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SAMPLE REPORT

Ordered By	Contact ID:8021877	Org ID:8141	Patient Legal Name: **Last, First**		
Medical Professional:	Unknown, Unknown, MD		Accession #: **01-495585**	Specimen #:	
Client:	MOCKORG44 (10829)		AP2 Order #: 3774889	Specimen: Blood EDTA (Purple top)	
			Birthdate: 01/01/1998	Sex assigned at birth: F	
			MRN #: N/A	Collected: 07/07/2026	
			Indication: Diagnostic/Family History	Received: 07/07/2026	
				Test Started: 07/07/2026	

CancerNext-Expanded®: Analyses of Genes Associated with Hereditary Cancer (78 genes)

RESULTS

BRCA2 **Pathogenic Mutation: c.5946delT**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **c.5946delT (p.S1982Rfs*22)** pathogenic mutation in the *BRCA2* gene.
- This result is consistent with a diagnosis of *BRCA2*-related cancer predisposition.
- **Risk estimate**: increased lifetime risks for female breast cancer (55-69%), ovarian cancer (13-29%), male breast cancer (1.8-7.1%), pancreatic cancer (5-10%) and prostate cancer (19-61%); increased risk for melanoma.
- 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 (78 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CHEK2, DICER1, ETV6, FH, FLCN, GATA2, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RPS20, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** **and** ***WT1*** **(sequencing and deletion/duplication);** ***AXIN2, CTNNA1, DDX41, EGFR, HOXB13, KIT, MBD4, MITF, MLH3, MSH3, PDGFRA, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only)**.

***BRCA2* Additional Information**

The **c.5946delT** pathogenic mutation is located in coding exon 10 of the *BRCA2* gene and is one of the well-described Ashkenazi Jewish founder mutations. This mutation results from a deletion of one nucleotide at position 5946, causing a translational frameshift with a predicted alternate stop codon (p.S1982Rfs*22). This mutation has been reported in numerous families affected with breast, ovarian, prostate, pancreatic, and other HBOC-related cancers (Agalliu I et al. *Clin. Cancer Res.* 2009 Feb;15:1112-20; Walsh T et al. *Proc. Natl. Acad. Sci. USA*. 2011 Nov;108:18032-7; Johnston JJ et al. *Am. J. Hum. Genet*. 2012 Jul;91:97-108; Bayraktar S et al. *Cancer*. 2012 Mar;118:1515-22; George J et al. *Clin. Cancer Res.* 2013 Jul;19:3474-84; Lucas AL et al. *Clin. Cancer Res*. 2013 Jul;19:3396-403; Salo-Mullen EE et al. *Cancer.* 2015 Dec;121:4382-8; Susswein LR et al. *Genet. Med.* 2016 Aug;18:823-32). This variant has also been reported in trans with a second pathogenic mutation in individuals affected with Fanconi anemia (Offit K et al. *J Natl Cancer Inst*. 2003 Oct;95(20):1548-51; Dewire MD et al. *Pediatr Blood Cancer.* 2009 Dec;53(6):1140-2). One study indicated that carriers of the c.5946delT mutation may have a lower relative risk for breast cancer when compared to carriers of other non-Ashkenazi Jewish *BRCA2* mutations (Finkelman BS et al. *J. Clin. Oncol*. 2012 Apr;30:1321-8); however other studies have reported the overall risk as similar to that of other pathogenic mutations in the ovarian cancer cluster region (OCCR) of coding exon 10 of *BRCA2* (Kuchenbaecker KB et al. *JAMA*. 2017 Jun;317(23):2402-2416). Of note, this mutation is also designated as 6174delT 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 *BRCA2* gene (NM_000059.3) is located on chromosome 13q13.1, encodes the breast cancer type 2 susceptibility protein, and contains 26 coding exons. Pathogenic variants in this gene are known to cause *BRCA2*-related cancer predisposition, which is inherited in an autosomal

dominant fashion, and *BRCA2*-related Fanconi anemia, which is inherited in an autosomal recessive fashion. *BRCA2*-related cancer predisposition is characterized by a significantly increased cumulative lifetime risk for female breast cancer (55-69%), male breast cancer (1.8-7.1%), epithelial ovarian cancer (13-29%), pancreatic cancer (5-10%), prostate cancer (19-61%), and melanoma. *BRCA2*-related cancer predisposition is also associated with a contralateral female breast cancer risk of up to 26% 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 *BRCA2*-related cancer predisposition 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 *BRCA2* gene predict sensitivity to chemotherapy agents that induce DNA damage and have been included in some indications for approved poly(ADP-ribose) polymerase (PARP) inhibitor therapies (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). Loss of function has been reported as the mechanism of disease for *BRCA2*-related cancer predisposition. *BRCA2*-related 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. *BRCA2*-related Fanconi anemia can be established in a patient following cytogenetic 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: *GeneReview*s [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022). Individuals with *BRCA2*-related 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 *BRCA2*. Biallelic loss of function, with at least one hypomorphic allele, has been reported as the mechanism of disease for *BRCA2*-related 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-Expanded® (Product Code 8875)

ASSAY INFORMATION

General methodology: Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's specimen using standardized methodology and quantified. 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). 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. Gross deletion/duplication analysis is performed using a customized pipeline using a combination of third-party coverage-based tools and custom methodologies followed by a confirmatory orthogonal method, as needed. Mobile element insertions, if detected, are confirmed by PCR and Sanger sequencing and/or gel electrophoresis.

Additional methodology:

- ***MSH2***: The inversion of coding exons 1-7 is detected by NGS and confirmed by multiplex ligation-dependent probe amplification (MLPA) or PCR and agarose gel electrophoresis.
- ***PMS2****:* 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.

NCBI reference sequences: *AIP*- NM_003977.2, *ALK*- NM_004304.4, *APC*- NM_000038.5 & NM_001127511.2, *ATM*- NM_000051.3, *ATRIP*- NM_130384.1, *AXIN2*- NM_004655.3, *BAP1*- NM_004656.2, *BARD1*- NM_000465.2, *BMPR1A*- NM_004329.2, *BRCA1*- NM_007294.3, *BRCA2*- NM_000059.3, *BRIP1*- NM_032043.2, *CDC73*- NM_024529.4, *CDH1*- NM_004360.3, *CDK4*- NM_000075.3, *CDKN1B*- NM_004064.3, *CDKN2A*- NM_000077.4 & NM_058195.3, *CEBPA*- NM_004364.3, *CFTR*- NM_000492.3, *CHEK2*- NM_007194.3, *CPA1*- NM_001868.2, *CTNNA1*- NM_001903.2, *CTRC*- NM_007272.2, *DDX41*- NM_016222.2, *DICER1*- NM_177438.2, *EGFR*- NM_005228.3, *EGLN1*- NM_022051.2, *EPCAM*- NM_002354.2, *ETV6*- NM_001987.4, *FH*- NM_000143.3, *FLCN*- NM_144997.5, *GATA2*- NM_032638.4, *GREM1*- NM_013372.6, *HOXB13*- NM_006361.5, *KIF1B*- NM_015074.3, *KIT*- NM_000222.2, *LZTR1*- NM_006767.3, *MAX*- NM_002382.3, *MBD4*- NM_001276270.2, *MEN1*- NM_130799.2, *MET*- NM_001127500.1, *MITF*- NM_000248.3, *MLH1*- NM_000249.3, *MLH3*- NM_001040108.1, *MSH2*- NM_000251.1, *MSH3*- NM_002439.3, *MSH6*- NM_000179.2, *MUTYH*- NM_001128425.1, *NF1*- NM_000267.3, *NF2*- NM_000268.3, *NTHL1*- NM_002528.5, *PALB2*- NM_024675.3, *PALLD*- NM_001166110.1, *PDGFRA*- NM_006206.4, *PHOX2B*- NM_003924.3, *PMS2*- NM_000535.5, *POLD1*- NM_002691.2, *POLE*- NM_006231.2, *POT1*- NM_015450.2, *PRKAR1A*- NM_002734.3, *PRSS1*- NM_002769.4, *PTCH1*- NM_000264.3, *PTEN*- NM_000314.4, *RAD51B* - NM_133510.3, *RAD51C*- NM_058216.1, *RAD51D*- NM_002878.3, *RB1*- NM_000321.2, *RET*- NM_020975.4, *RNF43*- NM_017763.4, *RPS20*- NM_001023.3, *RUNX1*- NM_001754.4, *SDHA*- NM_004168.2, *SDHAF2*- NM_017841.2, *SDHB*- NM_003000.2, *SDHC*- NM_003001.3, *SDHD*- NM_003002.2, *SMAD4*- NM_005359.5, *SMARCA4*- NM_001128849.1, *SMARCB1*- NM_003073.3, *SMARCE1*- NM_003079.4, *SPINK1*- NM_003122.3, *STK11*- NM_000455.4, *SUFU*- NM_016169.3, *TERT* - NM_198253.2, *TMEM127*- NM_017849.3, *TP53*- NM_000546.4, *TSC1*- NM_000368.4, *TSC2*- NM_000548.3, *VHL*- NM_000551.3, and *WT1*- NM_024426.4.

Analytical range: This test detects variants in the coding domains and well into the flanking 5' and 3' ends of 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.

Analytical range exceptions:

- ***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.
- ***EPCAM***: only gross deletions limited to the 3' end of the gene are reported.
- ***GREM1***: only the status of the 40kb 5'UTR gross duplication is routinely analyzed and reported.
- ***MITF***: only the c.952G>A (p.E318K) variant is reported.
- ***MSH3*** and ***PHOX2B***: the polyalanine repeat regions are excluded from analysis.
- ***NTHL1***: only full-gene gross deletions and duplications are detected.
- **Gross deletion/duplication analysis is not performed for the following genes:** *ATRIP, AXIN2, CFTR, CPA1, CTNNA1, CTRC, DDX41, EGFR, EGLN1, HOXB13, KIT, MBD4, MITF, MLH3, MSH3, PALLD, PDGFRA, POLD1, POLE, PRSS1, RAD51B, RNF43, SPINK1*, and *TERT*.

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

- **Pathogenic Variant**: variants 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 variant carriers recommended. Previously described pathogenic variants, including intronic variants at any position, are always reported when detected.
- **Variant, Likely Pathogenic (VLP)**: variants 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, Uncertain Significance (VUS)**: variants 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.

Variants 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” variants. Classification and interpretation of variants may change over time with accumulating evidence and scientific advancements. Updated classifications may be reported through reclassification notices; however, clients should re-contact the laboratory or visit ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) for the most up to date information regarding the current interpretation of results.

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

Gender identity (if provided) is not used in the interpretation of results, and sex assigned at birth is used in the interpretation of results only when necessary. Currently, there are insufficient data to determine specific cancer risk adjustments for transgender, nonbinary, or intersex individuals.

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.
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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).
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8. Grantham R. Amino acid difference formula to help explain protein evolution. *Science.* 1974;185(4151):862-864.
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12. Feng BJ. PERCH: A Unified Framework for Disease Gene Prioritization. *Hum Mutat.* 2017 Mar;38(3):243-251.
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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 (FDA). 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 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. 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, this test is not intended to analyze the following types of alterations: gross rearrangements, deep intronic variations, mobile element insertions, and other unknown abnormalities. The pattern of mutation types varies by gene, and this test detects a high but variable percentage of known and unknown mutations 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 ~99.9% of described mutations in the genes represented on the test, listed above (analytical sensitivity). The clinical sensitivity of this test may vary widely according to the specific clinical and family history. Mutations in other genes or the regions not analyzed by this test can also give rise to similar clinical conditions. 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.

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Clinician Management Resource for *BRCA2*

This overview of clinical management guidelines is based on this patient's positive test result for a pathogenic or likely pathogenic variant in the *BRCA2* gene. 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.	Individualized	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
Consider options for risk reduction agents	Individualized	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Ovarian Cancer		
Consultation with gynecologic oncologist or gynecologist with expertise/experience in genetic susceptibility to gynecologic cancer is recommended	Individualized	Individualized
Consideration of combination estrogen/progestin contraception (such as oral contraceptive pills) to reduce risk for ovarian cancer	Individualized	Individualized
Recommend risk-reducing salpingo-oophorectomy (RRSO)^	35 to 40 years old. (reasonable to delay until 40 to 45 years old)	N/A
CA-125 and pelvic ultrasound are recommended for preoperative planning	Individualized	Individualized
Salpingectomy		
Salpingectomy is an option for premenopausal patients with hereditary cancer risk who are not yet ready for oophorectomy	Individualized	Individualized
Completion oophorectomy is recommended as per gene-specific guidelines, unless specified by clinical trial protocol	Individualized	Individualized
Consider continuation of combination oral contraceptive pills or hormonal IUD for continued ovarian cancer risk reduction while ovaries remain in place.	Individualized	Individualized
Hysterectomy		
Discuss the risks and benefits of concurrent hysterectomy at the time of RRSO prior to surgery	Individualized	Individualized
Individuals who undergo hysterectomy at the time of RRSO are candidates for estrogen-alone HRT	Individualized	Individualized

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
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		
Recommend prostate cancer screening with PSA	40 years old	Every 12 months
Screening may also include a baseline mpMRI, preferably on clinical trial^^	50 years old (or 10 years younger than the earliest prostate cancer diagnosis in the family)	N/A
Melanoma		
General risk management, such as annual full-body skin examination and minimizing UV exposure	Individualized	Annual, or at clinician's discretion
Pancreatic Cancer		
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)
Other		
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.

** Screening with clinical breast exam should continue after risk-reducing mastectomy. Routine screening with mammogram and breast MRI are not indicated.

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

^ See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer- Principles of Surgery. Ovarian cancer onset in patients with BRCA2 mutations is an average of 8-10 years later than in patients with BRCA1 mutations. Therefore, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40-45y in patients with BRCA2 mutations, unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. Individuals 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 prostate cancer screening with mpMRI, screening in experienced high-volume centers is recommended. It is recommended 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 abnormalities, and uncertainties about the potential benefits of prostate cancer screening with mpMRI.

^^^ 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, Pancreatic, and Prostate. v2.2026. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed October 14, 2025. 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.

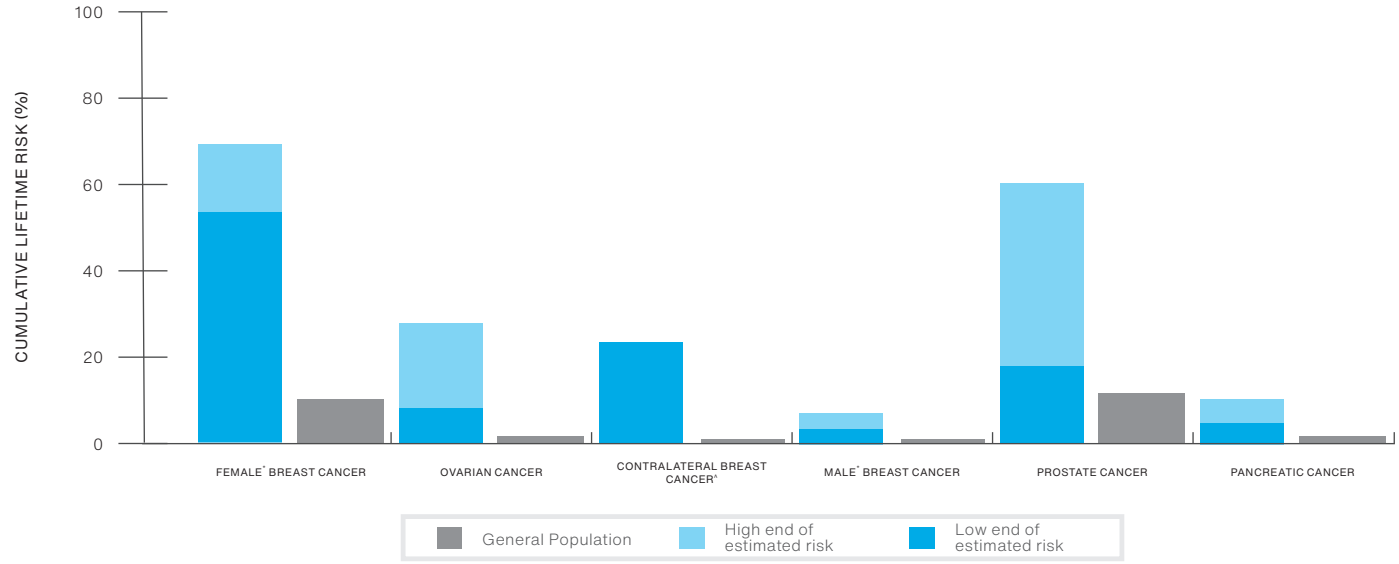
Understanding Your Positive *BRCA2* Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC OR LIKELY PATHOGENIC VARIANT

6 Things To Know

1	Result	Your testing shows that you have a pathogenic or likely pathogenic variant in the *BRCA2* gene.
2	*BRCA2*-related cancer predisposition	People with a pathogenic or likely pathogenic *BRCA2* variant have hereditary *BRCA2*-related cancer predisposition.
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 healthcare provider and decide on a plan that works for you.
5	Other medical concerns	Individuals with a pathogenic or likely pathogenic *BRCA2* variant may have an increased risk to have a child with Fanconi anemia, but only if their partner also carries a pathogenic or likely pathogenic variant in the *BRCA2* 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 pathogenic or likely pathogenic *BRCA2* 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.

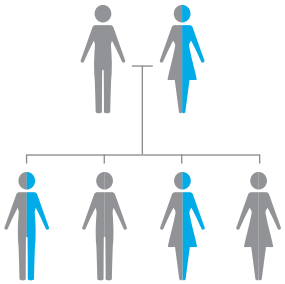
BRCA2 Cancer Risks**



* Refers to sex assigned at birth
** Refers to lifetime risk unless otherwise noted. Because risk estimates vary in different studies, only approximate risks are given. Cancer risks will differ based on individual and family history.
^ 20-year cumulative risk

BRCA2 in the Family

There is a 50/50 random chance to pass on the pathogenic or likely pathogenic *BRCA2* variant to each of your children.



Has a pathogenic or likely pathogenic *BRCA2* variant

No pathogenic or likely pathogenic *BRCA2* variant

RESOURCES

- American Cancer Society cancer.org
- 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
- 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 *BRCA2* 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.

1 Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 **ambrygen.com**

MKT-ONCO-FLYR-10023-EN v8 11.05.25

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.

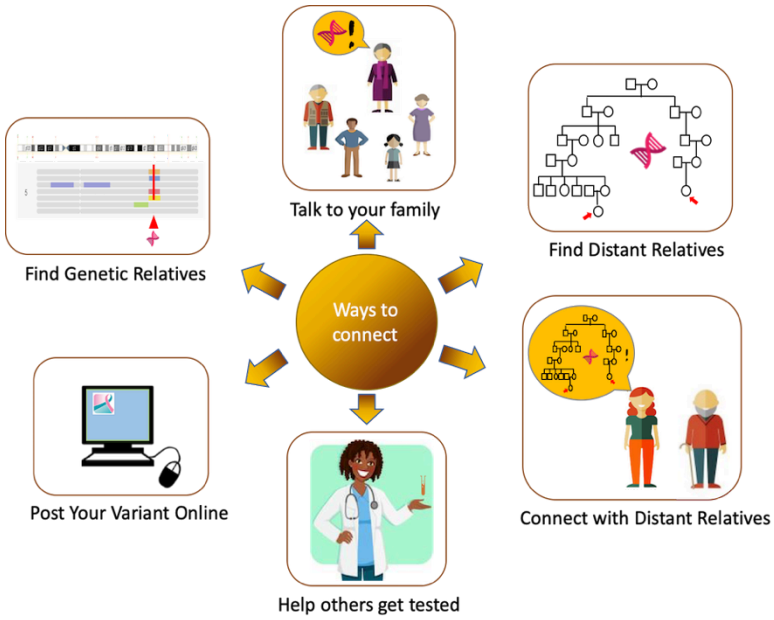
The ConnectMyVariant initiative seeks to help people like you:

- 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 preventive removal of the ovaries in women with a ***BRCA*** mutation was associated with a much lower risk of death from any cause.[1]
- found that breast MRIs for surveillance among women with a ***BRCA1*** mutation was associated with a much lower risk of death from breast cancer, compared to those who did not get breast MRIs.[2]

Get care updates personalized to you

As the National Comprehensive Cancer Network (NCCN) or other professional organizations update guidelines, we may alert you to share this information with your healthcare provider. This might include refining your cancer risks or finding additional ways to detect cancer early.

Be a part of other studies

to learn more about...

- risks and treatment outcomes among individuals with multiple cancer types and a mutation in high (***BRCA1***, ***BRCA2***, ***PALB2***) and moderate risk (***ATM***, ***CHEK2***, ***RAD51C***, ***RAD51D***) genes.
- breast cancers in women with ***BRCA1***, ***BRCA2***, ***PALB2***, ***ATM***, and ***CHEK2*** mutations through doing tumor genomic testing, to learn more about 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. 2024 Apr 1;10(4):484-492. PMID: 38421677;* [2] *Lubinski J, et al. 2024 Apr 1;10(4):493-499. PMID: 38421676.*

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

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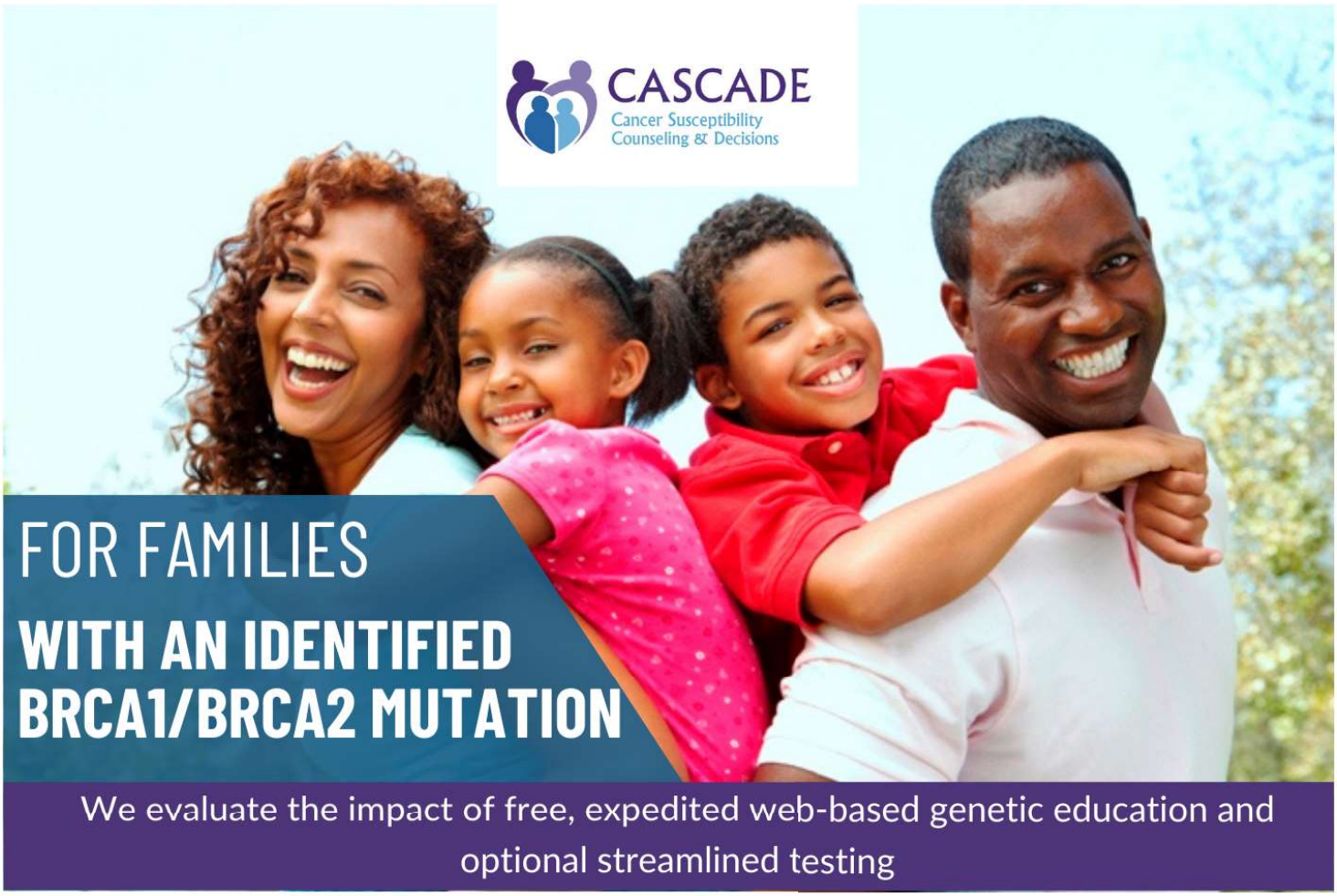
CASCADE
Cancer Susceptibility Counseling & Decisions



FOR FAMILIES
WITH AN IDENTIFIED BRCA1/BRCA2 MUTATION

We evaluate the impact of free, expedited web-based genetic education and optional streamlined testing

About CASCADE

Communicating with relatives about your BRCA mutation is key to ensuring that your family gets the information they need to make good decisions about their health. The "Cancer Susceptibility Counseling and Decisions" (CASCADE) study is a National Cancer Institute funded clinical study testing individualized web-based genetic education and optional genetic testing for your adult relatives.

CASCADE and You

- Our goal is to help individuals who are at risk of having a BRCA1/2 mutation. To do this, we need your help. We are asking you to put us in touch with your untested relatives so that we can send them print information about CASCADE.
- If your relatives choose to participate, they will be given access to either: an individually-tailored genetic education website or standard resources about BRCA1/2 testing. These resources will provide them with important cancer risk information.
- Even if your relatives are not interested in genetic information, we would still like them to complete our survey so we can understand why they are not interested.
- All participants will have the option to pursue genetic testing if they so choose. All information gathered during this study will remain completely confidential.
- To get started, go to **https://redcap.link/CASCADE** and complete our breif screener to confirm your eligibility.

The Jess and Mildred Fisher Center for Hereditary Cancer and Clinical Genomics Research

Georgetown University | Georgetown Lombardi Comprehensive Cancer Center
2115 Wisconsin Avenue, NW | Suite 300 | Washington, DC 20007
email: cascadestudy@georgetown.edu

NCI Comprehensive Cancer Center
A Cancer Center designated by the National Cancer Institute

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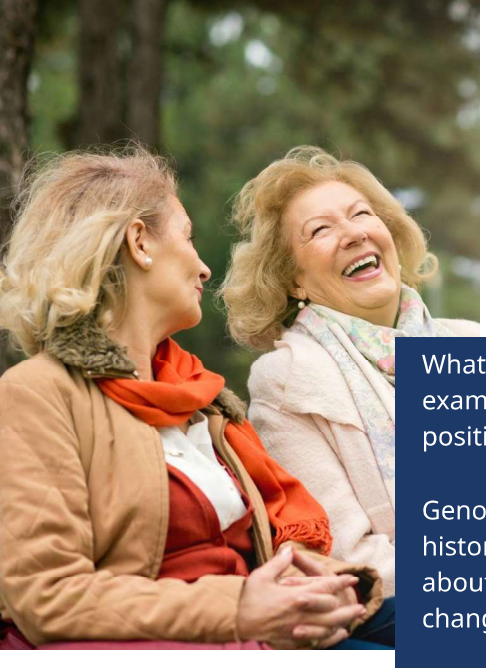
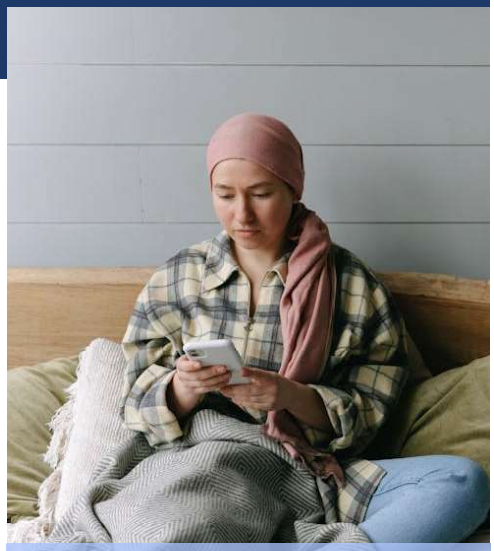


GenomeConnect
The ClinGen Patient Portal

What we know about genetic changes (also called variants) can change over time. For example, a result that is classified as uncertain (called a VUS) might later be changed to a positive or negative result.

GenomeConnect is a registry that helps you share your genetic test results and health history. Sharing your genetic changes and health history helps scientists learn more about genes and health and can help identify changes in variant classification over time.



Who can participate in GenomeConnect?

Anyone who has had genetic testing can join GenomeConnect. It doesn't matter what your results were—positive, negative, or uncertain (VUS). People with results in any gene can take part. GenomeConnect is available in English and Spanish.

Why join GenomeConnect?

Sometimes, when a lab finds a genetic change, they don't know what it means for health. These are called "uncertain" or "VUS" results. Even when a change is well understood, more information can help scientists learn more about the condition and how to treat it.

By joining GenomeConnect, you can securely share your genetic test results and health history with databases like ClinVar and with experts from ClinGen. ClinGen has a focus in cancer including through expert panels working to better understand genetic changes that increase cancer risk.

The more people who share their information, the more scientists can learn about how genes and genetic variants affect health and, ultimately, how best to care for patients.

By participating in GenomeConnect, you can:

- Share your information securely and safely.
- Help **increase our understanding of genetics and health** that might help you and other families.
- Have the option to **receive genetic result updates** from GenomeConnect. This can be particularly helpful for individuals with uncertain (VUS) results.
- Learn about other relevant **research opportunities.**
- **Connect with other participants** with similar results.

What are the steps to participate in GenomeConnect?

Participation is simple

- Sign up and consent www.genomeconnect.org
- Share a copy your genetic test results (no new sample needed)
- Fill out surveys to share your health history
- Update your information once a year

"It's just reassuring, really comforting to get updates and that I don't have to worry about it and just to know that the genetic industry or the genetic world, there is someone that we can rely on."

- GenomeConnect Participant discussing the option to receive genetic result updates

Learn More and Register:
www.genomeconnect.org

Questions:
info@genomeconnect.org

GenomeConnect is a project of the Clinical Genome Resource (ClinGen), an NIH funded research project.

ClinGen
Clinical Genome Resource

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