Ambry Genetics®
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SAMPLE REPORT - 04/09/2026

Ordered By	Contact ID:7640656	Org ID:1	Patient Legal Name: **Unknown, Unknown**
Medical Professional:	Unknown, Unknown, MD		Accession #: **01-272294** Specimen #:
Client:	Ambry		AP2 Order #: 3625031 Specimen: Blood EDTA (Purple top)
Additional Authorized Recipient:			Birthdate: 01/01/9999 Sex assigned at birth: U
			MRN #: N/A Collected: 04/06/2026
			Indication: Internal Testing Received: 04/06/2026
			Test Started: 04/06/2026

CardioNext®: Analyses of 92 Genes Associated with Inherited Cardiomyopathies and Arrhythmias

RESULTS

MYBPC3 **Pathogenic Mutation: c.3491-2A>T**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **c.3491-2A>T** pathogenic mutation in the *MYBPC3* gene.
- This result is consistent with a diagnosis of hypertrophic cardiomyopathy (HCM) or other *MYBPC3*-related cardiomyopathy.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (92 total): ***ABCC9, ACTC1, ACTN2, AKAP9, ALPK3, ANK2, ANKRD1, BAG3, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, EMD, EYA4, FKRP, FKTN, FLNC, GATAD1, GLA, GPD1L, HCN4, JPH2, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNQ1, LAMA4, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, NKX2-5, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN1B, SCN2B, SCN3B, SCN4B, SCN5A, SNTA1, TAZ, TBX20, TBX5, TCAP, TGFB3, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, TXNRD2*** **and** ***VCL*** **(sequencing and deletion/duplication);** ***ALMS1, CALM2, CALM3, DOLK, FHL1, RIT1, SCN10A, SOS1*** **and** ***TECRL*** **(sequencing only)**.

MYBPC3 **Additional Information**

The **c.3491-2A>T** intronic pathogenic mutation results from an A to T substitution two nucleotides before coding exon 32 of the *MYBPC3* gene. This alteration has been detected in a hypertrophic cardiomyopathy (HCM) genetic testing cohort in individuals who were reported to have HCM (Alfares AA et al. *Genet Med.* 2015;17:880-8; Walsh R et al. *Genet Med.* 2017 Feb;19:192-203). This variant is considered to be rare based on population cohorts in the Genome Aggregation Database (gnomAD). *In silico* splice site analysis predicts that this alteration will weaken the native splice acceptor site. In addition to the clinical data presented in the literature, alterations that disrupt the canonical splice site are expected to cause aberrant splicing, resulting in an abnormal protein or a transcript that is subject to nonsense-mediated mRNA decay. As such, this alteration is classified as a disease-causing mutation.

The *MYBPC3* gene (NM_000256.3), which contains 34 coding exons and is located on chromosome 11p11.2, encodes the cardiac myosin-binding protein C. Pathogenic variants in this gene have been associated with a spectrum of *MYBPC3*-related cardiomyopathies, including hypertrophic cardiomyopathy (HCM) and left ventricular noncompaction cardiomyopathy (LVNC), which can be inherited in an autosomal dominant or autosomal recessive fashion. HCM is defined by unexplained left ventricular hypertrophy with increased septal or posterior wall thickness, often leading to early onset syncope, ventricular fibrillation, episodic chest pain, dyspnea, and cardiac arrest. LVNC is characterized by excessive and prominent trabeculations of the left ventricle with deep intertrabecular recesses and a thickening of the endocardial noncompacted layer. Variable expression and reduced penetrance are observed in heterozygous individuals. Autosomal recessive *MYBPC3*-related cardiomyopathy is typically more severe with an earlier age of onset, during adolescence through early adulthood, although some patients with neonatal-onset have also been reported (Wessels MW et al. *Eur J Hum Genet*, 2015 Jul;23:922-8; Marian AJ et al. *Circ Res*, 2017 Sep;121:749-770; Sedaghat-Hamedani F et al. *Eur Heart J*, 2017 Dec;38:3449-3460; Ingles J et al. *Circ Genom Precis Med*, 2019 02;12:e002460; van Waning JI et al. *J Am Heart Assoc*, 2019 12;8:e012993; Allouba M et al. *Eur Heart J*, 2023 Dec;44:5146-5158). Loss of function has been reported as the mechanism of disease for *MYBPC3*-related cardiomyopathies.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- CardioNext® (Product Code 8911)

ELECTRONICALLY SIGNED BY

C. Christopher Lau, Ph.D., FACMG, CGMBS, on 04/09/2026 at 17:05:15 pm

ASSAY INFORMATION

General methodology: Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's specimen using standardized methodology and quantified. Sequence enrichment of the targeted coding exons and adjacent intronic nucleotides is carried out by a bait-capture methodology using long biotinylated oligonucleotide probes followed by polymerase chain reaction (PCR) and Next-Generation sequencing (NGS). Variants in regions complicated by pseudogene interference, variant calls not satisfying depth of coverage and variant allele frequency quality thresholds, and potentially homozygous variants are verified by Sanger sequencing. Gross deletion/duplication analysis is performed using a custom pipeline based on read-depth from NGS data followed by a confirmatory orthogonal method, as needed. Mobile element insertions, if detected, are confirmed by a confirmatory orthogonal method, as needed.

NCBI reference sequences: *ABCC9*- NM_005691.2, *ACTC1*- NM_005159.4, *ACTN2*- NM_001103.2, *AKAP9*- NM_005751.4, *ALMS1*- NM_015120.4, *ALPK3*- NM_020778.4, *ANK2*- NM_001148.4, *ANKRD1*- NM_014391.2, *BAG3*- NM_004281.3, *CACNA1C*- NM_000719.6, *CACNA2D1*- NM_000722.2, *CACNB2*- NM_201590.2, *CALM1*- NM_006888.4, *CALM2*- NM_001743.4, *CALM3*- NM_005184.2, *CASQ2*- NM_001232.3, *CAV3*- NM_033337.2, *CRYAB*- NM_001885.1, *CSRP3*- NM_003476.3, *DES*- NM_001927.3, *DMD*- NM_004006.2, *DOLK*- NM_014908, *DSC2*- NM_024422.3, *DSG2*- NM_001943.3, *DSP*- NM_004415.2, *EMD*- NM_000117.2, *EYA4*- NM_004100.4, *FHL1*- NM_001449, *FKTN*- NM_001079802.1, *FKRP*- NM_024301.4, *FLNC*- NM_001458.4, *GATAD1*- NM_021167.3, *GLA*- NM_000169.2, *GPD1L*- NM_015141.3, *HCN4*- NM_005477.2, *JPH2*- NM_020433.4, *JUP*- NM_002230.2, *KCND3*- NM_004980.4, *KCNE1*- NM_000219.3, *KCNE2*- NM_172201.1, *KCNE3*- NM_005472.4, *KCNH2*- NM_000238.3, *KCNJ2*- NM_000891.2, *KCNJ5*- NM_000890.3, *KCNJ8*- NM_004982.2, *KCNQ1*- NM_000218.2, *LAMA4*- NM_002290.3, *LAMP2*- NM_002294.2, *LDB3*- NM_007078.2, *LMNA*- NM_170707.2, *MYBPC3*- NM_000256.3, *MYH6*- NM_002471.3, *MYH7*- NM_000257.4, *MYL2*- NM_000432.3, *MYL3*- NM_000258.2, *MYOZ2*- NM_016599.4, *MYPN*- NM_032578.2, *NEXN*- NM_144573.3, *NKX2-5*- NM_004387.3, *PKP2*- NM_004572.3, *PLN*- NM_002667.3, *PRKAG2*- NM_016203.3, *PTPN11*- NM_002834.3, *RAF1*- NM_002880.3, *RBM20*- NM_001134363.1, *RIT1*- NM_006912.4, *RYR2*- NM_001035.2, *SCN10A*- NM_006514.3, *SCN1B*- NM_001037.4, *SCN2B*- NM_004588.4, *SCN3B*- NM_018400.3, *SCN4B*- NM_174934.3, *SCN5A*- NM_198056.2, *SNTA1*- NM_003098.2, *SOS1*- NM_005633.3, *TAZ*- NM_000116.3, *TBX5*- NM_000192.3, *TBX20*- NM_001077653.2, *TCAP*- NM_003673.3, *TECRL*- NM_001010874.4, *TGFB3*- NM_003239.2, *TMEM43*- NM_024334.2, *TNNC1*- NM_003280.2, *TNNI3*- NM_000363.4, *TNNT2*- NM_001001430.1, *TPM1*- NM_001018005.1, *TRDN*- NM_006073.2, *TRPM4*- NM_017636.3, *TTN*- NM_003319.4, *TTR*- NM_000371.3, *TXNRD2*- NM_006440.3, *VCL*- NM_014000.2.

Analytical range: This test detects variants in the coding domains and well into the flanking 5' and 3' ends of the introns and untranslated regions. Unless explicitly stated, sequence and copy number variants in the promoter, non-coding exons, or 3' untranslated regions are not routinely reported.

Analytical range exceptions:

- ***ALPK3:*** only full gene deletion/duplications are routinely reported.
- ***ANK2:*** variants in the brain-specific exon 38 are not reported.
- ***FLNC*:** sequence variations of exons 46-48 are not analyzed or reported. Only full gene deletion/duplications are routinely reported.
- ***TTN*:** only truncating variants are routinely reported.
- **Gross deletion/duplication analysis is not performed for the following genes:** *ALMS1, CALM2, CALM3, DOLK, FHL1, RIT1, SCN10A, SOS1,* and *TECRL.*

Reporting: Results reported herein may be of constitutional or somatic origin. This methodology cannot differentiate between these possibilities. In result reports, variants in the following classifications are always reported, and are based on the following definitions and clinical recommendations:

- **Pathogenic Variant:** variants with sufficient evidence to classify as pathogenic (capable of causing disease). Targeted testing of at-risk relatives and appropriate changes in medical management for pathogenic variant carriers recommended. Previously described pathogenic variants, including intronic variants at any position, are always reported when detected.
- **Variant, Likely Pathogenic (VLP):** variants with strong evidence in favor of pathogenicity. Targeted testing of at-risk relatives and appropriate changes in medical management for VLP carriers typically recommended. Previously described likely pathogenic variants, including intronic VLPs at any position, are always reported when detected.
- **Variant, Uncertain Significance (VUS):** variants with limited and/or conflicting evidence regarding pathogenicity. Familial testing via the Family Studies Program may be recommended. Medical management to be based on personal/family clinical histories, not VUS carrier status. Note, intronic VUSs are always reported out to 5 base pairs from the splice junction when detected.

Variants of unlikely clinical significance (those with strong/very strong evidence to argue against pathogenicity) are not routinely included in results. These include findings classified as "likely benign" and "benign" variants. Classification and interpretation of variants may change over time with accumulating evidence and scientific advancements. Updated classifications may be reported through reclassification notices; however, clients should re-contact the laboratory or visit ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) for the most up to date information regarding the current interpretation of results.

All results, including those from prior genetic testing for themselves and/or family members, will be reported as described above.

Gender identity (if provided) is not used in the interpretation of results, and sex assigned at birth is used in the interpretation of results only when

necessary. Currently, there are insufficient data to determine specific risk adjustments for transgender, nonbinary, or intersex individuals.

Assay Information Continued on Next Page

ASSAY INFORMATION *(Supplement to Test Results - Continued)*

Resources: The following references are used in variant analysis and classification when applicable for observed genetic alterations.

1. The 1000 Genomes Project Consortium. An integrated map of genetic variation from 1092 human genomes. *Nature*. 2012;491:56-65.
2. ACMG Standards and guidelines for the interpretation of sequence variants. *Genet Med.* 2015 May;17(5):405-23.
3. Ambry Genetics Variant Classification Scheme. http://www.ambrygen.com/variant-classification.
4. Berkeley Drosophila Genome Project [Internet]. Reese MG et al. *J Comp Biol.* 1997;4:311-23. http://www.fruitfly.org/seq_tools/splice.html.
5. Database of Single Nucleotide Polymorphisms (dbSNP) [Internet]. Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine (dbSNP Build ID:135) Available from: www.ncbi.nlm.nih.gov/SNP. Accessed Jan 2012).
6. ESEfinder [Internet]. Smith PJ, et al. (2006) *Hum Mol Genet.* 15(16):2490-2508 and Cartegni L, et al. *Nucleic Acid Research.* 2003;31(13):3568-3571. http://rulai.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home.
7. Exome Variant Server, NHLBI Exome Sequencing Project (ESP) [Internet], Seattle WA. Available from: evs.gs.washington.edu/EVS.
8. Grantham R. Amino acid difference formula to help explain protein evolution. *Science.* 1974;185(4151):862-864.
9. HGMD® [Internet]: Stenson PD et al. *Genome Med.* 2009;1(1):13. www.hgmd.cf.ac.uk.
10. Landrum MJ et al. ClinVar: public archive of relationships among sequence variation and human phenotype. *Nucleic Acids Res*. 2014 Jan 1;42(1):D980-5. doi: 10.1093/nar/gkt1113. PubMed PMID: 24234437.
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12. Feng BJ. PERCH: A Unified Framework for Disease Gene Prioritization. *Hum Mutat.* 2017 Mar;38(3):243-251.
13. Exome Aggregation Consortium (ExAC) [Internet], Cambridge, MA. Available from: http://exac.broadinstitute.org.
14. Genome Aggregation Database (gnomAD) [Internet], Cambridge, MA. Available from: http://gnomad.broadinstitute.org.
15. Lek M et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016 Aug 17;536(7616):285-91. PMID: 27535533
16. Mu W et al. *J Mol Diagn*. 2016 Oct 4. PubMed PMID: 27720647
17. Karczewski KJ et al. *Nature*. 2020 May;581(7809):434-443. PMID: 32461654
18. Splicing Prediction: Jaganathan K et al. *Cell.* 2019 Jan 24; 176(3):535-548.e24. PMID: 30661751

Disclaimer: This test was developed, and its performance characteristics were determined by Ambry Genetics Corporation. It has not been cleared or approved by the US Food and Drug Administration (FDA). The FDA does not require this test to go through premarket FDA review. It should not be regarded as investigational or for research. This test should be interpreted in context with other clinical findings. This report does not represent medical advice. Any questions, suggestions, or concerns regarding interpretation of results should be forwarded to a genetic counselor, medical geneticist, or physician skilled in interpretation of the relevant medical literature. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. This test analyzes the following types of mutations: nucleotide substitutions, small deletions (up to 25 bp), small insertions (up to 10 bp), small indels, and gross deletions/duplications. Unless otherwise noted in the methodology section above, this test is not intended to analyze the following types of alterations: gross rearrangements, deep intronic variations, mobile element insertions, and other unknown abnormalities. The pattern of mutation types varies by gene, and this test detects a high but variable percentage of known and unknown mutations of the classes stated. A negative result from the analysis cannot rule out the possibility that the tested individual carries a rare unexamined mutation or mutation in the undetectable group. This test is designed and validated to be capable of detecting ~99.9% of described mutations in the genes represented on the test, listed above (analytical sensitivity). The clinical sensitivity of this test may vary widely according to the specific clinical and family history. Mutations in other genes or the regions not analyzed by this test can also give rise to similar clinical conditions. Although molecular tests are highly accurate, rare diagnostic errors may occur. Possible diagnostic errors include sample mix-up, erroneous paternity identification, technical errors, clerical errors, and genotyping errors. Genotyping errors can result from trace contamination of PCR reactions, from maternal cell contamination in fetal samples, from rare genetic variants that interfere with analysis, germline or somatic mosaicism, presence of pseudogenes, technical difficulties in regions with high GC content or homopolymer tracts, active hematologic disease, a history of allogeneic bone marrow or peripheral stem cell transplant, or from other sources. Rare variants present in the human genome reference sequence (GRCh37.p5/hg19) or rare misalignment due to presence of pseudogenes can lead to misinterpretation of patient sequence data.

Ambry Genetics®

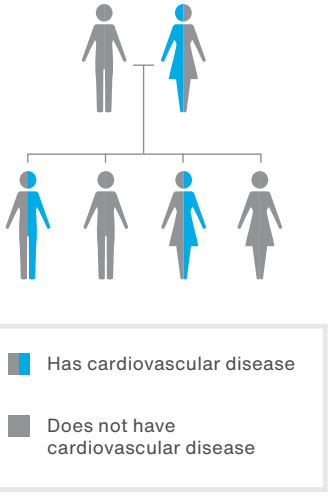
Understanding Your Positive Cardiovascular Genetic Test Result

INFORMATION FOR PATIENTS WITH A PATHOGENIC MUTATION OR VARIANT THAT IS LIKELY PATHOGENIC

Result	POSITIVE	Your testing shows that you have a pathogenic (disease-causing) mutation, or a variant that is likely disease-causing, in a gene that causes an inherited cardiovascular disorder. Both mutations and variants that are likely disease-causing should be treated as the same type of positive result.
Gene	DEFINITION	Everyone has two copies of each gene. We get one copy from each of our parents. Mutations (changes in the gene, like spelling mistakes) in one copy of any of the genes in this test can cause an inherited cardiovascular disorder (like cardiomyopathy or arrhythmia).
Management Options	PATIENTS WITH CARDIOMYOPATHY OR ARRHYTHMIA	Treatment options include: medications, surgery, pacemakers, implantable cardioverter defibrillators (ICDs), or avoiding certain athletic activities. Talk to your doctor about which may be right for you.
Screening Options	FAMILY MEMBERS	Options for screening and early detection for inherited cardiomyopathy or arrhythmia include: physical exams, echocardiograms, electrocardiograms (EKGs), and cardiac MRI. Talk to your doctor about which may be right for you and/or your family.
Next Steps	DISCUSS	Please share this with family members so they can talk with their doctors and learn more. They can now be tested for this same mutation, if they choose to.
Reach Out	RESOURCES	• Ambry's Cardiology Site for Families patients.ambrygen.com/cardiology • National Society of Genetic Counselors nsgc.org • Hypertrophic Cardiomyopathy Association 4hcm.org • Sudden Arrhythmia Death Syndromes (SADS) Foundation sads.org • Children's Cardiomyopathy Foundation childrenscardiomyopathy.org • Genetic Information Nondiscrimination Act (GINA) ginahelp.org

Cardiovascular Mutations in the Family

Your close family members (like your parents, brothers, sisters, children) have a 50/50 chance of having the mutation that you carry, and other family members (like your aunts, uncles, cousins) may also have it. Your relatives can now be tested for this same mutation. Those who DO NOT have this mutation may not be at risk for your cardiovascular disease and can avoid unneeded screening.



Please talk with your doctor or genetic counselor about this. The field of genetics is continuously changing, so updates related to your result, medical recommendations, and/or potential treatments may be available over time. This information is not meant to replace a discussion with a healthcare provider, and should not be considered or taken as medical advice.

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