frequency quality thresholds, and potentially homozygous variants are verified by Sanger sequencing. The *BRCA2* Portuguese founder mutation, c.156_157insAlu (also known as 384insAlu), and the *MSH2* coding exons 1-7 inversion are detected by NGS and confirmed by multiplex ligation-dependent probe amplification (MLPA) or PCR and agarose gel electrophoresis. Gross deletion/duplication analysis of the genes sequenced (excluding *AXIN2, HOXB13, MSH3, POLD1,* and *POLE*) is performed using a custom pipeline based on read-depth from NGS data and/or targeted chromosomal microarray with confirmatory MLPA when applicable. Gross deletions and duplications of exons 11-15 of *PMS2* are reflexed to long-range PCR and gel electrophoresis and/or sequencing to determine if the event occurs within *PMS2* or *PMS2CL*. The most likely deletion/duplication configuration that is consistent with the long-range PCR results is reported; however, rare complex rearrangements in *PMS2* and *PMS2CL* cannot be ruled out. All sequence analysis is based on the following NCBI reference sequences: *APC*- NM_000038.5 & NM_001127511.2, *ATM*- NM_000051.3, *AXIN2*- NM_004655.3, *BARD1*- NM_000465.2, *BMPR1A*- NM_004329.2, *BRCA1*- NM_007294.3, *BRCA2*- NM_000059.3, *BRIP1*- NM_032043.2, *CDH1*- NM_004360.3, *CDK4*- NM_000075.3, *CDKN2A*- NM_000077.4 and NM_058195.3 (p14ARF), *CHEK2*- NM_007194.3, *DICER1*-NM_177438.2, *HOXB13*- NM_006361.5, *MUTYH*- NM_001128425.1, *MLH1*- NM_000249.3, *MSH2*- NM_000251.1, *MSH3*- NM_002439.3, *MSH6*- NM_000179.2, *NF1*- NM_000267.3, *NTHL1*- NM_002528.5, *PALB2*- NM_024675.3, *PMS2*- NM_000535.5, *POLD1*- NM_002691.2, *POLE*-NM_006231.2, *PTEN*- NM_000314.4, *RAD51C*- NM_058216.1, *RAD51D*- NM_002878.3, *SMAD4*- NM_005359.5, *SMARCA4*- NM_001128849.1, *STK11*- NM_000455.4, *TP53*- NM_000546.4.

Analytical Range: The **CancerNext® +RNAinsight®** test detects variants in the sequenced genes (*APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, HOXB13, MLH1, MSH2, MSH3, MSH6, MUTYH, NF1, NTHL1*, *PALB2, POLD1, POLE, PMS2, PTEN, RAD51C, RAD51D, SMAD4, SMARCA4, STK11,* and *TP53)* by either Next-Generation or Sanger sequencing of all coding domains and well into the flanking 5' and 3' ends of all the introns and untranslated regions. Unless explicitly stated, sequence and copy number variants in the promoter, non-coding exons, or 3' untranslated regions are not routinely reported. For *HOXB13*, only variants impacting codon 84 are routinely reported. For *POLD1* and *POLE*, only missense variants and in-frame insertions/deletions in the exonuclease domains (codons 311-541 and 269-485, respectively) are routinely reported. The *MSH3* polyalanine repeat region is excluded from analysis. Gross deletion/duplication analysis determines gene copy number for the covered exons and untranslated regions of sequenced genes (excluding *AXIN2, HOXB13, MSH3, POLD1,* and *POLE*) as well as *GREM1* and *EPCAM*. For *GREM1,* only the status of the 40kb 5'UTR gross duplication is analyzed and reported. For *EPCAM*, only gross deletions encompassing the 3' end of the gene are reported. For *NTHL1*, only full-gene gross deletions and duplications are detected. For *APC*, all promoter 1B gross deletions as well as single nucleotide substitutions within the promoter 1B YY1 binding motif (NM_001127511 c.-196_-186) are analyzed and reported. RNA transcripts are screened and compared to a human reference pool. The presence of RNA transcripts meeting quality thresholds is incorporated as evidence for the assessment and classification of DNA variants. Any regions not meeting RNA quality thresholds, including regions with chronically low expression in human peripheral lymphocytes, are excluded from analysis. RNA transcripts derived from genes with limited gene-disease validity or with an inconsistent mechanism of disease do not routinely contribute to variant interpretation.

Result Reports: Results reported herein may be of constitutional or somatic origin. This methodology cannot differentiate between these possibilities. In result reports, alterations in the following classifications are always reported, and are based on the following definitions and clinical recommendations.

- **Pathogenic Mutation**: alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk relatives and appropriate changes in medical management for pathogenic mutation carriers recommended. Previously described pathogenic mutations, including intronic mutations at any position, are always reported when detected.
- **Variant, Likely Pathogenic (VLP)**: alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk relatives and appropriate changes in medical management for VLP carriers typically recommended. Previously described likely pathogenic variants, including intronic VLPs at any position, are always reported when detected.
- **Variant, Unknown Significance (VUS)**: alterations with limited and/or conflicting evidence regarding pathogenicity. Familial testing via the Family Studies Program may be recommended. Medical management to be based on personal/family clinical histories, not VUS carrier status. Note, intronic VUSs are always reported out to 5 base pairs from the splice junction when detected.

Alterations of unlikely clinical significance (those with strong/very strong evidence to argue against pathogenicity) are not routinely included in results. These include findings classified as "likely benign" and "benign" alterations.

All results, including those from prior genetic testing for themselves and/or family members, will be reported as described above.

Assay Information Continued on Next Page

ASSAY INFORMATION *(Supplement to Test Results - Continued)*

Resources: The following references are used in variant analysis and classification when applicable for observed genetic alterations.

1. The 1000 Genomes Project Consortium. An integrated map of genetic variation from 1092 human genomes. *Nature*. 2012;491:56-65.
2. ACMG Standards and guidelines for the interpretation of sequence variants. *Genet Med.* 2015 May;17(5):405-23.
3. Ambry Genetics Variant Classification Scheme. http://www.ambrygen.com/variant-classification.
4. Berkeley Drosophila Genome Project [Internet]. Reese MG et al. *J Comp Biol.* 1997;4:311-23. http://www.fruitfly.org/seq_tools/splice.html.
5. Database of Single Nucleotide Polymorphisms (dbSNP) [Internet]. Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine (dbSNP Build ID:135) Available from: www.ncbi.nlm.nih.gov/SNP. Accessed Jan 2012).
6. ESEfinder [Internet]. Smith PJ, et al. (2006) *Hum Mol Genet.* 15(16):2490-2508 and Cartegni L, et al. *Nucleic Acid Research.* 2003;31(13):3568-3571. http://rulai.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home.
7. Exome Variant Server, NHLBI Exome Sequencing Project (ESP) [Internet], Seattle WA. Available from: evs.gs.washington.edu/EVS.
8. Grantham R. Amino acid difference formula to help explain protein evolution. *Science.* 1974;185(4151):862-864.
9. HGMD® [Internet]: Stenson PD et al. *Genome Med.* 2009;1(1):13. www.hgmd.cf.ac.uk.
10. Landrum MJ et al. ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res*. 2014 Jan 1;42(1):D980-5. doi: 10.1093/nar/gkt1113. PubMed PMID: 24234437.
11. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), Copyright® 1966-2012. World Wide Web URL: http://omim.org.
12. Feng BJ. PERCH: A Unified Framework for Disease Gene Prioritization. *Hum Mutat.* 2017 Mar;38(3):243-251.
13. Exome Aggregation Consortium (ExAC) [Internet], Cambridge, MA. Available from: http://exac.broadinstitute.org.
14. Genome Aggregation Database (gnomAD) [Internet], Cambridge, MA. Available from: http://gnomad.broadinstitute.org.
15. Lek M et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016 Aug 17;536(7616):285-91. PMID: 27535533
16. Mu W et al. *J Mol Diagn*. 2016 Oct 4. PubMed PMID: 27720647
17. Karczewski KJ et al. *Nature*. 2020 May;581(7809):434-443. PMID: 32461654
18. Splicing Prediction: Jaganathan K et al. *Cell.* 2019 Jan 24; 176(3):535-548.e24. PMID: 30661751

Disclaimer: This test was developed and its performance characteristics were determined by Ambry Genetics Corporation. It has not been cleared or approved by the US Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. It should not be regarded as investigational or for research. This test should be interpreted in context with other clinical findings. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. This test analyzes the following types of mutations: nucleotide substitutions, small deletions (up to 25 bp), small insertions (up to 10 bp), small indels and gross deletions/duplications. Unless otherwise noted in the methodology section above, it is not intended to analyze the following types of alterations: gross rearrangements, deep intronic variations, Alu element insertions, and other unknown abnormalities. The pattern of mutation types varies with the gene tested and this test detects a high but variable percentage of known and unknown mutants of the classes stated. A negative result from the analysis cannot rule out the possibility that the tested individual carries a rare unexamined mutation or mutation in the undetectable group. This test is designed and validated to be capable of detecting ~99% of described mutations in the 36 genes represented on the panel (analytical sensitivity). The clinical sensitivity of this test may vary widely according to the specific clinical and family history. Breast, ovarian and colon cancers are complex clinical disorders. Mutations in other genes or the regions not analyzed by this test can also give rise to clinical conditions similar to breast cancer, ovarian or colon cancer. Although molecular tests are highly accurate, rare diagnostic errors may occur. Possible diagnostic errors include sample mix-up, erroneous paternity identification, technical errors, clerical errors, and genotyping errors. Genotyping errors can result from trace contamination of PCR reactions, from maternal cell contamination in fetal samples, from rare genetic variants that interfere with analysis, germline or somatic mosaicism, presence of pseudogenes, technical difficulties in regions with high GC content or homopolymer tracts, active hematologic disease, a history of allogeneic bone marrow or peripheral stem cell transplant, or from other sources. Rare variants present in the human genome reference sequence (GRCh37.p5/hg19) or rare misalignment due to presence of pseudogenes can lead to misinterpretation of patient sequence data can lead to misinterpretation of patient sequence data**.** This report does not represent medical advice. Any questions, suggestions, or concerns regarding interpretation of results should be forwarded to a genetic counselor, medical geneticist, or physician skilled in interpretation of the relevant medical literature.

Ambry Genetics®

Clinician Management Resource for *BRCA1*

This overview of clinical management guidelines is based on this patient's positive test result for a *BRCA1* gene mutation. Unless otherwise stated, medical management guidelines used here are limited to those issued by the National Comprehensive Cancer Network® (NCCN®)[1] in the U.S. Please consult the referenced guideline for complete details and further information.

Clinical correlation with the patient's past medical history, treatments, surgeries and family history may lead to changes in clinical management decisions; therefore, other management recommendations may be considered. Genetic testing results and medical society guidelines help inform medical management decisions but do not constitute formal recommendations. Discussions of medical management decisions and individualized treatment plans should be made in consultation between each patient and his or her healthcare provider, and may change over time.

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast awareness* ▪ Women should be familiar with their breasts and promptly report changes to their healthcare provider.	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old	Every 6-12 months
Breast Screening** ▪ Breast MRI with and without contrast ▪ Mammography	25-29 years old (MRI only***)	Every 12 months or individualized based on family history
	30-75 years old (MRI and mammography)	Every 12 months
	>75 years old	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Consider options for risk reduction agents	Individualized	Individualized
Ovarian Cancer		
Recommend risk-reducing salpingo-oophorectomy (RRSO)^	Typically 35 to 40 years old, recognizing that childbearing is a consideration	N/A
Consider options for risk reduction agents	Individualized	Individualized
Male Breast Cancer		
Breast self-exam training and education	35 years old	Periodic and consistent
Clinical breast exam	35 years old	Every 12 months
Consider mammogram screening	50 years or 10 years before the earliest known male breast cancer in the family (whichever comes first)	Every 12 months
Prostate Cancer		
Consider prostate cancer screening	40 years old	Clinician's discretion
Melanoma		
General risk management, such as annual full-body skin examination and minimizing UV exposure	Individualized	Annual, or at clinician's discretion
Pancreatic Cancer		
For individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening using contrast-enhanced MRI/MRCP and/or EUS.^^	50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)	Annually (with consideration of shorter intervals if potentially concerning abnormalities seen on screening)

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Other		
For individuals of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic testing and donor gametes. Discussion should include known risks, limitations, and benefits of these technologies.	Individualized	N/A
Counsel for risk of autosomal recessive condition in offspring.	Individualized	N/A

* Breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

** Women treated for breast cancer who have not undergone bilateral mastectomy: follow screening as described

***Mammography may be considered only if MRI is unavailable

^ Limited data suggest that there may be a slight increased risk of serous uterine cancer among women with a *BRCA1* mutation. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the BRCA population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* mutation prior to surgery. Women who undergo hysterectomy at the time of RRSO are candidates for estrogen alone hormone replacement therapy (HRT), which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which is required when the uterus is left in situ (Chlebowski R, *et al*. JAMA Oncol 2015; 1:296-305). HRT recommendations should be tailored depending on each patient's personal history of breast cancer and/or breast cancer risk reduction strategies. HRT is a consideration for premenopausal patients who do not carry a diagnosis of breast cancer or have other contraindications for HRT.

^^ For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. Most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V2.2024. Accessed September 27, 2023. 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.

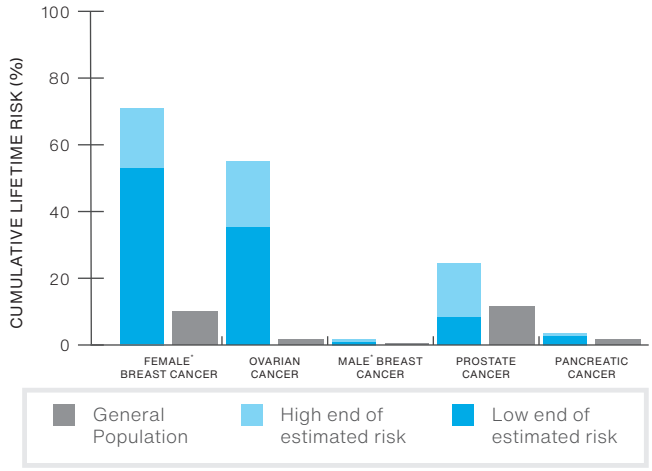
Understanding Your Positive *BRCA1* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC MUTATION OR VARIANT, LIKELY PATHOGENIC

6 Things To Know

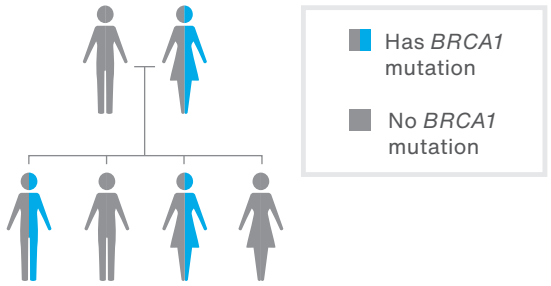
1	*BRCA1* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *BRCA1* gene.
2	Hereditary breast and ovarian cancer (HBOC)	People with *BRCA1* mutations have hereditary breast and ovarian cancer (HBOC).
3	Cancer risks	You have an increased chance to develop breast cancer, ovarian cancer, pancreatic cancer, prostate cancer, and possibly other types of cancer.
4	What you can do	Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your doctor and decide on a plan that works for you.
5	Other medical concerns	Individuals with *BRCA1* mutations may have an increased risk to have a child with Fanconi anemia, but only if their partner also carries a mutation in the *BRCA1* gene. Fanconi anemia is a rare condition that can cause specific physical characteristics, bone marrow failure, and an increased risk of certain cancers.
6	Family	Family members may also be at risk – they can be tested for the *BRCA1* mutation that was identified in you. It is recommended that you share this information with your family members so they can learn more and discuss with their healthcare providers.

BRCA1 Mutation Lifetime Cancer Risks**



BRCA1 Mutations in the Family

There is a 50/50 random chance to pass on a *BRCA1* mutation to each of your children. The image below shows that everyone can carry and pass on these mutations, regardless of their sex at birth.



* Refers to sex assigned at birth
** Because risk estimates vary in different studies, only approximate risks are given. Cancer risks will differ based on individual and family history.

RESOURCES

- Ambry's Hereditary Cancer Site for Families patients.ambrygen.com/cancer
- Bright Pink brightpink.org
- FORCE facingourrisk.org
- ICARE Inherited Cancer Registry InheritedCancer.net
- Imerman Angels imermanangels.org
- Sharsheret sharsheret.org
- Susan G. Komen Foundation komen.org
- Genetic Information Nondiscrimination Act (GINA) ginahelp.org
- National Society of Genetic Counselors nsgc.org
- Canadian Society of Genetic Counsellors cagc-accg.ca

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *BRCA1* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

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PROMPT

Prospective Registry Of MultiPlex Testing

Opportunity to Enroll in Hereditary Cancer Research

Genetic testing can help individuals and families by giving them a clearer idea of their cancer risks. Genetic tests (called multi-gene or multiplex panels) look for changes in several different genes, all in a single test. While all of the genes on these panels have been tied to an increased risk of cancer, we understand the risks associated with some of the genes better than we understand others. One way to help improve our understanding is to enroll people with pathogenic mutations or variants of unknown significance in registries. Registries typically follow people over many years to learn more about these alterations and how they impact their health.

How can I find a research registry?

There are several hereditary cancer research registries that are studying individuals who have had multiplex panel testing. One registry that is open to individuals nationwide is PROMPT (or **P**rospective **R**egistry **O**f **M**ulti**P**lex **T**esting). PROMPT is an online registry for patients and families who have had multiplex testing and have been found to have a genetic variation which may be linked to an increased risk of cancer. PROMPT is a joint effort involving several academic medical centers and commercial laboratories, working together to learn more about the genes that are studied on multiplex panels. PROMPT will allow researchers to better understand the cancer risks associated with changes in these genes and thus provide a better understanding of the best way to take care of individuals who have such changes.

What is involved in participation?

Participation in the study simply involves completing online surveys. Additionally, the PROMPT team may reach out to you to talk about ways that you can get more involved with the research effort. Your participation will help researchers learn more and improve the ability of this genetic testing to help people.

How do I enroll?

You can learn more about or register for PROMPT by going to www.promptstudy.info or by scanning the QR code below.

Thank you again for considering taking part in PROMPT!

If you would like to read more about multiplex panels, including details about specific genes, please visit our informational website at www.promptstudy.info.

Opportunity to connect and help prevent cancer in your family

Did you recently have genetic testing for a cancer gene variant (or mutation) known to be in your family? Questions such as “Where did this variant come from?” or “What can I do to help others in my family?” are common. ConnectMyVariant can help!

ConnectMyVariant provides resources for people who want help talking with relatives about cancer risk or finding new relatives who might be at risk to help them get genetic testing and prevent cancer.

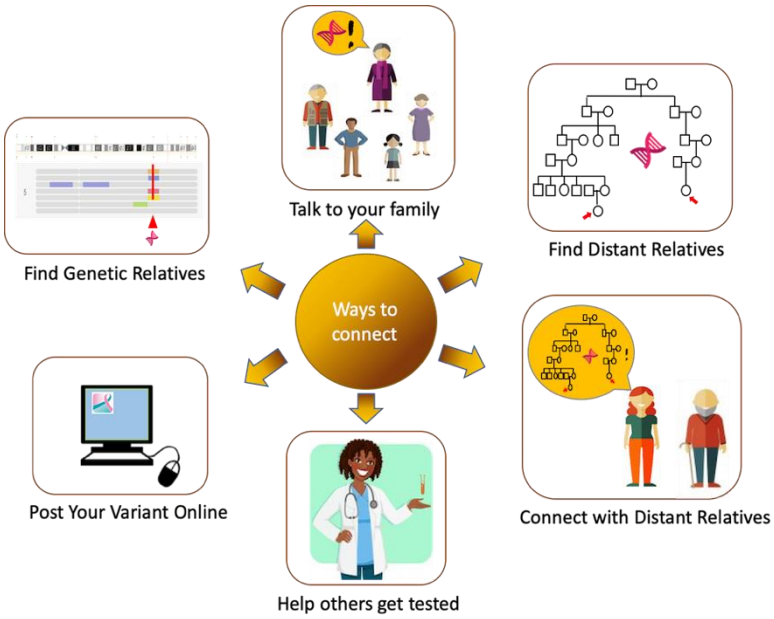
The ConnectMyVariant initiative seeks to help people like you:

- Talk to their relatives
- Share important genetic information
- Expand family trees to identify and connect with distant at-risk relatives
- Guide at-risk relatives to cancer prevention.

“Prevention Through Connection”

People with the same genetic variant may be distantly related through a long-ago ancestor. This means that your family’s variant may be a key to understanding your family’s past. It is also a key that you can use to help both close and distant family members prevent cancer before it happens.

You may have received genetic testing because someone cared enough to warn you about your risk. Now you can find and warn other at-risk relatives. Reaching out and speaking to other at-risk relatives to help them get genetic testing may help prevent cancer and save lives. These are the goals of ConnectMyVariant.



You can learn more and sign up at http://connectmyvariant.org/
Questions? info@connectmyvariant.org

ICARE
INHERITED CANCER REGISTRY

WHY PARTICIPATE IN ICARE?

Be a part of new discoveries.

Studies that used information from ICARE participants have...

found that removing the ovaries may not lower breast cancer risk for women with a ***BRCA*** mutation.[1]

improved cancer risk estimates for people with ***PALB2*** mutations.[2]

Get care updates personalized to you

as new guidelines and other information come out – for example:

ICARE participants with mutations in ***PALB2***, ***CHEK2***, and ***ATM*** were given updates that might affect their care because new National Comprehensive Cancer Network (NCCN) Genetics Guidelines were released in September 2022.

Find out about other studies.

Examples of studies include:

A study providing free resources to help with managing cancer risks and family communication of test results.

A study doing free genomic studies on breast cancers in people with ***BRCA1***, ***BRCA2***, ***PALB2***, ***ATM***, and ***CHEK2*** mutations to learn more about how these tumors develop and how we might best treat them.

Enroll online by visiting
https://redcap.link/ICAREconsent
or **scan the below QR code**:

[1] *Kotsopoulos J, et al. Bilateral Oophorectomy and the Risk of Breast Cancer in BRCA1 Mutation Carriers: A Reappraisal. Cancer Epidemiol Biomarkers Prev. 2022 Jul 1;31(7):1351-1358. PMID: 35477169;* [2] *Yang X, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020 Mar 1;38(7):674-685. PMID: 31841383.*

WHAT ARE PARTICIPANTS SAYING ABOUT ICARE?

Participant Testimonials:

"I absolutely love being a part of ICARE... and enjoy receiving their periodic newsletters on clinical and research updates."

"As much as it might seem frightening to some to join a registry like this, I am grateful for the opportunity to help pay it forward by supporting inherited cancer studies in the hopes we can all live well and have long healthy lives."

"I participate in ICARE and other related activities in hopes that continued research will positively impact all of us with hereditary cancers, and especially my three children who are now young adults."

615-875-2444 ICARE@vumc.org InheritedCancer.net

Version 10/28/2022

Salpingectomy: an approach to reduce the risk of ovarian cancer while preserving hormonal function

NRG ONCOLOGY
Advancing Research. Improving Lives.™

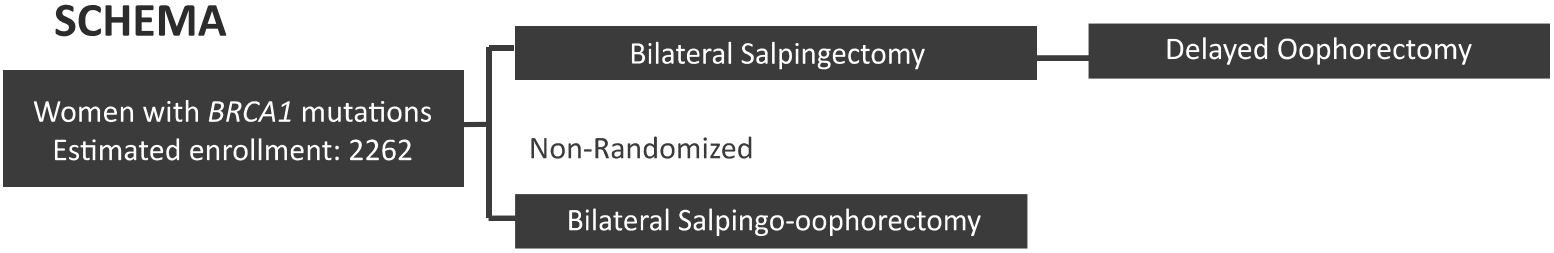
NCI Community Oncology Research Program
A program of the National Cancer Institute of the National Institutes of Health

NOW ENROLLING *BRCA1* CARRIERS

Clinical Trial • NCT04251052 • NRG-CC008

NCI-sponsored study to compare two surgical procedures in women with *BRCA1* mutations to assess reduced risk of ovarian cancer

SCHEMA



STUDY ENDPOINTS

Primary Outcome Measures:

- Non-inferiority of salpingectomy compared to bilateral salpingo-oophorectomy to reduce the risk of ovarian cancer

Secondary Outcome Measures:

- Estrogen deprivation symptoms
- Health-related quality of life
- Sexual function
- Cancer distress
- Quality of life
- Medical decision making
- Adverse events

For information regarding patient eligibility or clinical questions, contact the NRG-CC008 Co-Principal Investigators:

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ClinicalTrials.gov Identifer: NCT04251052

Study sponsored by the National Cancer Institute and conducted by NRG Oncology.

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