Guideline

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

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Substantial progress has been made recently in understanding the genetic basis of cardiomyopathy. Cardiomyopathies with known genetic cause include hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and left ventricular noncompaction (LVNC). HCM, DCM, and RCM have been recognized as distinct clinical entities for decades, whereas ARVD/C and LVNC are relative newcomers to the field. Hence the clinical and genetic knowledge for each cardiomyopathy varies, as do the recommendations and strength of evidence. (*J Cardiac Fail 2009;15:83–97*)

The evidence indicating that HCM has a genetic basis is extensive: HCM is now understood largely to be a genetic disease of contractile proteins, although less commonly, infiltrative etiologies may also be causative (Table 1). The evidence supporting a genetic basis for DCM, after other more common causes have been excluded (eg, ischemic disease, hypothyroidism, cardiotoxic agents such as Adriamycin), is now substantial for familial dilated cardiomyopathy (FDC), where FDC is defined as DCM of unknown cause in 2 or more closely related family members (Table 2). However, whether sporadic DCM has a genetic basis remains an open question, especially when detectable familial disease has been clinically excluded by testing closely related family members. Thus, although some recommendations formulated for the genetic evaluation of cardiomyopathy, such as the need for family history, apply to all entities, other recommendations must be tailored to account for these differences. This is particularly relevant as these guidelines use the generic term ''cardiomyopathy'' to imply possible familial or genetic cause, assuming that all other detectable causes of cardiomyopathy have been ruled out. This is particularly relevant for DCM where multiple nongenetic causes are possible as noted previously.

Recent discoveries indicate that ARVD/C is largely caused by mutations in genes encoding proteins of the desmosome (Table 3). Although initially recognized predominantly in the right ventricle, left ventricular involvement in 20% to 40% of patients has prompted the change in nomenclature from ARVD to ARVD/C.[1]

Discovering the genetic basis of RCM has been more challenging, because RCM is much less common than DCM or HCM, and less commonly presents with familial disease (Table 3).

LVNC is an anatomic abnormality of left ventricular myocardial development: left ventricular compaction is incomplete, leaving deep trabeculations in the LV myocardium. LVNC was categorized as a specific type of cardiomyopathy by an expert panel in 2006,[2] and some genetic association has been observed (Table 3). Although initially reported to be a rare condition associated with adverse outcome,[3] more recent reports[4–6] have called into question those preliminary conclusions.[7] Three different echocardiographic criteria have been used for diagnosis.[6] These authors suggested that the diagnostic criteria for LVNC might be too sensitive. Because of the uncertainty of diagnostic standards leading to difficulty clarifying its phenotype, we suggest that the LVNC recommendations in this document be limited to those individuals with only the most prominent disease.

This guideline organizes recommendations by cardiac phenotype. We acknowledge that there is substantial overlap among phenotypes and some mutations are associated with more than 1 phenotype. However, therapeutic decision-

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Table 1. Genetic Causes of Hypertrophic Cardiomyopathy

Gene*	Protein	OMIM†	Frequency, Familial‡	Frequency, Sporadic†	Comments	Selected References
Autosomal Dominant Hypertrophic Cardiomyopathy: Genes Encoding Sarcomeric Proteins						
MYH7	β-myosin heavy chain	160760	30%−40%	30%−40%	Wide age range; severe LVH; heart failure, SCD	11, 12, 38, 39
MYBPC3	Myosin-binding protein C	600958	30%−40%	30%−40%	Usually milder disease, although can be severe; some older onset	11, 12, 39, 40
TNNT2	Cardiac troponin T	191045	10%−20%	10%−15%	Mild LVH; SCD more common	11, 12, 39, 41
TPM1	α-tropomyosin	191010	2%−5%	?		11, 12, 39, 40
TNNI3	Cardiac troponin I	191044	2%−5%	?		11, 12, 39, 42
MYL2	Myosin regulatory light chain	160781	Rare	Rare		43
MYL3	Myosin essential light chain	160790	Rare	Rare		43
ACTC	Cardiac actin	102540	Rare	Rare		44
TTN	Titin	188840	Rare	Rare		45
MYH6	α-myosin heavy chain	160710	Rare	Rare		46
TCAP	Titin-cap or telethonin	604488	Rare	Rare		47
Hypertrophic Cardiomyopathy Caused by Metabolic/Infiltrative Disease						
PRKAG2	AMP-activated protein kinase subunit	602743	?	?	HCM, with WPW	48
GLA	α-galactosidase	300644	?	?	Fabry disease, X-linked	49
LAMP2	Lysosome-associated membrane protein 2	309060	?	?	Danon disease, X-linked	50

*Genes within each category are ordered by publication.
†OMIM is Online Mendelian Inheritance in Man (accessed via http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim).
‡Rare denotes a frequency usually <1%.

making is generally dictated by phenotype making this approach the most helpful for the clinician.

The available clinical genetics data for each of the cardiomyopathies varies greatly in content and quality, and thus the quality and certainty of genetic counseling information is also variable. So too, the evidence that supports clinical genetic testing varies greatly. Although analytic validity (the ability of the test to detect a mutation) is attainable with current methods, evidence to support clinical validity (the ability of the test to detect the condition) remains quite limited for most cardiomyopathies, the exception being HCM. A separate measurement, clinical utility, defines the global risks and benefits of any test, asking the all-important question: how will the genetic information, whether positive or negative, affect clinical decision-making for the patient or the patient's family? Clinical utility remains to be defined for all genetic testing of cardiomyopathies.

Although each recommendation has been designed for adult and pediatric patients, many of the references used to formulate these guidelines have focused primarily on adults. A section devoted to pediatric genetic cardiomyopathies provides additional specific information.

Despite these limitations, recent progress makes it possible to propose guidelines for the genetic evaluation of cardiomyopathy. These guidelines will evolve and mature as more robust clinical genetics knowledge becomes available.

HFSA Guideline Approach to Medical Evidence for Genetic Evaluation of Cardiomyopathy

Each recommendation in the general HFSA clinical guideline has both a strength of recommendation and a weight of evidence supporting that recommendation.[8] The strengths of recommendations in this guideline are identical to those in the general guideline.

The strength of recommendation is contained in the following 4 categories: (1) "Is recommended" as part of routine care, and exceptions should be minimized; (2) "Should be considered" indicates that the majority of patients should receive the intervention, with some discretion in application to individual patients; (3) "May be considered" indicates that individualization of therapy is indicated; and (4) "Is not recommended" indicates that the therapeutic intervention should not be used.

However, because genetic testing is relatively new, randomized clinical trials demonstrating that performing the specific genetic test improves outcomes are not available. Thus, we have used a different format for level of evidence that describes evidence for clinical validity that asks the question "Does the test correlate with the outcome of interest?"[9] The hierarchy of types of evidence includes the following.

Level A: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in reasonably large studies from multiple centers.
Level B: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in small or single center studies.
Level C: The specific genetic test or clinical test correlates with the cardiomyopathic disease of interest in case reports.

The second criterion, clinical utility strength of evidence criteria, follow the criteria used for overall strength of evidence in the general guideline (shown in the following section),[9] and asks the question, "Does performing the test result in improved patient outcomes?"

Level A: randomized, controlled, clinical trials. May be assigned on the basis of a single randomized trial.
Level B: Cohort and case control studies. Post-hoc, subgroup analysis, and meta-analysis. Prospective observational studies or registries.

Table 2. Genetic Causes of Dilated Cardiomyopathy

Gene*	Protein	OMIM	Frequency, Familial†	Frequency, Sporadic†	Comments‡	References
Autosomal Dominant FDC Dilated Cardiomyopathy Phenotype						
ACTC	Cardiac actin	102540	rare	rare		51–55
DES	Desmin	125660	?	?		54, 56–58
LMNA	Lamin A/C	150330	7.3%	3.0%	5.5% overall (41/748, 6 studies, see text)	22–27, 59–65
SGCD	δ-sarcoglycan	601411	rare	rare		57, 66, 67
MYH7	β-myosin heavy chain	160760	6.3%	3.2%	4.8% overall (22/455, 3 studies)	20, 68–70
TNNT2	Cardiac troponin T	191045	2.9%	1.6%	2.3% overall (15/644, 3 studies)	20, 68, 70–73
TPM1	α-tropomyosin	191010	rare	rare		74
TTN	Titin	188840	?	?		75
VCL	Metavinculin	193065	rare	rare		70, 76
MYBPC3	Myosin-binding protein C	600958	?	?		69
CSRP3	Muscle LIM protein	600824	rare	rare		20, 77
ACTN2	α-actinin-2	102573	?	?		78
PLN	Phospholamban	172405	rare	rare		70, 79, 80
ZASP/ LDB3	Cypher/LIM binding domain 3	605906	?	?		20, 81
MYH6	α-myosin heavy chain	160710	?	?		46
ABCC9	SUR2A	601439				82
TNNC1	Cardiac troponin C	191040	?	?		73
TCAP	Titin-cap or telethonin	604488	rare	rare		20, 47
SCN5A	Sodium channel	600163	?	?	2.3% overall (11/469, 2 studies)	83–85
EYA4	Eyes-absent 4	603550	?	?		86
TMPO	Tthymopoietin	188380	?	?		87
PSEN1	Presenilin 1 / 2	104311	?	?		88
PSEN2		600759				
X-linked Familial Dilated Cardiomyopathy						
DMD	Dystrophin	300377				89, 90
TAZ/G4.5	Tafazzin	300394				91, 92
Autosomal Recessive Familial Dilated Cardiomyopathy						
TNNI3	Cardiac troponin I	191044	?	?		93

*Genes are ordered by publication year.
†Rare indicates less than 1%; frequencies are provided only with two or more publications.
‡Overall frequencies may include studies that did not distinguish between familial and sporadic cases.

Level C: Expert opinion. Observational studies—epidemiologic findings. Safety reporting from large-scale use in practice.

However, as noted previously for clinical validity, randomized or controlled clinical trials or large cohort and case/control studies are seldom available from genetic cardiomyopathy studies. Hence the authors graded strength of evidence based upon the totality of information available.

17.1. A careful family history for ≥3 generations is recommended for all patients with cardiomyopathy.

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmogenic right ventricular dysplasia (ARVD)	**A**
Left ventricular noncompaction (LVNC)	**A**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extracardiac manifestations (Table 4)	**A**

Background. The family history, long established as an essential component of any medical evaluation, is particularly relevant for the cardiomyopathies.[10] The first goal of the family history is to ascertain if the cardiomyopathy is familial, and, if so, to identify those individuals who may be at risk. Because of reduced penetrance observed in some families with cardiomyopathy, a family history extending to at least 3 generations improves recognition that a cardiomyopathy is inherited and helps define dominant or recessive transmission. Patients unprepared for a recitation of their family history may only provide general information suggestive of cardiovascular disease in their relatives. Not uncommonly, the cause of any cardiovascular condition resulting in hospitalization may be described as a "heart attack," as is the case with sudden cardiac death (SCD). Hence, when the diagnosis of cardiomyopathy is suggested, the patient should be requested to obtain additional information to confirm or exclude the cardiomyopathy diagnosis. Specific medical information pertinent to the patient's diagnosis should be sought regarding the patient's relatives. For example, in HCM or

Table 3. Genetic Causes of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Left Ventricular Noncompaction, and Restrictive Cardiomyopathy

Gene	Protein	OMIM	Frequency*	Comments	Selected References
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy					
JUP	Plakoglobin	173325	Rare	Naxos disease, autosomal recessive	94–96
DSP	Desmoplakin	125647	6%–16%		1, 97
PKP2	Plakophilin-2	602861	11%–43%		1, 98, 99
DSG2	Desmoglein-2	125671	12%–40%		1, 100, 101
DSC2	Desmocollin-2	125645	Rare		1, 102, 103
RYR2	Ryanodine receptor	180902	Rare		104
TGFB3	Transforming growth factor beta-3	190230	Rare		97, 105, 106
Left Ventricular Noncompaction					
MYH7	β-myosin heavy chain	160760	?		107
LDB3	Limb domain binding protein 3	605906	?		81
DTNA	α-dystrobrevin	601239	?		108
TAZ	Taffazzin	300394	?		108
Restrictive Cardiomyopathy					
MYH7	β-myosin heavy chain	160760	?		107, 109
TNNI3	Troponin I	191044	?		110

*Frequency estimates for arrhythmogenic right ventricular dysplasia/cardiomyopathy are from Genetests.

ARVD/C, targeted questions relating to SCD in teenagers and young adults should be sought. Increasingly, practitioners record a pedigree to illustrate the family history data.

When taking a family history, it is imperative that the professional recording it makes no a priori assumptions of which side of the family the disease originated[10] and should consider bilineal inheritance (transmission of a disease-causing mutation in the same or a different gene from both mother and father). In HCM, reports of large series of patients undergoing comprehensive genetic screening have shown compound or double mutations in 5%.[11–13] It has been suggested that some of these individuals may have had more severe disease related to a "double-dose" effect incurred from the 2 mutations.[13]

A second goal, after a cardiomyopathy is suspected or proven to be familial, is to ascertain the inheritance pattern. Pedigree analysis is undertaken to determine if the inheritance is autosomal dominant or recessive, X-linked dominant or recessive, or mitochondrial[10] and thus provide an accurate risk assessment. Most genes known to cause cardiomyopathies are transmitted in an autosomal dominant manner. Autosomal dominant inheritance implies that only one copy of the mutation is needed to cause the disease phenotype, and that each child has a 50% chance to inherit the mutation. For X-linked inheritance, the mutation is carried in a gene on the X-chromosome.

Expanding a family history beyond the 3rd generation and collecting medical data from relatives known or suspected to manifest clinical disease consistent with the cardiomyopathy in question can be enormously informative. With additional family and clinical data, further analysis of the pedigree may suggest the age of onset, penetrance, lethality, response to treatment, and other aspects of the condition. However, because obtaining a family history and related activities outlined are time and effort intensive, busy practitioners may choose to refer patients with cardiomyopathy to centers expert in genetic cardiomyopathies. Such centers may also provide genetic counseling and genetic testing, compile clinical and genetic databases, and offer research opportunities that are essential for progress in the field.

17.2. Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended.

a. Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmogenic right ventricular dysplasia (ARVD)	**A**
Left ventricular noncompaction (LVNC)	**B**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extracardiac manifestations (Table 4)	**A**

b. Clinical screening for cardiomyopathy is recommended at intervals (see below) in asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s). (Level of Evidence = A)

c. Clinical screening for cardiomyopathy is recommended for asymptomatic at-risk first-degree relatives when genetic testing has not been performed or has not identified a disease-causing mutation. (Level of Evidence = A)

d. It is recommended that clinical screening consist of:

- **History (with special attention to heart failure symptoms, arrhythmias, presyncope, and syncope)**
- **Physical examination (with special attention to the cardiac and skeletal muscle systems)**
- **Electrocardiogram**
- **Echocardiogram**
- **CK-MM (at initial evaluation only)**
- **Signal-averaged electrocardiogram (SAECG) in ARVD only**
- **Holter monitoring in HCM, ARVD**
- **Exercise treadmill testing in HCM**
- **Magnetic resonance imaging in ARVD**

(Level of Evidence = B)

e. 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
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter.	B
Dilated	Every 3–5 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	B
ARVD/C	Every 3–5 years after age 10	Yearly after age 10 to 50 years of age.	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	C
Restrictive	Every 3–5 years beginning in adulthood	Yearly in childhood; every 1–3 years in adults.	C

f. At-risk first-degree relatives with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at 1 year. (Level of Evidence = C).

Background. The basis for these extensive clinical screening recommendations (and the counseling and molecular recommendations in the sections that follow) is because cardiomyopathy can be treated in almost all cases, improving survival and/or enhancing quality of life.[14,15] In contrast, many other genetic diseases have no useful medical treatment. Further, determining genetic risk of cardiomyopathy before disease presentation guides the recommendations for increased surveillance to detect early disease onset and medical intervention. All of these measures may delay disease presentation and progression, thereby avoiding advanced therapies such as cardiac transplantation, or averting the sequelae of life-threatening events, such as sudden cardiac death.[15]

Most cardiomyopathies are adult onset, and as is common for adult-onset genetic disease, show a variable age of onset and variable penetrance. Hence, clinical screening of first-degree relatives of adults diagnosed with cardiomyopathy is recommended, regardless of whether a disease-causing mutation has been identified in the index patient. Because of the variable age of onset, clinical screening repeated at intervals is recommended, even if clinical genetic testing has not identified a disease-causing mutation in the family. If a disease-causing mutation is identified, the frequency of presymptomatic clinical screening in relatives known to be mutation carriers is recommended with increased frequency, because the probability of future disease is increased among carriers. Increased frequency of follow-up clinical screening should also be undertaken for at-risk relatives if clinical screening has shown that the disease is familial, even if a mutation has not been found. This is because for genetic cardiomyopathy, familial disease strongly suggests genetic cause. Further, the sensitivity of genetic testing varies greatly (reviewed in Section 3). Conversely, as the table in Table 17.2 shows, if the clinical screening of first-degree relatives is negative, or a disease-causing mutation has not been identified, the intervals for clinical screening are recommended to be less frequent because of the reduced evidence of genetic risk.

The rationale for this latter recommendation, although reasonable, is based on limited data. With clinical screening, whether the lack of clinical evidence of cardiomyopathy in first-degree family members is helpful to predict the presence or absence of genetic cause of the proband's cardiomyopathy has not yet been resolved. This is because of the variable age of onset and variable penetrance. Resolution of this issue will require data from additional large, rigorously designed clinical and genetic studies. Despite these uncertainties, we suggest that negative molecular genetic findings in the proband or no clinical evidence of disease in their family members, integrated with the type of cardiomyopathy, may be helpful to estimate the family members' genetic risk. We emphasize that these risk assessments will vary greatly with the type of cardiomyopathy, because of the varied sensitivity of genetic testing (reviewed in Section 17.3). Thus, we have recommended longer intervals between clinical screening with less evidence of disease, recognizing that lack of evidence may not necessarily be synonymous with lack of risk. We also acknowledge that while genetic testing is recommended

(Section 17.3), in some circumstances genetic testing cannot be performed because of a variety of issues (eg, the proband is deceased or unavailable, funding issues). Hence, the clinician must integrate all data—clinical and genetic—from the patient and his/her family members, to support the clinical decision analysis in genetic cardiomyopathy.

Integration of all of these considerations given above, most importantly the type of cardiomyopathy, should also be taken into account in screening of children. Although children can manifest clinical cardiomyopathy, most disease is adolescent (HCM) or adult onset. Hence these recommendations should be integrated with the type of cardiomyopathy, the age of onset of other affected members in the pedigree when such data are available, the identity of the cardiomyopathy gene, and other features.

Recommendations for testing modalities by diagnosis are given in the previous section. All are screening tests to be performed during an initial evaluation of someone of unknown disease status. If any cardiovascular abnormalities are detected, additional testing specific for the cardiomyopathy should be obtained to secure a diagnosis and prognosis and formulate an appropriate treatment plan.

The risks for developing HCM after 50 years of age are reduced but not eliminated[16] as are those for ARVD after 50 years of age.[17] The utility and role of Holter monitoring and the signal-averaged ECG in the diagnosis of ARVD has been reviewed.[17] Magnetic resonance imaging is useful for the diagnosis of ARVD in centers experienced in its use and interpretation for ARVD[18]; data are not yet available to guide the frequency of its application for screening at-risk family members.

The patient should be encouraged to communicate with at-risk relatives regarding the presenting symptoms of cardiomyopathy, regardless of whether clinical genetic testing is undertaken, or if undertaken, whether the results are positive or negative. They should be counseled to seek medical assistance with symptoms, and in particular be counseled that potentially imminently life-threatening symptoms, such as presyncope or syncope, should be brought to immediate medical attention.

Less evidence is available to support of the genetic basis of RCM than for the other cardiomyopathies, hence its reduced level of evidence in these guidelines.

17.3. Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered. (Level of Evidence = B)

Background. The processes involved in clinical and genetic evaluation and testing for cardiomyopathies, integrated with up-to-date genetic counseling, are complex processes. Such complexity results in part because these recommendations are rapidly evolving. Those practicing cardiovascular genetic medicine must remain up to date with the accelerating developments in the field, integrating clinical and genetic evaluations with genetic counseling. This includes knowledge of recent discoveries of mutations in genes not previously implicated in the cardiomyopathies, as well as emerging gene-phenotype and genotype-phenotype correlations. Complexity also results from the extensive locus (many genes) and allelic (many different mutations within those genes) heterogeneity. Advances in genetic testing technology are also leading to a proliferation of new genetic tests for the cardiomyopathies, which are all confounded by this locus and allelic heterogeneity.

The second sentence of this recommendation states that referral to centers expert in genetic evaluation and family-based management should be considered. The ''should be considered'' language has been selected because the strength of the evidence varies with the cardiomyopathy phenotype, the details of the clinical and family information, and other aspects of each situation. Some practitioners with experience in the field may be able to provide appropriate care for cardiomyopathy patients without referral to a geneticist or a cardiomyopathy center with expertise in genetics. In addition to clinical care for the patient's cardiomyopathy, the practitioner will need to select the indicated genetic tests, counsel the patient on the purpose and outcomes of the possible results prior to the collection of blood or other tissue for the test, and then interpret the results to the patient upon receiving test results.[19] Whether positive or negative, the practitioner also will need to counsel the patient on potential reproductive risks should the patient wish to have children. Referral to genetic counseling services should be considered if these genetic counseling activities exceed the practitioner's skill, interest, or available time.

We present selected diverse patient situations to help a reader understand this recommendation. The first is that of a cardiomyopathy patient whose parents are deceased, and has no siblings or offspring. The primary need for this patient is reproductive counseling; that is, counseling on the risks of transmitting his or her cardiomyopathy to offspring. As presented in the following section, genetic testing is primarily indicated for risk assessment in at-risk relatives, and because this patient has no first-degree relatives, counseling for genetic testing would be directed to reproductive risk assessment.

A second case is that of a case of restrictive cardiomyopathy with no obvious family history. Because the genetic testing indicated for restrictive cardiomyopathy, as discussed in the section that follows, is much less established than that for HCM or DCM, efforts should be directed to acquiring a complete and comprehensive three to four generation family history. Although the practitioner needs to understand that the only known genetic basis of familial restrictive cardiomyopathy stems from

genes associated with HCM, in most other respects obtaining the family history is similar to that of the other cardiomyopathies.[10] A skilled practitioner can accomplish this, but if obtaining a complete and comprehensive family history exceeds the skill, interest, or available time, then referral should be considered.

In contrast to the RCM illustration in the previous section, the genetic information, genetic testing, and counseling available for HCM is extensive. Incumbent on the professional ordering genetic testing for HCM is the need to be skilled in interpreting the genetic test results and the consequent counseling based on the integration of the results (positive or negative), the family history, the clinical data of the patient, and any other known affected or unaffected family members. Ideally, the practitioner will also be skilled in the management of the clinical aspects of HCM, integrating the clinical, diagnostic, and therapeutic recommendations based on a synthesis of all data.[15] This latter point is particularly relevant with HCM because of the complexity of decision analysis for clinical interventions (eg, the assessment of outflow tract obstruction, and if present, selection of a treatment plan that may involve surgical or catheter-based interventions). In most centers, expert in providing care for genetic cardiomyopathies, cardiovascular clinicians knowledgeable and skilled in genetics rely on genetic counselors or geneticists to provide comprehensive services.[14,15,19] If executing and completing these aspects of management exceed the practitioner's skill, training, interest, or available time, then referral to a cardiovascular center specializing in dealing with genetic cardiomyopathy should be considered.

A final example is the question of genetic testing for FDC. Even though mutations in >20 genes have been implicated as causative in FDC (Table 2), the role of genetic testing for DCM at this time remains less certain because of the low test sensitivity. We have provided recommendations in the section that follows (17.4) based in part on the frequency of mutations of certain genes (Table 2), and this integrated with certain phenotypic characteristics of DCM (eg, the almost universal conduction system disease observed in LAMIN A/C cardiomyopathy, discussed in the following section). The field is rapidly evolving, and no one simple, comprehensive standard for risk assessment or genetic testing is presently applicable. Referral to a cardiovascular center specializing in genetic cardiomyopathy can assist in defining the appropriateness of genetic testing for DCM patients.

Practitioners may also consider referral to cardiovascular genetics centers to promote the engagement of patients in research. Patient involvement is critical for continued discovery of unknown genes that cause cardiomyopathy, for establishing long-term natural history studies, and for harnessing this information to improve diagnosis and to improve treatments.

The recommendation for genetic counseling for cardiomyopathy follows (17.6).

Molecular Genetic Testing

17.4. Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

a. Cardiomyopathy phenotype

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	B
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	C
Restrictive cardiomyopathy (RCM)	C
Cardiomyopathies associated with other extracardiac manifestations	A

b. Specific genes available for screening based on cardiac phenotype

Cardiomyopathy Phenotype	Gene Tests Available*	Yield of Positive Results
HCM	MYH7, MYBPC3, TNNT2 TNNI3, TPMI, ACTC, MYL2, MYL3.	MYH7, MYBPC3 each account for 30%−40% of mutations, TNNT2 for 10%−20%. Genetic cause can be identified in 35%−45% overall; up to 60%−65% when the family history is positive.
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3 and TAZ.	5.5%, 4.2%, 2.9%, for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts.
ARVD	DSP, PKP2, DSG2, DSC2	6%−16%, 11%−43%, 12%−40%, for DSP, PKP2, and DSG2, respectively
LVNC	Uncertain—see discussion	Uncertain—see discussion
RCM	Uncertain—see discussion	Uncertain—see discussion

*GeneTests (www.genetests.org) is a National Institutes of Health–funded resource that lists clinical (and research) molecular genetic testing laboratories for the cardiomyopathies.

c. Screening for Fabry disease is recommended in all men with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy.

(Level of Evidence = B)

Background. This guideline is quite restrictive in its recommendation despite the extensive genetic information available, as reviewed in this section. The rationale for the level of evidence is derived largely from the published sensitivity of genetic testing, as presented in Tables 1−3. These guidelines do not address molecular testing in prenatal, newborn screening or in vitro fertilization settings. Additional information for specific genes or genetic diagnoses are available at the Online Mendelian Inheritance in Man

Table 4. Cardiomyopathies Associated With Systemic Disease

Dilated Cardiomyopathy
Duchenne muscular dystrophy
Becker muscular dystrophy
Emery-Dreifuss muscular dystrophy
Limb Girdle muscular dystrophy
Myotonic muscular dystrophy
Mitochondrial myopathy
Kearns-Sayre syndrome
Myotubular (centronuclear) myopathy
Nemaline myopathy
Cytochrome C oxidase deficiency
Barth syndrome
Danon disease
Fanconi anemia
Diamond-Blackfan syndrome
Sickle cell anemia
Medium-chain acyl CoA dehydrogenase deficiency (MCAD)
Long-chain acyl CoA dehydrogenase deficiency (LCAD)
Maroteaux-Lamy syndrome
Fabry disease
Hypertrophic Cardiomyopathy
Fabry disease
Friedreich's ataxia
Noonan syndrome
Costello syndrome
LEOPARD syndrome
Cardio-Facio-cutaneous syndrome
Hunter syndrome
Hurler syndrome
Hurler-Scheie syndrome
Maroteaux-Lamy syndrome
I-cell disease
Pompe syndrome
Beckwith-Wiedemann syndrome
Mitochondrial myopathy
Cytochrome C oxidase deficiency
Barth syndrome
Danon disease
Down syndrome
Proteus syndrome
Yunis-Varon syndrome
Pallister-Killian mosaic syndrome
Medium-chain acyl CoA dehydrogenase deficiency (MCAD)
Long-chain acyl CoA dehydrogenase deficiency (LCAD)
Multiple sulfatase deficiency
Restrictive Cardiomyopathy
Amyloidosis
Sarcoidosis
Fabry disease
Endomyocardial fibrosis
Loffler's eosinophilic endomyocardial disease
Pseudoxanthoma elasticum
Desmin myopathy
Gaucher disease
Left Ventricular Noncompaction
Mitochondrial myopathy
Barth syndrome
Arrhythmogenic Right
Ventricular Dysplasia
Naxos disease
Carvajal syndrome

(OMIM) website (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim) that can be accessed using OMIM numbers assigned to genes (Tables 1−3) or genetic conditions (Table 4) associated with cardiomyopathy.

Within the written text of the guideline are 2 aspects, the first of which recommends that the individual with the most evident disease should be the individual selected from a family to undergo genetic testing. This is a well-established principle in clinical genetics, as selecting the individual with the most evident disease that has been clinically confirmed to a high degree of certainty decreases the probability of testing a phenocopy (someone who clinically has the disease from another cause and does not carry the family mutation) and thereby increases the likelihood of finding a genetic cause. Usually the individual with more evident disease will also provide a more compelling phenotype, usually with greater numbers of features of the disease so that the most accurate classification of the cardiomyopathy can be achieved. Procurement of a tissue sample (preferentially tissue that has not been fixed) from an autopsy specimen can provide DNA for genetic testing. At times a DNA-containing sample from the family member with the most evident disease is not available, commonly because of death antecedent to the genetic analysis. Thus, another individual from the family must be selected for testing. As developed in the following section, selection of a secondary individual for testing requires careful consideration, especially because of the low sensitivity for genetic testing for many cardiomyopathies. The professional selecting the individual for testing will need to consider the implications of negative genetic test results for that subject, and have a plan for any additional testing for the remaining at-risk family members. On the other hand, if a mutation can be identified and the evidence supports its role as the disease-causing mutation, testing can be performed in relatives regardless of their clinical status.

The second aspect of this guideline restricts the indication for genetic testing to that of *facilitation of family screening and management*. Simply put, this guideline recognizes that at this time the primary value, and the primary reason to seek genetic testing for the genetic cardiomyopathies, is to more accurately predict the risk of a family member developing cardiomyopathy who at the present has little or no clinical evidence of cardiovascular disease.

If a disease-causing mutation is identified in the affected family member initially tested, and subsequent genetic testing of an at-risk but presymptomatic family member is negative, that family member's risk of developing the cardiomyopathy is substantially reduced. In this situation, the need for ongoing clinical screening in such a mutation-negative family member is not recommended. On the other hand, if a disease-causing mutation is identified in an asymptomatic, at-risk family member, the confidence is much greater to infer risk for that individual. The individual should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, the associated reduced penetrance and variable expressivity, and the rationale and frequency of the recommended clinical surveillance.

Notably, these recommendations are silent for any additional interventions specific for a disease-causing mutation. The reason for this stems from the lack of validated genotype-phenotype correlations of specific mutations with specific clinical cardiovascular outcomes. Unless or until

specific mutations have been shown to reliably predict specific clinical outcomes (eg, increased or reduced risk of a specific event such as the development of symptomatic heart failure or the high probability of SCD), the recommendations will refer to the general behavior of each disease gene.

The general characteristics of disease presentation and progression may be suggestive of involvement of specific genes. We refer to this herein as ''gene-phenotype relationships'' in contrast to the more commonly used ''genotype-phenotype relationships,'' the latter commonly used to indicate phenotypic characteristics of specific mutations. The strongest evidence for gene-phenotype relationships is present for HCM and DCM (Table 5).

This recommendation, focused on genetic testing to facilitate family screening and management, is also silent for specific recommendations for apparent sporadic (nonfamilial) disease. However, considerable evidence suggests that HCM results from both sporadic and familial genetic disease.[12] In contrast, the etiology of DCM that does not appear to be familial remains enigmatic, as is the evidence to support an underlying genetic cause. Some patients with DCM, but without a positive family history, have been shown to harbor mutations consistent with genetic causation of their disease (Table 2). Further, the largest genetic survey to date of 6 DCM disease genes in 313 unrelated probands observed a similar frequency of mutations attributed to familial versus sporadic disease.[20] However, patient acquisition for that study was not specifically designed to address the frequency of the genetic basis of sporadic DCM versus familial disease, and familial disease was not excluded with prospective clinical screening of first-degree relatives in those assigned to have sporadic DCM. This latter point is particularly relevant, as conducting clinical screening of first-degree family members with echocardiography and ECG has been shown to have 4-fold greater sensitivity to detect familial DCM compared with obtaining a careful 3-generation family history.[21] Thus, a genetic etiology for the bulk of nonischemic, presumably nonfamilial (sporadic) DCM, although plausible, has had no rigorous studies that provide robust, reliable estimates of the frequency of genetic causation.

HCM has the strongest evidence to support genetic testing (Table 1). ARVD/C, although quite rare, also has good evidence to support genetic testing (Table 3).

Testing for DCM is confounded by the question of etiology of sporadic DCM discussed previously. It is also greatly confounded by the extensive genetic heterogeneity, as well as the relatively low frequency of involvement of any 1 gene in DCM. Technologic advances will continue to improve testing methods, thereby dramatically decreasing costs. Although such progress will make it possible to test many DCM genes simultaneously, it is likely that sequence variations of unknown significance will be discovered that may confound test interpretation.

However, testing for the *LMNA* gene is recommended in patients with prominent conduction disease with or without supraventricular or ventricular arrhythmias (Table 5), 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 (Table 5). *LMNA* molecular genetic testing may be considered for all DCM patients based on its overall higher frequency in DCM (Table 5: a mean of 7.3% of those with familial disease, or 3.0% of those with apparent sporadic disease, or 5.5% overall, as summarized from 6 studies),[22–27] and because of its diagnosis on prognosis and management.[28]

Data are only now emerging describing the genetic basis of LVNC, limiting strength of recommendations, as is the case for RCM (Table 3).

Clinical genetic testing should be carried out in a fully accredited molecular genetic testing laboratory that has met Clinical Laboratory Improvement Amendment (CLIA) standards. Clear distinctions should be made between testing for clinical purposes, as advocated by these guidelines in CLIA-accredited laboratories and that undertaken for research purposes that cannot be used to direct

Table 5. Cardiomyopathy Phenotypes Suggestive of Specific Disease Genes

Gene	Protein	Phenotype Summary	Comments	References
Dilated Cardiomyopathy Phenotype				
LMNA	Lamin A/C	Prominent conduction system disease and arrhythmias, then DCM and heart failure	Asymptomatic electrocardiogram abnormalities, then sinus/AV node dysfunction; 1st-, 2nd-, 3rd-degree heart block; Aflutter/Afib, tachy/brady syndrome, pacemakers common. Onset of DCM, with mild-severe LV dysfunction, then HF, SCD, advanced disease requiring cardiac transplantation	22–27, 59–65
Hypertrophic Cardiomyopathy Phenotype				
MYH7	β-myosin heavy chain	Wide age range; severe LVH; heart failure, SCD		11, 12, 38, 39
MYBPC3	Myosin-binding protein C	Usually milder disease; some older onset		11, 12, 39, 40
TNNT2	Cardiac troponin T	Mild LVH; SCD common		11, 12, 39, 41

Aflutter/Afib: atrial flutter/atrial fibrillation; AV: atrioventricular; SCD: sudden cardiac death; LVH: left ventricular hypertrophy.

clinical care (unless conducted in a CLIA-certified research laboratory that provides clinical reports). Because the genetic knowledge base of cardiomyopathy is still emerging, practitioners caring for patients and families with genetic cardiomyopathy are encouraged to consider research participation. Referral centers expert in genetic cardiomyopathy are experienced in explaining the roles and outcomes of clinical testing versus research participation (that may include research genetic testing) and are able to facilitate both objectives (see previous work for review of these issues).[29]

Genetic Counseling

17.5. Genetic and family counseling is recommended for all patients and families with cardiomyopathy. (Level of Evidence = A)

Background. Genetic counseling is the process of communicating relevant genetic information, including genetic risks, to patients and their families, so that they may understand the genetic information presented and use it to make informed decisions regarding genetic testing or other therapeutic decisions. The process also helps individuals to adapt to the medical, psychological, and familial implications of genetic contributions to disease.[30] The majority of genetic counseling is performed by board-certified Master's-level genetic counselors or by board-certified medical geneticists. Genetic counseling for the cardiomyopathies is undertaken by genetic counselors or geneticists who are knowledgeable of the cardiovascular clinical features of the type of cardiomyopathy in question, or by cardiologists who are expert in the cardiomyopathy in question and are fluent in the content and nature of genetic counseling for the patient and their family members.[14,19,31] Alliances of cardiologists with special interest and expertise in genetic cardiomyopathies with genetics professionals, usually Master's-level trained genetic counselors or nurses trained in genetics, are beginning to emerge. In a survey of Dutch cardiologists and geneticists regarding the provision of care for HCM, most cardiologists preferred that pedigree construction, counseling, and genetic testing be handled by geneticists, although a significant trend for collaborative arrangements between geneticists and cardiologists was also noted.[32]

Regardless of who provides it, genetic counseling is an essential component of the evaluation, diagnosis, and management of the cardiomyopathies.[14,19,31] Essential activities completed by a genetic counselor are obtaining a careful and comprehensive 3- to 4-generation family history, educating the patient and family regarding the disease transmission and family risks, counseling regarding any genetic testing to be undertaken including the implications of positive, negative, or uncertain results, providing key information to other at-risk family members as identified by the index patient, and assisting with the interpretation of genetic test results and their integration into the overall treatment plan. Counseling is also aimed to promote informed choices and adaptation to the risk or condition in terms of medical facts, and options and social implications.

The first essential activity, obtaining a comprehensive family history, has already been recommended and reviewed (Section 17.1). The next objective is to educate the patient and family regarding the disease transmission and family risks. If genetic testing has identified a plausible genetic cause, counseling regarding transmission is conducted (autosomal or X-linked, either dominant or recessive). The pedigree is commonly utilized to inform the patient and family of at-risk members. If the patient presents without prior genetic testing but testing is indicated, counseling is undertaken regarding the utility, sensitivity, analytic validity, and the implications of all possible testing outcomes based on the prior items. The patient or family members also need to be counseled on the possibility of identifying genetic variants of unknown significance. Counseling also involves exploring the psychosocial issues that are relevant to the condition or risk that the individual is facing, as well as addressing family dynamics, which could potentially impact dissemination of genetic information to at-risk family members.

Therapy Based on Genetic Testing

As discussed previously (Section 17.4), the finding of any specific mutation as the cause of the cardiomyopathy does not in itself guide therapy. However, the clinical characteristics associated with some disease genes (Table 5), when integrated with the clinical and family data, may influence the overall case assessment, and may appropriately impact all aspects of the clinical recommendations. This includes the frequency and stringency of presymptomatic screening for signs of disease, the strength of interventions to educate family members of risks and symptoms, the threshold for presymptomatic initiation of preventive (eg, implantable cardiac defibrillators [ICDs] in certain HCM, DCM or ARVD/C settings, see the following section) or therapeutic (eg, β-blockers or angiotensin-converting enzyme inhibitors in presymptomatic DCM) interventions.

Therapy Based on Cardiac Phenotype

17.6. Medical therapy based on cardiac phenotype is recommended as outlined in the general guidelines. (Level of Evidence = A)

Background. Guidelines for clinical care of the patient with cardiomyopathies have been published for HCM[33] and DCM.[8,34] These guidelines provide comprehensive guidance for care of those who are presymptomatic or have had the onset of clinical disease. Guidelines for the

clinical care for ARVD, LVNC, and RCM are not yet available.

17.7. Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended as outlined in the general guidelines. (Level of Evidence = B)

Background. In brief, ICDs are indicated for symptomatic or life-threatening arrhythmias regardless of the type of cardiomyopathy diagnosis or ventricular function. The indications for ICDs are summarized for DCM in guideline statements.[8,34] For DCM, a left ventricular ejection less than 30% to 35% is usually an indication for an ICD, regardless of etiology.

17.8. In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Level of Evidence = C)

Background. Electrophysiologic disease can be considered broadly as conduction system disease and arrhythmia. Conventional guidelines apply for symptomatic or presymptomatic conduction system disease regardless of other aspects of the patient's clinical situation.[35] Pacemakers are indicated for symptomatic bradycardia, high-grade atrioventricular block regardless of symptoms, for any other symptomatic conduction system disease. In this setting of lamin A/C cardiomyopathy requiring pacemaker placement, the use of an ICD rather than a pacemaker has been recommended.[35] Such a course appears reasonable. Patients with a dilated cardiomyopathy but with ejection fraction >30% to 35% may be considered for an ICD if the family history is positive for SCD or for patients with *LMNA* mutations.[36]

Pediatric Forms of Inherited Cardiomyopathies. All phenotypes of cardiomyopathy presenting in childhood can occur as a genetic disorder. Unlike adult disease, pediatric cardiomyopathies, particularly those presenting in the first year of life, have an increased likelihood of being mitochondrial or metabolic-based. Evaluation of these young children must include studies aimed at determining whether mitochondrial dysfunction or metabolic derangement is central to the underlying basis of the cardiac disorder. In the case of mitochondrial disease, mitochondrial DNA mutations inherited from the mother (maternal inheritance), or autosomal recessive inheritance underlie these disorders. Metabolic defects most commonly are inherited as autosomal recessive traits.

In the remaining cases of inherited cardiomyopathies of childhood, the same inheritance patterns as seen in adulthood are expected.

HCM of Childhood. Young children with left ventricular hypertrophy (LVH) may have an underlying mitochondrial or metabolic disease, whereas others have early clinical expression of HCM from a sarcomere gene mutation. For instance, the deadly infiltrative lysosomal storage disorder Pompe disease, or the benign infant of a diabetic mother form of LVH may appear to be similar by echocardiography. In addition, syndromes such as Noonan syndrome, overgrowth disorders such as Beckwith-Wiedeman syndrome or Sotos syndrome, or children with chromosomal disorders may present with LVH. A subgroup of these young children with LVH, however, has the typical ''adult form'' of disease caused by mutations in genes encoding sarcomere proteins.[37] Children may have inherited these mutations or the gene defects can arise de novo, and therein cause sporadic disease.

Children with HCM from mutations in sarcomeric genes typically demonstrate the classical clinical phenotypic features of HCM seen in adults. Phenotypic heterogeneity is common in children with familial forms of disease, both in clinical expression and outcome. For these reasons, the clinical follow-up of children with HCM tends to differ from that outlined for adults. Children younger than 1 year of age with HCM are usually seen frequently, commonly every 3 months. Siblings without clinical features of disease are followed yearly in most cases until reaching puberty. At that time, follow-up is every 1 to 2 years depending on their specific clinical, echocardiographic, and electrocardiographic features. In cases where HCM presents in older children, the siblings are usually seen every 3 years unless a defect is identified.

DCM of Childhood. Inherited forms of DCM in childhood appear to exist in approximately 50% of affected subjects presenting by 18 years of age. As with HCM and mitochondrial and metabolic disease, chromosomal defects and dysmorphic syndromes may be responsible for a substantial subgroup of cases. In the remaining inherited forms, autosomal and X-linked inheritance is most common. A substantial subgroup of children has associated skeletal myopathy and some of these will also have conduction system disease. In inherited cases, similar to that described for HCM, onset of clinical features is age-dependent. In families with earlier onset of symptoms, follow-up of at-risk relatives should begin earlier. Relatives, particularly siblings, also follow a similar pattern as those outlined for relatives of HCM patients.

RCM of Childhood. Restrictive cardiomyopathy in childhood is an uncommon but serious form of cardiomyopathy. Inherited forms are infrequent, but when they occur appear to be associated with defective sarcomeric genes or mutations in desmin. Associated skeletal myopathy is common. In children with RCM, autosomal dominant inheritance predominates. Family evaluation for siblings tends to be approximately every 3 years unless a defect is identified.

LVNC of Childhood. Left ventricular noncompaction is seen during all ages of childhood from birth onward. Mitochondrial, metabolic, syndromic, chromosomal, and neuromuscular abnormalities are common. In addition, autosomal dominant inheritance is notable. LVNC is subdivided into dilated, hypertrophic, and hypertrophic/dilated forms, isolated LVNC without other abnormalities of size, thickness or function, and LVNC associated with

congenital heart disease. Family members are followed every 3 years unless a defect is identified.

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