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 Hereditary Aortopathy Test

GENES ANALYZED

ACTA2, ARIH1, BGN, CBS, COL3A1, COL5A1, COL5A2, FBN1, FBN2, FLNA, FOXE3, LOX, LTBP3, MED12, MFAP5, MYH11, MYLK, NOTCH1, PKD2, PLOD1, PLOD3, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1, TGFBR2

PRIMARY TEST RESULTS SUMMARY

POSITIVE - FBN1- clinically significant finding(s)

One heterozygous pathogenic variant detected in FBN1, associated with Marfan syndrome.

GENE	VARIANT	PROTEIN CHANGE	ZYGOSITY	CLASSIFICATION
FBN1	c.7775G>T	p.Cys2592Phe	Heterozygous	Pathogenic

Variants are reported using the GRCh38/hg38 human reference genome assembly.

Detailed findings continued on next page.

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PRIMARY FINDING **FBN1** Pathogenic variant

GENE CONTEXT

FBN1, heterozygous: FBN1 encodes fibrillin-1, a major structural component of the extracellular matrix, and underlies Marfan syndrome and related type-1 fibrillinopathies with autosomal dominant inheritance. Heterozygous pathogenic variants confer susceptibility to a multisystem phenotype whose prominent features include ascending aortic root dilatation with risk of aortic dissection, ectopia lentis, and skeletal manifestations such as long-bone overgrowth; mitral valve abnormalities and additional skeletal, skin, and dural findings are also reported. Clinical expression is variable within and between families and is age-related, with cardiovascular involvement representing the principal source of clinical significance across the lifespan. [1]

INTERPRETATION

The FBN1 c.7775G>T; p.Cys2592Phe variant is absent from gnomAD v2.1.1, supporting PM2. This variant has been identified in at least two additional individuals with clinical features of Marfan syndrome, supporting PS4. This variant affects a cysteine residue in a calcium-binding EGF-like domain, where cysteine residues are essential for disulfide bridge formation and protein structure, supporting PM1 [2,3]. Computational prediction tools support a damaging effect on protein function (REVEL 0.839), supporting PP3. The high missense constraint z-score for FBN1 (z=8.18) supports PP2[4]. This variant is classified as Pathogenic according to 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. Takeda N et al. Impact of pathogenic FBN1 variant types on the progression of aortic disease in patients with Marfan syndrome. Circ Genom Precis Med. 2018 Jun;11(6):e002058. doi: 10.1161/CIRCGEN.117.002058. PMID: 29848614.
2. Zeyer KA et al. Engineered mutations in fibrillin-1 leading to Marfan syndrome act at the protein, cellular and organismal levels. Mutat Res Rev Mutat Res. 2015 Jul-Sep;765:7-18. doi: 10.1016/j.mrrev.2015.04.002. Epub 2015 May 5. PMID: 26281765.
3. Muiño-Mosquera L et al. Tailoring the American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for the interpretation of sequenced variants in the FBN1 gene for Marfan syndrome. Circ Genom Precis Med. 2018 Jun;11(6):e002039. doi: 10.1161/CIRCGEN.117.002039. PMID: 29875124.
4. Arnaud P et al. Clinical relevance of genotype-phenotype correlations beyond vascular events in a cohort study of 1500 Marfan syndrome patients with FBN1 pathogenic variants. Genet Med. 2021 Jul;23(7):1296-1304. doi: 10.1038/s41436-021-01132-x. Epub 2021 Mar 17. PMID: 33731869; PMCID: PMC8257477.

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TECHNICAL AND REGULATORY INFORMATION

GENE AND TRANSCRIPT PAIRS

GENE	TRANSCRIPT	GENE	TRANSCRIPT	GENE	TRANSCRIPT
ACTA2	NM_001613.4	**LOX**	NM_002317.7	**SKI**	NM_003036.4
ARIH1	NM_005744.5	**LTBP3**	NM_001130144.3	**SLC2A10**	NM_030777.4
BGN	NM_001711.6	**MED12**	NM_005120.3	**SMAD2**	NM_005901.6
CBS	NM_000071.3	**MFAP5**	NM_003480.4	**SMAD3**	NM_005902.4
COL3A1	NM_000090.4	**MYH11**	NM_002474.3	**SMAD4**	NM_005359.6
COL5A1	NM_000093.5	**MYLK**	NM_053025.4	**SMAD6**	NM_005585.5
COL5A2	NM_000393.5	**NOTCH1**	NM_017617.5	**TGFB2**	NM_003238.6
FBN1	NM_000138.5	**PKD2**	NM_000297.4	**TGFB3**	NM_003239.5
FBN2	NM_001999.4	**PLOD1**	NM_000302.4	**TGFBR1**	NM_004612.4
FLNA	NM_001110556.2	**PLOD3**	NM_001084.5	**TGFBR2**	NM_003242.6
FOXE3	NM_012186.3	**PRKG1**	NM_006258.4		

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TEST METHODOLOGY

The Arboretum Hereditary Aortopathy Test is performed on genomic DNA extracted from buccal swabs, saliva, or whole blood. Nucleic acid extraction, library preparation, and sequencing were performed by GenebyGene, Ltd. Variant calling, interpretation, and reporting are performed by Arboretum Clinical, LLC. 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. Bioinformatics pipeline versions, configuration, and analysis records are maintained by the laboratory and are traceable to the patient report.

The test analyzes the 32 genes listed above for sequence variants and multi-exon copy number variants in genes selected for aortopathy 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.

Pathogenic and likely pathogenic variants are reported. Likely benign and benign variants are not reported. Only in rare cases are Variants of Uncertain Significance (VUS) reported. Absence from the report does not mean that no such variants were detected. A primary positive result is reported when one or more pathogenic or likely pathogenic variants are identified in genes associated with a hereditary aortopathy. Pathogenic and likely pathogenic variants in targeted genes that are not part of the primary aortopathy-risk result, including variants associated with carrier status for autosomal recessive conditions, 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%. Variant calls were filtered based on a quality score that incorporates per-site coverage depth, base quality, mapping quality, and variant allele fraction thresholds. 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

This monogenic panel does not assess polygenic risk, environmental risk, lifestyle risk, or all possible genetic contributors to disease. A positive genetic result alone does not establish an aortopathy 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 aortopathy predisposition. A negative result does not exclude a hereditary aortopathy syndrome due to variants in genes not covered by this panel. A likely pathogenic or pathogenic result is identified in approximately 3-35% of individuals with both thoracic aortic disease and at least one family member with an aneurysm [Hicks et al. *J Vasc Surg,* 2017; Jabagi et al, *Genet Med*, 2026].

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. This assay may not detect all single-exon copy number variants, complex structural rearrangements, deep intronic variants, regulatory variants, tissue-specific splice effects, variants in transcript isoforms outside the analyzed transcript set, low-level mosaicism, variants in regions of low or complex coverage, or variant types outside the validated scope of the assay.

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.

Unless specifically stated, this assay does not determine whether multiple variants are in cis or trans. For autosomal recessive genes, phase is often necessary to distinguish biallelic disease risk, when variants are in trans, from carrier status, when variants are in cis. For autosomal dominant genes, phase may affect interpretation in selected contexts. Parental, family, or orthogonal testing may be needed to establish phase.

Mosaic variants with variant allele fractions outside the assay's validated reporting range, including variants with greater than 20% variant allele frequency deviation for germline heterozygous calls, may not be reliably detected or interpreted. Variant allele fraction may not reflect the proportion of affected tissues. Bone marrow or stem-cell 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. The laboratory maintains a procedure for variant reassessment and report amendment or addendum when appropriate.

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: Feng Zhou, PhD, HCLD(ABB), MB(ASCP). Both laboratories are certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to 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

- Albornoz G et al. Familial thoracic aortic aneurysms and dissections--incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg. 2006 Oct;82(4):1400-5. doi: 10.1016/j.athoracsur.2006.04.098. PMID: 16996941.
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RELEVANT LITERATURE

- Jabagi H et al. Utilization of current ACC/AHA genetic testing recommendations for thoracic aortic disease at a large adult aortic center. Genet Med. 2026 Apr;28(4):102069. doi: 10.1016/j.gim.2026.102069. Epub 2026 Jan 21. PMID: 41581011.
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