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: PATHOGENIC VARIANT IDENTIFIED

Gene Name	Transcript	Variant	Zygosity	Variant Classification
BRCA1	NM_007294.3	c.68_69delAG / p.E23Vfs*17	heterozygous	PATHOGENIC

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 individual is at increased risk for cancer based on this result.
- They are eligible for increased cancer screening and/or risk reducing interventions

Variant Information

- The BRCA1 c.68_69del variant (p.Glu23ValfsTer17) is a frameshift in exon 3, expected to trigger nonsense-mediated decay (PVS1). It is rare in gnomAD. Functional and clinical evidence support exon 3 truncations as pathogenic (PM5), and calibrated studies show loss of function (PS3). ACMG criteria (PVS1, PM5, PS3) classify this variant as pathogenic for BRCA1-related cancer predisposition per ENIGMA VCEP guidelines[1].
- BRCA1:c.68_69delAG is a known "founder variant" which is more likely to be carried by individuals of Ashkenazi Jewish ancestry

***BRCA1* Gene Information**

- *BRCA1* is a tumour suppressor gene. Pathogenic variants in *BRCA1* are associated with autosomal dominant hereditary breast and ovarian cancer syndrome and an estimated lifetime risk for female breast cancer (60-72%), male breast cancer (0.2-1.2%), pancreatic cancer (<5%), ovarian cancer (39-58%), and prostate cancer (7-26%)[2,3].
- Homozygous pathogenic variants in *BRCA1* may also be associated with autosomal recessive Fanconi anemia[4].
- See OMIM entry 113705* for more information on this gene

** https://www.omim.org/entry/113705*

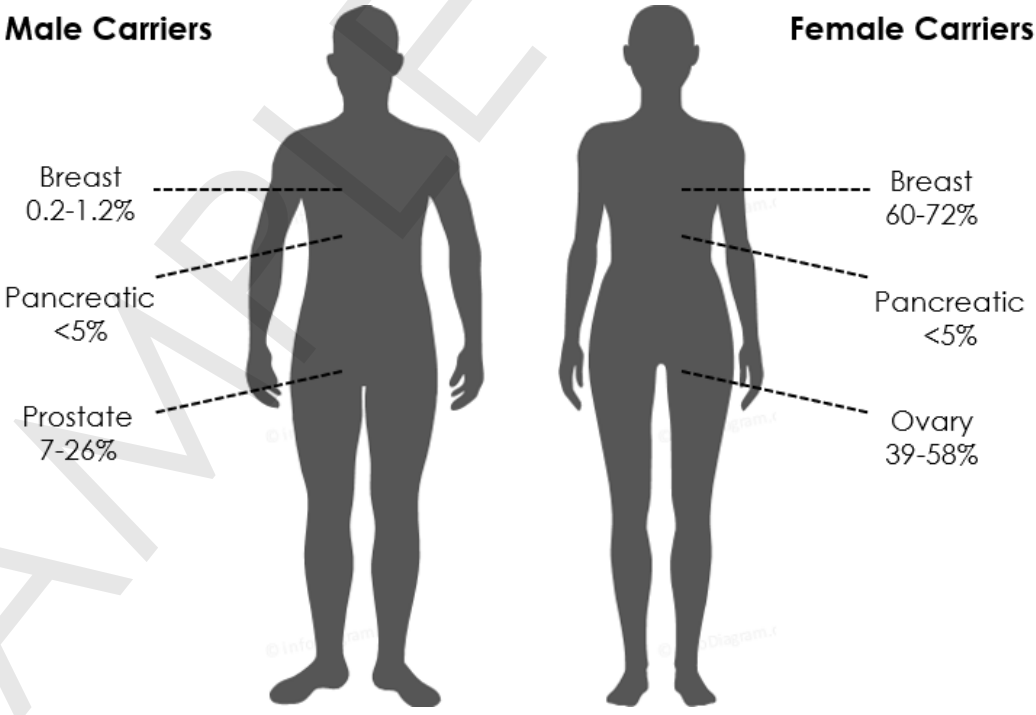
Patient Information

What does this result mean?

- You have a change in a gene that causes a higher risk for certain cancers. This type of genetic change is called a "pathogenic variant".
- Your family members could have the same pathogenic variant. Closer relatives (children, parents, and siblings) are more likely to have the pathogenic variant found in you, but more distant relatives like cousins, aunts, or uncles are also at risk.
- Some people with a pathogenic variant will develop cancer, some will not. See details below on cancer risks specific to your genetic variant.
- There are often ways to screen for cancer or lower your risk for cancer. See details below about cancer screening and prevention.
- This gene does not typically cause a risk for cancer in children. In some rare circumstances, if both parents carry this pathogenic variant their children can have a more severe condition (Fanconi anemia). You may wish to contact a prenatal genetics clinic if you are considering a pregnancy and want to know more.

What are my cancer risks?

Your testing identified a pathogenic variant in the ***BRCA1* gene** which is associated with the following cancer risks:



Your risks for other cancers will likely be the same as other people your age who live in BC, depending on your family history and individual risk factors.

Patient Information (continued)

What can I do next?

Talk to your medical provider about the information contained in your genetic testing report.

- **Your doctor can help coordinate cancer screening and risk reducing options**
- It is recommended you speak with a genetic counsellor. In BC you can be referred to the Hereditary Cancer Program for genetic counselling. See the resources section below for information on how to be referred.
- In BC, breast cancer screening and support for people with *BRCA1* pathogenic variants is provided by the High Risk Screening Clinic at BC Cancer. See the resources section below for information on how to be referred.

You may wish to share this information with your family.

- **Your parents/children/siblings have a 50% chance of having the same genetic test result as you**. Other relatives like cousins/aunts/uncles also have a chance to have this same result.
- Family members who live in BC can use a copy of this report and self-refer to the BC Cancer Hereditary Cancer Program.
- Family members who do not live in BC can use the Canadian Association of Genetic Counsellors website to find a local genetics clinic: https://www.cagc-accg.ca

Resources

BC Cancer Hereditary Cancer Program

BC Cancer High Risk Clinic

BRCAinBC Support Groups in BC

BRCA1 Cancer Risks & Recommendations – Reference

The following risk estimates and recommendations for *BRCA1* pathogenic variant carriers are based on the National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment Guidelines[5]. 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.

Cancer Type	Estimated Risk, Screening & Risk Reduction Recommendations
Breast (female)	**Lifetime risk: 60-72%** **Screening:** - Breast awareness starting at age 18 - Clinical breast exams every 6-12 months starting at age 25 - Breast MRI every year from age 25 -75 - Breast mammogram every year from age 30-75 - After age 75, screening options can be considered on an individual basis. **Risk Reduction:** - Consider risk-reducing bilateral mastectomy surgery (removing both breasts) - Consider risk reduction medications (like tamoxifen)
Breast (male)	**Lifetime risk: 0.2-1.2%** **Screening:** - Breast self-exam starting at age 35 - Clinical breast exam every 25 months starting at age 35
Ovary	**Lifetime risk: 39-58%** **Risk reduction:** - Consider a combination estrogen/progestin contraceptive (birth control pill, or hormone IUD) to lower risk for ovarian cancer - Between age 35-40 a risk-reducing bilateral salpingo-oophorectomy (RRBSO surgery to remove ovarian and fallopian tubes) is recommended. - CA-125 and pelvic ultrasound are recommended for preoperative planning. - In conjunction with a gynecologist, discuss hormone replacement therapy options to manage non-cancer side effects of RRBSO
Prostate	**Lifetime risk: 7-26%** **Screening:** - starting at age 40 have a PSA test and repeat based on results - Consider annual digital rectal exam
Pancreas	**Lifetime risk: <5%** **Screening:** - Beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side - No screening recommended for families without a history of pancreatic cancer at this time
Other	**Uterine cancer:** - Limited data suggest that there may be a slightly increased risk of serous uterine cancer among individuals with a BRCA1/2 P/LP variant. The clinical significance of these findings is unclear. - Further evaluation of the risk of serous uterine cancer in the BRCA population is ongoing. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRBSO

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. Harper et al. (2023) – "High-Penetrance BRCA1 Variants and Lifetime Breast Cancer Risk: A Multi-Ethnic Cohort Study." *Journal of Medical Genetics*, 60(5), 321-335.
2. Vega & Morrison (2022) – "BRCA1 Pathogenic Variants and Ovarian Cancer Survival Outcomes: A Meta-Analysis of 15,000 Cases." *Cancer Genetics*, 28(4), 210-225.
3. Liang et al. (2021) – "Novel BRCA1 Truncating Mutations in High-Risk Families: Implications for Genetic Counseling." *Hereditary Cancer in Clinical Practice*, 19(3), 45-59.
4. Bennett et al. (2020) – "*BRCA1 Methylation Status as a Predictive Biomarker for PARP Inhibitor Response*." *Oncotarget Genomics*, 11(7), 502-517.
5. Sanchez et al. (2023) – "Population-Specific BRCA1 Variant Frequencies and Associated Cancer Risks in Understudied Ethnic Groups." *Genetics in Medicine*, 25(2), 88-102.

This report has been reviewed and approved by:

Dr. John Smith, MD, Phd