Cincinnati Children's
Heart Institute

Heart Institute Diagnostic Lab
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Comprehensive Cardiomyopathy Panel

The Comprehensive Cardiomyopathy Panel offers Next Generation Sequencing of 37 genes associated with dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular noncompaction (LVNC), and restrictive cardiomyopathy (RCM).
The Comprehensive Cardiomyopathy Panel can be ordered as a first line test, or can be ordered as a cost-effective reflex following targeted disease testing (DCM, HCM, LVNC, or RCM).

HCM

Hypertrophic Cardiomyopathy (HCM) is relatively common, with a prevalence of 1 in 500 adults. HCM is a primary disorder of the heart muscle characterized by left ventricular hypertrophy. The most classic finding in HCM is asymmetric septal hypertrophy, with or without left ventricular outflow tract obstruction. The disease demonstrates extensive clinical variability with regard to age of onset, severity and progression of disease. HCM can affect infants and children although it is more typically identified in adolescence or adulthood. Approximately 50-65% of individuals with a known or suspected diagnosis of familial HCM have a mutation in one of a number of genes encoding components of the sarcomere and cytoskeleton.

DCM

Dilated Cardiomyopathy (DCM) is characterized by left ventricular enlargement and systolic dysfunction. DCM can either be acquired though environmental causes (most commonly through ischemic injury following myocardial infarction or coronary artery disease), or can be inherited. DCM is commonly an adult-onset disease, but demonstrates extensive variability with regard to age of onset and reduced penetrance. It is estimated that 20-50% of cases of DCM have a genetic basis.

DCM and DMD related Cardiomyopathy

DMD-associated DCM can be identified in individuals with subclinical Becker muscular dystrophy. Sequencing and deletion/duplication analysis of the *DMD* gene is available as part of the DCM and *DMD* related Cardiomyopathy panel.

LVNC

Left Ventricular Noncompaction (LVNC) is characterized by a spongy morphologic appearance of the myocardium, occurring primarily in the left ventricle with the abnormal trabeculations typically being most evident in the apical portion of the left ventricle. LVNC can be seen in isolation or in association with other cardiomyopathies (HCM or DCM) or congenital heart disease. It is estimated that up to 44% of LVNC cases are inherited.

RCM

Restrictive Cardiomyopathy (RCM) is characterized by increased stiffness of the ventricular chambers leading to abnormal filling and relaxation. Generally the ventricular wall thickness and systolic function remains within normal limits. Approximately 35% of individuals with RCM will have a mutation identified with currently available genetic testing.

Test Indication

This test is indicated for individuals with a primary cardiomyopathy in the absence of identifiable acquired causes.

Genes on Comprehensive Cardiomyopathy Panels

- Comprehensive Cardiomyopathy Panel – 37 genes
- HCM Panel – 23 genes*
- DCM Panel – 30 genes*
  - DCM and DMD related Panel – 31 genes*
- LVNC Panel – 13 genes*
- RCM Panel – 9 genes*

**Optional reflex to remaining genes*

Shipping Instructions

Please enclose a test requisition form with sample. All information must be complete before sample can be processed. Samples may be shipped at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship To:

Cincinnati Children's
Hospital Medical Center
Attn: Heart Institute Diagnostic Lab
240 Albert Sabin Way,
Room S4.381
Cincinnati, OH 45229-3039

Methodology:

Next Generation Sequencing: All coding exons and the flanking 15 bases (splice sites or untranslated regions of the genes listed in the panel, as well as 22 reported non-coding region mutations in *DMD*, are enriched from the patient's genomic DNA and sequenced using a solid-state sequencing-by-synthesis process. DNA sequences are assembled and compared to the published genomic reference sequences in Genome Reference Consortium Build 37. Dideoxy DNA sequencing is used to provide data for bases with insufficient coverage and to confirm the reported variants from next-generation sequencing. This assay does not detect variants in the promoter regions, deep intronic regions, or other regulatory elements, and does not detect large deletions or mosaicisms. Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

Multiplex ligation-dependent probe amplification (MLPA): MLA is utilized to detect large coding region deletions/duplications in the *DMD* gene (NM_004006.2; NM_000109.3 (exon 1 only)). Long range PCR or qPCR are used to confirm deletions/duplications detected by a single MLPA probe. This assay is over 99% sensitive in identifying large coding region deletions/duplications in the *DMD* gene (analytic sensitivity). It will not detect point mutations, inversions, translocations, mosaicism, nor copy number changes that lie outside the target sequence of the MLPA probes.

Sensitivity & Accuracy:

Validation testing indicates an analytic sensitivity of 99.8% and an analytic specificity of 100%.

Clinical Sensitivity
Based on the literatures, the clinical validity is determined to be:

- Greater than 93% for HCM
- Greater than 26% for DCM
- Approximately 30% for LVNC
- Approximately 35% for RCM

Specimen:

Peripheral blood in EDTA tube
Adult: 3-5mL
Child: 3-5mL
Infant: 1-3mL
For other specimen types, please contact Amy Shikany at 513-803-3317

Turnaround Time:

Full Mutation and Deletion/Duplication Analysis 8-10 weeks
Known Mutation Analysis 1-2 weeks

CPT Codes:

Comprehensive Cardiomyopathy Panel: 81403, 81404, 81405x12, 81406x5, 81407x4, 81479x14

Dilated Cardiomyopathy Panel: 81403, 81405 x9, 81406 x4, 81407 x4, 81479 x12

DCM and DMD related Cardiomyopathy Panel: 81161, 81403, 81405 x9, 81406 x4, 81407 x4, 81408, 81479 x12

Hypertrophic Cardiomyopathy Panel: 81403, 81404x2, 81405x9, 81406x3, 81407x3, 81479 x5

Left Ventricular Noncompaction Panel: 81405 x5, 81406 x4, 81407 x2, 81479 x2

Restrictive Cardiomyopathy Panel: 81404, 81405 x3, 81406, 81407 x2, 81479 x2

Known Mutation Analysis: 81403

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Comprehensive Cardiomyopathy Panel Gene List

Gene	DCM	DCM + DMD	HCM	LVNC	RCM
ABCC9	x	x			
ACTC1	x	x	x	x	x
ACTN2	x	x	x	x	
ANKRD1*	x	x	x		
BAG3	x	x			x
CAV3			x		
CRYAB	x	x			x
CSRP3	x	x	x		
DES	x	x		x	x
DMD		x			
EMD	x	x			
LAMP2	x	x	x		
LMNA	x	x		x	
MYBPC3	x	x	x	x	x
MYH6	x	x	x		
MYH7	x	x	x	x	x
MYL2			x	x	
MYL3			x	x	
MYPN	x	x			
NEBL*	x	x			
NEXN	x	x	x		
PLN	x	x	x		
PRKAG2			x		
RBM20	x	x			
SCN5A	x	x			
SCO2			x		
SGCD	x	x			
SURF1			x		
TAZ	x	x		x	
TCAP	x	x			
TNNC1	x	x	x		
TNNI3	x	x	x		x
TNNT2	x	x	x	x	x
TPM1	x	x	x	x	
TTN	x	x			
TTR			x		x
VCL	x	x	x	x	
ZASP/LDB3	x	x	x	x	

*CCHMC was the lead in identifying these novel genes

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