Ambry Genetics®

SAMPLE REPORT

Ordered By	Contact ID:5075949	Org ID:8141	Patient Legal Name:	**Unknown, Unknown**	
Medical Professional:	Unknown, Unknown, MD		Accession #:	**00-230828**	Specimen #:
Client:	MOCKORG44 (10829)		AP2 Order #:	2609137	Specimen: Blood EDTA (Purple top)
			Birthdate:	09/09/1990	Sex assigned at birth: U
			MRN #:	N/A	Collected: 08/21/2024
			Indication:	Family history	Received: 08/23/2024
					Test Started: 08/23/2024

CancerNext-Expanded® +RNAinsight®: Analyses of Genes Associated with Hereditary Cancer (90 genes)

RESULTS

FH **Pathogenic Mutation: p.R343***

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.R343* (c.1027C>T)** pathogenic mutation in the *FH* gene.
- This result is consistent with a diagnosis of hereditary leiomyomatosis and renal cell cancer (HLRCC).
- **Risk estimate**: lifetime risk of up to 20% for renal cell carcinoma (RCC).
- 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 (90 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CFTR, CHEK2, DICER1, ETV6, FH, FLCN, GATA2, KIF1B, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** **and** ***WT1*** **(sequencing and deletion/duplication); *ATRIP, AXIN2, CPA1, CTNNA1, CTRC, DDX41, EGFR, EGLN1, HOXB13, KIT, MBD4, MITF, MLH3, MSH3, PALLD, PDGFRA, POLD1, POLE, PRSS1, RAD51B, RNF43, RPS20, SPINK1*** **and** ***TERT*** **(sequencing only); *EPCAM*** **and** ***GREM1*** **(deletion/duplication only)**. RNA data is routinely analyzed for use in variant interpretation for all genes.

FH **Additional Information**

The **p.R343*** pathogenic mutation (also known as c.1027C>T), located in coding exon 7 of the *FH* gene, results from a C to T substitution at nucleotide position 1027. This changes the amino acid from an arginine to a stop codon within coding exon 7. This mutation was first reported in a hereditary leiomyomatosis and renal cell carcinoma (HLRCC) kindred with cutaneous and uterine leiomyomata and type II papillary renal cell cancer (RCC) (Tomlinson IP et al. *Nat Genet.* 2002 Apr;30(4):406-10). This mutation has also been reported in individuals with multiple leiomyomata but no personal history of RCC (Kiuru M et al. *Cancer Res.* 2002 Aug;62(16):4554-7; Gardie B et al. *J. Med. Genet.* 2011 Apr;48(4):226-34; Venables Z et al. *Clin. Exp. Dermatol.* 2015 Jan;40(1):99-100). Of note, this alteration is also designated as c.898C>T and p.Arg300X 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 *FH* gene (NM_000143.3) is located on chromosome 1q42.1, encodes the fumarate hydratase mitochondrial protein, and contains 10 coding exons. Pathogenic variants in this gene have been detected in individuals diagnosed with hereditary leiomyomatosis and renal cell cancer (HLRCC), which is inherited in an autosomal dominant fashion, and fumarate hydratase deficiency (FHD), which is inherited in an autosomal recessive fashion. HLRCC is characterized by an increased risk of developing cutaneous and uterine leiomyomas (fibroids) as well as renal

tumors. The majority of individuals with HLRCC develop cutaneous leiomyomata, and most females develop uterine leiomyomata, with penetrance estimates ranging from 50-90% (Toro J et al. *Am. J. Hum. Genet.* 2003. Jul;73(1):95-106; Muller M et al. *Clin Genet*. 2017 Dec;92(6):606-615; Forde C et al. *Eur Urol Oncol*. 2020 Dec;3(6):764-772; Bhola P et al. *Fam Cancer.* 2018 Oct;17(4):615-620). The lifetime risk for renal cell cancer with HLRCC is up to 20%, with a median age of diagnosis in the fourth decade of life. HLRCC-associated renal tumors are typically classified as type 2 papillary cancers and have an aggressive disease course (Gardie B et al. *J. Med. Genet*. 2011 Apr;48(4):226-34; Forde C et al.). In addition, specific pathogenic alterations in this gene have been reported in individuals with pheochromocytomas and/or paragangliomas (Fuchs T et al. *Am J Surg Pathol* 2023 Jan; 47(1): 25–36; Clark G et al. *J. Clin. Endocrinol. Metab*. 2014 Oct;99(10):E2046-50; Castro-Vega L et al. *Hum. Mol. Genet*. 2014 May;23(9):2440-6); however, these tumors are reported less frequently in HLRCC cohorts, and data is currently insufficient to determine cumulative lifetime risks (Forde et al.). FHD is characterized by early-onset hypotonia, severe global developmental delay, and cerebral underdevelopment which may be described on neuroimaging as white matter volume loss, cerebral atrophy and/or ventriculomegaly. Other features seen in a minority of patients include premature birth, poor feeding, failure to thrive, seizures, cortical visual impairment, microcephaly, polymicrogyria, open sylvian operculum, and dysmorphic facial features including frontal bossing, depressed nasal bridge, and widely spaced eyes. Biochemical findings include increased urine fumaric acid and reduced fumarate hydratase enzyme activity in fibroblasts or leukocytes (Allegri G, et al. (2010) J *Inherit Metab Dis* 33(4):411-9; Kerrigan JF et al. *Ann. Neurol*. 2000 May;47(5):583-8; Ottolenghi C et al. *Hum Mutat*. 2011 Sep;32(9):1046-52). Some pathogenic alterations reported in association with FHD have not been shown to confer risk for HLRCC-associated tumors in the heterozygous state (Kamihara J et al. *JCO Precis Oncol* 2021;5(0):1568-1578; Zhang L et al. *Hum Mutat*. 2020 January; 41(1):103–109). Loss of function has been reported as the mechanism of disease for both HLRCC and FHD.

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 8875-R)

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 with confirmatory MLPA and/or targeted chromosomal microarray. Mobile element insertions, if detected, are confirmed by PCR and Sanger sequencing and/or gel electrophoresis.

Ribonucleic acid (RNA) is 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 is carried out by a bait-capture methodology using long biotinylated oligonucleotide probes followed by polymerase chain reaction (PCR) and Next-Generation sequencing (NGS). 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 region not meeting RNA quality thresholds, including regions with chronically low expression in human peripheral lymphocytes, are excluded from analysis.

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 encompassing the 3' end of the gene are reported.
- ***GREM1***: only the status of the 40kb 5'UTR gross duplication is 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, RPS20, 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 Mutation**: 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 mutation carriers recommended. Previously described pathogenic mutations, including intronic mutations 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, Unknown 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.

RNA transcripts derived from genes with limited gene-disease validity or with an inconsistent mechanism of disease do not routinely contribute to variant interpretation.

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 frequently used in variant analysis and classification for observed genetic alterations.

1. ACMG Standards and guidelines for the interpretation of sequence variants. *Genet Med.* 2015 May;17(5):405-23.
2. Ambry Genetics Variant Classification Scheme. http://www.ambrygen.com/variant-classification.
3. Grantham R. Amino acid difference formula to help explain protein evolution. *Science.* 1974;185(4151):862-864. PMID: 4843792.
4. Stenson PD et al. The Human Gene Mutation Database: 2008 update. *Genome Med.* 2009 Jan 22;1(1):13. doi: 10.1186/gm13. PMID: 19348700; PMCID: PMC2651586.
5. 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.
6. Feng BJ. PERCH: A Unified Framework for Disease Gene Prioritization. *Hum Mutat.* 2017 Mar;38(3):243-251. PMID: 27995669.
7. Genome Aggregation Database (gnomAD) [Internet], Cambridge, MA. Available from: http://gnomad.broadinstitute.org.
8. Tavtigian SV et al. Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. *Genet Med.* 2018 Sep;20(9):1054-1060. PubMed PMID: 29300386
9. Karczewski KJ et al. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*. 2020 May;581(7809):434-443. PMID: 32461654.
10. Collins RL et al. A structural variation reference for medical and population genetics. *Nature*. 2020 May;581(7809):444-451. PMID: 32461652.
11. Jaganathan K et al. Predicting Splicing from Primary Sequence with Deep Learning. *Cell.* 2019 Jan 24; 176(3):535-548.e24. PMID: 30661751.
12. Tavtigian SV et al. Fitting a naturally scaled point system to the ACMG/AMP variant classification guidelines. *Hum Mutat.* 2020 Oct;41(10):1734-1737. PMID:32720330.
13. Pejaver et al. Calibration of computational tools for missense variant pathogenicity classification and ClinGen recommendation for PP3/BP4 criteria. *Am J Hum Genet.* 2022 Dec 1;109(12):2163-2177. PMID:36413997.
14. Walker LC et al. Using the ACMG/AMP framework to capture evidence related to predicted and observed impact on splicing: Recommendations from the ClinGen SVI Splicing Subgroup. *Am J Hum Genet.* 2023. PMID: 37352859.
15. Whiffin N et al. Using high-resolution variant frequencies to empower clinical genome interpretation. *Genet Med.* 2017 Oct;19(10):1151-1158. PMID: 28518168.

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.

Ambry Genetics®

Clinician Management Resource for *FH*

This overview of clinical management guidelines is based on this patient's positive test result for *FH* gene mutation. Unless otherwise stated, medical management guidelines used here are limited to those published in GeneReviews[1]. Please consult the referenced website link 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 decision 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.

SURVEILLANCE CONSIDERATIONS[1,^]	AGE TO START	FREQUENCY
Cutaneous leiomyoma		
Detailed skin exam by dermatologist to evaluate extent of disease and presence of atypical lesions and to discuss treatment options, if necessary.	At diagnosis	Annually to every 2 years
Uterine leiomyoma		
Gynecology consult to assess the severity of fibroids and to discuss treatment options, if necessary.	Beginning at age 20 years, or earlier if symptomatic	Annually
Renal tumors		
MRI with contrast with 1-3mm slices through kidney. Abdominal CT scan with contrast may also be performed, although MRI is preferred.	Beginning at age 8 years	Annually
Suspicious lesions (indeterminate lesion, questionable or complex cysts) should have prompt follow up. Renal tumors should be evaluated by a urologic oncology surgeon familiar with *FH* tumor predisposition syndrome to discuss treatment options.	Individualized	Individualized
Pheochromocytoma/paraganglioma		
Baseline blood pressure	At diagnosis	Individualized*
For genotypes associated with paraganglioma or patients with a personal or family history of paraganglioma, consider baseline MRI from skull base through pelvis and fractionated plasma metanephrines.	Individualized	Individualized
Counseling		
Genetic counseling by a genetic counselor, cancer genetics program, and/or a clinical geneticist.	At diagnosis	Individualized

^ Regular surveillance with an emphasis on early detection of renal cell carcinoma by clinicians familiar with the clinical manifestations of *FH* tumor predisposition syndrome is recommended. Surveillance may also be considered for individuals with a suspected diagnosis in whom an *FH* pathogenic variant has not been identified, as well as for at-risk family members who have not undergone molecular genetic testing.

* No uniform guidelines currently exist.

1. Kamihara J, et al. 2006 Jul 31 [Updated 2020 Aug 13]. In: GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. https://www.ncbi.nlm.nih.gov/books/NBK1252/

Ambry Genetics®

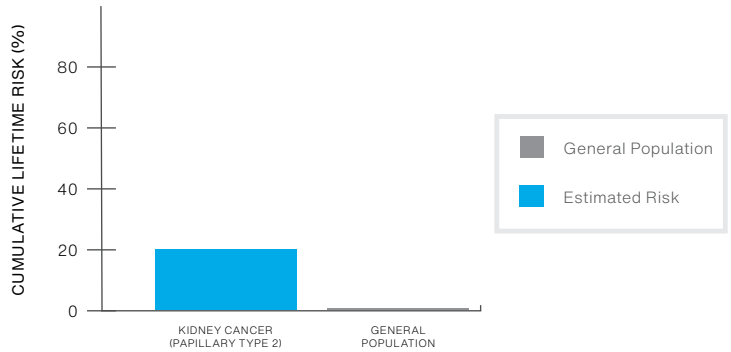
Understanding Your Positive *FH* Genetic Test Result

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

7 Things to know

1	*FH* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *FH* gene.
2	Hereditary leiomyomatosis and renal cell cancer	People with one *FH* mutation have hereditary leiomyomatosis and renal cell cancer (HLRCC).
3	Cancer risks	You have an increased chance to develop kidney (renal cell) cancer.
4	Tumor risks	▪ **For women:** Women with *FH* mutations have a higher chance to develop multiple uterine leiomyomas (uterine fibroids), which usually occur at a younger age compared to the general population. ▪ **For men and women:** Many people with *FH* mutations develop skin leiomyomas, which appear as skin-colored or light brown bumps. ▪ You may also have a slightly increased risk to develop paragangliomas or pheochromocytomas, which are rare tumors that affect the endocrine system (the body system that makes and controls hormones).
5	Other medical concerns	Individuals with *FH* mutations may have an increased risk to have a child with fumarate hydratase deficiency (FHD), but only if their partner also carries a mutation in the *FH* gene. FHD is a rare, severe condition of infancy that can cause abnormal brain development, weak muscle tone, and seizures.
6	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.
7	Family	Family members may also be at risk – they can be tested for the *FH* mutation that was found 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.

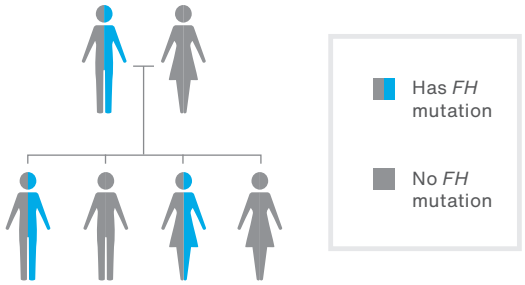
FH Mutation Lifetime Cancer Risks (%)*



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

FH Mutations in the Family

There is a 50/50 random chance to pass on an *FH* 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.



Reach Out

RESOURCES

- HLRCC Family Alliance hlrccinfo.org
- National Society of Genetic Counselors nsgc.org
- 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 *FH* 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.

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

MKT-ONCO-FLYR-20097-EN v4 05.10.24

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.

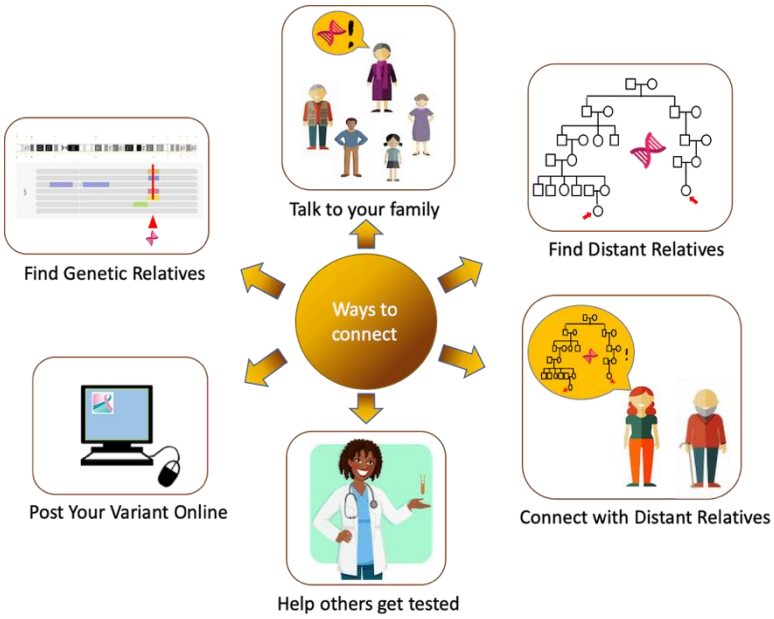
The ConnectMyVariant initiative seeks to help people like you:

- 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