The Heart Center

What Pediatricians Should Know About Genetic Testing for Cardiomyopathies

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Cardiomyopathy Phenotypes Often Overlap

Cardiomyopathy is a chronic disease that affects patients of all ages. However, it most often has adolescent or adult onset. Cardiomyopathy is a complex disease consisting of five primary phenotypes:

- Hypertrophic (HCM)
- Dilated (DCM)
- Arrhythmogenic right ventricular (ARVC)
- Restrictive (RCM)
- Left ventricular non-compaction (LVNC)

Substantial overlap exists between the cardiomyopathy phenotypes. Basic diagnosis of these phenotypes should be done with ECG and echocardiography; additional phenotyping options are listed in the table below.

Additionally, syndromic and metabolic causes comprise a higher portion of the cardiomyopathy cases in newborns and young children. Extracardiac findings might include:

- Dysmorphic features
- Short stature
- Congenital abnormalities
- Muscle weakness
- Sensory deficits of unknown cause
- Intellectual disability of unknown cause

If a patient is confirmed to have cardiomyopathy, all at-risk first-degree relatives should receive screening and be offered genetic testing based on the results in the patient.

PHENOTYPE	INCIDENCE (PER 100,000)	SYMPTOMS	RECOMMENDED BASELINE CLINICAL PHENOTYPING
HCM	0.2 adult prevalence 0.3-0.5 children	Shortness of breath Fatigue Orthopnea Paroxysmal nocturnal Dyspnea Edema	ECG EST Holter monitoring CMR Metabolic disease screening (for infants only) ECHO
DCM	5-8 adult 0.57 children	Same as HCM	CK-MM ECG CMR Metabolic disease screening (for infants) ECHO
ARVC	Rare	Syncope Atypical chest pain Ventricular tachycardia	ECG Holter monitoring CMR ECHO
RCM	Rare	Pulmonary congestion Dyspnea on exertion Decreased cardiac output Syncope	ECG EST Holter monitoring CMR Metabolic disease screening ECHO
LVNC	Rare	Often asymptomatic Shortness of breath Fatigue Atypical chest pain	CK-MM ECG CMR Metabolic disease screening ECHO

All Cardiomyopathy Patients Should See a Specialist

Patients with genetic, familial or unexplained forms of cardiomyopathy should be referred to centers with expertise in the evaluation, diagnosis, and management of genetic heart disease, such as The Heart Center at Nationwide Children's Hospital. In particular, infants and young children with syndromic or nonsyndromic cardiomyopathy should be evaluated by a specialist team.

Genetic Evaluation Is Recommended for the Family

The family is considered the unit of care for genetic cardiomyopathies. After a patient with a primary cardiomyopathy phenotype is referred, genetics professionals will obtain a detailed family history of at least three generations and will create a pedigree to identify at-risk family members.

Genetic evaluation includes a comprehensive family history, phenotypic evaluation of all at-risk family members, genetic counseling, genetic testing, and guidance on treatment and therapeutic intervention.

Genetic testing is recommended for:

- Identifying pathogenic or likely pathogenic genetic variants can facilitate patient management and family screening. An individual may not have symptoms of cardiomyopathy until late in the disease course, and thus first presentation may be sudden cardiac death.Therefore, it is critical that patients or family members found to be at-risk undergo interval screening to detect the earliest signs of any cardiomyopathy phenotype.
- Any patient with confirmed cardiomyopathy, preferably as soon as the diagnosis is made. If a pathogenic or likely pathogenic variant in one or more cardiomyopathy gene is identified, cascade genetic testing testing of at-risk relatives should be conducted.
  - Should an unaffected family member test positive, this individual should receive serial phenotypic screening for emergent cardiomyopathy.
  - Should an unaffected family member test negative, the risk for that individual is greatly reduced but is not reduced to zero.
- If a patient who has genetic testing for another disorder is identified as having a pathogenic or likely pathogenic cardiomyopathy genetic variant, cascade genetic screening of at-risk relatives should be considered.

What Tests Are Ordered?

Thousands of pathogenic and likely pathogenic variants have been identified in key cardiomyopathy genes. Currently, multigene panels are available to test a patient for genetic variants associated with syndromic, metabolic, and nonsyndromic forms of cardiomyopathy. Many of the cardiomyopathy genes can cause more than one cardiomyopathy phenotypes, and rarely a patient may carry more than one disease-causing variant. Genetics counselors or clinical geneticists, preferably with specialty in cardiovascular disease, will select the appropriate genetic test for referred cardiomyopathy patients. Subsequent test result interpretation is critical for establishing whether the variants found are consistent with the patient's phenotype and appropriate family cascade testing. Periodic test result reinterpretation or retesting is recommended as knowledge about specific variants accumulates over time and genetic testing technology changes.

PHENOTYPE	DIAGNOSTIC YIELD OF GENETIC TESTING	CELLULAR COMPONENTS ASSOCIATED WITH DISEASE
HCM	30 – 60%	Sarcomere Mitochondria
DCM	10 – 40%	Sarcomere Mitochondria Cytoskeletal proteins Desmosome
ARVC	10 – 50%	Desmosome
RCM	10 – 60%	See HCM and DCM
LVNC	Unknown	See DCM, HCM, and ARVC

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Referrals and Consultations

Online: **NationwideChildrens.org**
Phone: **(614) 722-6200** or **(877) 722-6220** | Fax: **(614) 722-4000**
Physician Direct Connect Line for 24-hour urgent physician consultations: **(614) 355-0221** or **(877) 355-0221**.

Laboratory Testing and Pathology Consultations

Online: **NationwideChildrens.org/Lab**
Phone: **(614) 722-5477** or **(800) 934-7575**

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W477450 11/3/2021