NutriPATH
INTEGRATIVE PATHOLOGY SERVICES

INFORMATION SHEET

Comprehensive Cardiomyopathy Panel

Clinical Summary

The Comprehensive Cardiomyopathy Panel analyzes **106 genes** associated with inherited cardiomyopathy: A2ML1, ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ANKRD1, BAG3, BRAF, CACNA1C, CALR3, CAV3, CBL, CHRM2, CPT2, CRYAB, CSRP3, CTF1, CTNNA3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, DTNA, ELAC2, EMD, EYA4, FHL1, FHL2, FKRP, FKTN, FLNC, GAA, GATA4, GATA6, GATAD1, GLA, HCN4, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3, LMNA, LRRC10, MAP2K1, MAP2K2, MTO1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NF1, NKX2-5, NPPA, NRAS, PDLIM3, PKP2, PLEKHM2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RRAS, RYR2, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, SPRED1, TAZ, TBX20, TCAP, TGFB3, TMEM43, TMEM70, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, TXNRD2, VCL.

Comprehensive testing allows for the evaluation of multiple cardiomyopathy conditions. In the meantime, panels including subsets of these genes are also available based on specific indications.

Cardiomyopathies are a group of diseases in the heart muscle associated with mechanical and/or electrical dysfunction. Cardiomyopathies are a broad classification of diseases that include diseases with genetic origins, acquired and mixed (both genetic and non-genetic) (1). However, a significant percentage of cardiomyopathies are inheritable diseases and are a major cause of morbidity and mortality (2).

Inherited cardiomyopathies include (among others):

Hypertrophic Cardiomyopathy (HCM): This disease is defined as a hypertrophied, nondilated left ventricle in the absence of other systemic or cardiac causes (1) (3). Hypertrophic cardiomyopathy has a relatively common genetic heart disease (primarily dominant inheritance) with a prevalence of about 1:625 to 1:344 in the general population and a major cause of sudden cardiac death in young individuals (1) (3). About 60% of patients with hypertrophic cardiomyopathy have a clearly defined familial disease.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVD): Predominantly involves the right ventricle, consists of replacement of cardiac muscle cells with fibrofatty tissue. It has an estimated prevalence of 1:1000 to 1:5000 in the population, with primarily dominant inheritance and variable penetrance. Genetic screening has been shown to locate genetic abnormalities in approximately 50% of cases (4) (5).

LV Noncompaction (LVNC): Characterized by a “spongy” appearance of the left ventricle. Genetics play an important role in this disease with up to 50% of patients having family history of cardiomyopathy (6).

Dilated Cardiomyopathy: Characterized by ventricular chamber enlargement and systolic dysfunction. Dilated Cardiomyopathy can lead to progressive heart failure, decline in left ventricle contractibility, arrhythmias, conduction system abnormalities, Thromboembolic disease, as well as sudden heart failure. About 20% to 35% of Dilated Cardiomyopathy cases have been reported as familial. However, penetrance is incomplete and age related. Dilated cardiomyopathy can be inherited in an autosomal dominant or X-linked manner, with most cases being autosomal dominant (7) (1).

Secondary cardiomyopathies are also found as part of systemic conditions. A common secondary cardiomyopathy is **Noonan syndrome (NS)**, a genetic multisystem disorder, due to misregulation of the RAS-MAPK signaling pathway and part of family of syndromes known as RASopathies. Noonan syndrome is characterized by dysmorphic features, developmental delay, heart defects, short stature as well as other symptoms. Noonan syndrome has an autosomal dominant inheritance pattern and variably expression. Estimated prevalence of the condition is 1:1000 to 1:2500 (8) (1).

Diagnostic testing for the various Cardiomyopathy diseases may help establish a diagnosis, inform management and clarify risks.

Technical Summary

We evaluated the accuracy of the NGS panel assay using benchmark samples with true positive/negative sites based on GeT-RM and NIST GIAB data. The technical sensitivity and specificity are ~99%. The average depth of coverage of the current test is > 100X with ~ 98% of targeted regions covered >=10X.

This assay also detects large deletions and duplications (CNVs) using the Atlas-CNV method (9).

Genes and Associated Disorders

GENE	INHERITANCE	ASSOCIATED DISEASE	HCM[1]	ARDV[2]	LVNC[3]	DCM[4]	NS[5]
A2ML1	AD	Noonan Syndrome 1					√
ABCC9	AD	Atrial fibrillation familial 12, Cardiomyopathy dilated 1O, Hypertrichotic osteochondrodysplasia				√	
ACADVL	AR	VLCAD deficiency	√				
ACTC1	AD	Atrial septal defect 5, Cardiomyopathy dilated 1R, Cardiomyopathy hypertrophic 11, Left ventricular noncompaction 4	√		√	√	
ACTN2	AD	Cardiomyopathy dilated 1AA with or without LVNC, Cardiomyopathy hypertrophic 23 with or without LVNC	√	√	√	√	
AGL	AR	Glycogen storage disease IIIa, Glycogen storage disease IIIb	√				

Genes and Associated Disorders (Cont'd)

ALMS1	AR	Alstrom syndrome				√	
ANKRD1	AD/AR	Familial dilated cardiomyopathy				√	
BAG3	AD	Cardiomyopathy dilated 1HH, Myopathy myofibrillar 6	√			√	
BRAF	AD	Cardiofaciocutaneous syndrome, LEOPARD syndrome 3, Noonan syndrome 7					√
CACNA1C	AD	Brugada syndrome 3, Long QT syndrome 8, Timothy syndrome	√				
CALR3	AD	Familial hypertrophic cardiomyopathy (?)	√				
CAV3	AD	Cardiomyopathy familial hypertrophic, Creatine phosphokinase elevated serum, Long QT syndrome 9, Myopathy distal Tateyama type, Rippling muscle disease 2	√			√	
CBL	AD	Noonan syndrome-like disorder with or without juvenile myelomonocytic leukemia					√
CHRM2	AD	Familial dilated cardiomyopathy				√	
CPT2	AD/AR	CPT II deficiency infantile, CPT II deficiency lethal neonatal, CPT II deficiency myopathic stress-induced	√				
CRYAB	AD/AR	Cardiomyopathy dilated 1II, Myopathy myofibrillar 2, Myopathy myofibrillar fatal infantile hypertonic alpha-B crystallin-related				√	
CSRP3	AD	Cardiomyopathy dilated 1M, Cardiomyopathy hypertrophic 12	√			√	
CTF1	AD/AR	Neonatal Stroke, Hypertensive Heart Disease				√	
CTNNA3	AD	Arrhythmogenic right ventricular dysplasia familial 13	√	√			
DES	AD/AR	Cardiomyopathy dilated 1I, Myopathy myofibrillar 1, Scapuloperoneal syndrome neurogenic Kaeser type	√	√		√	
DMD	X-linked	Becker muscular dystrophy, Cardiomyopathy dilated 3B, Duchenne muscular dystrophy				√	
DNAJC19	AR	3-methylglutaconic aciduria type V			√	√	
DOLK	AR	Congenital disorder of glycosylation type Im				√	
DSC2	AD/AR	Arrhythmogenic right ventricular dysplasia 11, Arrhythmogenic right ventricular dysplasia 11 with mild palmoplantar keratoderma and woolly hair		√		√	

Genes and Associated Disorders (Cont'd)

DSG2	AD	Arrhythmogenic right ventricular dysplasia 10, Cardiomyopathy dilated 1BB		√		√	
DSP	AD/AR	Arrhythmogenic right ventricular dysplasia 8, Cardiomyopathy dilated with woolly hair and keratoderma,		√	√	√	
DTNA	AD	Left ventricular noncompaction 1 with or without congenital heart defects			√		
ELAC2	AR	Combined oxidative phosphorylation deficiency 17	√				
EMD	X-linked	Emery-Dreifuss muscular dystrophy 1 X-linked		√		√	
EYA4	AD	Cardiomyopathy dilated 1J , Deafness autosomal dominant 10				√	
FHL1	X-linked	Emery-Dreifuss muscular dystrophy 6 X-linked, Myopathy X-linked with postural muscle atrophy, Reducing body myopathy X-linked, Uruguay faciocardiomusculoskeletal syndrome	√				√
FHL2	AD/AR	Familial dilated cardiomyopathy				√	
FKRP	AR	Muscular dystrophy-dystroglycanopathy				√	
FKTN	AR	Cardiomyopathy dilated 1, Muscular dystrophy-dystroglycanopathy				√	
FLNC	AD	Cardiomyopathy familial restrictive 5, Myopathy distal 4, Myopathy myofibrillar 5	√	√		√	
GAA	AR	Glycogen storage disease II	√				
GATA4	AD	Atrial septal defect, Tetralogy of Fallot, Ventricular septal defect 1	√	√		√	
GATA6	AD	Atrial septal defect 9, Atrioventricular septal defect 5, Pancreatic agenesis and congenital heart defects, Persistent truncus arteriosus, Tetralogy of Fallot	√	√		√	
GATAD1	AR	Cardiomyopathy dilated 2B				√	
GLA	X-linked	Fabry disease, Fabry disease cardiac variant	√				
HCN4	AD	Brugada syndrome 8, Sick sinus syndrome 2			√		
HRAS	AD	Congenital myopathy with excess of muscle spindles, Costello syndrome,					√
ILK	AD	Cardiomyopathy dilated, Cardiomyopathy hypertrophic	√			√	
JPH2	AD	Cardiomyopathy hypertrophic 17	√				
JUP	AD/AR	Arrhythmogenic right ventricular dysplasia 12, Naxos disease		√		√	
KRAS	AD	Cardiofaciocutaneous syndrome 2, Noonan syndrome 3, Oculoectodermal syndrome					√
LAMA4	AD	Cardiomyopathy dilated 1JJ			√	√	

Genes and Associated Disorders (Cont'd)

LAMP2	X-linked	Danon disease	√		√	√	
LDB3	AD	Cardiomyopathy dilated 1C with or without LVNC, Cardiomyopathy hypertrophic 24, Left ventricular noncompaction 3, Myopathy myofibrillar 4	√	√	√	√	
LMNA	AD/AR	Cardiomyopathy dilated 1A, Charcot-Marie-Tooth disease type 2B1, Emery-Dreifuss muscular dystrophy, Heart-hand syndrome Slovenian type, Hutchinson-Gilford progeria, Lipodystrophy familial partial type 2, Malouf syndrome, Muscular dystrophy congenital		√		√	
LRRC10	AD	Dilated Cardiomyopathy				√	
MAP2K1	AD	Cardiofaciocutaneous syndrome 3					√
MAP2K2	AD	Cardiofaciocutaneous syndrome 4					√
MTO1	AR	Combined oxidative phosphorylation deficiency 10	√	√			
MYBPC3	AD/AR	Cardiomyopathy dilated 1MM, Cardiomyopathy hypertrophic 4, Left ventricular noncompaction 10	√		√	√	
MYH6	AD	Atrial septal defect 3, Cardiomyopathy dilated 1EE, Cardiomyopathy hypertrophic 14, Sick sinus syndrome 3	√			√	
MYH7	AD/AR	Cardiomyopathy dilated 1S, Cardiomyopathy hypertrophic 1, Laing distal myopathy, Left ventricular noncompaction 5, Myopathy myosin storage	√		√	√	
MYL2	AD	Cardiomyopathy hypertrophic 10	√				
MYL3	AD/AR	Cardiomyopathy hypertrophic 8	√				
MYLK2	AD	Cardiomyopathy hypertrophic 1 digenic	√				
MYOM1	AD/AR	Cardiomyopathy hypertrophic	√				
MYOZ2	AD	Cardiomyopathy hypertrophic 16	√				
MYPN	AD/AR	Cardiomyopathy dilated 1KK, Cardiomyopathy familial restrictive 4, Cardiomyopathy hypertrophic 22, Nemaline myopathy 11 autosomal recessive	√			√	
NEBL		Endocardial Fibroelastosis				√	
NEXN	AD	Cardiomyopathy dilated 1CC, Cardiomyopathy hypertrophic 20	√			√	
NF1	AD	Neurofibromatosis-Noonan syndrome					√
NKX2-5	AD	Atrial septal defect 7 with or without AV conduction defects, Conotruncal heart malformations variable, Hypoplastic left heart syndrome 2, Tetralogy of Fallot, Ventricular septal defect 3	√	√			

Genes and Associated Disorders (Cont'd)

NPPA	AD/AR	Atrial fibrillation familial 6, Atrial standstill 2		√		√	
NRAS	AD	Noonan syndrome 6					√
PDLIM3	AD	Cardiomyopathy hypertrophic, Cardiomyopathy, dilated	√			√	
PKP2	AD	Arrhythmogenic right ventricular dysplasia 9		√		√	
PLEKHM2	AD	Left Ventricular Noncompaction, Dilated Cardiomyopathy			√	√	
PLN	AD	Cardiomyopathy dilated 1P, Cardiomyopathy hypertrophic 18	√	√	√	√	
PRDM16	AD	Cardiomyopathy dilated 1LL, Left ventricular noncompaction 8			√	√	
PRKAG2	AD	Cardiomyopathy hypertrophic 6, Glycogen storage disease of heart lethal congenital, Wolff-Parkinson-White syndrome	√	√			
PTPN11	AD	LEOPARD syndrome 1, Noonan syndrome 1					√
RAF1	AD	Cardiomyopathy dilated 1NN, LEOPARD syndrome 2, Noonan syndrome 5	√			√	√
RASA1	AD	Capillary malformation-arteriovenous malformation 1					√
RBM20	AD	Cardiomyopathy dilated 1DD		√		√	
RIT1	AD	Noonan syndrome 8	√				√
RRAS	AD	Noonan syndrome					√
RYR2	AD	Arrhythmogenic right ventricular dysplasia 2, Ventricular tachycardia catecholaminergic polymorphic 1		√	√	√	
SCN5A	AD/AR	Atrial fibrillation familial 10, Brugada syndrome 1, Cardiomyopathy dilated 1E, Heart block nonprogressive, Heart block progressive type IA, Long QT syndrome-3, Sick sinus syndrome 1, Susceptibility to Sudden infant death syndrome, Ventricular fibrillation familial 1		√	√	√	
SDHA	AD/AR	Cardiomyopathy dilated 1GG, Leigh syndrome, Mitochondrial respiratory chain complex II deficiency				√	
SGCD	AR	Cardiomyopathy dilated 1L, Muscular dystrophy limb-girdle autosomal recessive 6				√	
SHOC2	AD	Noonan syndrome-like with loose anagen hair					√
SLC22A5	AR	Carnitine deficiency systemic primary				√	
SOS1	AD	Noonan syndrome 4					√
SOS2	AD	Noonan syndrome 9					√
SPRED1	AD	Legius syndrome					√
TAZ	X-linked	Barth syndrome			√	√	

TBX20	AD	Atrial septal defect 4, Cardiomyopathy hypertrophic, Cardiomyopathy dilated, LV Noncompaction	√		√	√	
TCAP	AD/AR	Cardiomyopathy hypertrophic 25, Muscular dystrophy limb-girdle autosomal recessive 7	√			√	
TGFB3	AD	Arrhythmogenic right ventricular dysplasia 1, Loeys-Dietz syndrome 5		√			
TMEM43	AD	Arrhythmogenic right ventricular dysplasia 5, Emery-Dreifuss muscular dystrophy 7		√		√	
TMEM70	AR	Mitochondrial complex V (ATP synthase) deficiency nuclear type 2					
TMPO		Dilated Cardiomyopathy				√	
TNNC1	AD	Cardiomyopathy dilated 1Z, Cardiomyopathy hypertrophic 13	√			√	
TNNI3	AD/AR	Cardiomyopathy dilated 1FF, Cardiomyopathy dilated 2A, Cardiomyopathy familial restrictive 1, Cardiomyopathy hypertrophic 7	√	√	√	√	
TNNT2	AD	Cardiomyopathy dilated 1D, Cardiomyopathy familial restrictive 3, Cardiomyopathy hypertrophic 2, Left ventricular noncompaction 6	√	√	√	√	
TPM1	AD	Cardiomyopathy dilated 1Y, Cardiomyopathy hypertrophic 3, Left ventricular noncompaction 9	√		√	√	
TTN	AD/AR	Cardiomyopathy dilated 1G, Cardiomyopathy familial hypertrophic 9, Muscular dystrophy limb-girdle autosomal recessive 10, Salih myopathy	√	√		√	
TTR	AD	Amyloidosis hereditary transthyretin-related	√			√	
TXNRD2	AR	Glucocorticoid deficiency 5, dilated cardiomyopathy				√	
VCL	AD	Cardiomyopathy dilated 1W, Cardiomyopathy hypertrophic 15	√		√	√	

[1] Hypertrophic Cardiomyopathy Panel (50 genes), [2] Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia Panel (28 genes), [3] LV Noncompaction Panel (22 genes), [4]Dilated Cardiomyopathy (66), and [5] included in Noonan syndrome and other RASopathies panel, see comprehensive RASopathies panel for complete list (26 genes).

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