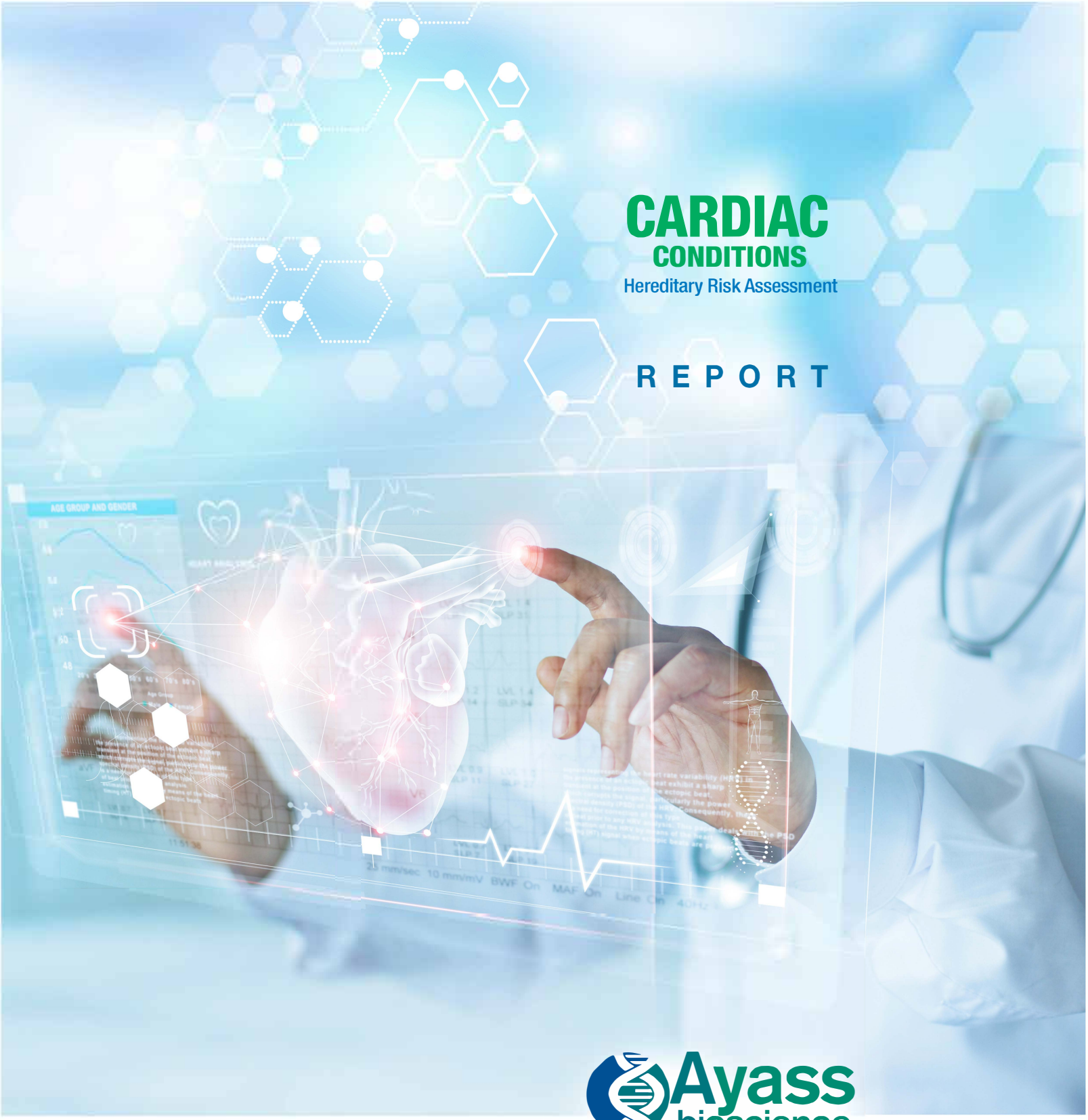
CARDIAC CONDITIONS

Hereditary Risk Assessment

REPORT



Ayass bioscience LLC™
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Patient Name: XXXXXXXXX

Date of Birth: XX/XX/XXXX

Accession #: XXXXXXXXX

Hereditary Cardio Screening Result

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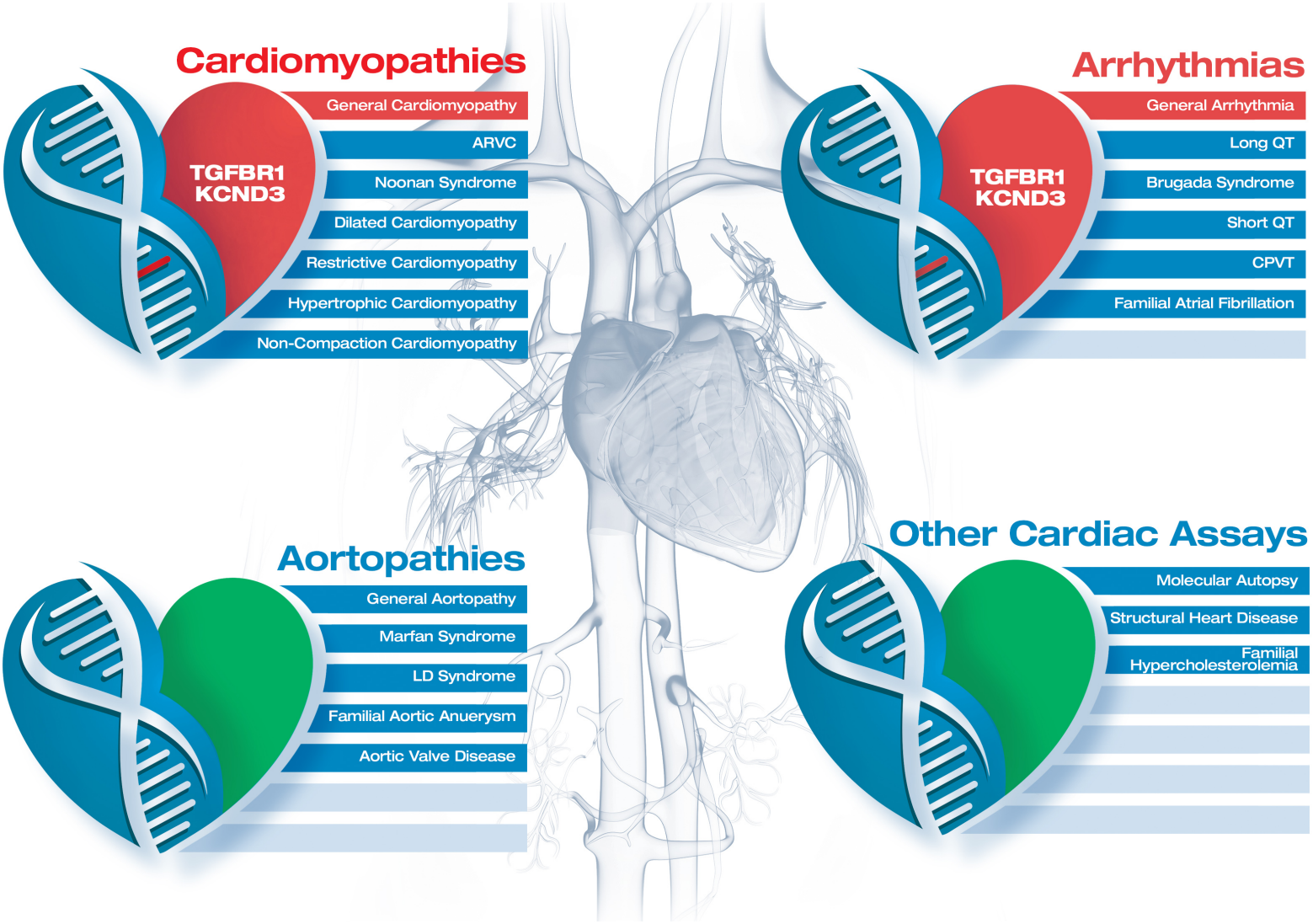
Patient Name: XXXXXX
DOB: XX/XX/XXXX
Accession #: XXXXXX
Collection Date: XX/XX/XXXX



Legend:

Red: One or more pathogenic or likely pathogenic variants were detected on the indicated genes for the related condition(s)

Orange: One or more variants of unknown significance (VUS) were detected on the indicated genes for the related condition(s)

Green: No significant variants were detected on genes related to the indicated conditions.

Hereditary Cardio Screening Result

Ayass bioscience LLC©
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Patient Name: XXXXXX
Accession #: XXXXXX

DOB: XX/XX/XXXX
Collection Date: XX/XX/XXXX

RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT
	Specimen Type:	Name: XXXXXX
	Collection Date:	Date of Birth:
	Accession Date:	Gender:
	Received Date:	Accession #: XXXXXX
	Report Date: 13 Sep XXXX	File: XXXXXX
ORDERING PHYSICIAN:		
CLINICAL BACKGROUND / INDICATIONS:		

RESULT: POSITIVE - CLINICALLY SIGNIFICANT VARIANT IDENTIFIED

Note: "CLINICALLY SIGNIFICANT", as defined in the report, is a genetic change that has been directly reported to contribute to the development of disease and is associated with the potential to alter medical intervention.

CLINICALLY SIGNIFICANT VARIANTS

Note: "CLINICALLY SIGNIFICANT", as defined in the report, is a genetic change that has been directly reported to contribute to the development of disease and is associated with the potential to alter medical intervention.

CLASSIFICATION	GENE	RSID	MUTATION	INTERPRETATION
Pathogenic	**TGFBR1**		**c.1041C>A (p.Cys347*)** HET	**HIGH RISK FOR GENERAL CARDIOMYOPATHY AND GENERAL ARRHYTHMIA**

DETAILS ABOUT c.1041C>A (p.Cys347*): NM_004612.3

Functional Significance:
The heterozygote germline TGFBR1 variant c.1041C>A is predicted to result in abnormal protein translation of the TGFBR1 protein at amino acid position 347 (p.Cys347*) .
Predicted effect(s) on the protein: Nonsense

Clinical Significance: High Risk for General Cardiomyopathy and General Arrythmia
This mutation is associated with increased risk for Cardiac Conditions and should be regarded as clinically significant.

Evidence

*** FROM OMIM SELECTION ***

Disease Summary: Loeys-Dietz syndrome is a disorder that affects the connective tissue in many parts of the body. Connective tissue provides strength and flexibility to structures such as bones, ligaments, muscles, and blood vessels.

There are five types of Loeys-Dietz syndrome, labelled types I through V, which are distinguished by their genetic cause. Regardless of the type, signs and symptoms of Loeys-Dietz syndrome can become apparent anytime from childhood through adulthood, and the severity is variable.

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Loeys-Dietz syndrome is characterized by enlargement of the aorta, which is the large blood vessel that distributes blood from the heart to the rest of the body. The aorta can weaken and stretch, causing a bulge in the blood vessel wall (an aneurysm). Stretching of the aorta may also lead to a sudden tearing of the layers in the aorta wall (aortic dissection). People with Loeys-Dietz syndrome can also have aneurysms or dissections in arteries throughout the body and have arteries with abnormal twists and turns (arterial tortuosity).

Individuals with Loeys-Dietz syndrome often have skeletal problems including premature fusion of the skull bones (craniosynostosis), an abnormal side-to-side curvature of the spine (scoliosis), either a sunken chest (pectus excavatum) or a protruding chest (pectus carinatum), an inward- and upward-turning foot (clubfoot), flat feet (pes planus), or elongated limbs with joint deformities called contractures that restrict the movement of certain joints. A membrane called the dura, which surrounds the brain and spinal cord, can be abnormally enlarged (dural ectasia). In individuals with Loeys-Dietz syndrome, dural ectasia typically does not cause health problems. Malformation or instability of the spinal bones (vertebrae) in the neck is a common feature of Loeys-Dietz syndrome and can lead to injuries to the spinal cord. Some affected individuals have joint inflammation (osteoarthritis) that commonly affects the knees and the joints of the hands, wrists, and spine.

People with Loeys-Dietz syndrome may bruise easily and develop abnormal scars after wound healing. The skin is frequently described as translucent, often with stretch marks (striae) and visible underlying veins. Some individuals with Loeys-Dietz syndrome develop an abnormal accumulation of air in the chest cavity that can result in the collapse of a lung (spontaneous pneumothorax) or a protrusion of organs through gaps in muscles (hernias). Other characteristic features include widely spaced eyes (hypertelorism), eyes that do not point in the same direction (strabismus), a split in the soft flap of tissue that hangs from the back of the mouth (bifid uvula), and an opening in the roof of the mouth (cleft palate).

Individuals with Loeys-Dietz syndrome frequently develop immune system-related problems such as food allergies, asthma, or inflammatory disorders such as eczema or inflammatory bowel disease.

Population Frequency: The prevalence of Loeys-Dietz syndrome is unknown. Loeys-Dietz syndrome types I and II appear to be the most common forms.

References (PubMed ID#):

- FBN1, TGFBR1, and the Marfan-craniosynostosis/mental retardation disorders revisited. (PMID: 16596670)
- Evolution of the face in Loeys-Dietz syndrome type II: longitudinal observations from infancy in seven cases. (PMID: 18978651)
- Revised diagnostic criteria for the Marfan syndrome. (PMID: 8723076)
- Identification of a novel TGFBR1 mutation in a Loeys-Dietz syndrome type II patient with vascular Ehlers-Danlos syndrome phenotype. (Letter) (PMID: 18070134)
- New marfanoid syndrome with craniosynostosis. (PMID: 3565476)
- International registry of patients carrying TGFBR1 or TGFBR2 mutations: results of the MAC (Montalcino Aortic Consortium). (PMID: 27879313)
- Marfanoid features and craniosynostosis: report of one case and review. (PMID: 8287183)
- A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. (PMID: 15731757)
- Aneurysm syndromes caused by mutations in the TGF-beta receptor. (PMID: 16928994)
- Loeys-Dietz syndrome: a primer for diagnosis and management. (PMID: 24577266)
- Identification and in silico analyses of novel TGFBR1 and TGFBR2 mutations in Marfan syndrome-related disorders. (PMID: 16791849)
- Craniosynostosis and marfanoid habitus without mental retardation: report of a third case. (Letter) (PMID: 9605294)
- Familial aortic dissecting aneurysm. (PMID: 2647812)
- Mutations in transforming growth factor-beta receptor type II cause familial thoracic aortic aneurysms and dissections. (PMID: 16027248)

- Dural ectasia in Loeys-Dietz syndrome: comprehensive study of 30 patients with a TGFBR1 or TGFBR2 mutation. (PMID: 24344637)
- Analysis of multigenerational families with thoracic aortic aneurysms and dissections due to TGFBR1 or TGFBR2 mutations. (PMID: 19542084)

*** FROM VARELECT EVIDENCE SELECTION ***

Diseases inferred to be associated with TGFBR1:

- Marfan Syndrome

LIKELY CLINICALLY SIGNIFICANT VARIANTS

Note: "LIKELY CLINICALLY SIGNIFICANT" as defined in the report, is a genetic change that likely contributes to the development of disease, but current evidence is insufficient to prove conclusively.

CLASSIFICATION	GENE	RSID	MUTATION	INTERPRETATION
Uncertain Significance	**KCND3**	**rs747057931**	**c.897G>T (p.Lys299Asn)** HET	**MEDIUM RISK FOR GENERAL CARDIOMYOPATHY AND GENERAL ARRHYTHMIA**

DETAILS ABOUT c.897G>T (p.Lys299Asn): NM_004980.4

Functional Significance:
The heterozygote germline KCND3 variant c.897G>T is predicted to result in abnormal protein translation of the KCND3 protein at amino acid position 299 (p.Lys299Asn) .
Predicted effect(s) on the protein: Missense

Clinical Significance: Medium Risk for General Cardiomyopathy and General Arrythmia
This mutation is associated with increased risk for Cardiac Conditions and should be regarded as clinically significant.

Evidence

*** FROM OMIM SELECTION ***

References (PubMed ID#):

- A novel autosomal dominant spinocerebellar ataxia (SCA22) linked to chromosome 1p21-q23. (PMID: 12764052)
- Reply to: SCA-19 and SCA-22: evidence for one locus with a worldwide distribution. (Letter) (PMID:)
- Mutations in potassium channel KCND3 cause spinocerebellar ataxia type 19. (PMID: 23280838)
- Mutations in KCND3 cause spinocerebellar ataxia type 22. (PMID: 23280837)
- Clinical and genetic analysis of a four-generation family with a distinct autosomal dominant cerebellar ataxia. (PMID: 11284128)
- SCA19 and SCA22: evidence for one locus with a worldwide distribution. (Letter) (PMID: 14679032)
- Identification of a novel SCA locus (SCA19) in a Dutch autosomal dominant cerebellar ataxia family on chromosome region 1p21-q21. (PMID: 12384780)

Disease Summary: Brugada syndrome is characterized by ST segment elevation in the right precordial electrocardiogram leads (so-called type 1 ECG) and a high incidence of sudden death in patients with structurally normal hearts. The syndrome typically manifests during adulthood, with a mean age of sudden death of 41 +/- 15 years, but also occurs in infants and children (summary by {1:Antzelevitch et al., 2005}). For a discussion of genetic heterogeneity of Brugada syndrome, see BRGDA1 ({601144}).

References (PubMed ID#):

- Brugada syndrome: report of the second consensus conference. (PMID: 15655131)
- Novel mutations in the KCND3-encoded Kv4.3 K+ channel associated with autopsy-negative sudden unexplained death. (PMID: 22457051)
- Transient outward current (I-to) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. (PMID: 21349352)

*** FROM VARELECT EVIDENCE SELECTION ***

Diseases inferred to be associated with KCND3:

- Heart Conduction Disease

Disorders from UniProtKB/Swiss-Prot:

- Brugada syndrome 9 (BRGDA9) [MIM:616399]: A tachyarrhythmia...individual will faint and may die in a few minutes if the *heart* is not reset. {ECO:0000269 PubMed:21349352, ECO:0000269...

Summaries:

- EntrezGene: Voltage-gated potassium (Kv) channels represent the...functions include regulating neurotransmitter release, *heart* rate, insulin secretion, neuronal excitability, epithelial...

References:

- The potential role of Kv4.3 K+ channel in *heart* hypertrophy. (PMID: 24762397)

Pathways:

- regulation of *heart* rate by cardiac conduction

No additional pathogenic/likely pathogenic variants found in the panel genes tested (refer to the Methodology and Limitations section of this report for a complete list of the genes).

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SECONDARY FINDINGS: VARIANTS OF UNKNOWN SIGNIFICANCE

GENE	MUTATION	INTERPRETATION
GCKR	**c.1337T>C** (HET)	**UNKNOWN**

*** FROM OMIM DATA ***

Evidence

Diseases directly associated with GCKR:

- FASTING PLASMA GLUCOSE LEVEL QUANTITATIVE TRAIT LOCUS 5; FGQTL5 (OMIM: 613463)
  References:
  - The P446L variant in GCKR associated with fasting plasma glucose and triglyceride levels exerts its effect through increased glucokinase activity in liver. (PMID: 19643913)
  - Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. (PMID: 17463246)
  - New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. (PMID: 20081858)
  - The GCKR {dbSNP rs780094} polymorphism is associated with susceptibility of type 2 diabetes, reduced fasting plasma glucose levels, increased triglycerides levels and lower HOMA-IR in Japanese population. (PMID: 20574426)
  - Common missense variant in the glucokinase regulatory protein gene is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. (PMID: 18678614)
  - The GCKR {dbSNP rs780094} polymorphism is associated with elevated fasting serum triacyglycerol, reduced fasting and OGTT-related insulinaemia, and reduced risk of type 2 diabetes. (PMID: 18008060)
  - The common P446L polymorphism in GCKR inversely modulates fasting glucose and triglyceride levels and reduces type 2 diabetes risk in the DESIR prospective general French population. (PMID: 18556336)

TTN	**c.13282+22832C>T** (HET)	**UNKNOWN**
ANK2	**c.11791G>A** (HET)	**UNKNOWN**
MYPN	**c.2863C>T** (HET)	**UNKNOWN**

*** FROM OMIM DATA ***

Evidence

Diseases directly associated with MYPN:

- Cardiomyopathy, Dilated, 1kk

APOE	**c.526C>T** (HET)	**UNKNOWN**
FKRP	**c.427C>A** (HET)	**UNKNOWN**

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants) and most variants do not increase an individual's risk of Cardiac Conditions. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause an increased risk for Cardiac Conditions. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by personal and family history and any other significant clinical findings.

Patient Name: XXXXXX **DOB:** XX/XX/XXXX

Accession #: XXXXXX **Collection Date:** XX/XX/XXXX

ADDITIONAL INFORMATION

Assay was performed in a CLIA certified laboratory (CLIA#45D2034851).

METHODOLOGY AND LIMITATIONS

Assay

This test is a performed using next generation sequencing methodology for genetic profiling of 174 genes with known associations to 17 Inherited Cardiac Conditions. This is a target enrichment assay and does not cover all the regions of the gene. Blood and Saliva are the only validated sample types accepted for the assay.
Laboratory process: Total genomic DNA was extracted from biological samples using the AGENCOURT® GENFINDTM V2 DNA Extraction procedure. The DNA quality and quantity was assessed using the nanodrop and Qubit. Library was prepared according to existing SOP for Performing Trusight Cardio Assay on Miseq and MiseqDx Systems and loaded on the sequencers. Prepared libraries are loaded on to a flow cell for sequencing with the MiSeq or MiSeqDx sequencer. Sequencing-derived raw image files were processed using a base-calling software (Illumina) and the sequence data was transformed into FASTQ format using Illumina Basespace. Each sample is sequenced with high coverage uniformity across the target region, with 98% of targeted regions covered at minimum of 20X— and a mean coverage of 150X— or above. For the alignment human genome reference sequence (GRCh37.p5/hg19) is used. The analytical sensitivity and accuracy of this assay are greater than 99% for single nucleotide variants (SNVs) and small insertions/deletions (INDELs).

Interpretation:

This report is made using Tgex. Pathogenic and likely pathogenic variants are reported; likely benign and benign variants were not reported. The pathogenicity potential of the identified variants were assessed by considering the predicted consequence, the biochemical properties of the codon change and the degree of evolutionary conservation as well as a number of reference population databases and mutation databases such as, but not limited, to the 1000 Genomes Project, gnomAD, ClinVar, and HGMD. The variants are evaluated by reviewing the relevant literature and databases such as 1000 Genomes Project, Database of Genomic Variants, ExAC, and DECIPHER. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines.

Disclaimer:

This test has not been cleared or approved by the US Food and Drug Administration. 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 laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. The test analyzes the following types of mutations: single nucleotide variations, nucleotide substitutions, small deletions (up to 10 bp), small insertions (up to 10 bp). It is not intended to analyze the following types of alterations: Copy number variations, gross rearrangements, deep intronic variations, Alu element insertions, and other unknown abnormalities.
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 rare genetic variants that interfere with analysis, low level mosaicism, presence of pseudogenes, technical difficulties in regions with high GC content or homo polymertracts, or from other sources. This report does not represent medical advice.

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Patient Name: XXXXXX **DOB:** XX/XX/XXXX

Accession #: XXXXXX **Collection Date:** XX/XX/XXXX

Gene list

The following 174 genes will be sequenced and analyzed for all samples.

Cardiomyopathies

General Cardiomyopathy: DSC2, DSG2, DSP, LMNA, MYBPC3, MYH6, MYH7, PKP2, SCN5A, TNNI3, TNNT2, TTN, ABCC9, ACTA1, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, BRAF, CALR3, CASQ2, CAV3, CBL, COX15, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DTNA, EMD, EYA4, FHL1, FHL2, FKRP, FKTN, FXN, GAA, GATAD1, GLA, HADHA, HFE, HRAS, ILK, JPH2, JUP, KLF10, KRAS, LAMA2, LAMA4, LAMP2, LDB3, MAP2K1, MAP2K2, MIB1, CAVIN4, MYL2, MYL3, MYLK2, MYO6, MYOZ2, MYPN, NEXN, NPPA, NRAS, PDLIM3, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN2B, SCO2, SDHA, SGCB, SGCD, SGCG, SHOC2, SLC25A4, SOS1, TAZ, TBX20, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TPM1, TRIM63, TRPM4, TXNRD2, VCL

Hypertrophic Cardiomyopathy: MYBPC3, MYH7, TNNI3, TNNT2, ACTA1, ACTC1, ACTN2, ANKRD1, BRAF, CALR3, CASQ2, CAV3, COX15, CRYAB, CSRP3, DES, FHL1, FXN, GAA, GLA, JPH2, KLF10, LAMP2, LDB3, MAP2K1, MAP2K2, MYH6, MYL2, MYL3, MYLK2, MYO6, MYOZ2, MYPN, NEXN, PDLIM3, PLN, PRKAG2, PTPN11, RAF1, SLC25A4, SOS1, TCAP, TNNC1, TPM1, TRIM63, TTN, VCL

Dilated Cardiomyopathy: LMNA, MYH6, MYH7, SCN5A, TNNT2, TTN, ABCC9, ACTA1, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FKRP, FKTN, GATAD1, HADHA, HFE, ILK, JUP, LAMA2, LAMA4, LAMP2, LDB3, CAVIN4, MYBPC3, MYPN, NEXN, NPPA, PDLIM3, PKP2, PLN, PRDM16, RBM20, SDHA, SGCB, SGCD, SGCG, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNI3, TPM1, TXNRD2, VCL

ARVC: DSC2, DSG2, DSP, PKP2, CTF1, DES, JUP, LMNA, RYR2, TGFB3, TMEM43, TTN

Noonan Syndrome: KRAS, PTPN11, RAF1, SOS1, BRAF, CBL, HRAS, MAP2K1, MAP2K2, NRAS, SHOC2

Non-compaction cardiomyopathy: MYBPC3, MYH7, ACTC1, CASQ2, DTNA, MIB1, PRDM16, TAZ, TNNT2, TPM1

Restrictive Cardiomyopathy: TNNI3, ACTC1, DES, MYH7, MYL2, MYL3, MYPN, TNNT2, TPM1

Arrhythmias

General Arrhythmia: KCNH2, KCNQ1, RYR2, SCN5A, ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, DSC2, EMD, GJA5, GPD1L, HCN4, JPH2, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ5, KCNJ8, LMNA, MYH6, NKX2-5, NPPA, PKP2, RANGRF, SCN1B, SCN3B, SCN4B, SNTA1, TRDN
Long QT: KCNE1, KCNE2, KCNH2, KCNQ1, SCN5A, AKAP9, ANK2, CACNA1C, CAV3, KCNE3, KCNJ2, KCNJ5, RYR2, SCN4B, SNTA1
Brugada Syndrome: SCN5A, CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND3, KCNE3, KCNJ8, PKP2, RANGRF, SCN1B, SCN3B
Short QT: KCNH2, KCNJ2, KCNQ1, CACNA2D1
CPVT: RYR2, CALM1, CASQ2, KCNE1, KCNJ2, TRDN

Familial Atrial Fibrillation: GJA5, KCNQ1, SCN5A, ABCC9, DSC2, EMD, HCN4, JPH2, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ8, LMNA, MYH6, NKX2-5, NPPA, SCN3B, SCN4B

Aortopathies

General Aortopathy: ACTA2, ELN, FBN1, NOTCH1, TGFBR1, TGFBR2, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN2, LTBP2, MYH11, MYLK, MYLK2, SLC2A10, SMAD3, SMAD4, TGFB2
Marfan Syndrome: FBN1, TGFBR1, TGFBR2
LD Syndrome: TGFBR1, TGFBR2, SMAD3, TGFB2
Familial aortic anuerysm: ACTA2, COL3A1, EFEMP2, ELN, FBN1, FBN2, MYH11, MYLK, MYLK2, NOTCH1, SLC2A10, SMAD3, SMAD4, TGFB2, TGFBR1, TGFBR2
Aortic Valve Disease: ELN, NOTCH1, FBN1

Other cardiac assays

Familial Hypercholesterolemia: LDLR, APOB, APOE, CETP, LDLRAP1, PCSK9, SREBF2
Structural Heart Disease: CRELD1, JAG1, MYH6, NKX2-5, NODAL, PRKAR1A, TBX5, ZIC3, ABCC9, ACTC1, ELN, FBN2, SALL4, TBX20, TBX3

Molecular Autopsy: DSC2, DSG2, DSP, KCNH2, KCNQ1, PKP2, RYR2, SCN5A, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, DES, GPD1L, HCN4, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ5, KCNJ8, LMNA, RANGRF, SCN1B, SCN3B, SCN4B, SNTA1, TGFB3, TMEM43, TRDN, TTN

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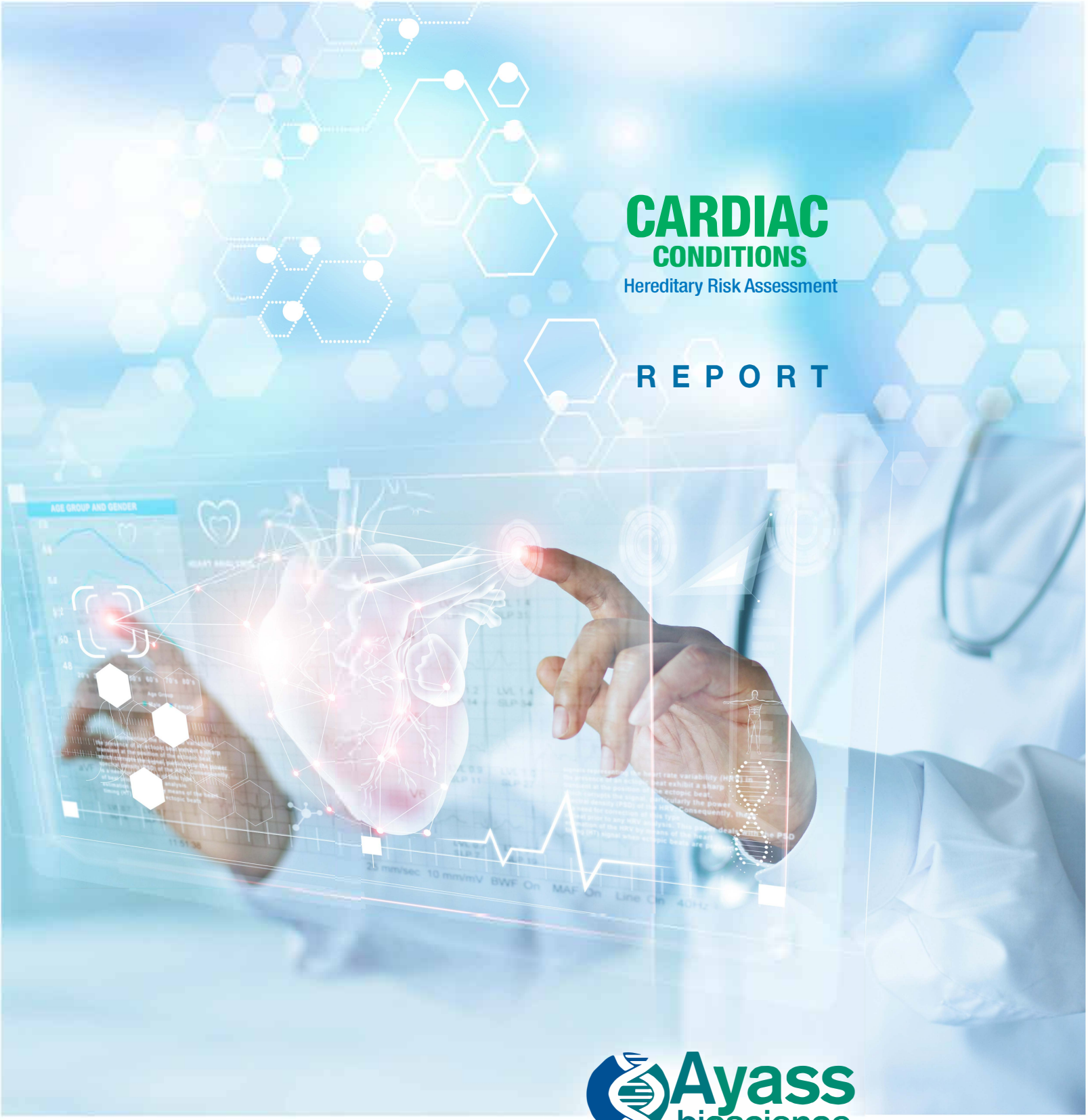
CARDIAC CONDITIONS

Hereditary Risk Assessment

REPORT



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Patient Name: XXXXXXXXX

Date of Birth: XX/XX/XXXX

Accession #: XXXXXXXXX

Hereditary Cardio Screening Result

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Patient Name: XXXXXX
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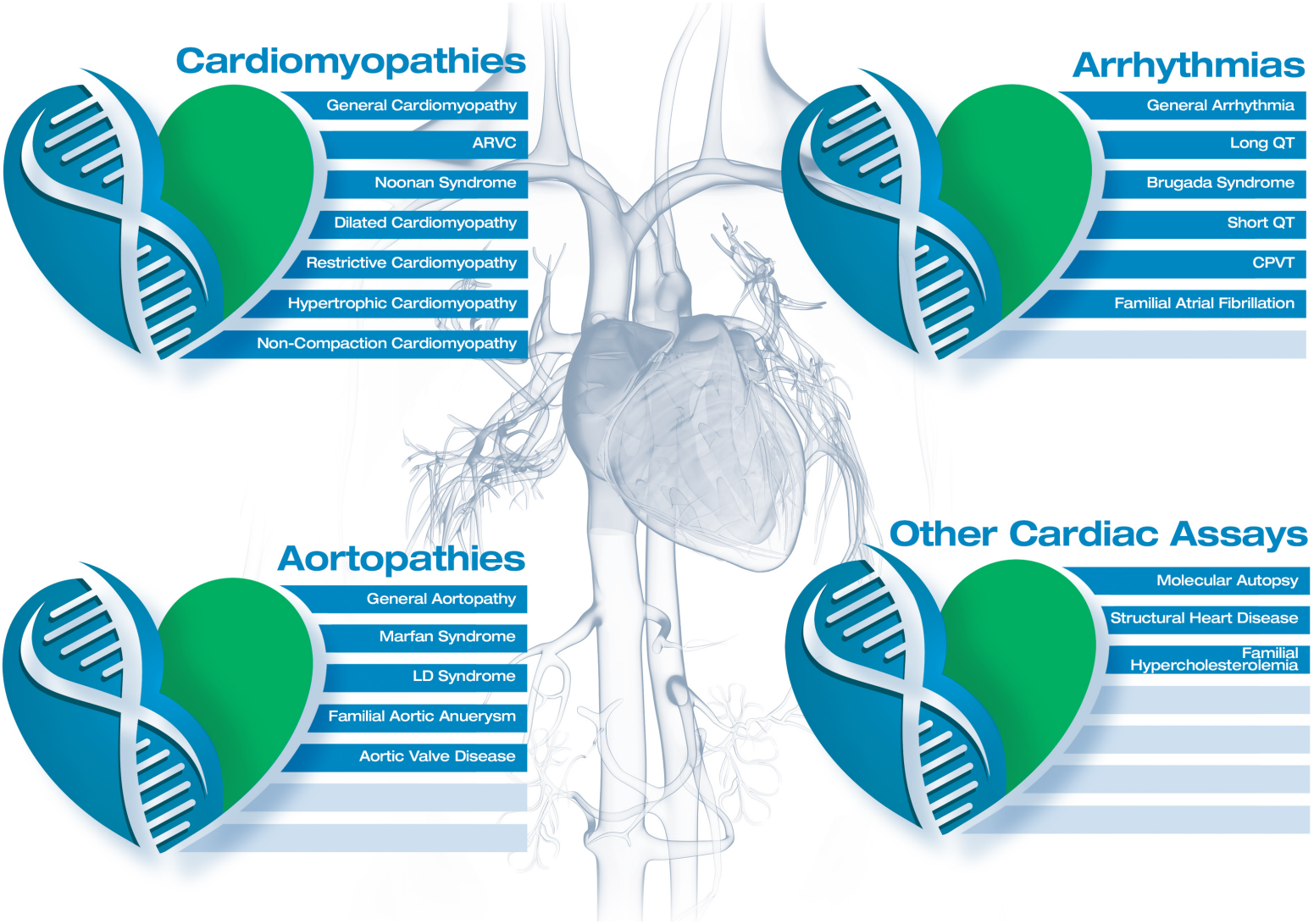
Collection Date: XX/XX/XXXX



Legend:

Red: One or more pathogenic or likely pathogenic variants were detected on the indicated genes for the related condition(s)

Orange: One or more variants of unknown significance (VUS) were detected on the indicated genes for the related condition(s)

Green: No significant variants were detected on genes related to the indicated conditions.

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Hereditary Cardio Screening Result

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Patient Name: XXXXXX
Accession #: XXXXXX

DOB: XX/XX/XXXX
Collection Date: XX/XX/XXXX

RECEIVING HEALTHCARE PROVIDER	SPECIMEN	PATIENT
	Specimen Type: Collection Date: Accession Date: Received Date: Report Date: **13 Sep XXXX**	Name: **XXXXXX** Date of Birth: Gender: Accession #: **XXXXXX** File: **XXXXXX**
ORDERING PHYSICIAN:		
CLINICAL BACKGROUND / INDICATIONS:		

RESULT: NEGATIVE---NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT", as defined in the report, as a genetic change that is associated with the potential to alter medical intervention.

All 174 genes listed in the Gene List section of this report have been sequenced and evaluated for the presence of genetic variants that may predispose to cardiac conditions. No pathogenic (disease causing) or likely pathogenic genetic changes (mutations) have been identified. No further medical action is necessary. However, behavioral counseling on lifestyle changes to mitigate environmental risks is encouraged. Development of cardiac conditions is multifactorial, often involving an interplay of genetic and environmental risk factors. Relevant lifestyle changes (where applicable) are recommended, for instance:

- Cessation of smoking
- Limited alcohol consumption
- Regular exercise
- Healthy diet and weight management

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Patient Name: XXXXXX **DOB:** XX/XX/XXXX

Accession #: XXXXXX **Collection Date:** XX/XX/XXXX

ADDITIONAL INFORMATION

Assay was performed in a CLIA certified laboratory (CLIA#45D2034851).

METHODOLOGY AND LIMITATIONS

Assay

This test is a performed using next generation sequencing methodology for genetic profiling of 174 genes with known associations to 17 Inherited Cardiac Conditions. This is a target enrichment assay and does not cover all the regions of the gene. Blood and Saliva are the only validated sample types accepted for the assay.
Laboratory process: Total genomic DNA was extracted from biological samples using the AGENCOURT® GENFINDTM V2 DNA Extraction procedure. The DNA quality and quantity was assessed using the nanodrop and Qubit. Library was prepared according to existing SOP for Performing Trusight Cardio Assay on Miseq and MiseqDx Systems and loaded on the sequencers. Prepared libraries are loaded on to a flow cell for sequencing with the MiSeq or MiSeqDx sequencer. Sequencing-derived raw image files were processed using a base-calling software (Illumina) and the sequence data was transformed into FASTQ format using Illumina Basespace. Each sample is sequenced with high coverage uniformity across the target region, with 98% of targeted regions covered at minimum of 20X— and a mean coverage of 150X— or above. For the alignment human genome reference sequence (GRCh37.p5/hg19) is used. The analytical sensitivity and accuracy of this assay are greater than 99% for single nucleotide variants (SNVs) and small insertions/deletions (INDELs).

Interpretation:

This report is made using TGex. Pathogenic and likely pathogenic variants are reported; likely benign and benign variants were not reported. The pathogenicity potential of the identified variants were assessed by considering the predicted consequence, the biochemical properties of the codon change and the degree of evolutionary conservation as well as a number of reference population databases and mutation databases such as, but not limited, to the 1000 Genomes Project, gnomAD, ClinVar, and HGMD. The variants are evaluated by reviewing the relevant literature and databases such as 1000 Genomes Project, Database of Genomic Variants, ExAC, and DECIPHER. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines.

Disclaimer:

This test has not been cleared or approved by the US Food and Drug Administration. 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 laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing. The test analyzes the following types of mutations: single nucleotide variations, nucleotide substitutions, small deletions (up to 10 bp), small insertions (up to 10 bp). It is not intended to analyze the following types of alterations: Copy number variations, gross rearrangements, deep intronic variations, Alu element insertions, and other unknown abnormalities.
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 rare genetic variants that interfere with analysis, low level mosaicism, presence of pseudogenes, technical difficulties in regions with high GC content or homo polymertracts, or from other sources. This report does not represent medical advice.

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Patient Name: XXXXXX **DOB:** XX/XX/XXXX

Accession #: XXXXXX **Collection Date:** XX/XX/XXXX

Gene list

The following 174 genes will be sequenced and analyzed for all samples.

Cardiomyopathies

General Cardiomyopathy: DSC2, DSG2, DSP, LMNA, MYBPC3, MYH6, MYH7, PKP2, SCN5A, TNNI3, TNNT2, TTN, ABCC9, ACTA1, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, BRAF, CALR3, CASQ2, CAV3, CBL, COX15, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DTNA, EMD, EYA4, FHL1, FHL2, FKRP, FKTN, FXN, GAA, GATAD1, GLA, HADHA, HFE, HRAS, ILK, JPH2, JUP, KLF10, KRAS, LAMA2, LAMA4, LAMP2, LDB3, MAP2K1, MAP2K2, MIB1, CAVIN4, MYL2, MYL3, MYLK2, MYO6, MYOZ2, MYPN, NEXN, NPPA, NRAS, PDLIM3, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN2B, SCO2, SDHA, SGCB, SGCD, SGCG, SHOC2, SLC25A4, SOS1, TAZ, TBX20, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TPM1, TRIM63, TRPM4, TXNRD2, VCL

Hypertrophic Cardiomyopathy: MYBPC3, MYH7, TNNI3, TNNT2, ACTA1, ACTC1, ACTN2, ANKRD1, BRAF, CALR3, CASQ2, CAV3, COX15, CRYAB, CSRP3, DES, FHL1, FXN, GAA, GLA, JPH2, KLF10, LAMP2, LDB3, MAP2K1, MAP2K2, MYH6, MYL2, MYL3, MYLK2, MYO6, MYOZ2, MYPN, NEXN, PDLIM3, PLN, PRKAG2, PTPN11, RAF1, SLC25A4, SOS1, TCAP, TNNC1, TPM1, TRIM63, TTN, VCL

Dilated Cardiomyopathy: LMNA, MYH6, MYH7, SCN5A, TNNT2, TTN, ABCC9, ACTA1, ACTC1, ACTN2, ALMS1, ANKRD1, BAG3, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FKRP, FKTN, GATAD1, HADHA, HFE, ILK, JUP, LAMA2, LAMA4, LAMP2, LDB3, CAVIN4, MYBPC3, MYPN, NEXN, NPPA, PDLIM3, PKP2, PLN, PRDM16, RBM20, SDHA, SGCB, SGCD, SGCG, TAZ, TBX20, TCAP, TMPO, TNNC1, TNNI3, TPM1, TXNRD2, VCL

ARVC: DSC2, DSG2, DSP, PKP2, CTF1, DES, JUP, LMNA, RYR2, TGFB3, TMEM43, TTN

Noonan Syndrome: KRAS, PTPN11, RAF1, SOS1, BRAF, CBL, HRAS, MAP2K1, MAP2K2, NRAS, SHOC2

Non-compaction cardiomyopathy: MYBPC3, MYH7, ACTC1, CASQ2, DTNA, MIB1, PRDM16, TAZ, TNNT2, TPM1

Restrictive Cardiomyopathy: TNNI3, ACTC1, DES, MYH7, MYL2, MYL3, MYPN, TNNT2, TPM1

Arrhythmias

General Arrhythmia: KCNH2, KCNQ1, RYR2, SCN5A, ABCC9, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, DSC2, EMD, GJA5, GPD1L, HCN4, JPH2, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ5, KCNJ8, LMNA, MYH6, NKX2-5, NPPA, PKP2, RANGRF, SCN1B, SCN3B, SCN4B, SNTA1, TRDN
Long QT: KCNE1, KCNE2, KCNH2, KCNQ1, SCN5A, AKAP9, ANK2, CACNA1C, CAV3, KCNE3, KCNJ2, KCNJ5, RYR2, SCN4B, SNTA1
Brugada Syndrome: SCN5A, CACNA1C, CACNA2D1, CACNB2, GPD1L, HCN4, KCND3, KCNE3, KCNJ8, PKP2, RANGRF, SCN1B, SCN3B
Short QT: KCNH2, KCNJ2, KCNQ1, CACNA2D1
CPVT: RYR2, CALM1, CASQ2, KCNE1, KCNJ2, TRDN

Familial Atrial Fibrillation: GJA5, KCNQ1, SCN5A, ABCC9, DSC2, EMD, HCN4, JPH2, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ8, LMNA, MYH6, NKX2-5, NPPA, SCN3B, SCN4B

Aortopathies

General Aortopathy: ACTA2, ELN, FBN1, NOTCH1, TGFBR1, TGFBR2, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, FBN2, LTBP2, MYH11, MYLK, MYLK2, SLC2A10, SMAD3, SMAD4, TGFB2
Marfan Syndrome: FBN1, TGFBR1, TGFBR2
LD Syndrome: TGFBR1, TGFBR2, SMAD3, TGFB2
Familial aortic anuerysm: ACTA2, COL3A1, EFEMP2, ELN, FBN1, FBN2, MYH11, MYLK, MYLK2, NOTCH1, SLC2A10, SMAD3, SMAD4, TGFB2, TGFBR1, TGFBR2
Aortic Valve Disease: ELN, NOTCH1, FBN1

Other cardiac assays

Familial Hypercholesterolemia: LDLR, APOB, APOE, CETP, LDLRAP1, PCSK9, SREBF2
Structural Heart Disease: CRELD1, JAG1, MYH6, NKX2-5, NODAL, PRKAR1A, TBX5, ZIC3, ABCC9, ACTC1, ELN, FBN2, SALL4, TBX20, TBX3

Molecular Autopsy: DSC2, DSG2, DSP, KCNH2, KCNQ1, PKP2, RYR2, SCN5A, AKAP9, ANK2, CACNA1C, CACNA2D1, CACNB2, CALM1, CASQ2, CAV3, DES, GPD1L, HCN4, JUP, KCND3, KCNE1, KCNE2, KCNE3, KCNJ2, KCNJ5, KCNJ8, LMNA, RANGRF, SCN1B, SCN3B, SCN4B, SNTA1, TGFB3, TMEM43, TRDN, TTN

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