Pediatric Cardiomyopathy Panel

Panel Gene List: ABCC9, ACTC1, ACTN2, AKAP9, ALMS1, ALPK3, ANKRD1, BAG3, BRAF, CAV3, CHRM2, CRYAB, CSRP3, CTNNA3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATAD1, GLA, HCN4, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, LRRC10, MAP2K1, MAP2K2, MIB1, MTND1, MTND5, MTND6, MTTD, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, MURC, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, NKX2-5, NRAS, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SOS1, TAZ, TBX20, TCAP, TGFB3, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TOR1AIP1, TPM1, TTN, TXNRD2, VCL

Clinical Features:

Cardiomyopathy is defined as disease of the heart muscle and has many different presentations. **Hypertrophic cardiomyopathy (HCM)** is characterized by myocardial hypertrophy and myocyte disarray in the absence of other cardiac or systemic causes.[1-3] **Dilated cardiomyopathy (DCM)** usually presents with one or more of the following: i) heart failure with symptoms of congestion (edema, orthopnea or paroxysmal dyspnea), ii) reduced cardiac output resulting in fatigue or dyspnea on exertion, arrhythmias and/or conduction system disease and iii) thromboembolic disease or stroke, mainly from left ventricular mural thrombus. However, some individuals with a DCM pathogenic variant may also be asymptomatic.[4,5] **Left ventricular non-compaction (LVNC)** is characterized by abnormal trabeculations in the left ventricle, most frequently at the apex, and can share the same clinical presentation as DCM, ranging from asymptomatic disease to progressive deterioration of cardiac function, arrhythmias, thromboembolic events, or sudden cardiac death.[4,6] **Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC)** is a disorder that affects the cardiac desmosome, which is a protein complex that maintains cell-to-cell connections and provides mechanical attachments between adjacent cells. ARVC is characterized by myocyte death and replacement by fat and fibrous tissue in the right ventricle.[7,8] **Noonan syndrome (NS)** is a relatively common multi-system disorder with features including HCM, facial dysmorphism, congenital heart defects, short stature, skeletal malformations, motor delay, learning disabilities, and impaired blood clotting ability.[9] Cardiomyopathy can also be a presenting feature of other inherited disorders, such as Danon disease, Fabry disease, Pompe disease, mitochondrial myopathy, or muscular dystrophy.[1-5,10]

Inheritance Pattern/Genetics: Autosomal Dominant, Autosomal Recessive, X-linked, or Mitochondrial

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV) (excluding exon 6 of the *PKP2* gene and the following genomic regions of the *TTN* gene: chr2:179527692-

179527782, 179523898-179523982, 179523731-179523815). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request. Sequencing and deletion/duplication analysis of the remaining genes on the Pedtric Combined Cardiac Panel is available as a separate test if the Cardiomyopathy Panel is negative.

Test Sensitivity:

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Cardiomyopathy Panel depends in part on the patient's clinical phenotype and family history. In general, the sensitivity is highest for individuals with clearly defined cardiomyopathy and a family history of disease. The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For FKRP, HRAS and the mitochondrial genes, sequencing but not deletion/duplication analysis, is performed. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: TAZ and TBX20 genes only whole gene deletions or duplications may be detected.

Gene	Protein	Inheritance	Disease Association(s)
ABCC9	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9	AD	DCM, Brs, ERS, Cantu syndrome and related disorders
ACTC1	ACTIN, ALPHA, CARDIAC MUSCLE	AD	CHD, DCM, HCM, LVNC
ACTN2	ACTININ, ALPHA-2	AD	HCM, DCM
AKAP9	A-KINASE ANCHOR PROTEIN 9	AD	LQTS, cardiomyopathy
ALMS1	CENTROSOME AND BASAL BODY ASSOCIATED PROTEIN	AR	Alstrom syndrome, mitogenic cardiomyopathy, infantile DCM
ALPK3	ALPHA KINASE 3	AR	HCM, DCM
ANKRD1	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 1	AD	DCM
BAG3	BCL2-ASSOCIATED ATHANOGENE 3	AD	DCM, myofibrillar myopathy
BRAF	V-RAF MURINE SARCOMA VIRAL ONCOGENE HOMOLOG B1	AD	Noonan/CFC/Costello syndromes
CAV3	CAVEOLIN 3	AD	HCM, LQTS, LGMD, Tateyama-type distal myopathy, SIDS, rippling muscle disease
CHRM2	M2-MUSCARINIC ACETYLCHOLINE RECEPTOR	AD	DCM
CRYAB	CRYSTALLIN, ALPHA-B	AD, AR	DCM, myofibrillar myopathy
CSRP3	CYSTEINE- AND GLYCINE-RICH PROTEIN 3	AD	HCM, DCM
CTNNA3	CATENIN ALPHA 3	AD	ARVC, Autism

Gene (cont.)	Protein	Inheritance	Disease Association(s)
DES	DESMIN	AD, AR	DCM, ARVC, myopathy, AV block , LGMD
DMD	DYSTROPHIN	XL	DMD, BMD, DCM
DOLK	DOLICHOL KINASE	AR	DCM, congenital disorder of glycosylation type 1m
DSC2	DESMOCOLLIN	AD, AR	ARVC, ARVC+skin and hair findings, DCM
DSG2	DESMOGLEIN	AD	ARVC, DCM
DSP	DESMOPLAKIN	AD, AR	ARVC, DCM, Carvajal syndrome and related disorders
DTNA	DYSTROBREVIN, ALPHA	AD	LVNC, CHD
EMD	EMERIN	XL	EMD
EYA4	EYES ABSENT, DROSOPHILA, HOMOLOG OF, 4	AD	DCM, Hearing loss
FHL1	FOUR-AND-A-HALF LIM DOMAINS 1	XL	HCM, EMD, myofibrillar myopathy, reducing body myopathy
FKRP	FUKUTIN RELATED PROTEIN	AR	muscular dystrophy, dystroglycanopathies
FKTN	FUKUTIN	AR	DCM, LGMD, Fukuyama Congenital Muscular Dystrophy
FLNC	FILAMIN C	AD	RCM, HCM, ARVC, DCM, myopathy
GAA	GLUCOSIDASE, ALPHA, ACID	AR	Pompe Disease (Glycogen storage disease II)
GATA4	GATA-BINDING PROTEIN 4	AD	AF, CHD, cardiomyopathy, SUDS
GATAD1	GATA ZINC FINGER DOMAIN-CONTAINING PROTEIN 1	AR	DCM
GLA	GALACTOSIDASE, ALPHA	XL	Fabry disease
HCN4	HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED POTASSIUM CHANNEL 4	AD	LVNC, AF, AV block, bradycardia, BrS, SSS, tachycardia
HRAS	V-HA-RAS HARVEY RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Costello syndrome
ILK	INTEGRIN-LINKED KINASE	AD	DCM
JPH2	JUNCTOPHILIN 2	AD	HCM
JUP	JUNCTION PLAKOGLOBIN	AD, AR	ARVC, Naxos disease and related disorders
KRAS	V-KI-RAS2 KIRSTEN RAT SARCOMA VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello syndromes
LAMA4	LAMININ, ALPHA-4	AD	DCM
LAMP2	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2	XL	Danon disease
LDB3	LIM DOMAIN-BINDING 3	AD	DCM, LVNC, ARVC, LDB3-related myopathies
LMNA	LAMIN A/C	AD, AR	DCM, LMNA-related neuromuscular disorder, ARVC/ARVC-like disease, lipodystrophy, and premature aging disorders
LRRC10	LEUCINE-RICH REPEAT-CONTAINING PROTEIN 10	AD, AR	DCM
MAP2K1	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 1	AD	Noonan/CFC/Costello syndromes
MAP2K2	MITOGEN-ACTIVATED PROTEIN KINASE KINASE 2	AD	Noonan/CFC/Costello syndromes
MIB1	MINDBOMB E3 UBIQUITIN PROTEIN LIGASE 1	AD	LVNC
MTND1	mtDNA ENCODED COMPLEX I, SUBUNIT ND1	MITO	Cardiomyopathy, myopathy
MTND5	mtDNA ENCODED COMPLEX I, SUBUNIT ND5	MITO	Cardiomyopathy, myopathy
MTND6	mtDNA ENCODED COMPLEX I, SUBUNIT ND6	MITO	Cardiomyopathy, myopathy
MTTD	MITOCHONDRIAL tRNA FOR ASPARTIC ACID	MITO	Cardiomyopathy, myopathy
MTTG	MITOCHONDRIAL tRNA FOR GLYCINE	MITO	Cardiomyopathy, myopathy
MTTH	MITOCHONDRIAL tRNA FOR HISTIDINE	MITO	Cardiomyopathy, myopathy
MTTI	MITOCHONDRIAL tRNA FOR ISOLEUCINE	MITO	Cardiomyopathy, myopathy
MTTK	MITOCHONDRIAL tRNA FOR LYSINE	MITO	Cardiomyopathy, myopathy
MTTL1	MITOCHONDRIAL tRNA FOR LEUCINE 1	MITO	Cardiomyopathy, myopathy
MTTL2	MITOCHONDRIAL tRNA FOR LEUCINE 2	MITO	Cardiomyopathy, myopathy
MTTM	MITOCHONDRIAL tRNA FOR METHIONINE	MITO	Cardiomyopathy, myopathy

Gene (cont.)	Protein	Inheritance	Disease Association(s)
MTTQ	MITOCHONDRIAL tRNA FOR GLUTAMINE	MITO	Cardiomyopathy, myopathy
MTTS1	MITOCHONDRIAL tRNA FOR SERINE 1	MITO	Cardiomyopathy, myopathy
MTTS2	MITOCHONDRIAL tRNA FOR SERINE 2	MITO	Cardiomyopathy, myopathy
MURC	MUSCLE-RELATED COILED-COIL PROTEIN	AD	DCM
MYBPC3	MYOSIN-BINDING PROTEIN C, CARDIAC	AD	HCM, DCM
MYH6	MYOSIN, HEAVY CHAIN 6, CARDIAC MUSCLE, ALPHA	AD	CHD, DCM, HCM, SSS
MYH7	MYOSIN, HEAVY CHAIN 7, CARDIAC MUSCLE, BETA	AD	DCM, HCM, myopathy
MYL2	MYOSIN, LIGHT CHAIN 2, REGULATORY, CARDIAC, SLOW	AD	HCM, muscle fiber disease
MYL3	MYOSIN, LIGHT CHAIN 3, ALKALI, VENTRICULAR, SKELETAL, SLOW	AD, AR	HCM
MYLK2	MYOSIN LIGHT CHAIN KINASE 2	AD	HCM
MYOZ2	MYOZENIN 2	AD	HCM
MYPN	MYOPALLADIN	AD	DCM, RCM, HCM
NEBL	NEBULETTE	AD	DCM, endocardial fibroelastosis
NEXN	NEXILIN	AD	DCM, HCM
NKX2-5	NK2 HOMEOBOX 5	AD	CHD, CCD
NRAS	NEUROBLASTOMA RAS VIRAL ONCOGENE HOMOLOG	AD	Noonan/CFC/Costello syndromes
PDLIM3	PDZ AND LIM DOMAIN PROTEIN 3	AD	HCM, DCM
PKP2	PLAKOPHILIN 2	AD	ARVC, BrS
PLN	PHOSPHOLAMBAN	AD	DCM, HCM, ARVC
PRDM16	PR DOMAIN CONTAINING 16	AD	DCM, LVNC
PRKAG2	PROTEIN KINASE, AMP-ACTIVATED, NONCATALYTIC, GAMMA2	AD	HCM, Wolff-Parkinson-White syndrome
PTPN11	PROTEIN-TYROSINE PHOSPHATASE, NONRECEPTOR-TYPE 11	AD	Noonan/CFC/Costello syndromes
RAF1	V-RAF-1 MURINE LEUKEMIA VIRAL ONCOGENE HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
RBM20	RNA-BINDING MOTIF PROTEIN 20	AD	DCM
RIT1	RAS-LIKE WITHOUT CAAX 1	AD	Noonan syndrome
RYR2	RYANODINE RECEPTOR 2	AD	ARVC, CPVT, DCM
SCN5A	SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT	AD	DCM, ARVC/ARVC-like disease, BrS, Heart block, LQTS, SIDS, SSS
SGCD	SARCOGLYCAN, DELTA	AD, AR	DCM, LGMD
SHOC2	SOC-2 HOMOLOG	AD	Noonan-like syndrome with loose anagen hair
SOS1	SON OF SEVENLESS, DROSOPHILA, HOMOLOG 1	AD	Noonan/CFC/Costello syndromes
TAZ	TAFAZZIN	XL	DCM, LVNC, Barth syndrome
TBX20	T-BOX 20	AD	CHD, DCM, LVNC
TCAP	TITIN-CAP (TELETHONIN)	AD, AR	HCM, DCM, LGMD
TGFB3	TRANSFORMING GROWTH FACTOR BETA 3	AD	ARVC, Loeys-Dietz syndrome-5, TAAD
TMEM43	TRANSMEMBRANE PROTEIN 43	AD	ARVC, EMD
TMPO	THYMOPOIETIN	AD	DCM
TNNC1	TROPONIN C, SLOW	AD	DCM, HCM
TNNI3	TROPONIN I, CARDIAC	AD	DCM, HCM, RCM
TNNT2	TROPONIN T2, CARDIAC	AD	DCM, HCM, RCM, LVNC
TOR1AIP1	TORSIN-1A-INTERACTING PROTEIN 1	AR	LGMD, Contractures, DCM
TPM1	TROPOMYOSIN 1	AD	DCM, HCM
TTN	TITIN	AD, AR	ARVC, DCM, TTN-related myopathies and muscular dystrophies
TXNRD2	THIOREDOXIN REDUCTASE 2	AD, AR	DCM, glucocorticoid deficiency
VCL	VINCULIN	AD	HCM, DCM, LVNC

Abbreviations: AD – Autosomal dominant; AF – Atrial fibrillation; AR – Autosomal recessive; ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy; AV block- Atrioventricular Block; BMD – Becker Muscular Dystrophy; BrS – Brugada Syndrome; CCD- Cardiac Conduction Disease; CHD – Congenital Heart Defects; CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia; DCM – Dilated Cardiomyopathy; DMD- Duchenne Muscular Dystrophy; EMD – Emery Dreifuss Muscular Dystrophy; ERS- Early repolarization syndrome; HCM – Hypertrophic Cardiomyopathy; JLNS – Jervell and Lange-Nielsen Syndrome; LGMD – Limb Girdle Muscular Dystrophy; LQTS – Long QT Syndrome; LVNC

– Left Ventricular Non-Compaction; RCM – Restrictive Cardiomyopathy; SIDS – Sudden Infant Death Syndrome; SSS – Sick Sinus Syndrome; TAAD- Thoracic Aortic Aneurysm and Dissection; XL – X-linked

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