

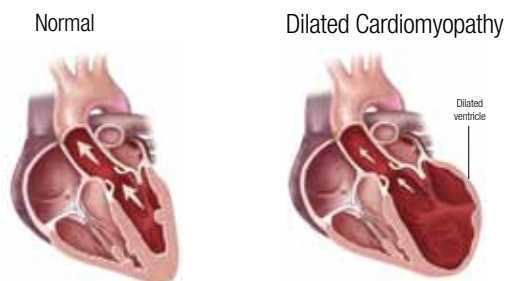
## Dilated Cardiomyopathy (DCM) and Conduction Disease Associated with DCM

### Disease States Overview

According to the Centers for Disease Control and Prevention, each year in the United States, more than 600,000 people die from heart disease. Approximately 22,000 of those deaths occur in young, seemingly healthy people  $\leq 44$  years of age. Many of these deaths are caused by a group of progressive heart muscle diseases called cardiomyopathies. These diseases may cause the heart's mechanical and/or electrical systems to malfunction. Dilated cardiomyopathy (DCM) is the most commonly diagnosed cardiomyopathy, the third leading cause of heart failure and the leading cause of heart transplant.<sup>1,2</sup> In a significant percentage of familial DCM patients the malformation of the heart is preceded by conduction disease (AV block being most common). Echocardiogram findings are often inconclusive in these patients therefore familial conduction disease associated with DCM is often overlooked. For many DCM patients, conduction disease causes sudden cardiac death before they start to experience the signs and symptoms of heart failure.<sup>3</sup>

DCM is characterized by ventricular chamber dilation and reduced force of contraction (Figure 1). The causes of DCM can be acquired and/or genetic. Common causes of acquired DCM include: ischemic injury related to coronary artery disease, myocarditis, chronic high blood pressure and/or chronic alcoholism.<sup>1</sup> After acquired causes have been ruled-out, DCM is referred to as 'idiopathic' (no identifiable cause). One study estimated the prevalence of idiopathic DCM to be 1 in every 2,500 individuals; many DCM experts believe this to be an underestimate.<sup>4</sup> Among DCM patients with conduction disease, 40-50% have a *LMNA* mutation.<sup>5,6</sup>

Figure 1: The Clinical Presentation of DCM



DCM Patients can present at any age, however, symptoms most commonly manifest during the 4th and 5th decades of life. Patients with CD-DCM tend to present at a younger age (between the 2nd and 4th decades of life), but either disease can present at any age. The clinical presentation of DCM is heterogeneous and is associated with progressive heart failure, reduced cardiac output, supraventricular and ventricular arrhythmias, conduction system abnormalities,

thromboembolic events including stroke, and sudden death or heart failure related death. DCM patients may remain symptomless until the disease has substantially progressed. Symptoms associated with DCM include: heart palpitations, syncope, fatigue, breathlessness, intolerance to exercise, and sudden cardiac death.<sup>2,3</sup> Five-year survival post a diagnosis is ~50%.<sup>2</sup>

The primary goals of therapy are symptom management and prevention of disease progression. ACE inhibitors and angiotensin II receptor antagonists have both been found to prevent disease progression.<sup>3</sup> Other treatments include pace maker and implantable cardiac defibrillator device placement.

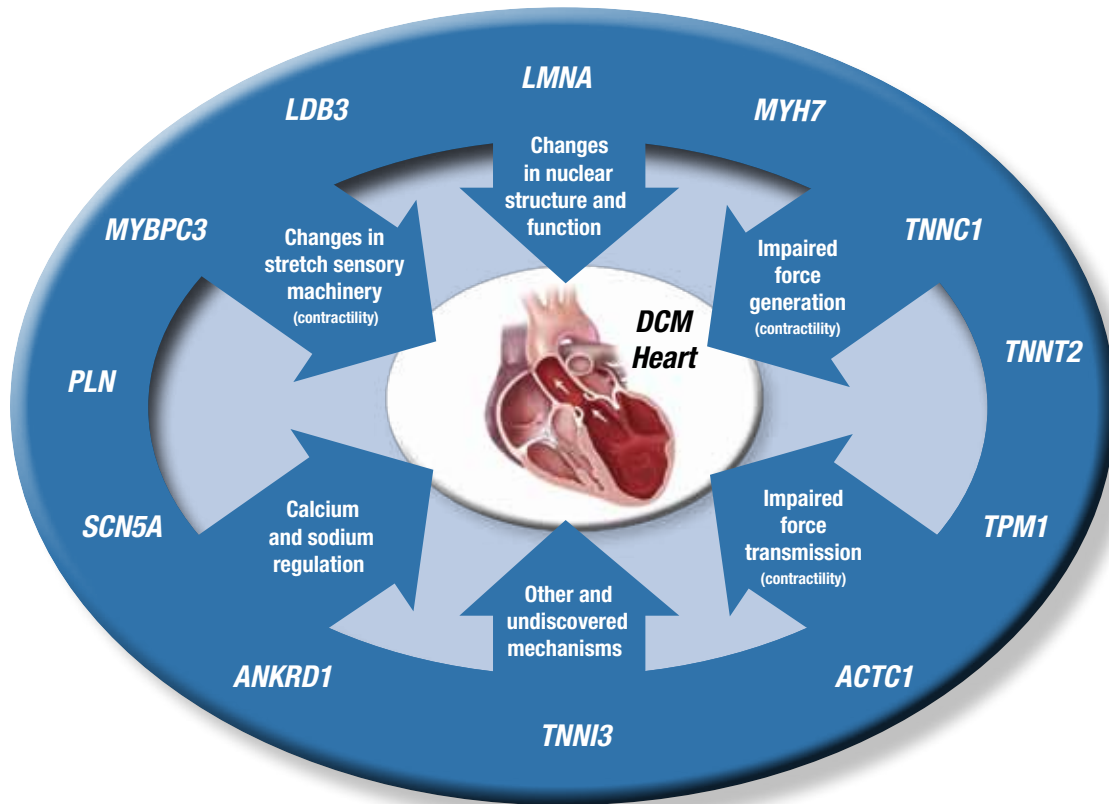
### The Genetic Cause of DCM

Familial DCM is a genetically heterogeneous disease that is most commonly inherited as an autosomal dominant trait. Over 20 genes are associated with DCM; however, the vast majority of known DCM mutations occur in 12 genes (Figure 2).<sup>5</sup> Approximately 25% of idiopathic DCM patients will have a mutation in 1 of these 12 DCM genes.<sup>5,6</sup>

Figure 2. Estimated Percentage of Familial DCM

Gene	Estimated Percentage of Idiopathic DCM Patients <sup>4,5</sup>
<i>LMNA</i>	6%, also associated with CD-DCM
<i>SCN5A</i>	3%, also associated with CD-DCM
<i>MYH7</i>	4%
<i>LDB3</i>	3%
<i>MYBPC3</i>	3%
<i>ANKRD1</i>	2%
<i>TNNT2</i>	2%
<i>PLN</i>	<1%
<i>ACTC1</i>	<1%
<i>TPM1</i>	<1%
<i>TNNC1</i>	<1%
<i>TNNI3</i>	<1%

Figure 3: Disruption of Diverse Molecular Mechanisms by Single Gene Mutations Causes Familial DCM



The proteins encoded by DCM genes have diverse biological roles and the precise molecular mechanisms that lead to the development of clinically recognized DCM are still largely unknown. However, some diverse DCM-causing mechanisms have been uncovered and include defects in force generation and transmission, nuclear structure and function, stretch sensor mechanisms, and calcium signaling (Figure 3).<sup>7</sup> Interestingly, hypertrophic cardiomyopathy (HCM) and DCM share a partially overlapping molecular etiology as both of these cardiomyopathies can result from sarcomeric gene mutations, although the specific mutations associated with each cardiomyopathy and resulting molecular mechanisms can be different.<sup>8</sup>

Between 20-50% of idiopathic DCM has a genetic etiology.<sup>5,9,10,11</sup> Mutations in *LMNA* are the most common cause of familial DCM and are identified in ~6% of idiopathic DCM patients. Approximately 35% of idiopathic DCM patients with conduction disease (e.g., AV Block) will have a *LMNA* mutation.<sup>5,12</sup> *LMNA* mutations are highly penetrant and ~50% of patients with *LMNA* mutations suffer sudden cardiac death.<sup>2,12,13</sup> These facts illustrate a clear need for the early identification of all family members harboring these mutations.

## Clinical Diagnosis of Idiopathic DCM

A diagnosis of idiopathic DCM is made if all of the following criteria are met:<sup>2</sup>

- Ejection fraction <45% and/or a fractional shortening of <25%
- Left ventricle end diastolic diameter of >117%

And the **absence** of the following criteria:

- Absence of systemic hypertension (>160/100 mmHg)
- Coronary artery disease (50% in one or more branches)
- Chronic excess alcohol (>40 g/day for female, >80 g/day for male)
- Systemic disease known to cause idiopathic dilated cardiomyopathy
- Pericardial disease
- Congenital heart disease
- Cor pulmonale (pulmonary heart disease)

## Challenges Diagnosing DCM and CD-DCM

### 1. Identifying Early-stage DCM.

- DCM symptoms generally manifest during end-stage disease.<sup>3</sup>

### 2. Connecting Non-ischemic Induced Cardiac Conduction

Disease With Familial DCM in the Absence of an Echocardiogram Showing LV Dilation.

### 3. Identifying the Cause of DCM or CD-DCM.

- Clinical investigations of DCM often yield non-specific findings and do not necessarily identify the etiology of DCM.<sup>3</sup>

## Genetic Analysis Can Help Overcome Diagnostic Challenges

For many patients with idiopathic DCM genetic testing can help identify the etiology of their disease. Once a proband is identified cascade testing of family members is possible. Genetic testing is the most reliable way to identify pre-symptomatic or asymptomatic family members, creating the opportunity for aggressive clinical surveillance and earlier intervention with disease modifying therapy.

## The *FAMILION* DCM and CD-DCM Tests

The *FAMILION* DCM Test includes 12 genes and the *FAMILION* CD-DCM Test includes 2 genes (Figure 4). The *FAMILION* DCM Test is the only DCM panel that includes *SCN5A* and *ANKRD1*, two genes that combine to account for 5% of gene mutations in familial DCM patients.<sup>6</sup>

The tests are indicated for:

- Patients with clinical features consistent with DCM or CD-DCM.
- Relatives of patients with a known DCM or CD-DCM gene mutation.

Figure 4: The *FAMILION* DCM and CD-DCM Tests

Gene	Included in DCM Test	Included in CD-DCM Test
<i>LMNA</i>	✓	✓
<i>SCN5A</i>	✓	✓
<i>MYH7</i>	✓	–
<i>LDB3</i>	✓	–
<i>MYBPC3</i>	✓	–
<i>ANKRD1</i>	✓	–
<i>TNNT2</i>	✓	–
<i>PLN</i>	✓	–
<i>ACTC1</i>	✓	–
<i>TPM1</i>	✓	–
<i>TNNC1</i>	✓	–
<i>TNNI3</i>	✓	–

The *FAMILION* DCM Test will find a mutation in approximately 25% of idiopathic DCM patients.<sup>4,5</sup>

The *FAMILION* CD-DCM will find a mutation in 40-50% of familial DCM patients with conduction disease.<sup>5,13</sup>

## The Role of the *FAMILION* DCM and/or CD-DCM Tests

By reducing uncertainty and finding the specific cause of DCM or conduction disease associated with DCM, the *FAMILION* DCM and/or CD-DCM Tests provide the following benefits:

- Diagnose or confirm the diagnosis of familial DCM
- Distinguishes between idiopathic and familial DCM
- Identifies at-risk family members, creating the opportunity for early intervention
- Better enables genetic counseling
- Helps establish the need and schedule for clinical surveillance of family members
- Distinguishes between DCM, end-stage HCM and ARVC

## Genetic Evaluation of Cardiomyopathy - A Heart Failure Society of America Practice Guideline (2009)

The Heart Failure Society of America (HFSA) Practice Guideline supports genetic testing of DCM probands (Figure 5).<sup>5</sup> HFSA ratings are based on clinical validity and utility. Grades range from A to C; the letter grade A corresponds to the highest score while C is the lowest.

Figure 5: HFSA Grade for Genetic Testing of Proband

Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.	
Cardiomyopathy Phenotype	Level of Evidence
Dilated cardiomyopathy (DCM)	B

## The HFSA Guideline Supports Genetic Testing for Patients With Conduction Disease Associated With DCM

...[genetic] testing for the LMNA gene is recommended in patients with prominent conduction disease with or without supraventricular or ventricular arrhythmias, or with signs of skeletal muscle involvement shown most commonly by elevated creatine kinase because in either of these groups LMNA mutations appear to be at higher frequency...<sup>5</sup>

## HFSA Supports Genetic Screening of DCM Families

The proband's genetic status affects the need for and timing of clinical monitoring of family members. If a disease-causing mutation is identified in the proband but is NOT found in family members, the risk of developing DCM is significantly reduced and ongoing clinical screening is NOT recommended.<sup>5</sup> The recommendations for the clinical screening intervals vary based on genetic status (Figure 6).

Figure 6: HFSA Guidelines on Clinical Screening of DCM Families

Clinical screening for cardiomyopathy should be considered at the following times and intervals or at any time that signs or symptoms appear.			
Cardiomyopathy Phenotype	Interval if genetic testing* is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Level of Evidence
DCM	Every 3 to 5 years beginning with childhood	Yearly in childhood; every 1 to 3 years in adults	B

\*Genetic testing of proband is negative.

## ACC/AHA/ESC Guidelines (2006) Supports Genetic Testing for Identification of ALL Mutation Carriers in a DCM Family

"When a pathogenic mutation is identified, it becomes possible to establish a presymptomatic diagnosis of the disease among family members and to provide them with genetic counseling to monitor progression of the disease and to assess the risk of transmitting the disease to offspring."<sup>5</sup>

## PGxHealth Laboratory Process Highlights

PGxHealth sequences 12 genes associated with DCM, and 2 genes associated with CD-DCM. The following laboratory processes are among the reasons PGxHealth is a leader in genetic testing:

- Two technologists independently score all sequence variants, and a supervisor reconciles any discrepancy.
- All traces with variants are reviewed and approved by an American Board of Medical Genetics board certified molecular geneticist.
- For each class I or II mutation found, a second round of PCR amplification and sequencing are completed to confirm the initial finding.
- Identified variants are interpreted with respect to an ethnically diverse reference population of several hundred unrelated individuals (presumed non-cardiomyopathy), a database of known mutations and published medical literature (Figure 7).

Figure 7: The *FAMILION* Test Variant Classification

<b>Class I Mutation:</b> Deleterious and Probable Deleterious Mutations
<b>Class II Mutation:</b> Variant of Uncertain Significance
<b>Class III Variant:</b> Variant Not Generally Expected to Cause Disease
<b>Class IV Variant:</b> Non-protein-altering Variant

## PGxHealth Reimbursement Highlights

- PGxHealth is an approved Medicare provider.
- PGxHealth is an approved Medicaid provider in most states. PGxHealth reserves the right not to participate in any state's Medicaid program even if approved as a provider.
- A brief list of select insurance companies that have developed positive medical policies for all or select *FAMILION* tests include: BCBSA, United, Aetna, Cigna and Humana.

## Every Test Report is Accompanied by an Interpretation Guide

- All test reports include a test-specific interpretation guide. These were developed to better explain the system employed by PGxHealth for rating variants (Figure 8).

Figure 8: The *FAMILION* Tests Interpretation Guide

	← Related to Disease	Not Related to Disease →
	<b>Class I Mutation</b> (Deleterious or Probable Deleterious)	<b>Class II Mutation</b> (Variant of Uncertain Significance)
	<b>Class III Variants</b> (Not Expected to Cause Disease)	
Clinical Interpretation	<ul style="list-style-type: none"> <li>• Result strongly suggests an inherited cardiac disease.</li> </ul>	<ul style="list-style-type: none"> <li>• Mutation may be disease-causing or benign.</li> </ul>
Reasons for Classification	<ul style="list-style-type: none"> <li>• Strong evidence of deleteriousness.</li> <li>• “Probable,” if included, indicates that variant is predicted, but has not been demonstrated, to cause disease.</li> <li>• Typically absent from a healthy control population.</li> </ul>	<ul style="list-style-type: none"> <li>• Evidence is insufficient to determine whether the mutation is deleterious.</li> <li>• Typically absent from a healthy control population.</li> </ul>
Recommendations	<ul style="list-style-type: none"> <li>• Genetic testing of all first-degree relatives is recommended to identify those at risk for disease. Genetic counseling should be considered.</li> </ul>	<ul style="list-style-type: none"> <li>• Evidence indicates variant is not disease-causing.</li> <li>• Typically common in a healthy control population.</li> </ul>
	<ul style="list-style-type: none"> <li>• Genetic testing and clinical screening in family members may elucidate the significance of the mutation. Genetic counseling should be considered.</li> </ul>	<ul style="list-style-type: none"> <li>• Genetic testing of family members for Class III variants is not advised.</li> </ul>

## The FAMILION Family of Genetic Tests

Cardiac Channelopathies	Genes*				Clinical Sensitivity†
<b>LQTS Test</b>	<i>KCNQ1</i> (LQT1) <i>KCNE2</i> (LQT6) <i>SCN4B</i> (LQT10)	<i>KCNH2</i> (LQT2) <i>KCNJ2</i> (LQT7) <i>AKAP9</i> (LQT11)	<i>SCN5A</i> (LQT3) <i>CACNA1C</i> (LQT8) <i>SNTA1</i> (LQT12)	<i>KCNE1</i> (LQT5) <i>CAV3</i> (LQT9)	75-80% <sup>1,2</sup>
<b>BrS Test</b>	<i>SCN5A</i> <i>SCN1B</i>	<i>GPD1L</i> <i>KCNE3</i>	<i>CACNA1C</i> <i>SCN3B</i>	<i>CACNB2</i>	25-40% <sup>3,4,5,6,7,8,9</sup>
<b>CPVT Test</b>	<i>RYR2</i>	<i>KCNJ2</i>			65-75% <sup>10,11,12,13</sup>
<b>SQTS Test</b>	<i>KCNH2</i>	<i>KCNQ1</i>	<i>KCNJ2</i>		Unknown
Cardiomyopathies	Genes*				Clinical Sensitivity†
<b>ARVC Test</b>	<i>DSP</i> <i>PKP2</i>	<i>DSG2</i> <i>DSC2</i>	<i>TMEM43</i>		40-50% <sup>14</sup>
<b>DCM Test</b>	<i>LMNA</i> <i>ANKRD1</i> <i>TNNC1</i>	<i>SCN5A</i> <i>TPM1</i> <i>MYBPC3</i>	<i>ACTC</i> <i>LDB3</i> <i>PLN</i>	<i>MYH7</i> <i>TNNT2</i> <i>TNNI3</i>	~25% <sup>2,15</sup>
<b>CD-DCM Test</b>	<i>LMNA</i>	<i>SCN5A</i>			40-50% <sup>16,17</sup>
<b>HCM Test</b>	<i>MYH7</i> <i>TPM1</i> <i>MYBPC3</i>	<i>TNNC1</i> <i>TNNT2</i> <i>TNNI3</i>	<i>ACTC</i> <i>MYL2</i> <i>MYL3</i>	<i>GLA</i> <i>LAMP2</i> <i>PRKAG2</i>	50-60% <sup>18</sup>

\* See the FAMILION test specification sheet for coverage areas. † Percent of patients with a high index of suspicion for the cardiac syndrome that will have a mutation identified.

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For more information about reimbursement of the FAMILION tests or any other PGxHealth test please contact our Patient Services Team (1.877.274.9432) or visit [www.familion.com](http://www.familion.com).

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