ARBORETUM CLINICAL

617-465-0969 • support@arboretumclinical.com

LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)

LABORATORY NAME
Arboretum Clinical, LLC

FIRST NAME: Oscar
LAST NAME: Meyer
DOB: 01/01/1964
PATIENT ID: HDHD-1-1

SAMPLE ID: ASDFG123
SAMPLE TYPE: Buccal swab
COLLECTION DATE: 01/06/2026
ORDERING PROVIDER: Sherlock Holmes

ORDERING PROVIDER CONTACT: 555-555-5555
ORDER REQUISITION: XXXXX
DATA RECEIVED: 01/08/2026
REPORT DATE: 01/18/2026

Arboretum Cancer Risk Test

GENES ANALYZED

AIP, ALK, APC, ATM, ATRIP, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CFTR, CHEK2, CPA1, CTRC, CTNNA1, DDX41, DICER1, EGFR, EGLN1, EPCAM, ETV6, FH, FLCN, GATA2, GREM1, HOXB13, KIF1B, KIT, LZTR1, MAX, MBD4, MEN1, MET, MITF, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PALLD, PDGFRA, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PRSS1, PTCH1, PTEN, RAD51B, RAD51C, RAD51D, RB1, RET, RNF43, RPS20, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, SPINK1, STK11, SUFU, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WT1

PRIMARY TEST RESULTS SUMMARY

POSITIVE - one pathogenic variant detected

One heterozygous pathogenic variant detected in BRCA1, associated with BRCA1-associated hereditary breast and ovarian cancer syndrome (HBOC).

GENE	VARIANT	PROTEIN CHANGE	ZYGOSITY	CLASSIFICATION
BRCA1	c.5266dupC	p.Gln1756ProfsTer74	Heterozygous	Pathogenic

Detailed findings continued on next page.

This space left intentionally blank

ARBORETUM CLINICAL
617-465-0969 • support@arboretumclinical.com

LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)
LABORATORY NAME
Arboretum Clinical, LLC

FIRST NAME: Oscar LAST NAME: Meyer DOB: 01/01/1964 ORDER REQUISITION: XXXXX

PRIMARY FINDING

BRCA1, Pathogenic Heterozygous

GENE CONTEXT

BRCA1, Heterozygous: BRCA1 is associated with hereditary breast and ovarian cancer syndrome (HBOC), inherited in an autosomal dominant manner. Heterozygous pathogenic variants in BRCA1 confer susceptibility to female breast and ovarian cancer, with additional reported associations including contralateral breast cancer and, to a lesser extent, other BRCA1-related malignancies. The clinical phenotype is characterized by increased cancer susceptibility rather than a defined non-neoplastic presentation.[1,2,3,4]

INTERPRETATION

A frameshift variant was identified in BRCA1 (c.5266dup; p.Gln1756ProfsTer74). This variant has an estimated variant allele fraction of 0.61. This variant is reported in ClinVar as "Pathogenic" (status: "reviewed by expert panel"; ID: 17677). This variant is present in gnomAD with a maximum population allele frequency of 5.42407E-5. Loss of function is a known disease mechanism for this gene, and this frameshift variant is predicted to cause loss of function (PVS1). This frameshift variant meets gene-specific ClinGen expert panel loss-of-function criteria (PM5). Functional studies support pathogenicity of this variant (PS3)[5]. This variant has been found more frequently in affected individuals than in unaffected controls (PS4) [6,7]. Based on this evidence, this variant has been classified as Pathogenic per ACMG/AMP guidelines.

FOLLOW UP RECOMMENDATIONS

It is recommended that these results are discussed with a certified genetic counselor or other healthcare professional with genetics expertise.

REFERENCES

1. Kuchenbaecker KB et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. doi: 10.1001/jama.2017.7112. PMID: 28632866.
2. Chen J et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. JNCI Cancer Spectr. 2020 Apr 23;4(4):pkaa029. doi: 10.1093/jncics/pkaa029. PMID: 32676552; PMCID: PMC7353955.
3. Kobayashi H et al. Hereditary breast and ovarian cancer susceptibility genes (review). Oncol Rep. 2013 Sep;30(3):1019-29. doi: 10.3892/or.2013.2541. Epub 2013 Jun 19. PMID: 23779253.
4. Chen S et al. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007 Apr 10;25(11):1329-33. doi: 10.1200/JCO.2006.09.1066. PMID: 17416853; PMCID: PMC2267287.
5. Petrucelli N et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [updated 2025 Mar 20]. In: Adam MP, Bick S, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2026. PMID: 20301425.
6. Kobayashi H et al. Hereditary breast and ovarian cancer susceptibility genes (review). Oncol Rep. 2013 Sep; 30(3):1019-29. doi: 10.3892/or.2013.2541. Epub 2013 Jun 19. PMID: 23779253.
7. Yildiz Tacar S et al. Next generation sequencing analysis of BRCA1 and BRCA2 identifies novel variations in breast cancer. Life Sci. 2020 Nov 15;261:118334. doi: 10.1016/j.lfs.2020.118334. Epub 2020 Aug 23. PMID: 32846166.

ARBORETUM CLINICAL
617-465-0969 • support@arboretumclinical.com

LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)
LABORATORY NAME
Arboretum Clinical, LLC

FIRST NAME: Oscar LAST NAME: Meyer DOB: 01/01/1964 ORDER REQUISITION: XXXXX

TECHNICAL AND REGULATORY INFORMATION

GENE AND TRANSCRIPT PAIRS

GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT
AIP	NM_003977.4	FLCN	NM_144997.7	PRSS1	NM_002769.5
ALK	NM_004304.5	GATA2	NM_032638.5	PTCH1	NM_000264.5
APC	NM_000038.6	GREM1	NM_013372.7	PTEN	NM_000314.8
ATM	NM_000051.4	HOXB13	NM_006361.6	RAD51B	NM_133510.4
ATRIP	NM_130384.3	KIF1B	NM_001365951.3	RAD51C	NM_058216.3
AXIN2	NM_004655.4	KIT	NM_000222.3	RAD51D	NM_002878.4
BAP1	NM_004656.4	LZTR1	NM_006767.4	RB1	NM_000321.3
BARD1	NM_000465.4	MAX	NM_002382.5	RET	NM_020975.6
BMPR1A	NM_004329.3	MBD4	NM_001276270.2	RNF43	NM_017763.6
BRCA1	NM_007294.4	MEN1	NM_001370259.2	RPS20	NM_001023.4
BRCA2	NM_000059.4	MET	NM_000245.4	RUNX1	NM_001754.5
BRIP1	NM_032043.3	MITF	NM_001354604.2	SDHA	NM_004168.4
CDC73	NM_024529.5	MLH1	NM_000249.4	SDHAF2	NM_017841.4
CDH1	NM_004360.5	MLH3	NM_001040108.2	SDHB	NM_003000.3
CDK4	NM_000075.4	MSH2	NM_000251.3	SDHC	NM_003001.5
CDKN1B	NM_004064.5	MSH3	NM_002439.5	SDHD	NM_003002.4
CDKN2A	NM_000077.5	MSH6	NM_000179.3	SMAD4	NM_005359.6
CEBPA	NM_004364.5	MUTYH	NM_001048174.2	SMARCA4	NM_003072.5
CFTR	NM_000492.4	NF1	NM_001042492.3	SMARCB1	NM_003073.5
CHEK2	NM_007194.4	NF2	NM_000268.4	SMARCE1	NM_003079.5
CPA1	NM_001868.4	NTHL1	NM_002528.7	SPINK1	NM_001379610.1
CTNNA1	NM_001903.5	PALB2	NM_024675.4	STK11	NM_000455.5
CTRC	NM_007272.3	PALLD	NM_001166108.2	SUFU	NM_016169.4
DDX41	NM_016222.4	PDGFRA	NM_006206.6	TERT	NM_198253.3
DICER1	NM_177438.3	PHOX2B	NM_003924.4	TMEM127	NM_017849.4
EGFR	NM_005228.5	PMS2	NM_000535.7	TP53	NM_000546.6
EGLN1	NM_022051.3	POLD1	NM_002691.4	TSC1	NM_000368.5
EPCAM	NM_002354.3	POLE	NM_006231.4	TSC2	NM_000548.5
ETV6	NM_001987.5	POT1	NM_015450.3	VHL	NM_000551.4
FH	NM_000143.4	PRKAR1A	NM_002734.5	WT1	NM_024426.6

ARBORETUM CLINICAL
617-465-0969 • support@arboretumclinical.com

LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)
LABORATORY NAME
Arboretum Clinical, LLC

TECHNICAL AND REGULATORY INFORMATION

TEST METHODOLOGY

The Arboretum Hereditary Cancer Genetic Test is performed on genomic DNA extracted from buccal swabs, saliva, or whole blood. The test is validated for constitutional germline testing and is not intended for tumor testing. Next-generation sequencing is performed using a blended approach combining low-coverage whole genome sequencing with high-coverage exome sequencing. Variant calling is performed using the DRAGEN Bio-IT Platform version 4.3.13 with alignment to reference genome GRCh38. Copy number variant detection utilizes the GATK germline CNV (gCNV) pipeline.

The test analyzes the 90 genes listed above for sequence variants and multi-exon copy number variants in genes selected for hereditary cancer risk assessment and specified Additional Findings. Target regions include all coding exons and adjacent introns with at least 10x coverage for SNPs and 15x coverage for indels. Variants are classified according to ACMG/AMP 2015 guidelines with gene-specific modifications from the applicable ClinGen Variant Curation Expert Panels where available. Copy number variants are classified using 2020 ACMG/ClinGen CNV interpretation guidelines. Variants beyond the target regions are not reviewed nor classified as part of this test.

Only pathogenic and likely pathogenic variants are reported. Variants of uncertain significance (VUS), likely benign, and benign variants are not reported. A primary positive result is reported when one or more pathogenic or likely pathogenic variants are identified in genes associated with hereditary cancer risk.

Pathogenic and likely pathogenic variants in targeted genes that are not part of the primary hereditary cancer-risk result, including variants associated with chronic pancreatitis risk, carrier status for autosomal recessive conditions, or other non-cancer phenotypes, may be reported as Additional Findings according to laboratory reporting policy. Variants are reported using HGVS nomenclature.

Quality control acceptance criteria include: minimum mean coverage ≥20x across targeted gene regions, overall genotype concordance ≥95%, and contamination estimate <5%. Samples not meeting these quality thresholds are not reported and may require recollection.

Pathogenic and likely pathogenic variants with VAF ≥33% are reported as germline findings unless variant-, gene-, specimen-, or clinical factors suggest mosaicism, clonal hematopoiesis, transplant-related chimerism, tumor contamination, or another acquired/somatic source.

This sample and genetic data met Arboretum Clinical's quality standards for report generation.

TEST LIMITATIONS

The test does not assess polygenic risk or environmental factors that influence cancer risk. A positive genetic result alone does not establish a cancer diagnosis. Clinical correlation with family history, signs, symptoms, and physical examination findings is required for diagnosis.

Variant calling in PRSS1 and PMS2 is subject to elevated uncertainty due to high sequence similarity with paralogous sequences (PRSS2 and pseudogene PRSS3P3 for PRSS1 and pseudogene PMS2CL for PMS2 exons 11–15). While the DRAGEN variant calling platform incorporates algorithmic improvements for these regions, copy number variants in PMS2 exons 11–15 may involve PMS2CL rather than PMS2 itself, and novel or undocumented PRSS1 variants may warrant confirmatory orthogonal testing.

Some splice-site variants may be classified using computational prediction tools and curated database evidence without RNA-based confirmation, and a subset of variants predicted to affect splicing may not result in aberrant transcripts in practice.

The assay does not detect single-exon copy number variants, complex structural rearrangements, deep intronic variants with less than 10x coverage for SNPs and 15x coverage for indels, variants in transcript isoforms, tissue-specific splicing variants, or variants in regulatory regions.

The assay does not detect complex structural variants including translocations or inversions and does not determine the precise structural configuration of detected duplications. Tandem duplications (which typically disrupt gene function and are pathogenic) cannot be distinguished from non-tandem duplications (which may preserve gene function). Consequently, partial detected duplications cannot be definitively classified as pathogenic or benign based on structural characteristics alone and are classified as variants of uncertain significance (VUS) pending additional evidence from functional studies or alternative sequencing methodologies.

This panel does not include all genes associated with hereditary cancer predisposition. A negative result does not exclude a hereditary cancer syndrome due to variants in genes not covered by this panel.

Analytical validation included samples from European, East Asian, and African ancestry populations. Variant interpretation relies on population frequency databases and computational prediction tools trained primarily on individuals of European ancestry. Performance may be reduced for individuals from populations with limited representation in genomic reference databases, including but not limited to Native American, Pacific Islander, and some Central Asian ancestries, or individuals with complex admixed ancestry.

When two or more pathogenic or likely pathogenic variants are detected in the same gene, chromosomal phase cannot be determined by this assay. For autosomal dominant genes, clinical correlation with the patient's personal and family cancer history can help distinguish between trans configuration (more severe phenotype) and cis configuration (typical heterozygous phenotype). For autosomal recessive genes, clinical correlation is required to distinguish between trans configuration (disease-causing) and cis configuration (carrier status). Family segregation studies can definitively establish phase for any gene.

Individuals with significant germline mosaicism (>20% variant allele frequency deviation) may yield inaccurate variant calls. Bone marrow transplant recipients tested using blood-derived samples may reflect donor rather than recipient genotype. Buccal swab or saliva specimens may be preferred to blood for transplant recipients, but may still contain donor-derived hematopoietic cells.

Results may be unreliable in patients with active hematologic malignancy, as circulating tumor cells or clonally expanded hematopoietic populations may contaminate specimens and result in somatic variants being misinterpreted as germline findings. Testing should be deferred until remission where clinically feasible.

Variant classifications may change as new scientific evidence becomes available. All detected variants are retained in laboratory records for potential reclassification.

LABORATORY INFORMATION

This test was performed by Arboretum Clinical, LLC, 6901 Quaker Ave. Ste B, Lubbock TX 79413 CLIA: 45D2331659, CAP 7734236. Laboratory Director: Owatha Tatum, Ph.D., HCLD/CC(ABB). Sequencing services were provided by GenebyGene, Ltd., 1445 North Loop West, Suite 820 Houston, TX 77008, CLIA ID 45D1102202, CAP 7212851, Laboratory Director: Director: Dr. Feng Zhou, PhD, HCLD(ABB), MB(ASCP). Both laboratories are authorized under the Clinical Laboratory Improvement Amendments (CLIA) to develop and perform high complexity clinical laboratory testing. This test was developed and its performance characteristics determined by Arboretum Clinical. It has not been cleared or approved by the U.S. Food and Drug Administration. It is a laboratory-developed test (LDT) not reviewed by the U.S. Food and Drug Administration.

ARBORETUM CLINICAL
617-465-0969 • support@arboretumclinical.com

LAB DIRECTOR
Owatha Tatum, Ph.D. HCLD/CC(ABB)
LABORATORY NAME
Arboretum Clinical, LLC

FIRST NAME: Oscar LAST NAME: Meyer DOB: 01/01/1964 ORDER REQUISITION: XXXXX

RELEVANT LITERATURE

- Babadi M et al. GATK-gCNV enables the discovery of rare copy number variants from exome sequencing data. Nat Genet. 2023 Sep;55(9):1589-1597. doi: 10.1038/s41588-023-01449-0. Epub 2023 Aug 21. Erratum in: Nat Genet. 2024 Mar;56(3):553. doi: 10.1038/s41588-024-01663-4. PMID: 37604963; PMCID: PMC10904014.
- Garutti M et al. Hereditary Cancer Syndromes: A Comprehensive Review with a Visual Tool. Genes (Basel). 2023 Apr 30;14(5):1025. doi: 10.3390/genes14051025. PMID: 37239385; PMCID: PMC10218093.
- Manahan ER et al. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019 Oct;26(10):3025-3031. doi: 10.1245/s10434-019-07549-8. Epub 2019 Jul 24. PMID: 31342359; PMCID: PMC6733830.
- Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.
- Spier I et al. Gene-specific ACMG/AMP classification criteria for germline APC variants: Recommendations from the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel. Genet Med. 2024 Feb;26(2):100992. doi: 10.1016/j.gim.2023.100992. Epub 2023 Oct 4. PMID: 37800450; PMCID: PMC10922469.
- Tavtigian SV et al. Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. Genet Med. 2018 Sep;20(9):1054-1060. doi: 10.1038/gim.2017.210. Epub 2018 Jan 4. PMID: 29300386; PMCID: PMC6336098.
- Valle L et al. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. J Pathol. 2019 Apr;247(5):574-588. doi: 10.1002/path.5229. Epub 2019 Feb 20. PMID: 30584801; PMCID: PMC6747691.
- ClinGen Hereditary Breast, Ovarian, and Pancreatic Cancer Variant Curation Expert Panel (HBOPC VCEP). clinicalgenome.org.
- National Comprehensive Cancer Network. (2025). Genetic/familial high-risk assessment: Colorectal, endometrial, and gastric (Version 1.2025).
- National Comprehensive Cancer Network. (2026). Genetic/familial high-risk assessment: Breast, ovarian, pancreatic, and prostate (Version 3.2026).