

Dilated Cardiomyopathy via *PLN* Gene Sequencing (Test #148)

Brief Description of Clinical Features: Dilated cardiomyopathy (DCM, OMIM # 115200) is a heterogeneous disease of the heart muscle. It is characterized by dilatation of the left, right, or both ventricles, systolic dysfunction, and diminished myocardial contractility. Symptoms include arrhythmia, dyspnea, chest pain, palpitation, fainting, and congestive heart failure (Ikram et al. *Br Heart J* 57:521-527, 1987). Additional features may include woolly hair and myopathy (Moller et al. *Eur J Hum Genet* 17:1241-1249, 2009). Sudden death occurs in ~30% of patients with DCM (Tamburro and Wilber *Am Heart J* 124:1035-1045, 1992). Although symptoms of DCM usually begin in adulthood, extensive clinical variability between individuals concerning the age of onset, and extent of structural and functional abnormality has been documented. The prevalence of DCM has been estimated at ~1/2700 (Codd et al. *Circulation* 80:564-572, 1989). See also the Cardiomyopathy Association (<http://www.cardiomyopathy.org>) and Hershberger et al. (GeneReviews, 2009, www.genetests.org).

Genetics: Up to 30% of DCM cases are familial (Grunig et al. *J Am Coll Cardiol* 31:186-194, 1998). In about half of these families, DCM is inherited in an autosomal dominant manner (AD-DCM). Less commonly, the disease is transmitted with an autosomal recessive, X-linked, or mitochondrial inheritance. AD-DCM is caused by defects in 24 genes encoding myocardial proteins. One of these genes, *PLN*, encodes for a cardiac phospholamban, a transmembrane phosphoprotein expressed on the sarcoplasmic reticulum membrane. *PLN* mutations have been reported in patients with AD-DCM (Hershberger et al. *J Cardiac Fail* 15:83-97, 2009). *PLN*-associated DCM has incomplete penetrance (Haghighi et al. *Hum Mutat* 29:640-647, 2008). One missense mutation, p.Arg9Cys, has been found to segregate in a 4-generation family with DCM (Schmitt et al. *Science* 299:1410-1413). In addition, a nonsense mutation, p.Leu39Stop, has been identified in individuals with DCM and in individuals with hypertrophic cardiomyopathy (HCM) (Haghighi et al. *Hum Mutat* 29:640-647, 2008; Chiu et al. *J Mol Cell Cardiol* 43:337-343, 2007; Landstrom et al. *Am Heart J* 161:165-171, 2011).

Description of This Particular Test: This test involves bidirectional DNA sequencing of the single coding exon of the *PLN* gene. The coding sequence plus ~ 50 bp of non-coding flanking DNA are sequenced. As indicated, we will sequence the relevant portion of this exon (Test #100, \$190) in family members of patients with known mutation, or to confirm research results.

Reference Sequences: Genomic: NC_000006.11 mRNA: NM_002667.3 Protein: NP_002658.1 (CCDS 5120.1)

Indications for Test: Patients with symptoms suggestive of DCM or HCM and with no variants reported in genes that are more frequently associated with DCM or HCM.

Sensitivity of Test: The incidence of *PLN* mutations in DCM is unknown. Less than <1% of individuals with HCM have mutations in *PLN*.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of coding exon of the *PLN* Gene: \$ 340

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x2	83898 \$ 75	Sequencing x2	83904 \$ 95
Separation x2	83894 \$ 30	Interpretation/Report x1	83912 \$ 70

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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