Ambry Genetics®

**SAMPLE REPORT**

| | | | | | |
|---|---|---|---|---|---|
| **Ordered By** | Contact ID:405949 | Org ID:8141 | Patient Name: | **Last, First** | |
| Medical Professional: | Last, First, CGC | | Accession #: | **00-332044** | Specimen #: test |
| Client: | MOCKORG44 (10829) | | AP2 Order #: | 205722 | Specimen: Blood EDTA (Purple top) |
| **Additional Authorized Recipient:** | | | Birthdate: | 01/01/1980 | Sex at Birth: F |
| Sample Genetic Counselor MS, CGC | | | MRN #: | 12345 | Collected: 02/22/2021 |
| | | | Indication: | Internal Testing | Received: 02/23/2021 |

# *CancerNext-Expanded® +RNAinsight®: Analyses of 77 Genes Associated with Hereditary Cancer*

## RESULTS

***RAD51D*** **Pathogenic Mutation: c.326dupC**

## SUMMARY

## POSITIVE: Pathogenic Mutation Detected

## INTERPRETATION

- This individual is heterozygous for the **c.326dupC (p.G110Rfs*2)** pathogenic mutation in the *RAD51D* gene.
- **Risk estimate**: approximately a 10-12% cumulative risk for ovarian cancer and an increased risk for female breast cancer.
- 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.

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No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (77 total): ***AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, CTNNA1, DICER1, FANCC, FH, FLCN, GALNT12, KIF1B, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** **and** ***XRCC2*** **(sequencing and deletion/duplication);** ***EGFR, EGLN1, HOXB13, KIT, MITF, PDGFRA, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only)**. RNA data is routinely analyzed for use in variant interpretation for all genes.

***RAD51D* Additional Information**

The **c.326dupC** pathogenic mutation, located in coding exon 4 of the *RAD51D* gene, results from a duplication of C at nucleotide position 326, causing a translational frameshift with a predicted alternate stop codon (p.G110Rfs*2). 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 RAD51 homolog D (*RAD51D*, OMIM: *602954, NM_002878.3) gene, located at 17q12, encodes the 328 amino acid RAD51D protein, which is critical for DNA damage repair via homologous recombination. Monoallelic pathogenic germline mutations in *RAD51D* confer a cumulative lifetime risk for ovarian cancer between 10-12% (Loveday C et al. *Nat Genet*. 2011 Aug 7;43(9):879-82; Osher D et al. *Br J Cancer.* 2012 Apr 10;106(8):1460-3; Song H, et al. *J. Clin. Oncol.* 2015 Sep;33(26):2901-7). In addition, *RAD51D* mutations are associated with an increased risk for prostate and female breast cancer (Couch FJ, et al. *J. Clin. Oncol.* 2015 Feb;33(4):304-11; Pritchard CC et al. *N. Engl. J. Med.* 2016 Aug;375(5):443-53).

**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® +RNAinsight® (Product Code 8874-R)

## ASSAY INFORMATION

**Methodology:** The **CancerNext-*Expanded*® +RNAinsight®** test is a comprehensive screen of 77 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. 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. For *BRCA2* and *MSH2*, the Portuguese founder mutation, c.156_157insAlu (also known as 384insAlu), and the coding exons 1-7 inversion, respectively, are detected by next generation sequencing and confirmed by multiplex ligation-dependent probe amplification (MLPA) or PCR and agarose gel electrophoresis. Gross deletion/duplication analysis for the genes sequenced (excluding *EGFR, EGLN1*, *HOXB13, KIT, MITF, PDGRFA, POLD1, POLE,* and *PMS2*) is performed using a custom pipeline based on read-depth from NGS data and/or targeted chromosomal microarray with confirmatory MLPA when applicable. Gross deletion/duplication analysis of *PMS2* is performed using MLPA kit P008-B1. If a deletion is detected in exons 13, 14, or 15 of *PMS2*, double stranded sequencing of the appropriate exon(s) of the pseudogene *PMS2CL* will be performed to determine if the deletion is located in the *PMS2* gene or pseudogene. All sequence analysis is based on the following NCBI reference sequences: *AXIN2*- NM_004655.3, *AIP*- NM_003977.2, *ALK*- NM_004304.4, *APC*- NM_000038.5 & NM_001127511.2, *ATM*- NM_000051.3, *BAP1*- NM_004656.2, *BARD1*- NM_000465.2, *BLM*- NM_000057.2, *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 and NM_058195.3 (p14ARF), *CHEK2*- NM_007194.3, *CTNNA1*- NM_001903.2, *DICER1*-NM_177438.2, *EGFR*- NM_005228.3, *EGLN1*- NM_022051.2, *FANCC*- NM_000136.2, *FH*- NM_000143.3, *FLCN*- NM_144997.5, *GALNT12*- NM_024642.4, *HOXB13*- NM_006361.5, *KIF1B*- NM_015074.3, *KIT*- NM_000222.2, *LZTR1*- NM_0006767.3, *MAX*- NM_002382.3, *MEN1*-NM_130799.2, *MET*- NM_000245.1, *MITF*- NM_000248.3, *MUTYH*- NM_001128425.1, *MLH1*- NM_000249.3, *MSH2*- NM_000251.1, *MSH3*- NM_002439.3, *MSH6*- NM_000179.2, *NBN*- NM_002485.4, *NF1*-NM_000267.3, *NF2*- NM_000268.3, *NTHL1*- NM_002528.5, *PALB2*- NM_024675.3, *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, *PTCH1*- NM_000264.3, *PTEN*- NM_000314.4, *RAD51C*- NM_058216.1, *RAD51D*- NM_002878.3, *RB1*- NM_000321.2, *RECQL*- NM_002907.3, *RET*- NM_020975.4, *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_002079.4, *STK11*- NM_000455.4, *SUFU*- NM_016169.3, *TMEM127*- NM_017849.3, *TP53*- NM_000546.4, *TSC1*- NM_000368.4, *TSC2*- NM_000548.3, *VHL*- NM_000551.3, *XRCC2*- NM_005431.1.

**Analytical Range:** The **CancerNext-*Expanded*® +RNAinsight®** test targets detection of DNA sequence mutations in 75 genes 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. For *HOXB13*, only variants impacting codon 84 are routinely reported. For *MITF*, only the status of the c.952G>A (p.E318K) alteration is analyzed and reported. For *EGFR*, only the status of the c.2369C>T (p.T790M) and c.2327G>A (p.R776H) alterations are analyzed and reported. For *EGLN1*, only missense variants in the catalytic domain (codons 188-418) are reported. For *RECQL*, only missense variants in the helicase and RCQ domains (codons 63-592) and exonic truncating variants 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. For *ALK*, only variants located within the kinase domain (c.3286-c.4149) are reported. For *PDGFRA,* only missense variants or in-frame insertion/deletions located in coding exons 9, 11, 13, and 17 are reported. For *KIT,* only missense variants or in-frame insertion/deletions located in coding exons 8, 9, 11, 13, and 17 are reported. The *MSH3* exon 1 repeat region and the *PHOX2B* polyalanine repeat region are excluded from analysis Gross deletion/duplication analysis determines gene copy number for the covered exons and untranslated regions for the sequenced genes (excluding *EGFR, EGLN1, HOXB13, KIT, MITF, PDGRFA, POLD1, POLE*) plus *EPCAM* and *GREM1*. 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 for 18 genes (*APC, ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, NF1, PALB2, PMS2* exons 1-10, *PTEN, RAD51C, RAD51D*, and *TP53*) and compared to a human reference pool. The absence or presence of RNA transcripts meeting quality thresholds are incorporated as evidence towards assessment and classification of DNA variants. Any regions not meeting RNA quality thresholds are excluded from analysis. Regions routinely excluded due to chronically low expression in human peripheral lymphocytes include: *BRCA2* (exon 1), *BRIP1* (exons 18, 20), *CDH1* (Exons 1, 2, 16), and *CHEK2* (exons 1, 7, 8).

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

- **Pathogenic Mutation**: alterations with sufficient evidence to classify as pathogenic (capable of causing disease). 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. 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. Intronic VUSs are always

reported out to 5 basepairs 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 on results reports. These include findings classified as “likely benign” and “benign” alterations.

*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.

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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.
9. HGMD® [Internet]: Stenson PD et al. *Genome Med.* 2009;1(1):13. www.hgmd.cf.ac.uk.
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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

**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 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, 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 77 genes represented on the test (analytical sensitivity). The clinical sensitivity of this test may vary widely according to the specific clinical and family history. Cancer is a complex clinical disorder. 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 *RAD51D*

This overview of clinical management guidelines is based on this patient's positive test result for a *RAD51D* 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 | AGE TO START | FREQUENCY |
|---|---|---|
| **Ovarian Cancer[1]** | | |
| Consider risk-reducing salpingo-oophorectomy | 45-50 years old (or earlier based on a specific family history of an earlier onset ovarian cancer) | N/A |
| **Breast Cancer** | | |
| Potential increase in female breast cancer risk (including triple negative disease) with insufficient evidence for risk management | N/A | N/A |


1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.2021. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed October 1, 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.
2. Pritchard CC, *et al*. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016 Aug 4; 375(5):443-53.




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# Understanding Your Positive *RAD51D* Genetic Test Result

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

## 4 Things To Know

| | | |
|---|---|---|
| 1 | *RAD51D* mutation | Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *RAD51D* gene. |
| 2 | Cancer risks | You have an increased chance to develop ovarian cancer, and possibly other cancers, such as female breast cancer. Cancer risk estimates for male *RAD51D* mutation carriers are not currently available. |
| 3 | What you can do | There are risk management options to detect cancer early or lower your risk to develop cancer. It is important to discuss these options with your doctor, and decide on a plan that best manages your cancer risks. |
| 4 | Family | Family members may also be at risk – they can be tested for the *RAD51D* mutation that was identified in you. |

## *RAD51D* Mutations in the Family

There is a 50/50 random chance to pass on an *RAD51D* mutation to your sons and daughters. The image to the right shows that both men and women can carry and pass on these mutations.

# Understanding Your Positive *RAD51D* Genetic Test Result

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

| | | |
|---|---|---|
| Result | **MUTATION** | Your testing shows that you have a pathogenic mutation (a disease-causing change in the gene, like a spelling mistake) or a variant that is likely pathogenic in the *RAD51D* gene. Both of these results should be considered positive. |
| Gene | ***RAD51D*** | Everyone has two copies of the *RAD51D* gene, which we randomly inherit from each of our parents. Mutations in one copy of the *RAD51D* gene can increase the chance for you to develop certain types of cancer in your lifetime. |
| Cancer Risks | **INCREASED** | You have an increased chance to develop ovarian cancer (10-12%, compared to 2% in the average woman), and female breast cancer. Men have an increased chance to develop prostate cancer. |
| Management Options | **FOR WOMEN** | Options for early detection and prevention of cancer for women may include: breast exam, mammogram, breast MRI, transvaginal ultrasound, a blood test called CA-125, preventive medications, and options for preventive surgery. Talk to your doctor about what options may be right for you. |
| Risk Management | **VARIES** | Risk management decisions are very personal, and the best option depends on many factors. Screening typically begins earlier than in the general population, and is often done more frequently. It is important to discuss these options with your doctor. |
| Family Members | **50/50 CHANCE** | Your close relatives (like your parents, brothers, sisters, children) have a 50/50 random chance of inheriting the *RAD51D* mutation that you carry, and other family members (like your aunts, uncles, cousins) may also inherit it. Your relatives can be tested for this same mutation. Depending on the family history, those who DO NOT have it may not have an increased chance (above the general population) to develop cancer. |
| Next Steps | **DISCUSS** | It is recommended that you share this information with family members so they can learn more and discuss this with their healthcare providers. |
| Reach Out | **RESOURCES** | • Ambry's hereditary cancer site for families patients.ambrygen.com/cancer<br>• FORCE facingourrisk.org<br>• Genetic Information Nondiscrimination Act (GINA) ginahelp.org<br>• National Society of Genetic Counselors nsgc.org<br>• Canadian Association 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 *RAD51D* 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 for Connections

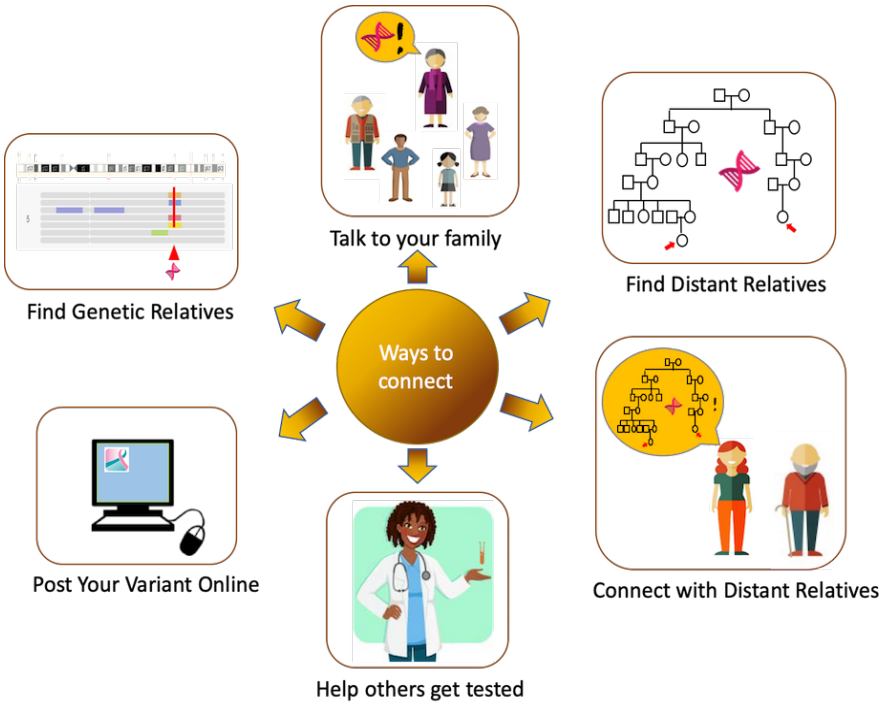
Receiving a positive genetic test for a cancer predisposition gene can feel like an isolating and confusing time for you and your family. Questions such as “Where did this variant come from?” or “What can I do to help others in my family?” are common. This is why the University of Washington has a public health initiative called ConnectMyVariant.

The ConnectMyVariant initiative seeks to help people talk to their relatives, share important genetic information, expand family trees, identify and connect with close and distant at-risk relatives, and help individuals guide others to get genetic testing.

### “Prevention Through Connection”

Almost all mutations (harmful genetic variants) happened for the first time with a single person in history. That person could be alive today or could have lived hundreds of years ago. Other people with your same genetic variant are probably related to you through the same ancestor. This means that your specific variant is a key to understanding your past. It is also a key that you can use to help many relatives prevent cancer before it happens.

Your close relatives may have your variant and you can talk to them about their possible genetic risk now. Your distant relatives could also share your same genetic variant and may not know about it. These relatives may have had similar experiences with their health and the disease, the same experiences with doctors, and have had to face the same life-planning decisions. Reaching out and helping at-risk relatives get genetic testing may help them prevent cancer and save lives.




Learn more about this public health initiative:
email: connectmyvariant@uw.edu phone: 206-598-2101 website: www.connectmyvariant.org