Patient Name: SMITH, Jane	Sample Type: blood
DOB: 01/01/1980	Collection date: 01/01/2025
Sex: F	Accession date: 01/13/2025
Patient ID: 123456789	Report date: 02/13/2025

Ordered by: Dr. John White
Organization: Community Health Clinic
Other recipients: Dr. Jane Black
Billing code: P12345

Tests performed: WGS Hereditary Cancer Complete (80 Gene) + ACMG Secondary Findings

Result: variant of uncertain significance identified

Gene Name	Transcript	Variant	Zygosity	Variant Classification
MLH1	NM_000249.4	c.59C>T / p.A20V	heterozygous	uncertain significance

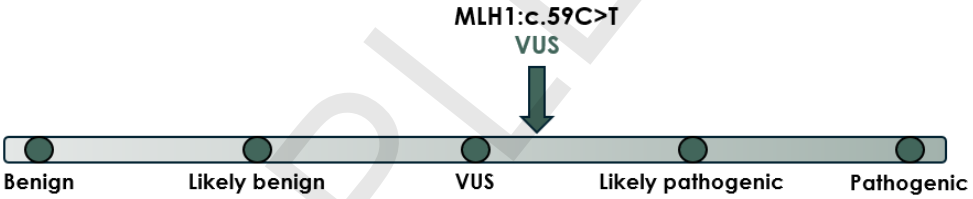
No other reportable variants were identified in the genes analyzed for this individual (80 gene hereditary cancer panel + ACMG secondary finding genes). See assay details for list of genes analyzed.

Summary of Results

Clinical Interpretation

- This result reduces the likelihood that this individual has a hereditary cancer predisposition.
- In the absence of an identifiable pathogenic variant, cancer screening and risk management should be based on individual risk factors and family history.

Variant Information



- The MLH1 c.59C>T variant (p.Ala20Val) is a missense substitution in exon 1, replacing alanine with valine at a highly conserved residue (PM1, physiochemically conservative). This variant is rare or absent in population databases (PM2) and is predicted to be deleterious by computational evidence (PP3). However, the clinical significance remains uncertain due to insufficient functional or segregation data. ACMG criteria (PM1, PM2, PP3) classify this variant as a variant of uncertain significance (VUS) for Lynch syndrome per current guidelines.

MLH1 Gene Information

- *MLH1* is a tumour suppressor gene. Pathogenic variants in *MLH1* are associated with autosomal dominant Lynch syndrome[1].
- See OMIM entry 120436* for more information on this gene.

** https://www.omim.org/entry/120436*

Patient Information

What does this result mean?

We did not identify any harmful genetic changes in you. **Your risk of hereditary cancer is low.**

- If you have a personal history of cancer, it is unlikely to have been caused by an inherited change in any of the genes analyzed by this test.
- We identified a "variant of uncertain significance" (VUS) in you. A VUS is a genetic change that we do not have enough information about to classify as either harmless (benign) or harmful (pathogenic). A VUS may be reclassified as either benign or pathogenic in the future, however most VUS are reclassified as benign
- It is important to know if your VUS is reclassified as pathogenic as it may impact your cancer risks and risk management options. See "What can I do next?" below for information on how to be notified about changes to your VUS classification.

What are my cancer risks?

- Your risk for cancer will depend on individual risk factors such as your sex, age, medical history, and family history.
- Every woman in British Columbia should have screening for breast cancer, colon cancer, and cervical cancer. People with a history of cigarette smoking may also qualify for lung cancer screening.
- As families share both genetic and environmental risk factors, people with a family history of a particular cancer may have a risk for the same type of cancer.

What can I do next?

Talk to your medical provider about the information contained in your genetic test report to make an individualized plan for your care.

- **Your doctor can help coordinate your cancer screening based on your medical history and family history.**
- Depending on your family history of cancer, other members of your family may be eligible for genetic testing for hereditary cancer. Residents of BC can be referred to the BC Cancer Hereditary Cancer Program for hereditary cancer risk assessment: http://www.bccancer.bc.ca/our-services/services/hereditary-cancer
- Those living outside of BC can use the Canadian Association of Genetic Counsellors website to find a local genetics clinic: https://www.cagc-accg.ca

BC Cancer Female Screening Recommendations – Reference

The following screening recommendations are provided by BC Cancer / BC Ministry of Health[2]. This information may change over time. Cancer risk interpretations and screening/risk reduction recommendations may differ by region and may be altered based on individual risk factors[3].

<table>
<tr><th colspan="5">General Population Screening</th></tr>
<tr><th>Age</th><th>Breast Cancer</th><th>Colon Cancer</th><th>Cervical Cancer</th><th>Lung Cancer</th></tr>
<tr><td><25</td><td rowspan="6">No screening recommended. See your doctor if you have concerning symptoms.</td><td rowspan="6">No screening recommended. See your doctor if you have concerning symptoms.</td><td>No screening recommended. See your doctor if you have concerning symptoms.</td><td rowspan="6">No screening recommended. See your doctor if you have concerning symptoms.</td></tr>
<tr><td>25</td><td rowspan="10">Every 5 years use a cervix-self screening kit or every 3 years see your doctor for a Pap test until age 69.</td></tr>
<tr><td>30</td></tr>
<tr><td>35</td></tr>
<tr><td>40</td></tr>
<tr><td>45</td></tr>
<tr><td>50</td><td rowspan="7">Mammogram every 2 years from age 50-74.</td><td rowspan="7">Fecal immunochemical test (FIT) every 2 years from age 50-74. This test will determine if colonoscopy is required.</td><td rowspan="2">If you have smoked tobacco for 20 years or more and are between the ages of 55-74 please call this number for assessment: 1-877-717-5864. You may be eligible for CT lung screening.</td></tr>
<tr><td>55</td></tr>
<tr><td>60</td></tr>
<tr><td>65</td></tr>
<tr><td>70</td></tr>
<tr><td><75</td><td>No screening recommended. See your doctor if you have concerning symptoms.</td></tr>
<tr><th colspan="5">With a Significant Family History of Cancer</th></tr>
<tr><td>Any age</td><td>If you have a family history of close relatives (parent/sibling) with breast cancer, you may be able to access mammogram screening before age 50.</td><td>If you have a family history of multiple relatives with colon cancer or early onset colon cancer, you may be recommended to have colonoscopy at a younger age, with or without FIT screening.</td><td>Cervical cancer is not a cancer that has a significant hereditary component. Screening does not change based on family history.</td><td>Lung cancer is not a cancer that has a significant hereditary component. Screening does not change based on family history.</td></tr>
</table>

Assay Details – WGS Hereditary Cancer Complete (80 gene)

Gene List

80 genes analyzed: *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). Additional genes analyzed per ACMG secondary finding guidelines: *ACTC1, APOB, ATP7B, BTD, CACNA1S, CASQ2, COL1A1, COL1A2, COL6A1, COL6A2, COL6A3, DSC2, DSG2, DSP, DMD, FBN1, GAA, G6PC, HFE, KCNH2, KCNQ1, LDLR, LMNA, MYBPC3, MYH7, MYL2, MYL3, OTC, PCSK9, PKP2, PRKAG2, RYR1, RYR2, SCN5A, SLC25A13, SLC37A4, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNT2, TNNI3.*

Method

Genomic DNA is extracted, quantified and subjected to PCR-free ligation-based library construction. Libraries are sequenced on Illumina PLATFORM using paired end 150bp reads. Sequences are aligned to hg38 human reference genome using Illumina DRAGEN. Single nucleotide variants, copy number variants, and sequencing quality metrics are processed by a customized pipeline. Annotation, filtering, and reporting are performed with the Illumina Connected Insights platform. This test was developed as a clinical assay by [lab partner]. Assay performance metrics are determined by [lab partner] with a reported sensitivity for germline SNVs, short indels, and CNVs of >NN% with NNx mean genomic coverage. Variants are annotated and interpreted according to ACMG clinical guidelines in the context of all clinical information provided by the ordering provider. cDNA nucleotide numbering begins at the A of the initiating codon (ATG) per HGVS convention. TransCan Genomics PolyScrypt is used for report generation following provider content guidelines when applicable. Reported variants are confirmed by orthogonal methods at TransCan Genomics discretion.

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.

Limitations

This genetic testing report provides insights based on current scientific knowledge and available testing methodologies. Not all pathogenic variants or genetic risk factors may be identified due to technological constraints, variant classification challenges, or the specific genes/regions analyzed. Genetic research is rapidly advancing, and variant interpretations may change as new evidence emerges. This report reflects classifications at the time of analysis. A positive result does not guarantee disease development, and a negative result does not eliminate all risk. Other genetic, environmental, and lifestyle factors contribute to cancer susceptibility. While this test assesses hereditary risk, family members may carry undetected variants due to incomplete penetrance or de novo mutations. Some variants may have uncertain significance (VUS) or differing risk associations across populations due to limited data in certain ethnic groups. This report is not a substitute for clinical evaluation. Genetic counselling is recommended to discuss results, risk management, and family implications.

References

1. U.S. National Library of Medicine. 2025. MLH1 gene. Genetics Home Reference.
2. BC Cancer. 2025. Hereditary cancer screening guidelines. BC Ministry of Health.
3. National Comprehensive Cancer Network. (Year). NCCN guidelines for genetic/familial high-risk assessment: Colorectal.

This report has been reviewed and approved by:

Dr. John Smith, MD, Phd