Ambry Genetics®

SAMPLE REPORT

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

Patient Name:	**Unknown, Unknown**		
Accession #:	**00-060386**	Specimen #:	
AP2 Order #:	638361	Specimen:	Blood EDTA (Purple top)
Birthdate:	01/01/1976	Sex at Birth:	F
MRN #:	N/A	Collected:	N/A
Indication:	Family history	Received:	02/04/2019
		Test Started:	10/12/2023

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

RESULTS

MSH2 **Pathogenic Mutation: p.Y769***

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.Y769* (c.2307C>G)** pathogenic mutation in the *MSH2* gene.
- This result is consistent with a diagnosis of Lynch syndrome (also known as hereditary non-polyposis colorectal cancer or HNPCC).
- **Risk estimate**: lifetime risks of 33-52% for colorectal cancer, 21-57% for endometrial cancer, 8-38% for ovarian cancer, and increased lifetime risks for gastric, small bowel, and renal/bladder (urothelial) cancers; risks may be increased for brain or prostate cancers.
- 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 (77 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, DICER1, FANCC, FH, FLCN, GALNT12, KIF1B, LZTR1, MAX, MEN1, MET, MLH1, MSH2, 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);** ***AXIN2, CTNNA1, EGFR, EGLN1, HOXB13, KIT, MITF, MSH3, 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.

MSH2 **Additional Information**

The **p.Y769*** pathogenic mutation (also known as c.2307C>G), located in coding exon 14 of the *MSH2* gene, results from a C to G substitution at nucleotide position 2307. This changes the amino acid from a tyrosine to a stop codon within coding exon 14. This variant is considered to be rare based on population cohorts in the Genome Aggregation Database (gnomAD). 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 *MSH2* gene (NM_000251.1) is located on chromosome 2p21, encodes the DNA mismatch repair protein Msh2, and contains 16 coding exons. Pathogenic variants in this gene are known to cause Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer or HNPCC), which is inherited in an autosomal dominant fashion. Pathogenic variants in *MSH2* confer a significantly increased risk for colon cancer (33-52% cumulative lifetime risk), endometrial cancer (21-57% cumulative lifetime risk in females), gastric cancer (0.2-9% cumulative lifetime risk), ovarian cancer (8-38% cumulative lifetime risk in females), renal/bladder (urothelial) cancers, and cancer of the pancreas and biliary tract. Risks for cancers of the sebaceous glands (a variant of Lynch syndrome also known as Muir Torre syndrome) and central nervous system may also be elevated in individuals with an *MSH2* pathogenic variant compared to the general population (Bonadona V et al. *JAMA*. 2011 Jun;305:2304-10; Møller P et al. *Gut*. 2018 07;67:1306-1316; Møller P et al. *Gut*. 2017 03;66:464-472; Engel C et al. *J Clin Oncol*. 2012

Dec;30:4409-15; Dominguez-Valentin M et al. *Genet Med.* 2020 01;22:15-25; Wang C et al. *JNCI Cancer Spectr.* 2020 Apr 23;4(5):pkaa027; Dowty J et al. *Hum Mutat.* 2013 Mar;34(3):490-7). Some studies have estimated that mutations in mismatch repair (MMR) genes may be related to an approximately 2-fold increase in prostate cancer risk; however, new data suggests that this risk may be attributed primarily to mutations in *MSH2*, and that this risk may be less significant for other MMR genes (Ryan S et al. *Cancer Epidemiol. Biomarkers Prev.* 2014 Mar;23(3):437-49; Dominguez-Valentin, 2020). Penetrance in Lynch syndrome due to *MSH2* pathogenic variants is incomplete, and variable expressivity is observed; therefore, specific cancer risks will differ based on individual and family history. Biallelic pathogenic variants in this gene are known to cause constitutional mismatch repair deficiency (CMMR-D) syndrome, which is inherited in an autosomal recessive fashion. CMMR-D is characterized by café au lait macules and an increased risk for hematologic malignancies, brain tumors, and early-onset Lynch syndrome-associated cancers (Aronson M et al. *J Med Genet.* 2022 Apr;59(4):318-327). Individuals of reproductive age are at 25% risk of having a child with CMMR-D with each pregnancy when both biological parents have a pathogenic variant in *MSH2*. Loss of function has been reported as the mechanism of disease for Lynch syndrome and CMMR-D.

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 *AXIN2, CTNNA1, EGFR, EGLN1*, *HOXB13, KIT, MITF, MSH3, 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. Unless explicitly stated, sequence and copy number variants in the promoter, non-coding exons or 3' untranslated regions are not routinely reported. For *HOXB13*, only variants impacting codon 84 are routinely reported. For *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 *AXIN2, CTNNA1, EGFR, EGLN1, HOXB13, KIT, MITF, MSH3, PDGRFA, POLD1,* and *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 and compared to a human reference pool. The presence of RNA transcripts meeting quality thresholds is incorporated as evidence for the assessment and classification of DNA variants. Any regions not meeting RNA quality thresholds, including regions with chronically low expression in human peripheral lymphocytes, are excluded from analysis. RNA transcripts derived from genes with limited gene-disease validity or with an inconsistent mechanism of disease do not routinely contribute to variant interpretation.

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

- **Pathogenic Mutation**: alterations with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk relatives and appropriate changes in medical management for pathogenic mutation carriers recommended. Previously described pathogenic mutations, including intronic mutations at any position, are always reported when detected.
- **Variant, Likely Pathogenic (VLP)**: alterations with strong evidence in favor of pathogenicity. Targeted testing of at-risk relatives and

appropriate changes in medical management for VLP carriers typically recommended. Previously described likely pathogenic variants, including intronic VLPs at any position, are always reported when detected.

- **Variant, Unknown Significance (VUS)**: alterations with limited and/or conflicting evidence regarding pathogenicity. Familial testing via the Family Studies Program may be recommended. Medical management to be based on personal/family clinical histories, not VUS carrier status. Note, intronic VUSs are always reported out to 5 base pairs from the splice junction when detected.

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

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

Assay Information Continued on Next Page

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

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

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

Disclaimer: This test was developed and its performance characteristics were determined by Ambry Genetics Corporation. It has not been cleared or approved by the US Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. It should not be regarded as investigational or for research. This test should be interpreted in context with other clinical findings. This 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 *MSH2* (Lynch syndrome)

This overview of clinical management guidelines is based on this patient's positive test result for a MSH2 gene mutation. Unless otherwise stated, medical management guidelines used here are limited to those issued by the National Comprehensive Cancer Network® (NCCN®)[1] in the U.S. Please consult the referenced guideline for complete details and further information.

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

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Colorectal Cancer		
Colonoscopy	20-25 years old (or 2-5 years prior to the earliest colorectal cancer in the family, if it is diagnosed before 25 years)	Every 1-2 years^
Consider daily aspirin to reduce future risk of colorectal cancer, including a discussion of risks and benefits.	Individualized	N/A
Endometrial Cancer		
Consider option of risk-reducing hysterectomy	Individualized	N/A
Encourage prompt response to symptoms (e.g. abnormal uterine bleeding, postmenopausal bleeding)	Individualized	Individualized
Consider screening via endometrial biopsy. Routine endometrial cancer screening does not have proven benefit.	30-35 years old	Every 1-2 years
Transvaginal ultrasound may be considered in post menopausal women.^^	Clinician's discretion	Clinician's discretion
Consider risk reduction agents, including a discussion of risks and benefits.	Individualized	Individualized
Ovarian Cancer		
Bilateral salpingo-oophorectomy (BSO) for women who have completed childbearing	Individualized	N/A
Educate women on the symptoms associated with ovarian cancer (e.g. pelvic/abdominal pain, bloating, difficulty eating, increased abdominal girth, etc.).	Individualized	Individualized
Transvaginal ultrasound and serum CA-125 may be considered. Data do not support routine ovarian screening.	Clinician's discretion	Clinician's discretion
Consider risk reduction agents, including a discussion of risks and benefits.	Individualized	Individualized
Urothelial Cancer		
Selected individuals such as with a family history of urothelial cancer or individuals with *MSH2* mutations (especially males) may consider urinalysis. There is insufficient evidence to recommend a particular surveillance strategy.	30-35 years old	Every 12 months
Gastric and Small Bowel Cancer		
Upper GI surveillance with EGD, preferably in conjunction with colonoscopy. Random biopsy of the proximal and distal stomach should at a minimum be performed on the initial procedure to assess for *H. pylori*, autoimmune gastritis, and intestinal metaplasia.	30-40 years old or earlier based on family history or high risk findings	Every 2-4 years or more frequently based on family history or high-risk findings
Individuals not undergoing endoscopic surveillance should have one-time noninvasive testing for *H. pylori* at time of Lynch syndrome diagnosis.	Individualized	N/A
Treatment for *H. pylori* if detected.	Individualized	N/A

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Pancreatic Cancer*		
For individuals with exocrine pancreatic cancer in >1 first- or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening.*	50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier)	Every 12 months (with consideration of shorter intervals if worrisome abnormalities seen on screening)
Prostate Cancer		
It is reasonable for men with Lynch syndrome to consider beginning shared decision-making about prostate cancer screening.	40 years old	Consider screening at annual intervals rather than every other year.
Breast Cancer		
Not enough evidence to support increased screening above average-risk screening recommendations or based on personal and/or family history.	Clinician's discretion	Clinician's discretion
Brain Cancer		
Patients should be educated regarding signs and symptoms of neurologic cancer and the importance of prompt reporting of abnormal symptoms to their physicians.	Individualized	Individualized
Skin Manifestations		
Consider skin exam with a health care provider skilled in identifying Lynch syndrome-associated skin manifestations.	Individualized	Every 1-2 years
Reproductive Options		
For patients of reproductive age, counsel about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic testing.	Individualized	N/A
If both parents are carriers of a pathogenic/likely pathogenic variant in *MSH2*, counsel for risk of a rare autosomal recessive condition called constitutional mismatch repair deficiency (CMMRD).	Individualized	N/A
Risk to Relatives		
Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management. Recommend genetic counseling and consideration of genetic testing for at-risk relatives.	Individualized	N/A

^ Individuals who may benefit from a shorter screening interval (ie, 1-year vs 2-year) include those with risk factors such as a history of colorectal cancer or adenoma, male sex, *MSH2* pathogenic variant, and age over 40 years.

^^ Transvaginal ultrasound is not highly sensitive or specific for endometrial cancer screening.

* For individuals considering pancreatic cancer screening, the guideline recommends that screening be performed in experienced high-volume centers. The guideline 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 intermediate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening. The guideline recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. The guideline emphasizes that 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: Colorectal. V2.2022.

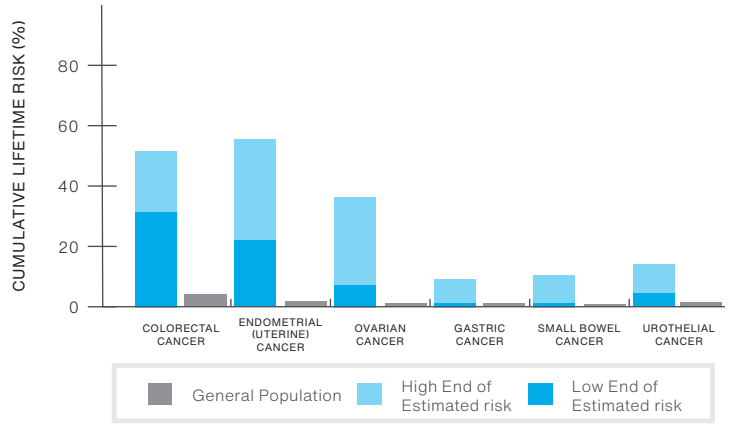
Understanding Your Positive *MSH2* Genetic Test Result

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

6 Things To Know

1	*MSH2* mutation	Your testing shows that you have a pathogenic mutation or a variant that is likely pathogenic in the *MSH2* gene.
2	Lynch syndrome	People with *MSH2* mutations have Lynch syndrome, previously known as hereditary non-polyposis colorectal cancer (HNPCC).
3	Cancer risks	You have an increased chance to develop colorectal, endometrial/uterine, stomach, ovarian, small bowel, and other types of cancer.
4	What you can do	Risk management decisions are very personal. There are options to detect cancer early or lower the risk to develop cancer. It is important to discuss these options with your doctor and decide on a plan that works for you.
5	Other Medical Concerns	Individuals with *MSH2* mutations may have an increased risk to have a child with constitutional mismatch repair deficiency (CMMRD), but only if their partner also carries a mutation in the *MSH2* gene. CMMRD is a multisystem disorder characterized by specific physical features and an increased risk for hematologic malignancies, brain tumors, and early-onset Lynch syndrome-associated cancers.
6	Family	Family members may also be at risk – they can be tested for the *MSH2* mutation that was identified in you. It is recommended that you share this information with family members so they can learn more and discuss this with their healthcare providers.

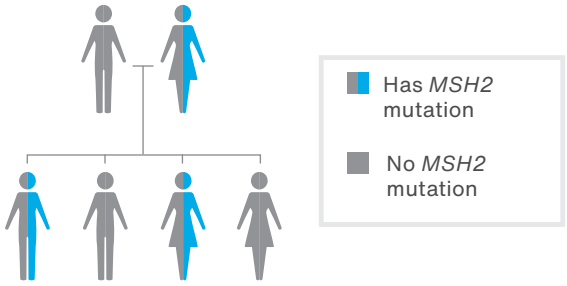
MSH2 Mutation Lifetime Cancer Risks (%)*



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

MSH2 Mutations in the Family

There is a 50/50 random chance to pass on a *MSH2* mutation to your sons and daughters. The image below shows that both men and women can carry and pass on these mutations.



Reach Out

RESOURCES

- Ambry's hereditary cancer site for families patients.ambrygen.com/cancer
- Hereditary Colon Cancer Foundation hcctakesguts.org
- I Have Lynch Syndrome ihavelynchsyndrome.com
- Lynch Syndrome International lynchcancers.com
- Genetic Information Nondiscrimination Act (GINA) ginahelp.org
- National Society of Genetic Counselors nsgc.org
- Canadian Association of Genetic Counsellors cagc-accg.ca
- AliveAndKickn (Patient Advocacy Group) aliveandkickn.org

Please discuss this information with your healthcare provider. The cancer genetics field is continuously evolving, so updates related to your *MSH2* result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or interpreted as medical advice.

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PROMPT

Prospective Registry Of MultiPlex Testing

Opportunity to Enroll in Hereditary Cancer Research

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

How can I find a research registry?

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

What is involved in participation?

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

How do I enroll?

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

Thank you again for considering taking part in PROMPT!

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

Opportunity to connect and help prevent cancer in your family

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

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

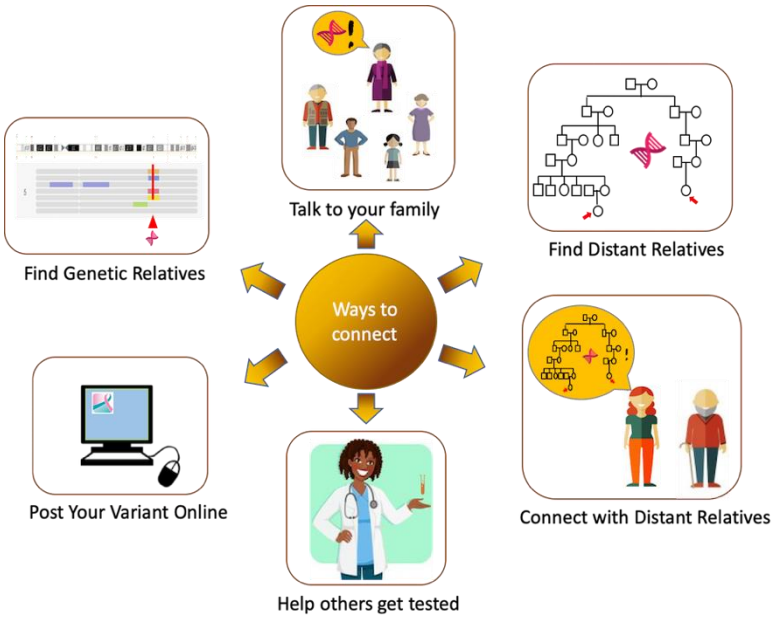
The ConnectMyVariant initiative seeks to help people like you:

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

“Prevention Through Connection”

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

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



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