



Test Information Sheet

Cardiology Genetics: Dilated Cardiomyopathy (DCM) Panel

Also known as: Idiopathic Dilated Cardiomyopathy (IDC); Familial Dilated Cardiomyopathy (FDC)

Mendelian Inheritance in Man Number: 115200

Clinical Features:

Dilated cardiomyopathy (DCM) usually presents with one or more of the following: heart failure with symptoms of congestion such as edema, orthopnea or paroxysmal dyspnea, and/or reduced cardiac output, such as fatigue or dyspnea on exertion; arrhythmias and/or conduction system disease; or thromboembolic disease, mainly from left ventricular mural thrombus, including stroke. However, individuals with DCM may also be asymptomatic. The diagnosis of DCM is established by the finding of both left ventricular enlargement and of systolic dysfunction, primarily determined by echocardiogram to measure cardiac chamber dimensions, ventricular thickness and ejection fraction.²

The prevalence of idiopathic DCM in the general population is at least 1/2,700. Dilated cardiomyopathy is due to inherited (genetic) or acquired (environmental or non-genetic) causes. DCM is most commonly due to acquired causes, such as ischemic injury from myocardial infarction, secondary to underlying coronary artery disease, or a variety of other insults or inflammatory conditions that cause damage to the myocardium. Hereditary DCM is characterized by left ventricular enlargement and systolic dysfunction, or a reduction in the myocardial force of contraction, in the absence of other cardiac, systemic or environmental causes. It is thought that approximately 20-50% of idiopathic DCM cases have a genetic basis.²

Inheritance Pattern: DCM can be inherited in an autosomal dominant, autosomal recessive or X-linked manner. The vast majority (90%) of familial cases are Autosomal dominant, where by definition an affected individual with a disease-causing mutation has a 50% chance of transmitting this mutation to a child.

Genetics:

DCM is genetically heterogeneous with mutations in more than 20 genes being identified to date. Up to one-half of patients diagnosed with DCM have at least one first-degree relative with features consistent with DCM. Molecular genetic testing also makes it possible to identify asymptomatic family members at risk for DCM.

Etiology:

Hereditary dilated cardiomyopathy can be caused by mutations in genes coding for cardiac proteins that are responsible for proper cardiac muscle contraction, either by impairing the production of such proteins and/or by reducing the force of which the heart muscle cells can contract. Mutations in genes encoding sarcomeric proteins, such as α -cardiac actin (ACTC1); β -myosin (MYH7); cardiac myosin-binding protein C (MYBPC3); heavy chain α -tropomyosin (TPM1); and troponins T (TNNT2) and I (TNNI3) account for the majority of identified mutations and are inherited in an autosomal dominant manner. Mutations in the gene encoding the nuclear envelope protein lamin A/C (LMNA) are also inherited in an autosomal dominant manner and are responsible for the development of DCM associated with atrioventricular (AV) conduction disorder and other electrophysiologic disturbances. Mutations in LMNA and other genes, such as DES may cause patients with DCM to also exhibit symptoms associated with skeletal myopathies, such as Emery-Dreyfuss muscular dystrophy and myofibrillar myopathy. Some genes cause DCM through metabolic effects on the cardiac myocyte including lysosome-associated membrane protein 2 (LAMP2), mitochondrial transfer RNA leucine/glutamine/histidine/lysine/serine 1/serine 2 (MTTL1, MTTQ, MTTH, MTTK, MTTS1, MTTS2), mitochondrial NADH dehydrogenase subunits 1/5/6 (MTND1, MTND5, MTND6), or due to abnormal protein deposition such as amyloid from a mutated transthyretin (TTR).

Reasons for Referral:

1. Confirmation of a clinical diagnosis in symptomatic patients
2. Risk assessment of asymptomatic family members of a proband with DCM
3. Genetic counseling and recurrence risk calculation
4. Differentiation of hereditary DCM from acquired (non-genetic) causes of DCM.
5. Prenatal diagnosis in families with a known mutation

Test Method:

Using genomic DNA obtained from a blood specimen (2-5 mL in EDTA), approximately 181 exons of 23 genes (LMNA, MYH7, TNNT2, ACTC1, DES, MYBPC3, TPM1, TNNI3, ZASP, TAZ, PLN, TTR, LAMP2, SGCD, MTTL1, MTTQ, MTTT, MTTK, MTTT1, MTTT2, MTND1, MTND5 and MTND6) including their splice junctions are sequenced using a novel solid-state sequencing-by-synthesis process that allows sequencing a large number of amplicons in parallel.³ For analysis, DNA sequence is assembled and compared to the published genomic reference sequences. The presence of any potentially disease-associated sequence variant(s) is confirmed by conventional dideoxy DNA sequence analysis. A reference library of almost 800 alleles is used to evaluate the frequency of novel sequence variants if indicated. If appropriate, testing of one affected relative or, if not available, of both biological parents, is performed to clarify variants of unknown significance at no additional charge.

Test Sensitivity:

Up to 50% of individuals with a clinical diagnosis of idiopathic DCM are due to genetic causes.² It is not currently known what percentage of these individuals would be expected to harbor a disease-causing mutation in the 23 genes tested for in this panel. It is estimated that this panel would detect a disease-causing mutation in at least 20% of patients with familial DCM.² The technical sensitivity of this testing approach is estimated to be 98%.

Specimen Requirements and Shipping/Handling:

- **Blood:** A single tube with 2-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** Not accepted at this time
- **Other Specimens:** Contact us for specific inquiries and specimen requests.
- **Prenatal Diagnosis:** Available only if a familial mutation has been identified. Contact us for more information.

Required Forms:

- Cardiology Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions
- We highly recommend submitting relevant clinical information (ECG/Echo/MRI Reports, etc) with specimens.

CPT Codes and Turn-Around-Times:

Test #	Description	CPT codes	Turnaround time
350	DCM panel in a new patient	83891x1, 83900x1, 83901x51, 83904x51, 83909x3, 83912x1	Approx. 8 weeks
901	DNA testing of a relative for a single known mutation	83891x2, 83898x2, 83894x2, 83904x4, 83892x2, 83912x2	Approx. 3 weeks
902	Prenatal diagnosis for a known mutation	83891x5, 83898x10, 83894x5, 83904x10, 83892x2, 83912x5	Approx. 2 weeks

Possible ICD9 Codes: Cardiomyopathy, Familial = 425.4 Metabolic Cardiomyopathy = 425.7
Syndromic Cardiomyopathy = 425.8 Family member is a carrier of a genetic disease = V18.9

References Cited:

1. Online Mendelian Inheritance in Man. www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
2. Hershberger RE, Kushner JD, Parks SB. Dilated Cardiomyopathy Overview. GeneReviews. 2008. www.genetests.org
3. Bennett S. Pharmacogenomics. 2004;5(4):433-8 (PubMed: 15165179)
4. Human gene mutation database (HGMD) www.hgmd.cf.ac.uk/ac/index.php
5. Hunt SA et al. Circulation. 2005; 112(12):e154-235. (PubMed: 16160202)

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