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 Combined Hereditary Cardiomyopathy and Arrhythmia Test

## GENES ANALYZED

ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, ANK2, BAG3, BRAF, CACNA1C, CALM1, CALM2, CALM3, CASQ2, CAV3, CBL, CDH2, CPT2, CSRP3, CTNNA3, DES, DMD, DSC2, DSG2, DSP, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATA6, GJA5, GLA, HAND1, HCN4, HFE, HRAS, JPH2, JUP, KCNA5, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, KRAS, LAMP2, LDB3, LMNA, LZTR1, MAP2K1, MAP2K2, MIB1, MRAS, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYPN, NEXN, NF1, NKX2-5, NPPA, NRAS, PKP2, PLN, PPP1CB, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, TAFAZZIN, TBX20, TCAP, TECRL, TGFB3, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, VCL

## PRIMARY TEST RESULTS SUMMARY

### POSITIVE - KCNQ1 - clinically significant finding(s)

One heterozygous pathogenic variant detected in KCNQ1, associated with Long QT Syndrome.

| GENE | VARIANT | PROTEIN CHANGE | ZYGOSITY | CLASSIFICATION |
|---|---|---|---|---|
| KCNQ1 | c.760G>A | p.Val254Met | Heterozygous | Pathogenic |

*Detailed findings continued on next page.*

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PRIMARY FINDING **KCNQ1** Pathogenic variant

## GENE CONTEXT

**KCNQ1, heterozygous:** KCNQ1 encodes the pore-forming alpha subunit of the cardiac IKs potassium channel, and heterozygous loss-of-function or dominant-negative variants reduce repolarizing current and prolong the cardiac action potential. This mechanism underlies type 1 long QT syndrome, an autosomal dominant condition that can present as syncope, cardiac arrest, or sudden death, often triggered by exertion. Certain gain-of-function variants in this gene are instead linked to familial atrial fibrillation. Clinical expression is variable, ranging from asymptomatic carriers to symptomatic arrhythmia. [1]

## INTERPRETATION

A missense variant was identified in KCNQ1 (c.760G>A; p.Val254Met). This variant is absent from gnomAD v4.1.0 (PM2). This variant has been reported in affected probands exhibiting QTc prolongation above 480 milliseconds and an exercise-associated event, which together are highly specific for long QT syndrome 1 (PP4) [2]. This variant has been reported in at least 4 additional probands affected with long QT syndrome 1 (PS4) [2]. The variant segregates with long QT syndrome through 10 affected family members across 5 probands (PP1) [2]. The computational predictor REVEL gives a score of 0.918, above the ClinGen Potassium Channel Arrhythmia VCEP threshold, predicting a damaging effect on protein function (PP3). Functional studies demonstrate a dominant negative electrophysiological defect in two manual patch-clamp studies (PS3) [3,4]. Based on this evidence, this variant has been classified as Pathogenic per ACMG/AMP guidelines as specified by the ClinGen Potassium Channel Arrhythmia VCEP.

## FOLLOW UP RECOMMENDATIONS

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

## REFERENCES

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## TECHNICAL AND REGULATORY INFORMATION

| GENE | TRANSCRIPT | GENE | TRANSCRIPT | GENE | TRANSCRIPT | GENE | TRANSCRIPT |
|---|---|---|---|---|---|---|---|
| **ABCC9** | NM_020297.4 | **FHL1** | NM_001159699.2 | **MAP2K2** | NM_030662.4 | **SCN5A** | NM_000335.5 |
| **ACADVL** | NM_000018.4 | **FKRP** | NM_024301.5 | **MIB1** | NM_020774.4 | **SDHA** | NM_004168.4 |
| **ACTC1** | NM_005159.5 | **FKTN** | NM_001079802.2 | **MRAS** | NM_001085049.3 | **SGCD** | NM_000337.6 |
| **ACTN2** | NM_001103.4 | **FLNC** | NM_001458.5 | **MTO1** | NM_012123.4 | **SHOC2** | NM_007373.4 |
| **AGL** | NM_000642.3 | **GAA** | NM_000152.5 | **MYBPC3** | NM_000256.3 | **SLC22A5** | NM_003060.4 |
| **ALMS1** | NM_001378454.1 | **GATA4** | NM_001308093.3 | **MYH6** | NM_002471.4 | **SOS1** | NM_005633.4 |
| **ALPK3** | NM_020778.5 | **GATA6** | NM_005257.6 | **MYH7** | NM_000257.4 | **SOS2** | NM_006939.4 |
| **ANK2** | NM_001148.6 | **GJA5** | NM_181703.4 | **MYL2** | NM_000432.4 | **TAFAZZIN** | NM_000116.5 |
| **BAG3** | NM_004281.4 | **GLA** | NM_000169.3 | **MYL3** | NM_000258.3 | **TBX20** | NM_001077653.2 |
| **BRAF** | NM_004333.6 | **HAND1** | NM_004821.3 | **MYPN** | NM_032578.4 | **TCAP** | NM_003673.4 |
| **CACNA1C** | NM_000719.7 | **HCN4** | NM_005477.3 | **NEXN** | NM_144573.4 | **TECRL** | NM_001010874.5 |
| **CALM1** | NM_006888.6 | **HFE** | NM_000410.4 | **NF1** | NM_001042492.3 | **TGFB3** | NM_003239.5 |
| **CALM2** | NM_001743.6 | **HRAS** | NM_005343.4 | **NKX2-5** | NM_004387.4 | **TMEM43** | NM_024334.3 |
| **CALM3** | NM_005184.4 | **JPH2** | NM_020433.5 | **NPPA** | NM_006172.4 | **TMEM70** | NM_017866.6 |
| **CASQ2** | NM_001232.4 | **JUP** | NM_002230.4 | **NRAS** | NM_002524.5 | **TMPO** | NM_001032283.3 |
| **CAV3** | NM_033337.3 | **KCNA5** | NM_002234.4 | **PKP2** | NM_001005242.3 | **TNNC1** | NM_003280.3 |
| **CBL** | NM_005188.4 | **KCNE1** | NM_000219.6 | **PLN** | NM_002667.5 | **TNNI3** | NM_000363.5 |
| **CDH2** | NM_001792.5 | **KCNE2** | NM_172201.2 | **PPP1CB** | NM_002709.3 | **TNNI3K** | NM_015978.3 |
| **CPT2** | NM_000098.3 | **KCNH2** | NM_000238.4 | **PRDM16** | NM_022114.4 | **TNNT2** | NM_001276345.2 |
| **CSRP3** | NM_003476.5 | **KCNJ2** | NM_000891.3 | **PRKAG2** | NM_016203.4 | **TPM1** | NM_001018005.2 |
| **CTNNA3** | NM_013266.4 | **KCNJ8** | NM_004982.4 | **PTPN11** | NM_002834.5 | **TRDN** | NM_006073.4 |
| **DES** | NM_001927.4 | **KCNQ1** | NM_000218.3 | **RAF1** | NM_002880.4 | **TRPM4** | NM_017636.4 |
| **DMD** | NM_004006.3 | **KRAS** | NM_004985.5 | **RBM20** | NM_001134363.3 | **TTN** | NM_001267550.2 |
| **DSC2** | NM_024422.6 | **LAMP2** | NM_002294.3 | **RYR2** | NM_001035.3 | **TTR** | NM_000371.4 |
| **DSG2** | NM_001943.5 | **LDB3** | NM_007078.3 | **SCN1B** | NM_001037.5 | **VCL** | NM_014000.3 |
| **DSP** | NM_004415.4 | **LMNA** | NM_170707.4 | **SCN2B** | NM_004588.5 | | |
| **EMD** | NM_000117.3 | **LZTR1** | NM_006767.4 | **SCN3B** | NM_001040151.2 | | |
| **EYA4** | NM_004100.5 | **MAP2K1** | NM_002755.4 | **SCN4B** | NM_174934.4 | | |

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## TECHNICAL AND REGULATORY INFORMATION

### TEST METHODOLOGY

The Arboretum Combined Hereditary Cardiomyopathy and Arrhythmia 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 109 genes listed above for sequence variants and multi-exon copy number variants in genes selected for cardiomyopathy and arrhythmia 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 and arrhythmia. Pathogenic and likely pathogenic variants in targeted genes that are not part of the primary cardiomyopathy and arrhythmia-risk result, including variants associated with carrier status for autosomal recessive conditions, variants in genes with preliminary evidence of cardiomyopathy and arrhythmia 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 or arrhythmia risk. A positive genetic result alone does not establish a cardiomyopathy or arrhythmia 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 cardiomyopathy or arrhythmia predisposition. A negative result does not exclude a hereditary cardiomyopathy or arrhythmia 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.

## RELEVANT LITERATURE


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## RELEVANT LITERATURE


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