ARBORETUM CLINICAL

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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 Hereditary Cardiomyopathy Test

GENES ANALYZED

ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, BAG3, BRAF, CBL, CDH2, CPT2, CSRP3, DES, DMD, DSC2, DSG2, DSP, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATA6, GLA, HAND1, HFE, HRAS, JPH2, JUP, KRAS, LAMP2, LDB3, LMNA, LZTR1, MAP2K1, MAP2K2, MIB1, MRAS, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYPN, NEXN, NF1, NKX2-5, NRAS, PKP2, PLN, PPP1CB, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, TAFAZZIN, TBX20, TCAP, TGFB3, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TTN, TTR, VCL

PRIMARY TEST RESULTS SUMMARY

POSITIVE - MYBPC3 - clinically significant finding(s)

One heterozygous pathogenic variant detected in **MYBPC3**, associated with familial hypertrophic cardiomyopathy.

GENE	VARIANT	PROTEIN CHANGE	ZYGOSITY	CLASSIFICATION
MYBPC3	c.1505G>A	p.Arg502Gln	Heterozygous	Pathogenic

Detailed findings continued on next page.

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PRIMARY FINDING **MYBPC3** Pathogenic variant

GENE CONTEXT

MYBPC3, heterozygous: MYBPC3 is associated with hypertrophic cardiomyopathy, a sarcomeric cardiomyopathy that follows autosomal dominant inheritance, and MYBPC3 is one of the most common causal genes. Heterozygous pathogenic variants, predominantly loss-of-function truncating variants acting through a locus-independent mechanism, confer susceptibility to unexplained left ventricular hypertrophy, with reported histologic features of myocyte hypertrophy, disarray, and myocardial fibrosis. Clinical expression is variable and age-dependent, and not all carriers develop overt disease; reported complications include left ventricular outflow tract obstruction, atrial fibrillation, heart failure, and increased susceptibility to sudden cardiac death. [1]

INTERPRETATION

A missense variant was identified in MYBPC3 (c.1505G>A; p.Arg502Gln). This variant is absent from gnomAD v2.1.1, supporting pathogenicity (PM2). This variant has been reported in numerous individuals with hypertrophic cardiomyopathy at a statistically increased frequency compared to controls, and has segregated with disease across multiple families (PS4, PP1) [2,3]. Another variant at this codon (p.Arg502Trp) has been classified as pathogenic by the ClinGen VCEP, supporting pathogenicity of variants at this residue (PM5) [4]. Computational prediction tools are inconclusive for this variant with a REVEL score below 0.7. Based on this evidence, this variant has been classified as Pathogenic for hypertrophic cardiomyopathy in an autosomal dominant manner 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. Tudurachi BS et al. An Update on MYBPC3 Gene Mutation in Hypertrophic Cardiomyopathy. Int J Mol Sci. 2023 Jun 22;24(13):10510. doi: 10.3390/ijms241310510. PMID: 37445689; PMCID: PMC10341819.
2. Olivotto I et al. Myosin-binding protein C mutations and outcome in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2008 Sep 16;52(12):1061-72. doi: 10.1016/j.jacc.2008.05.060. PMID: 18803133.
3. Helms AS et al. Spatial and functional distribution of MYBPC3 pathogenic variants and clinical outcomes in patients with hypertrophic cardiomyopathy. Circ Genom Precis Med. 2020 Oct;13(5):396-405. doi: 10.1161/CIRCGEN.120.002929. Epub 2020 Aug 25. PMID: 32841044; PMCID: PMC7676622.
4. Walsh R et al. Quantitative approaches to variant classification increase the yield and precision of genetic testing in Mendelian diseases: the case of hypertrophic cardiomyopathy. Genome Med. 2019 Jan 28;11(1):5. doi: 10.1186/s13073-019-0616-z. PMID: 30696458.

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TECHNICAL AND REGULATORY INFORMATION

GENE AND TRANSCRIPT PAIRS

GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT
ABCC9	NM_020297.4	FKRP	NM_024301.5	MTO1	NM_012123.4	SGCD	NM_000337.6
ACADVL	NM_000018.4	FKTN	NM_001079802.2	MYBPC3	NM_000256.3	SHOC2	NM_007373.4
ACTC1	NM_005159.5	FLNC	NM_001458.5	MYH6	NM_002471.4	SLC22A5	NM_003060.4
ACTN2	NM_001103.4	GAA	NM_000152.5	MYH7	NM_000257.4	SOS1	NM_005633.4
AGL	NM_000642.3	GATA4	NM_001308093.3	MYL2	NM_000432.4	SOS2	NM_006939.4
ALMS1	NM_001378454.1	GATA6	NM_005257.6	MYL3	NM_000258.3	TAFAZZIN	NM_000116.5
ALPK3	NM_020778.5	GLA	NM_000169.3	MYPN	NM_032578.4	TBX20	NM_001077653.2
BAG3	NM_004281.4	HAND1	NM_004821.3	NEXN	NM_144573.4	TCAP	NM_003673.4
BRAF	NM_004333.6	HFE	NM_000410.4	NF1	NM_001042492.3	TGFB3	NM_003239.5
CBL	NM_005188.4	HRAS	NM_005343.4	NKX2-5	NM_004387.4	TMEM43	NM_024334.3
CDH2	NM_001792.5	JPH2	NM_020433.5	NRAS	NM_002524.5	TMEM70	NM_017866.6
CPT2	NM_000098.3	JUP	NM_002230.4	PKP2	NM_001005242.3	TMPO	NM_001032283.3
CSRP3	NM_003476.5	KRAS	NM_004985.5	PLN	NM_002667.5	TNNC1	NM_003280.3
DES	NM_001927.4	LAMP2	NM_002294.3	PPP1CB	NM_002709.3	TNNI3	NM_000363.5
DMD	NM_004006.3	LDB3	NM_007078.3	PRDM16	NM_022114.4	TNNI3K	NM_015978.3
DSC2	NM_024422.6	LMNA	NM_170707.4	PRKAG2	NM_016203.4	TNNT2	NM_001276345.2
DSG2	NM_001943.5	LZTR1	NM_006767.4	PTPN11	NM_002834.5	TPM1	NM_001018005.2
DSP	NM_004415.4	MAP2K1	NM_002755.4	RAF1	NM_002880.4	TTN	NM_001267550.2
EMD	NM_000117.3	MAP2K2	NM_030662.4	RBM20	NM_001134363.3	TTR	NM_000371.4
EYA4	NM_004100.5	MIB1	NM_020774.4	SCN5A	NM_000335.5	VCL	NM_014000.3
FHL1	NM_001159699.2	MRAS	NM_001085049.3	SDHA	NM_004168.4		

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TECHNICAL AND REGULATORY INFORMATION

TEST METHODOLOGY

The Arboretum Hereditary Cardiomyopathy Test is performed on genomic DNA extracted from buccal swabs, saliva, or whole blood. The test is validated for germline constitutional specimens only. 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 83 genes listed above for sequence variants and multi-exon copy number variants in genes selected for cardiomyopathy 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 cardiomyopathy. Pathogenic and likely pathogenic variants in targeted genes that are not part of the primary cardiomyopathy-risk result, including variants associated with carrier status for autosomal recessive conditions, variants in genes with preliminary evidence of cardiomyopathy risk, or other non-cardiac 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.

This test is intended to identify germline variants within the genes and variant types included in the ordered report. Reported variants are interpreted as germline based on available laboratory, specimen, gene-, and variant-level evidence. Variants with evidence suggesting mosaicism, clonal hematopoiesis, transplant-related chimerism, tumor contamination, or another acquired/somatic source are not reported as germline findings unless additional evaluation supports germline origin.

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 cardiomyopathy risk. A positive genetic result alone does not establish a cardiomyopathy diagnosis. Clinical correlation with family history, signs, symptoms, and physical examination findings is required for diagnosis. This panel does not include all genes associated with hereditary cardiomyopathy predisposition. A negative result does not exclude a hereditary cardiomyopathy syndrome due to variants in genes not covered by this panel. A pathogenic or likely pathogenic result is identified in approximately 20-25% of patients evaluated for heritable cardiomyopathy or arrhythmia; yield varies by diagnostic indication.

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.

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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.

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 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. 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: 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.

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RELEVANT LITERATURE

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