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

RAY E. HERSHBERGER, MD<sup>1,2</sup>, MICHAEL M. GIVERTZ, MD<sup>3</sup>, CAROLYN Y. HO, MD<sup>3</sup>, DANIEL P. JUDGE, MD<sup>4</sup>, PAUL F. KANTOR, MD<sup>5</sup>, KIM L. MCBRIDE, MD<sup>6</sup>, ANA MORALES, MS, CGC<sup>1</sup>, MATTHEW R.G. TAYLOR, MD<sup>7</sup>, MATTEO VATTA, PhD<sup>8,9,10</sup>, STEPHANIE M. WARE, MD, PhD<sup>9,11</sup>

<sup>1</sup>Division of Human Genetics, Ohio State University Wexner Medical Center, Columbus, Ohio

<sup>2</sup>Division of Cardiovascular Medicine, Ohio State University Wexner Medical Center, Columbus, Ohio

<sup>3</sup>Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts

<sup>4</sup>Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina

<sup>5</sup>Division of Pediatric Cardiology, University of Alberta and Stollery Children's Hospital, Edmonton, Canada

<sup>6</sup>Center for Cardiovascular Research, Nationwide Children's Hospital, and Department of Pediatrics, Ohio State University, Columbus Ohio

<sup>7</sup>Adult Medical Genetics Program, Division of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, Colorado

<sup>8</sup>Invitae Corporation, San Francisco, California

<sup>9</sup>Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana

<sup>10</sup>Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana

<sup>11</sup>Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana.

### Abstract

This guideline describes the approach and expertise needed for the genetic evaluation of cardiomyopathy. First published in 2009 by the Heart Failure Society of America (HFSA), the guideline has now been updated in collaboration with the American College of Medical Genetics and Genomics (ACMG). The writing group, composed of cardiologists and genetics professionals with expertise in adult and pediatric cardiomyopathy, reflects the emergence and increased clinical activity devoted to cardiovascular genetic medicine. The genetic evaluation of cardiomyopathy is a rapidly emerging key clinical priority, because high-throughput sequencing is now feasible

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Reprint requests: Ray Hershberger, MD, Ohio State University Wexner Medical Center, Biomedical Research Tower, Room 304, 460 West 12th Avenue, Columbus, OH 43210. Tel: +1 614-688-1388; Fax: +1 614-688-1381. Ray.Hershberger@osumc.edu.

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for clinical testing and conventional interventions can improve survival, reduce morbidity, and enhance quality of life. Moreover, specific interventions may be guided by genetic analysis. A systematic approach is recommended: always a comprehensive family history; an expert phenotypic evaluation of the proband and at-risk family members to confirm a diagnosis and guide genetic test selection and interpretation; referral to expert centers as needed; genetic testing, with pre- and post-test genetic counseling; and specific guidance as indicated for drug and device therapies. The evaluation of infants and children demands special expertise. The approach to managing secondary and incidental sequence findings as recommended by the ACMG is provided. (*J Cardiac Fail* 2018;24:281–302)

## Keywords

Cardiomyopathy; genetics; genetic analysis; practice guideline; secondary findings

Continued rapid progress has been made in understanding the genetic basis of cardiomyopathy. The present work, which describes the content, approach, and expertise needed for a cardiomyopathy genetic evaluation, was first developed in a guideline statement in 2008 and published in 2009 for the Heart Failure Society of America (HFSA).<sup>1</sup> It has now been updated by a writing group organized with the American College of Medical Genetics and Genomics (ACMG) and the HFSA to serve as a practice resource (ACMG) and as a revised guideline statement (HFSA).

This collaboration of cardiovascular and genetics professionals mirrors a recent proliferation of specialized cardiovascular genetics clinics.<sup>2</sup> Most commonly, cardiologists, adult or pediatric, with special interest or training in cardiovascular genetics, team up with genetics professionals, usually board-eligible or board-certified genetic counselors and/or clinical geneticists, ideally with cardiovascular expertise, to provide state-of-the-art genetics services to the many patients and families with cardiomyopathy. This growth has been triggered by improvements in technology for clinical genetic testing, resulting in the availability of large clinical genetic testing panels, where numerous genes of interest can be sequenced quickly, efficiently, and accurately using continually developing massively parallel DNA sequencing technologies. This growth also recognizes the critical importance of integrating expert phenotypic information with final clinical recommendations in light of burgeoning sequence information.<sup>3</sup>

This collaboration also speaks to the recent prominence of cardiovascular genetics and genomics brought about by the emergence of clinical exome sequencing and the ACMG recommendation, first in 2013<sup>4</sup> and updated in 2016,<sup>5</sup> to return relevant and actionable secondary findings. Of the 59 medically actionable genes cited in 2016, 30 (51%) had cardiovascular phenotypes, and 16 (27%) were genes that included cardiomyopathy phenotypes. By request from the ACMG, we also provide guidance for secondary findings derived from cardiomyopathy genes.

The rationale for the inclusion of cardiomyopathy genes in the ACMG secondary findings list, and the basis for the clinical screening, counseling, and molecular recommendations contained herein, is that cardiomyopathies are medically actionable: well established

treatments or interventions are available to improve survival, reduce morbidity, and enhance quality of life.<sup>6,7</sup> Cardiomyopathies may present late in their course with advanced disease, which includes heart failure, heart block, and/or life-threatening arrhythmias, including sudden cardiac death, and thromboembolic events, including stroke from atrial arrhythmias or ventricular thrombus. Therefore, the rationale to identify genetic risk is compelling, so that those found to be at risk can undergo interval screening to detect the earliest manifestations of the cardiomyopathy phenotype. The first evidence of a phenotype then permits earlier interventions,<sup>7</sup> including lifestyle modifications, drugs to slow or halt disease progression or to prevent thromboembolism, and procedures, drugs, or devices to reduce the risk of sudden cardiac death.<sup>6</sup> Identification of at-risk individuals, whether affected but asymptomatic or clinically unaffected, may also have implications for genetic counseling and reproductive decision making.

Cardiovascular physicians are expert at assessing the nuances of cardiomyopathy phenotypes or subphenotypes, an essential contribution to cardiovascular genetics care. As in 2009,<sup>1</sup> our current approach continues to be stratified by cardiomyopathy phenotype, as clinical and genetic data collection, analysis, and decision making for the cardiomyopathies remain anchored by phenotypic categories.

## The Family as the Unit of Care

A critical transition for cardiovascular practitioners who wish to more fully actualize cardiovascular genetic medicine is to adopt the family as the unit of care, a concept inherently understood by genetics professionals. For cardiovascular providers, moving the care paradigm beyond the patient (proband), who often presents with a fully developed phenotype and at times with advanced life-threatening disease, to at-risk relatives is mandatory to fulfill the promises of precision medicine. Moreover, collaboration with and care for the family unit is an essential component of the genetic evaluation. This includes establishing a genetic etiology for the proband and affected family members, the clinical evaluation of at-risk family members, cascade genetic testing of family members as indicated, and genetic counseling at all steps. All of this will not only augment the evidence of variant pathogenicity but also will provide insight into penetrance, age of onset, pleiotropy, and disease expression.

Ideally, family-based cardiovascular genetic medicine also means developing integrated teams with pediatric and adult training and expertise that are able to provide coordinated care across all age groups. Identification of disease and pathogenic variants in an adult parent facilitates testing and potential treatment of pediatric-age children. Conversely, if the index case is a child, the testing and treatment of adult-age relatives may also be needed. Therefore, we recognize the critical need to address accessible delivery of care of the family across all ages. This also includes managing insurance coverage for the evaluation of asymptomatic relatives based on their family history.

Genetic cardiomyopathy has substantial complexity, as shown by overlaps in phenotype as well as an overlap of genes.<sup>8</sup> Despite this complex interplay of genes, variants, and phenotypes, current knowledge, when combined with expert phenotyping and the

sensitivity and specificity of current genetic testing, is sufficient to effectively conduct genetic cardiomyopathy evaluations. We caution, however, that variant interpretation must be thoughtful and rigorous and leverage the most up-to-date approaches, because not all variants identified by genetic testing will be clinically significant or disease causing. Key resources include use of the most recent ACMG/Association for Molecular Pathology guidance,<sup>5,9</sup> now being augmented by ClinGen, a National Human Genome Research Institute–sponsored initiative to curate genes and variants and place them into ClinVar, a publically accessible database,<sup>10,11</sup> and other large publicly accessible reference databases.

## Types of Cardiomyopathy

The genetic basis of hypertrophic cardiomyopathy (HCM) is well established as largely a disease caused by mutations in genes encoding sarcomeric proteins. That familial dilated cardiomyopathy (DCM) has a genetic basis is also well accepted. (The term DCM is used herein instead of the more technical attribution “idiopathic dilated cardiomyopathy,” where the other common and easily clinically detected causes of systolic dysfunction such as coronary artery disease, primary valvular or congenital heart disease, or previous exposure to cancer chemotherapy or other injurious drugs, have been excluded.) However, most DCM occurs without apparent familial disease, and whether nonfamilial DCM is principally a genetic condition remains uncertain.<sup>8,12,13</sup> The much greater numbers of genes and the diversity of variants identified (allelic and locus heterogeneity) with DCM is more extensive than with the other cardiomyopathies,<sup>8,12,14,15</sup> making genetic testing inherently more challenging. Arrhythmogenic right ventricular cardiomyopathy (ARVC), which is much less common than HCM or DCM, also has a well established genetic basis associated with mutations in genes that encode desmosomal elements. Restrictive cardiomyopathy (RCM), although quite rare, also shares in part a genetic basis with HCM.

In contrast to HCM, DCM, RCM and ARVC, the left ventricular noncompaction (LVNC) phenotype remains enigmatic and without consensus as to whether it should be considered a primary cardiomyopathy,<sup>13</sup> a variant morphologic trait,<sup>16</sup> or something else.<sup>17,18</sup> We favor describing it as a phenotype, because an increasing body of population-derived high-quality imaging evidence, not available when LVNC was deemed to be a primary cardiomyopathy,<sup>13</sup> now shows that increased ratios of noncompacted (trabeculated) to compacted (nontrabeculated) myocardium may be present in 2%–10% or more of the population depending on the definition and test sensitivity.<sup>16,19,20</sup> Furthermore, studies in highly trained athletes<sup>21,22</sup> and pregnancy<sup>23</sup> suggest that LVNC may progress and regress, akin to ventricular remodeling and reverse remodeling. Therefore, LVNC has been included and referred to as a noncompaction phenotype rather than a unique form of cardiomyopathy. Additional background is provided in the online supplement.

## Approaches to Review and Publication by the ACMG and HFSA

The writing group was established jointly with the ACMG and HFSA from 2013 to 2015. The approaches to creating, curating, and approving practice guidelines or practice resources for the HFSA and ACMG, respectively, have been outlined in each group’s publication. The material covered in this and the companion document<sup>24</sup> are congruent

with one another. Differences in scope, including supplemental materials, are denoted and cross-referenced.

The writing group was composed of a panel of experts—board-certified cardiologists and genetics professionals with experience and expertise in genetic cardiomyopathies (Appendix)—with the goal of revising an earlier HFSA publication in a conjoint effort to produce a new document for the ACMG. Each author was screened for relevant conflicts of interest, and all conflicts shown were considered to be nonsubstantial to influence the document. Dr Vatta was included in the writing group before his employment with a for-profit genetic testing company; after his employment, potential conflicts of interest regarding genetic testing indications were managed by his recusal from pertinent discussions.

## Use of Medical Evidence in This Guideline

We address 2 questions here. The 1st question is that of clinical validity: “Does the evaluation or test correlate with the outcome of interest?”<sup>25</sup> Because randomized clinical trials evaluating the clinical accuracy of diagnosis with or without a genetic evaluation or genetic testing are not generally feasible, as in the previous guideline<sup>1</sup> we have used a different format for level of evidence. By genetic evaluation we mean a systematic approach that includes a comprehensive family history, phenotypic evaluation of the proband and at-risk family members, genetic counseling, genetic testing, if indicated, with pre- and post-test genetic counseling, and guidance as indicated for specific drug and/or device or other specific therapeutic interventions. By genetic testing we mean DNA sequencing or other DNA testing modalities to identify DNA variants relevant for the phenotype of interest. **Level A:** genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in studies with a moderate or large sample size; **level B:** genetic evaluation or testing has a high correlation with the cardiomyopathic disease of interest in smaller or single-center studies; and **level C:** genetic evaluation or testing correlates with the cardiomyopathic disease of interest in case reports. All levels were assigned based on literature review and full consensus of the writing group.

The 2nd question is one of clinical effectiveness: “Does performing a genetic evaluation or test result in improved patient outcomes?” This question depends also on the multiple treatment options that follow from a firm genetic and phenotypic diagnosis in cardiomyopathy, as well as the perceived clinical utility, which in this context is the benefit of those who receive a genetic evaluation or test. Again, randomized studies to address this question controlling for genetic diagnosis are not feasible. Moreover, consensus on how to appropriately measure the impact of genetic evaluation and testing on personal utility of patients is still developing,<sup>26</sup> and the impact of genetic evaluation and testing on societal utility is a broader question beyond our current scope. Therefore, while acknowledging these constraints, we have interpreted the level of evidence within the existing HFSA framework<sup>27</sup> and have based the strength of recommendations on this level, as well as on our current knowledge of clinical effectiveness from the totality of information currently available.

Although we recognize that essentially no randomized controlled clinical trials have been conducted to support most of the recommendations herein, this also provides an opportunity for us to press our constituencies to design and conduct innovative and rigorous research studies to achieve a substantive evidentiary basis for these guidelines. Although the present guidance may be considered “expert,” it is well known that well designed and rigorously performed clinical studies have routinely shown that “conventional wisdom” may be simply wrong.

**Guideline 1 Obtaining a family history of at least 3 generations, including the creation of a pedigree, is recommended for all patients with a primary cardiomyopathy.**

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	A
Cardiomyopathies with extracardiac manifestations	A
Left ventricular noncompaction (LVNC)	See Background

**Key Points**—A genetics professional is skilled at obtaining a reliable family history and identifying those at risk, which is critically important once genetic results have been obtained. Specific questions should be focused to elicit possible affected relatives that may not be identified in a general family history. Primary clinical data should be reviewed, whenever possible, and may require collection of relatives’ records or postmortem reports. These may include relevant prenatal (including fetal loss), infant, pediatric, or adult records.

**Background**—The family history, a key component of any medical and genetic evaluation, is particularly relevant for the cardiomyopathies. The goals of a family history are to ascertain if the cardiomyopathy is inherited, establish the inheritance pattern, identify at-risk family members, and provide information on disease characteristics within the family (eg, age of onset, severity, phenotypic variability within the pedigree, and treatment response). Reduced penetrance, defined as individuals possessing a pathogenic variant but not manifesting any evidence of disease, and variable expressivity are not uncommon in cardiomyopathy. For this reason, a family history of at least 3 generations is needed to determine the pattern of inheritance (dominant, recessive, X-linked, or mitochondrial).<sup>28</sup> Family history of more distantly affected relatives may be informative regarding the pattern of disease within the family through increased numbers of affected individuals in the data set.

The writing group strongly recommends placing the family history into a graphic pedigree format to enhance genetic competency for data interpretation, managing family-based clinical screening, determining the mode of inheritance, facilitating the assessment of relatives at risk, and family counseling.<sup>2</sup>



Most cardiomyopathies presenting in adulthood are inherited in an autosomal dominant manner. Cardiomyopathy presenting in childhood is also frequently inherited as an autosomal dominant condition, but it is more likely to have autosomal recessive, X-linked, or mitochondrial inheritance than in adults. De novo variants may be found in children or adults. In children, de novo variants are most commonly identified for autosomal dominant and X-linked syndromic cardiomyopathies. A child may be the first individual in a family to come to attention with a primary HCM, DCM, or ARVC and have a negative family history. Studies have shown de novo events in up to one-third of cases with a negative family history, although cardiomyopathy may also occur due to inheritance from an affected but asymptomatic parent unaware that they have disease.<sup>29,30</sup>

Assumptions regarding paternal or maternal transmission should be avoided, because bilineal inheritance of autosomal dominant cardiomyopathy (transmission of disease from both mother and father) can occur and may incur more severe and earlier onset disease. Compound or digenic heterozygous variants classified in earlier studies have been shown in up to 5% of HCM and up to 20% of ARVC patients,<sup>31–33</sup> although a reevaluation of the previously published HCM double variants applying the 2015 ACMG approach<sup>9</sup> indicated that double pathogenic or likely pathogenic double variants were much less common.<sup>34</sup> Reliable data for DCM are not yet available but also may be prevalent in those patients.<sup>35</sup> If the inheritance pattern can be established, accurate risk assessment of relatives can be provided. Although some digenic conditions have been clearly established,<sup>36</sup> well designed rigorous studies investigating di- or multigenic inheritance for the cardiomyopathies are needed.

A family history provided by patients is frequently inadequate and may miss familial cardiomyopathy.<sup>37</sup> Details from patients regarding heart disease in their family may be lacking, and vague terms such as “heart attack” or “stroke” may be used for any sudden or unexplained death. Ideally, family history should be obtained from the most informed family member. Similarly to medical history, family history is dynamic and should be updated at regular intervals. Specific focused questions should be asked to ensure that affected relatives are identified. Key elements include: 1) cardiovascular symptoms (eg, shortness of breath, paroxysmal nocturnal dyspnea, or dyspnea on exertion) or symptoms suggestive of arrhythmia, including palpitations, presyncope, or syncope with or without exercise; 2) cardiovascular diagnoses such as cardiomyopathy, heart failure, or valve disease or previous procedures including cardiac catheterization, arrhythmia ablation, cardioversions, heart surgery, heart transplantation, or use of pacemakers or implantable cardioverter-defibrillators (ICDs); all of these should include age at the time of symptom onset, procedures, or death; 3) sudden death, particularly before the age of 40 years, with special attention to single-vehicle accidents, drowning, or sudden infant death; 4) previous genetic testing; 5) specific details on deaths attributed to “heart attack”; and 6) features of syndromes, especially any features suggesting skeletal muscle disease; also, if applicable, eg, short stature and learning problems suggesting Noonan syndrome, acroparesthesias, and renal failure consistent with Fabry or skeletal myopathy.

A critical component to validate family history often includes obtaining medical records and/or postmortem reports. Obtaining a family history and the related activities outlined

here are time and effort intensive. Alternatively, focused family history interviews can be accomplished by trained allied health professionals. Practitioners may choose to refer patients with cardiomyopathy to centers expert in genetic cardiomyopathies to obtain detailed family histories, provide genetic counseling and genetic testing, compile clinical and genetic databases, and provide opportunities to participate in research studies that are essential for progress in the field.

As noted in the introduction and in the supplemental material, LVNC observed in conjunction with HCM, DCM, ARVC, or RCM follows guidelines for that of the associated subtype of cardiomyopathy. If isolated noncompaction is identified serendipitously in an individual who is otherwise normal (asymptomatic with normal electrocardiography [ECG] and normal ventricular size and function), it is always reasonable to obtain a family history to ensure that there is no evidence of cardiomyopathy in the family, although formal population-based family studies of such individuals have not been published. Please see additional discussion at guidelines 2 and 4.

**Guideline 2 Clinical (phenotypic) screening for cardiomyopathy in at-risk 1st-degree relatives is recommended.**

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	A
Cardiomyopathies, overlapping, or extracardiac	A
Left ventricular noncompaction (LVNC)	See Background

**Key Points**—Cardiomyopathies are frequently clinically silent for extended periods of time. Thus, 1st-degree relatives may be reportedly unaffected, and cardiomyopathy can be detected only by clinical testing (denoted hereafter as “phenotype screening”). Relatives who complete phenotype screening with no evidence of disease are denoted as “clinically unaffected.” Relatives who are asymptomatic but have not completed phenotype screening are denoted as “reportedly clinically unaffected.” Development of disease is age dependent, so assessments of at-risk relatives may require repeated phenotype screening.

**2a. Baseline phenotype screening is recommended for all at-risk 1st-degree relatives, including those who have tested negative for a known familial variant. (Level of Evidence = A):**

The rationale for baseline phenotype screening for at-risk family members is that, as noted above, cardiomyopathy is commonly clinically silent and can be detected only by clinical screening. The rationale for phenotyping family members who test negative for a familial variant known to be actionable (ie, pathogenic or likely pathogenic) is that in some cases nonsegregation (an individual with the cardiomyopathy phenotype who tests negative for a pathogenic or likely pathogenic variant in the pedigree) will be unmasked, thus prompting the need for expanded genetic evaluation. We also note that determining whether a variant of uncertain significance (VUS) identified in the proband segregates with



cardiomyopathy in a family can be accomplished only with up-to-date clinical phenotype information about all at-risk members of the pedigree. Furthermore, many variants continue to be novel for the cardiomyopathies (the exception being some variants in *MYH7* and *MYBPC3*, where larger numbers of pathogenic variants have been identified in HCM<sup>38</sup>), and therefore if observed only in the proband, they will likely be assigned as a VUS, whereas knowledge of other affected family members who also carry a variant initially assigned as a VUS may enable its reclassification to likely pathogenic or pathogenic, which can then be used for predictive testing. For these reasons, we advocate that baseline clinical phenotype screening be conducted for all at-risk family members in conjunction with initial cascade genetic testing of a family's disease-causing variant or variants. Please see guideline 3 for comments specific to children.

**2b. Serial phenotype screening for cardiomyopathy is recommended in clinically unaffected at-risk relatives who are known to carry one or more disease-causing variants. (Level of Evidence = A):** Serial screening means that after a baseline screening event, regular and repeated phenotype screening events are then conducted over a period of years.

**2c. Serial phenotypic screening for the emergence of cardiomyopathy is recommended for clinically unaffected atrisk 1st-degree relatives whose genetic status is unknown. (Level of Evidence = A):** An unknown genetic status can occur when an at-risk individual has not yet been tested for a previously detected disease-causing variant in the family or if no pathogenic or likely pathogenic variant has been identified in the proband. It can also occur if a VUS has been identified in the proband and the family-based or other data are insufficient to allow reclassification as a likely pathogenic variant.

**2d. Serial screening of clinically unaffected relatives who have negative genetic testing for a pathogenic variant is not recommended. (Level of Evidence = A):** This recommendation is based on the certainty that the variant identified in a family is indeed pathogenic, as discussed below in guideline 4. However, relatives should be counseled to present for evaluation if they develop signs or symptoms suggestive of disease.

**2e. Clinical phenotype screening is recommended. (Level of Evidence =A):** Clinical phenotype screening (Table 1) includes:

- Medical history, with special attention to heart failure symptoms, arrhythmias, presyncope or syncope, and thromboembolism.
- Physical examination.
  - Special attention should be given to cardiac and neuromuscular systems.
  - Examination of the integumentary system is indicated when ARVC is suspected.
- Electrocardiography.

- Cardiovascular imaging. This includes, minimally, 2-dimensional transthoracic echocardiography for all cardiomyopathies, augmented with the use of tissue Doppler interrogation, if available, for HCM. Cardiac MRI is rapidly emerging as a definitive imaging modality; it should be used if echocardiographic imaging is inadequate or equivocal. Additional studies may be considered based on the type of cardiomyopathy and/or if symptoms are present.

**f. Suggested Clinical Screening Intervals for At-Risk Family Members..:** Clinical screening intervals are suggested in Table 2.

**Background**—Cardiomyopathies span all ages, from prenatal to elderly patients. The approach to clinical phenotype screening of family members always relies on cardiac electrical, structural, and functional evaluations, with age- or phenotype-specific additions as needed. ECG and an echocardiography are usually foundational in the initial phenotype screening for all ages of at-risk pediatric and adult 1st-degree relatives.

Integration of the considerations given above, most importantly the type of cardiomyopathy, should also be taken into account in screening of children. Although children, even neonates, do manifest cardiomyopathy, most disease is of adolescent or adult onset. Therefore these recommendations should be integrated with the type of cardiomyopathy, the age of onset in other affected members in the pedigree when such data are available, the identity of the cardiomyopathy gene, if known, and other features. Additional guidance for the evaluation of cardiomyopathy in pediatrics is covered in the next section.

Adult-onset cardiomyopathies commonly show variable expressivity, a variable age of onset, and reduced penetrance. Clinical screening of 1st-degree relatives of adults diagnosed with cardiomyopathy is indicated, regardless of whether or not a disease-causing variant has been identified in the index patient. In cases where 1st-degree relatives are all clinically unaffected, it is reasonable to initiate genetic testing in the affected patient because identification of a previously known disease-causing variant could lead to cascade testing in 1st-degree relatives. 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 variant in the proband.

The risk for developing HCM after the age of 50 years is reduced but not eliminated<sup>39</sup> as is that for ARVC after age 50.<sup>40</sup> The favorable utility and role of Holter monitoring in the diagnosis of ARVC has been reviewed.<sup>40</sup> Magnetic resonance imaging is useful for the diagnosis of ARVC in centers experienced in its use and interpretation for ARVC<sup>41</sup>; data are not yet available to guide the frequency of its application for screening at-risk family members.

As noted in the introduction and in the Supplemental Material, LVNC may be observed in conjunction with other cardiomyopathy phenotypes, and if so, recommendations for that cardiomyopathy drive clinical screening recommendations. We lack data on whether or not, in the setting of normal ventricular size and function, the LVNC phenotype foreshadows the later development of a specific cardiomyopathy or other forms of cardiovascular disease

in an extended pedigree. This is because the present literature of family-based screening has been derived from LVNC identified at referral centers, in most cases in the setting of other cardiovascular disease.<sup>42–44</sup> Large systematic population-based studies to identify individuals with the LVNC phenotype but otherwise with normal cardiac morphology and function, followed by studies of their family members, have not been done, although limited preliminary data are available.<sup>42,43</sup> Because of the high prevalence of the LVNC phenotype in otherwise normal individuals in population-based studies,<sup>19,20</sup> the limited evidence of disease causation from the LVNC phenotype itself, and the limited individual and pedigree natural history data from population-based studies, we provide no recommendations regarding family-based phenotype screening of LVNC that is not accompanied by other cardiovascular phenotypes with known disease risks.

**Guideline 3 Referral of patients with genetic, familial, or other unexplained forms of cardiomyopathy to expert centers is recommended.**

- 3a.** Infants and children with cardiomyopathy should be evaluated by clinicians with specific expertise in the recognition and testing of syndromic and nonsyndromic presentations of cardiomyopathy in this age group.

**Key Points**—Expert centers are those with expertise in the evaluation, diagnosis, and management of genetic heart disease. Core competencies of expert centers include expertise with cardiovascular phenotypes as well as the conduct of genetic evaluations. Such centers should also have expertise in adults and/or children, depending on the ages of patients referred. Especially for infants and children, this includes clinicians who are able to recognize and characterize syndromes, dysmorphology, and metabolic abnormalities. Personnel at expert centers include physicians who are board eligible or board certified in cardiovascular disease, working collaboratively with genetics professionals, including genetic counselors and/or clinical geneticists, ideally ones with cardiovascular expertise.

**Background**—This recommendation is based on the marked genetic heterogeneity observed in cardiomyopathy, the increasingly complicated interpretations of human DNA variation, and the syndromic associations with some forms of cardiomyopathy. As noted below, both pre- and post-test genetic counseling should be provided by a health professional who is board eligible or board certified in genetic counseling or clinical genetics, ideally with specialty training and experience in cardiovascular genetics. Although all health professionals are expected to have core competencies in genetics, most cardiovascular providers do not have specific training or certification in clinical genetics or genetic counseling.<sup>2</sup> The 2009 HFSA practice guideline in genetic evaluation of cardiomyopathy acknowledged the challenges of obtaining a family history.<sup>1</sup> The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines also highlight the importance of obtaining an at least 3-generation family history in the evaluation of cardiomyopathy.<sup>6</sup> However, the genetic evaluation of cardiomyopathy is more complex than identification of a familial pattern of disease. This includes expert phenotyping to guide test selection and rigorous interpretation of genetic testing results. It should also be kept in mind that a recent study of genetic testing in clinical practice cited problems with

incorrect or inappropriate ordering, errors in analysis, incorrect interpretations, and incorrect follow-up regarding VUSs, potentially jeopardizing patient safety.<sup>45</sup>

In contrast to other subspecialty areas in cardiovascular disease, no consensus or formal definition of the requirements for expertise in cardiovascular genetics is currently available. Some training programs in advanced heart failure and transplant cardiology or in cardiac electrophysiology include genetics exposure, but typically training is insufficient to achieve the expertise to conduct an independent cardiovascular genetic evaluation. Similarly, training programs in clinical genetics typically provide exposure to diagnostic evaluation of cardiomyopathy, but may not provide sufficient training or experience in the recognition, management, and risk stratification of the heterogeneous cardiac phenotypes found in this patient population. Clinical practice in cardiovascular genetics requires that practitioners remain up to date with the wide range of genes in which pathogenic variants cause cardiac phenotypes, including various forms of cardiomyopathy, arrhythmia, and syndromes in which these cardiovascular manifestations occur. For these reasons the ideal construct includes a close collaboration of specialists in both fields.

Because of the genetic and phenotypic heterogeneity inherent among different forms of cardiomyopathy, a single health care provider is unlikely to be able to provide expert care alone. Often, the range of expertise required is best achieved with a team of personnel who have complementary training and experience, because a multidisciplinary approach is frequently essential for optimizing diagnosis and management.<sup>2,46,47</sup> Often a board-eligible or board-certified genetics professional will work in conjunction with clinicians who are board eligible or board certified in cardiovascular disease—pediatric, adult, or both. One or more members of an expert team involved with evaluation of cardiomyopathies may have subspecialty certification in advanced heart failure and transplant cardiology and/or subspecialty certification in cardiac electrophysiology. The evaluation of genetic heart disease includes whole families, so expert centers ideally have teams of physicians and counselors who are experienced with providing care for both adults and children with genetic forms of heart disease. Expert centers should be able to advise patients properly about patterns of inheritance, family members who are at risk of developing genetic heart disease, and reproductive risks related to variants in genes involved with cardiomyopathies.

Although referral to an expert center is recommended for genetic evaluation of patients with familial or otherwise un-explained forms of cardiomyopathy, the practicality of this recommendation varies regionally. Travel to an expert center for genetic evaluation of cardiomyopathy may not be feasible for some patients and their families. Additional options through telephone-based genetic counseling and telemedicine-based genetic evaluation may help in part to address this shortcoming.<sup>48</sup>

### **The Evaluation of Cardiomyopathy in Children Requires Special Expertise**

Cardiomyopathy in children presents a unique differential diagnosis list, compared with adults, and geneticist evaluation may be required because syndromic and metabolic causes of disease represent a higher proportion in children than in the adult population.<sup>49,50</sup> This is particularly relevant in patients with intellectual disability of unknown cause. Other extracardiac findings that should prompt further evaluation and referral include dysmorphic

features, short stature, congenital anomalies, muscle weakness, or sensory deficits of unknown cause. Age at presentation may greatly aid in refining the differential list, with a specific set of disorders more common in infancy. Although there are many conditions that may cause cardiomyopathy in childhood (see Supplemental Table 1 for examples), a few are notable for having specific time-critical treatments available or because the identification of the cardiomyopathy in the presence of other findings may solidify the diagnosis of a specific syndrome. A number of conditions can be screened by relatively inexpensive and rapid biochemical tests, followed by genetic testing for a molecular diagnosis.

Aside from neuromuscular disorders, inborn errors of metabolism, and specific syndromes noted in children, the same causes of familial HCM and DCM common in adults are also encountered throughout childhood.<sup>51</sup>

Equally, syndromes with cardiomyopathy as a component may not be diagnosed until adulthood, and therefore syndromic cardiomyopathies should also be part of the differential diagnosis among adults. In some cases, the dysmorphic features that form an integral part of the diagnosis in infancy and childhood may not be as prominent later in life.

**Infancy.**—Inborn errors of metabolism (IEMs) constitute an important group of conditions that may manifest early in life. Although expanded newborn screening may identify potentially affected individuals, false negatives and missed screening confirmations can occur. Not all diseases are screened in all jurisdictions, and some conditions are not currently amenable to screening. Disorders of energy metabolism in particular should be considered: they may present as either HCM or DCM and include fatty acid oxidation defects (eg, very-long-chain acyl-CoA dehydrogenase [VLCAD], carnitine palmitoyl transferase 2 [CPT2], and long-chain 3-hydroxyacyl-CoA dehydrogenase [LCHAD] deficiency) and mitochondrial oxidative phosphorylation disorders. If suspected, acylcarnitine profile, serum amino acids, urine organic acids, liver transaminases, serum lactate, and comprehensive metabolic profile are recommended first-line studies. HCM in infancy should always invoke investigation for infantile Pompe disease (glycogen storage disease type II) by means of enzyme assay for acid alpha-glucosidase deficiency, because early diagnosis is crucial for successful treatment by enzyme replacement therapy. Of note, HCM may also occur secondary to corticosteroid use in preterm infants with respiratory distress syndrome<sup>52,53</sup> or maternal diabetes<sup>54</sup> and should resolve spontaneously. Persistence of HCM >4 weeks after cessation of steroids or past 6 months of age in an infant of a diabetic mother should prompt evaluation for other causes.

Some syndromes with cardiomyopathy may present in infancy. Noonan syndrome or other RASopathies are the most common syndromes associated with HCM and may have extracardiac manifestations of short stature and dysmorphic features which may be subtle and difficult to recognize. HCM occurs in up to 20%–30% of cases, with one-half presenting before 12 months of life with a more severe hypertrophy that paradoxically may improve over time.<sup>55,56</sup> This may be biventricular, or involve predominantly the right ventricle. HCM rarely newly develops past the age of 5 years.<sup>57</sup> Molecular testing for RASopathies may or may not be included with sarcomeric HCM genetic testing panels.

**Childhood.**—Cardiomyopathy due to IEMs may present in early or late childhood, typically in individuals previously diagnosed with a specific disorder who receive cardiac screening. Examples include the amino acid metabolism disorders methylmalonic acidemia and propionic acidemia, glycogen storage disease type III (or very rarely type IV), and mucopolysaccharidosis. Occasionally these conditions escape diagnosis or are misdiagnosed.

Neuromuscular disorders may first manifest with DCM in childhood, and they include muscular dystrophies (dystrophinopathies, laminopathies, desminopathies, sarcoglycanopathies, and other recessive and dominant limb-girdle muscular dystrophies) and Friedreich ataxia. Myotonic dystrophy, types I and II, also present with cardiomyopathy, though more commonly in adults, especially type II. Both types also have risk for conduction-system disease.<sup>58</sup> Mitochondrial disorders also may present primarily as symptomatic cardiomyopathy throughout childhood. Finally, boys with early-onset cardiomyopathy should be carefully evaluated for Barth syndrome (skeletal myopathy, small size, cyclical neutropenia, delayed puberty, and 3-methylglutaconic aciduria), an X-linked condition due to pathogenic variants in *TAZ*, which is important for mitochondrial function.<sup>59</sup> Mitochondrial disorders may exhibit HCM (~60%) or DCM (~30%).<sup>60</sup>

**Selected Syndromes with Cardiomyopathy.**—Careful history and physical exam are essential to identify possible extracardiac manifestations of syndromes that may change investigation and management. It is estimated that up to 10% of children with cardiomyopathy have an underlying genetic syndrome. More than 100 different syndromes have been described with cardiomyopathy as a feature. Although most are very rare, several occur with higher frequency and should be considered in the differential diagnosis (Supplemental Table 1).

Several syndromes present more commonly in childhood. Alström syndrome may present with transient DCM in infancy and with later reoccurrence of DCM or restrictive cardiomyopathy in adolescence. Other features include visual impairment (due to cone-rod dystrophy) with nystagmus, progressive sensorineural hearing loss, obesity, and diabetes (due to insulin resistance). Danon disease, an X-linked condition due to pathogenic variants in *LAMP2*, frequently manifests in early childhood.<sup>61</sup> It resembles infantile Pompe disease with severe HCM but less pronounced skeletal myopathy, and it has additional problems of cardiac preexcitation, intellectual disabilities, and retinal pigmentary disease. The variability in extracardiac features is not well understood. Female carriers may present with either HCM or DCM, most often in the second or third decades. Severe HCM due to 5' adenosine monophosphate-activated protein kinase (AMPK) deficiency encoded by *PRKAG2* leading to nonlysosomal glycogen accumulation may also present in childhood, frequently with arrhythmias, heart block, and Wolff-Parkinson-White syndrome.<sup>62</sup> Fabry disease, an X-linked disorder resulting from mutations in *GLA*, causes deficiency of alpha-galactosidase. Fabry disease may present as early as adolescence with LV hypertrophy. Manifestations of classic Fabry disease include extracardiac features of angiokeratomas, painful acroparesthesias, corneal opacities, reduced sweating, and endstage renal disease due to loss of enzyme activity (typically <1%). However, variants in *GLA* that leave some residual enzymatic function may result in cardiac variant Fabry disease, which usually



presents at the age of 40 years and older, in which left ventricular (LV) hypertrophy is identified with or without proteinuria and without other extracardiac manifestations.<sup>63</sup> Early enzyme replacement therapy, particularly for male and severely affected female individuals with this X-linked disorder, may slow progression of disease. Atypical forms of Fabry disease include a cardiac variant consisting of HCM, arrhythmia, and conduction abnormalities without renal failure, neuropathy, or skin findings and present at a later age.

**Guideline 4 Genetic testing is recommended for patients with cardiomyopathy.**

- 4a. Genetic testing is recommended for the most clearly affected family member.
- 4b. Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
- 4c. In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with other extracardiac manifestations	A
Left ventricular noncompaction (LVNC)	See Background

**Key Points**—Genetic testing is recommended to determine if a pathogenic variant can be identified to facilitate patient management and family screening. The identification of at-risk family members is critical, because the first presentation may be sudden death. Cascade genetic screening identifies asymptomatic affected family members and clinically unaffected carriers of pathogenic variants.<sup>64</sup> Institution of therapy in asymptomatic affected individuals improves outcomes and decreases hospitalization and death due to heart failure.<sup>65,66</sup> Preliminary studies indicate that treatment of clinically unaffected carriers of pathogenic variants may improve outcome as well, although larger studies are needed.<sup>67</sup> Genetic testing and cascade screening for HCM have been shown to be cost-effective in Australia and the United States.<sup>68,69</sup> The identification of a molecular cause may also lead to critical gene-specific cardiac or extracardiac management recommendations. For example, cardiac hypertrophy seen in *LAMP2*, *PRKAG2*, *PTPN11*, and *RAF1* pathogenic variant carriers can represent a genocopy of hypertrophy seen with sarcomeric pathogenic variants; yet *LAMP2*, *PRKAG2*, *PTPN11*, and *RAF1* patients have different clinical courses and management needs.<sup>70,71</sup> In sarcomeric carriers, genotype status is associated with long-term outcomes, including all-cause mortality.<sup>72,73</sup> In DCM, there is evidence for prognostication value of genetic testing<sup>74–77</sup> and management implications for specific genetic findings, such as consideration of ICD placement for primary prevention in carriers of *LMNA* pathogenic variants.<sup>78</sup> In ARVC, ICD placement for primary prevention in asymptomatic male carriers of a malignant pathogenic variant showed a significant effect on long-term clinical outcome.<sup>79</sup>

Testing should ideally be initiated on the person in a family with the most definitive diagnosis and most severe manifestations. This approach would maximize the likelihood of obtaining diagnostic results and detecting whether multiple pathogenic variants may be present and contributing to variable disease expression or severity. See guideline 3 for additional comments on specialized evaluation of infants and children.

**Background**—Nomenclature follows the ACMG approach<sup>9</sup> for calling variants pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign, and benign. The indications for genetic testing include guiding patient management and facilitating family screening and reproductive risk assessment.

**Test Selection: Genes and Gene Panels.** Since the 2009 HFSA guideline,<sup>1</sup> the number of genes known to harbor rare pathogenic variants that cause cardiomyopathy has increased, the number of clinical laboratories performing high-volume cardiovascular genetic testing has expanded, and the number, type, and technologies available for gene-based sequencing have been in continual evolution. Although the 2009 guideline suggested that “genetic testing should be considered,” additional data on the importance of genetic testing for prognostication and management as well as cascade screening and risk stratification of relatives support the current genetic testing recommendation. Furthermore, the cost for most large genetic panels is substantially lower than it was in 2009, with expectations for continued decline.<sup>80</sup> Nevertheless, genetic testing is probabilistic in nature, and interpretation of genetic variation will continue to be refined as additional sequencing information becomes available from both affected and unaffected individuals.

The rationale for level of evidence presented in this guideline is derived largely from the published sensitivity of genetic testing. These guidelines do not address molecular testing in prenatal, newborn screening, or in vitro fertilization settings.

We also note ongoing challenges of variant interpretation in non-white and non-northern European populations, because most genetic testing, and therefore repositories of known pathogenic variants, have been conducted principally in the white/ northern European population. The recent development of very large population databases (eg, ExAC [<http://exac.broadinstitute.org>] or gnomAD [<http://gnomad.broadinstitute.org>]) now provides limited numbers of reference alleles from non-European cohorts, which has greatly assisted variant interpretation. However, genetic test interpretation of variant alleles from ethnic groups not represented or represented in low numbers in reference datasets becomes extremely challenging and must be approached with considerable caution.

A variety of resources are publicly available that provide additional relevant information (eg, GeneReviews, <http://www.ncbi.nlm.nih.gov/books/NBK11116>) on individual genes (eg, Online Mendelian Inheritance in Man, <http://www.omim.org>), specific genetic variants and their population frequencies (eg, dbSNP [<http://www.ncbi.nlm.nih.gov/snp>], ExAC browser [<http://exac.broadinstitute.org>], Genome aggregation database [gnomAD, <http://gnomad.broadinstitute.org/>], exome variant server [<http://evs.gs.washington.edu/EVS>], and 1000 Genomes [<http://www.1000genomes.org>]) and information for the interpretation

of these variants (eg, ClinVar [<http://www.ncbi.nlm.nih.gov/clinvar>] and ClinGen [<http://www.clinicalgenome.org>]).

We also note that large insertion/deletion variants (eg, >25 nucleotides) and other structural changes in DNA, referred to as copy number variants represent <1% of cardiomyopathy cases, according to a preliminary study,<sup>81</sup> although structural variants have received minimal investigation in the cardiomyopathies and may have greater relevance than is currently understood.

**Whom to Test.:** To yield the most conclusive and informative results, diagnostic genetic testing is optimally initiated on a confirmed affected individual. Furthermore, because there are sometimes multiple genetic variants contributing to disease in a single family, the testing should ideally be initiated on the person who is most likely to harbor the disease-causing variant or variants. This is frequently the individual in the family with the most severe disease and/or the earliest disease onset. This is a well established principle in clinical genetics, because selecting the individual with the most evident disease increases the likelihood of finding a genetic cause. If the ideal person for initiation of genetic testing in a family is unavailable or unwilling to proceed, then comprehensive genetic testing should be considered for another affected family member.

**When to Test.:** The timing for ordering genetic testing in a patient with cardiomyopathy has not been studied. Because results may guide management, we recommend genetic testing at the time a new cardiomyopathy diagnosis is made, but it can be conducted at any time after diagnosis. Education and counseling regarding genetic testing options are a key component of the process. For those who have had genetic testing in the past, retesting may be appropriate if the previous testing produced negative or inconclusive results and the test's detection rate has improved. This latter point is particularly relevant for DCM, because the gene panels have rapidly expanded (eg, inclusion of *TTN*<sup>45,82,83</sup> and others) and are expected to continue expanding.

Genetic testing for the cardiomyopathies may best be viewed as continuously evolving as new genes, and therefore larger panels with greater sensitivity, continue to emerge. Although no data are available, we suggest that repeated genetic testing is reasonable if test sensitivity has increased by 5%–10%. An alternate approach is to tailor retesting if particular characteristics of the patient's phenotype are consistent with a newly identified gene. Furthermore, the genetics provider involved in a patient's care should periodically revisit results because variants may be reclassified over time.<sup>46,84,85</sup> Such reclassification includes upgrading variants from VUS to LP or P as additional probands and affected family members with the phenotype of interest are found to carry the variant. Conversely, some variants, previously considered to be P, are downgraded to VUS, or likely benign or benign, as larger datasets from expanded ethnicities become available.

**How to Test.:** With the development of next-generation sequencing (NGS), panels incorporating dozens of genes relevant to the phenotype have become the norm as they are technically feasible and less costly.<sup>80</sup> As a result, clinical genetic testing panels for these disorders are changing rapidly. Molecular genetic testing for multiple genes with the use

of a multigene panel is now the standard of practice for cardiovascular genetic medicine. Furthermore, multigene panel genetic testing is recommended over a serial single-gene testing approach owing to the genetically heterogeneous nature of cardiomyopathy. Genetic testing and cascade screening have been shown to be cost-effective.<sup>68,69</sup>

Large gene panels for cardiomyopathy may include genes that cause genetic syndromes associated with cardiomyopathy (eg, Fabry disease, Danon disease, Alström syndrome), neuromuscular conditions associated with cardiomyopathy (eg, limb girdle muscular dystrophies), or metabolic conditions. These large gene panels have the advantage of increasing the likelihood of identifying a molecular etiology, especially in patients with mixed phenotypes or those who lack pathognomonic features.<sup>86,87</sup> Considerable overlap of genes among different types of cardiomyopathy (and other phenotypes) is also well established (Supplemental Fig. S1). Panels also increase the likelihood of identifying individuals who carry disease-causing variants in multiple genes, and this knowledge is extremely important for appropriate targeted testing of family members.

With larger gene panels, the likelihood of identifying a VUS increases in proportion to the number of genes tested, increasing the complexity of the interpretation and genetic counseling. Importantly, the strength of evidence for gene-disease pairs on current panels differs, with some well established genes having a wealth of information regarding disease-causing variants and more recently identified genes having much less information available. The latter case increases the likelihood of a variant being classified as a VUS. The composition of gene panels varies by testing laboratory. It is critical that the ordering physician has an understanding of the uses, benefits, and limitations of specific test types to select the most appropriate test for their patient (Supplemental Table 2). Addition of *TTN* and *BAG3* to DCM panels increased genetic testing yield by more than 10%,<sup>15,82,83</sup> but for HCM recent studies have shown that expanded panels do not currently increase sensitivity.<sup>69</sup> Therefore the decision to order a panel that includes a larger number of genes should be based on the specifics of the patient's medical history, physical examination findings, and family history.

**HCM.:** The level of evidence for testing in HCM is based on studies showing a high diagnostic yield of genetic testing in children and adults and prognostic value of genotype status.<sup>30,69,72,73,88</sup> HCM is considered to be a disease of the sarcomere, and variations in genes encoding sarcomeric proteins, in which there is low tolerance for genetic variation, are common causes.<sup>89</sup> The diagnostic yield of HCM testing is ~30%–60% (Table 3). The yield of testing is higher in individuals who have a known family history of HCM.<sup>69,88</sup> Pathogenic variants in *MYH7* and *MYBPC3* account for ~80% of all cases for which a molecular diagnosis is achieved.<sup>90,91</sup> Beyond sarcomeric genes, core genes to screen in patients with HCM include *GLA*, *PRKAG2*, and *LAMP2*, as reviewed in the Background of guideline 3.

Infants and children with HCM may require more specialized evaluation and diagnostic testing, as noted in guideline 3, owing to the rate of syndromic conditions and inborn errors of metabolism associated with HCM at those ages.<sup>49,50,92</sup> Consultation with a geneticist is indicated.

**DCM.:** Evidence indicates that clinical genetic testing can identify the cause of DCM in families with autosomal dominant inheritance in ~25%–40% of cases, whereas in isolated cases of DCM the yield of testing is commonly estimated at 10%–25%.<sup>35,93–95</sup> Core genes to be tested in individuals with DCM include genes encoding sarcomeric and cytoskeletal proteins (Table 3), although DCM testing panels typically carry several dozen genes, some with uncertain significance. In most cases, all HCM and ARVC genes are included in DCM panels owing to gene/phenotype overlap.

Protein-truncating variants in *TTN* (*TTN*tv) represent the most common genetic testing finding in DCM, ranging from 10% to 20% of cases.<sup>15,82,83</sup> Although many commercial testing laboratories will deem all *TTN*vs, whether singleton or familial, as P or LP, variant interpretation is challenging because of the large size of the gene and the frequency of *TTN*vs in reference populations.<sup>82,83,96,97</sup> Most studies have not been family based, where segregation could be evaluated, but some nonsegregation of *TTN*vs has been identified.<sup>98</sup> Furthermore, recent cardiac magnetic resonance data of normal individuals from a population-based study showed a small but significant decrement in LV function with *TTN*vs in constitutive cardiac exons,<sup>97</sup> suggesting that in some cases a *TTN*tv may function as a risk allele.

The *LMNA* gene is the second most commonly identified cause of DCM, with a diagnostic yield of 5.5%, and gene-specific management recommendations, reviewed below, are available.<sup>99,100</sup> More recently identified genetic causes of DCM, such as *BAG3*, a chaperone regulator, and *RBM20*, a protein required for RNA splicing, identify novel molecular mechanisms for disease<sup>101,102</sup> and are each identified in ~2% of DCM cases. DCM is a common complication of neuromuscular disease such as Duchenne or Becker muscular dystrophy. Genetic testing is important in mothers of individuals with Duchenne or Becker muscular dystrophy to determine carrier status, because carrier women may develop DCM in the third to fifth decade of life.<sup>103</sup> As in HCM, infants and children with DCM may require additional diagnostic genetic evaluation.

**ARVC.:** The genetic basis of ARVC was initially identified as a disease of the desmosome.<sup>104</sup> Genetic testing of *PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, *TMEM43*, and *PLN* resulted in a molecular diagnosis in 63% of patients who fulfilled Task Force criteria for ARVC.<sup>105</sup> Digenic inheritance and compound heterozygosity are frequent<sup>106</sup> and, combined with the decreased penetrance that is a feature of ARVC, may significantly complicate genetic counseling. ARVC overlaps with arrhythmogenic LV cardiomyopathy (sometimes more broadly referred to as arrhythmogenic cardiomyopathy).<sup>107</sup> This reflects genetic and phenotypic overlap among these forms of cardiomyopathy. Accordingly, genetic testing for ARVC with the use of a larger cardiomyopathy panel may identify nondesmosomal genes with pathogenic variants. Similarly, desmosome gene mutations have been identified in patients diagnosed with DCM.<sup>108</sup> Exercise has a well established role in the pathogenesis of desmosomal cardiomyopathies, and recognition of a desmosome gene mutation can help to determine optimal exercise recommendations.<sup>109</sup>

**RCM.:** Genetic causes of RCM continue to be identified, but because RCM is a relatively rare form of cardiomyopathy, numbers remain limited. A recent study identified a pathogenic

variant in 60% of subjects, primarily occurring in genes known to cause HCM.<sup>110</sup> Family members were frequently identified with HCM or HCM with restrictive physiology. Cardiac amyloidosis resulting from pathogenic variants in *TTR* needs to be differentiated from other forms of RCM owing to the age demographic in which this occurs, the slowly progressive nature of this disease, and therefore the different management strategies.<sup>111,112</sup> The *TTR* allele p.Val142Ile (commonly referred to as Val122Ile based on nomenclature for the circulating protein after N-terminal peptide cleavage) has been found in 10% of African Americans older than 65 years with severe congestive heart failure.<sup>113</sup> Substantial recent progress with amyloidosis, both in imaging strategies, including cardiac magnetic resonance and pyrophosphate scanning, and therapeutic interventions in ongoing clinical trials, provides new incentives for genetic diagnosis.<sup>114</sup> Hemochromatosis is uncommon but easily excluded with iron studies, such as percent saturation of transferrin, and if present can be treated with iron removal.<sup>115</sup>

**LVNC.:** As noted above, the LVNC phenotype may be observed in conjunction with all other cardiomyopathy phenotypes, so considerations related to genetic testing should always be directed by findings of a cardiomyopathy (or other cardiovascular) phenotype.<sup>16,116</sup> Genetic testing is not recommended when the LVNC phenotype is identified serendipitously in asymptomatic individuals with otherwise normal cardiovascular structure and function.<sup>117</sup>

**Special Circumstances.:** A genetic etiology should be considered and a genetic evaluation conducted in cases of peripartum cardiomyopathy, as rare variants in genes known to cause DCM have been identified in patients with peripartum cardiomyopathy,<sup>118–120</sup> and *TTN* truncating variants are present at rates similar to those found in the DCM population.<sup>120</sup> In cases of sudden death with an autopsy diagnosis of cardiomyopathy, genetic testing may facilitate risk stratification of family members.<sup>121,122</sup>

**Interpretation of Genetic Testing.:** Genetic testing results are probabilistic rather than determinative, and therefore rely on strength of evidence, both for and against, of specific variants causing or contributing to disease. New guidelines have attempted to standardize and increase the stringency of interpretation, with greater clarity regarding the criteria for strength of evidence and the weighing of multiple sources of information that need to be incorporated to arrive at the interpretation.<sup>9</sup> Despite this, the interpretations provided for a given variant may differ between clinical genetic testing laboratories.<sup>123,124</sup> In addition, updates and revisions of the laboratory interpretation may occur as more information is obtained from larger cohorts, sometimes leading to reissuing of a clinical report with changed interpretation by diagnostic laboratories.

Because of their probabilistic nature, results of genetic testing must always be interpreted in the context of the patient's medical and family history.<sup>85</sup> For example, family history information and the segregation of a putative disease-causing variant within the family may be important information to guide clinical interpretation, especially in cases where novel genetic variants are identified. Also, family studies have noted >1 pathogenic variant in up to 10% of families with ARVC.<sup>125</sup> Two or more variants have been seen in 3%–5% of HCM cases,<sup>31–33</sup> particularly if onset is early or severe.<sup>30</sup> Although not reported systematically, digenic inheritance has been suggested to occur at even higher frequency with DCM.<sup>35</sup>



The diagnostic yield of genetic testing for each subtype of cardiomyopathy is much less than 100% (Table 2), and a negative genetic test result (in this setting including VUS and likely benign and benign variants) does not rule out a genetic cause. Such an uninformative result in a proband simply indicates that the genetic testing performed was unable to identify the specific cause of disease in the given family. In these circumstances, an uninformative genetic testing result can not be used for predictive cascade genetic testing in unaffected relatives. Rather, family screening with the use of phenotypic evaluations is recommended (guideline 2). Larger panels, better coverage of the relevant genes, analysis for deletions, duplications, and rearrangements in the genes of interest, or exome sequencing in families with multiple living affected individuals may identify a genetic etiology.

Finally, the recent availability of and much greater focus on extensive genetic testing panels should not diminish or distract from the critical importance of expert phenotyping of patients and families and the relevance of highly insightful phenotype and gene-variant correlations. Current genetics practice suggests that results provided by molecular genetics laboratories drive clinical decision making, specifically actionability, in a genetic evaluation. In the Family Management section below, this guidance states that a VUS cannot be used for predictive testing, which the writing group firmly supports. However, we acknowledge that compelling clinical data, for example, the pre-genetic test specification of a disease gene highly likely to harbor a disease-associated variant of interest, seldom affects the clinician's decision of whether a variant classified as a VUS by a laboratory report is actionable. More specifically, cardiovascular genetics experts have become quite sanguine, for example, about specifying the pretest likelihood of identifying an *LMNA* variant based on phenotype and/or family data. However, finding a novel missense or nonsense variant in any gene, even with such a pretest specification, cannot be classified under current ACMG rules as LP (or P), and thus actionable, unless data regarding the same variant are available from multiple probands and/or affected family members. Although we propose no solution to this conundrum, we acknowledge its existence. Efforts to accumulate extensive catalogs of expertly adjudicated phenotype and variant information, such as the ClinGen effort,<sup>10</sup> may eventually partially mitigate this situation.

### **Considerations of Family Management**

**Predictive Genetic Testing.** Risk stratification in family members is an important and valuable reason for genetic testing. If a pathogenic or likely pathogenic variant is identified in the index patient initially tested, opportunities emerge for the predictive testing of at-risk family members. As noted above, VUSs are not useful in predictive genetic testing.

**Negative Cascade Genetic Testing in an At-Risk Family Member.** If genetic testing is negative in an at-risk phenotype-negative family member for a P or LP variant present in the proband, that family member's risk of developing the cardiomyopathy is substantially reduced. In this situation the need for serial phenotype screening after a baseline clinical evaluation in such a genotype-negative family member in most cases is unnecessary, and the family member can be discharged from serial clinical phenotype screening. However, the strength of the recommendation to release a family member from ongoing interval phenotype screening is based on the strength of the evidence that the variant is indeed the

cause of disease in the family under care. In most cases, this evidence must be assembled from previous patients and families, usually in publicly accessible databases or the medical literature, and/or from data gathered and assessed from the family under care. The family member should be counseled that their risk has been substantially reduced, but is not reduced to zero, with the caveat that if they develop relevant symptoms, phenotype screening should be reconsidered owing to the possibility that one or more yet undetected variants may be at play.

**Positive Cascade Genetic Testing in an At-Risk Family Member.** On the other hand, if a P or LP variant is identified in an asymptomatic at-risk phenotype-negative family member, the confidence is much greater to infer risk for that individual. They should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, any associated reduced penetrance and variable expressivity, and the rationale and frequency of the recommended clinical surveillance (reviewed at guideline 2).

**Leveraging Family-Based Segregation Information to Affect Variant Analysis.** Some variants detected by means of cardiomyopathy genetic testing will be novel, that is, variants that have not been previously reported in publicly accessible databases, and will meet other usual criteria for pathogenicity. However, even if the variant is of the type that is known to be disease causing and has occurred in a well established gene associated with the cardiomyopathy phenotype in the family, such novel variants will often be deemed to be VUSs because of a lack of previous case or family data. In this circumstance, searching for segregation of the variant in question with the cardiomyopathy phenotype in additional family members can provide additional valuable information. Depending on the size of the pedigree, the number of individuals tested, and the genetic testing results, such information may help to reclassify a variant from VUS to P or benign. The ClinGen initiative<sup>10</sup> proposes to rectify this issue by aggregating all available disease-associated variants into ClinVar, a publicly accessible database using a standardized curation approach tailored after the ACMG/AMP recommendations,<sup>9</sup> and all professionals with any access to genetic data relevant to the cardiomyopathies are urged to contribute to this important database. However, because of the number of genes involved in the cardiomyopathies, many variants in the near term will likely be curated as VUS. For example, in one HCM study, the cardiomyopathy with the largest disease-specific databases and where ~80% of pathogenic variants can be identified in 2 genes, *MYPBC3* or *MYH7*, 30% and 35% of variants were novel for these 2 genes, respectively. In other well established HCM genes, 76% of variants were unique.<sup>38</sup>

The corollary of the above is that if the VUS does not segregate with affected family members, the likelihood that the VUS is relevant for the family phenotype is reduced. However, such analysis must encompass the growing reality of bilineal or multivariant disease, which has been postulated to be more common in DCM<sup>8,35</sup> and ARVC.<sup>126</sup>

In most clinical situations, sequencing a VUS is not undertaken in family members who have completed clinical screening and have been shown to be free of the phenotype (negative clinical phenotype screening), because genetic information will not inform variant pathogenicity. One important exception to this is parental sequencing to confirm the possibility of de novo occurrence of a variant. A second exception to this includes

sequencing older unaffected family members, who are highly informative when assessing the penetrance of a variant. Application of this principle depends greatly on the age of onset of the phenotype in the family (infant, pediatric, early adult, late adult), the clarity and severity of the phenotype, and the gene involved and disease mechanisms.

Finally, as noted above, variant calls may change. The most problematic is when a previously called variant, deemed to be P or LP, is downgraded to VUS. In this circumstance, recommendations for the clinical surveillance screening of at-risk family members change. Most importantly, a genotype-negative family member must now be counseled that they remain at risk for the family phenotype, and therefore need to reengage in clinical screening. The proband and any family members who tested positive for the variant, now downgraded to a VUS, must also be counseled that future genetic reevaluation may be appropriate. All clinicians participating in genetic evaluations must be aware of the implications of changes in variant calls, and the family members should be counseled regarding these possibilities during the initial genetic evaluation and the need for possible future contact. Given the seeming recent increase in downgrading to VUS, this high-impact change in variant status carries great potential for unintended clinical errors if not identified and communicated effectively to the relevant family unit.

**Guideline 5 Genetic counseling is recommended for all patients with cardiomyopathy and their family members. (Level of Evidence = A)**

**Key Points:** Genetic counseling for cardiomyopathy may be offered by board-certified or board-eligible genetic counselors, clinical geneticists, or, in the absence of available genetics professionals, clinicians who have the required background, expertise, and training. Genetic counseling for cardiomyopathy includes review of medical records essential for phenotyping, obtaining a pedigree, patient and family education, evaluating genetic testing options, obtaining consent for genetic testing, facilitating family communication, and ordering and interpreting genetic test results while addressing psychosocial issues.

**Background:** Genetic counseling facilitates understanding of and adaptation to the impact of a genetic condition at the medical, psychologic, and family levels<sup>127</sup> and is valued positively as an essential service by both caregivers and patients.<sup>1,46,128</sup> This service may be provided by clinical geneticists, genetic counselors, or specially trained nurses. In the United States it is performed mostly by genetic counselors, who are mid-level providers with a masters-level training in gathering, interpreting, and communicating medical genetics information. Their scope of practice also includes psychosocial assessment and support. Genetic counseling conceptualizes the family as the unit of care, with a broadened focus including preventive care for at-risk family members.

Genetic counseling is usually undertaken by genetic counselors and/or clinical geneticists who are knowledgeable in the cardiovascular features of the type of cardiomyopathy in question, or by cardiologists, adult or pediatric, who are expert in the cardiomyopathy in question and are fluent in the content and nature of genetic counseling. Cardiologists with special interest and expertise in genetic cardiomyopathies usually integrate genetic counselors into their practices.

Genetic counseling is an essential component of the evaluation, diagnosis, and management of the cardiomyopathies. Genetic counseling roles include review and gathering of medical records essential for phenotyping, obtaining a family history (guideline 1), educating the patient and family regarding the disease transmission and family risks, evaluating genetic testing options (guideline 4), obtaining consent for genetic testing, including discussing the implications of positive, negative, or uncertain results, providing key information to other at-risk family members as identified by the index patient, ordering testing, interpreting genetic test results, and communicating results and their clinical implications, including screening recommendations for family members (guideline 2).

Counseling also aims to promote informed choices and adaptation to risk or condition while exploring and addressing psychosocial issues as they emerge. Addressing family dynamics, which could potentially affect dissemination of genetic information to at-risk family members, is an active area of focus in genetic counseling that may be aided by the use of patient letters, educational materials, or other communication tools.

**Guideline 6 Focused cardiovascular phenotyping is recommended when pathogenic or likely pathogenic variants in cardiomyopathy genes, designated for reporting of secondary findings by the ACMG, are identified in an individual.**

- 6a.** If a cardiovascular phenotype is identified as would be predicted by currently available knowledge of the gene/ variant pair, all usual approaches described in this document for a genetic evaluation, including family-based approaches, are recommended.
- 6b.** If no cardiovascular disease phenotype is identified in the individual, recommendations for surveillance screening at intervals should be considered.
- 6c.** If no cardiovascular phenotype is identified in the individual, cascade evaluation of at-risk relatives may be considered, tempered by the strength of evidence supporting the pathogenicity of the variant, the usual age of onset of the gene/ variant pair, and pedigree information (eg, the ages of at-risk family members, other previously known cardiovascular clinical data in the pedigree, and related information).

**Background:** Across specialties, genetic testing is moving toward use of large gene panels, whole-exome sequencing, and potentially whole-genome sequencing. These tests may be performed for a wide variety of indications and diseases that do not include a cardiac phenotype. Individuals who undergo genetic testing for a disease that does not involve the heart may have a genetic variant discovered that may predispose that individual to a cardiomyopathy. This discovery may occur in 2 ways. 1) The gene, known to confer risk from high-penetrance variants that are medically actionable, may be intentionally analyzed, as recommended by the American College of Medical Genetics and Genomics. Variants identified from intentional analysis are termed secondary findings. 2) A variant is identified incidentally or accidentally through the analysis of genes related to the original phenotype for which the test was performed. These are termed incidental findings.

The ACMG has developed guidelines to manage secondary findings, which were first published in 2013<sup>4</sup> and updated in 2016.<sup>5</sup> The ACMG guidance directs the reporting only of known pathogenic (KP) or expected pathogenic (EP) variants,<sup>5</sup> the former defined as “sequence variation is previously reported and is a recognized cause of the disorder” and the latter as “sequence variation is previously unreported and is of the type expected to cause the disorder.” These definitions were taken from the ACMG 2008 guidance for variant interpretation,<sup>129</sup> which was updated by the ACMG/AMP in 2015<sup>9</sup> with modified nomenclature of P (pathogenic) and LP (likely pathogenic). The P and LP attributions are now nearly universally used in clinical genetic testing laboratories in the United States. This nomenclature is also used in ClinGen,<sup>10,11</sup> the ClinGen Cardiovascular Clinical Domain Working Group,<sup>130</sup> and the present guideline. Despite possible subtle differences of KP/EP and P/LP, because the P and LP attributions are used for the other specific numbered guidelines in this document, for simplicity and parsimony these attributions will be used in this section as well.

Variants in the ACMG-listed cardiomyopathy genes (Table 3) that have been identified as secondary findings and adjudicated as P or LP are considered to be medically actionable. In those cases, cardiac phenotyping should be conducted in the individuals who carry those variants, assuming that the individual has not opted out of notification.

Greater difficulty in determining whether a variant is medically actionable may occur for incidental findings reported by the diagnostic laboratory that fall outside the ACMG guidelines. Incidental findings may be classified as P, LP, VUS, likely benign, or benign, with specific criteria for the strength of assertion.<sup>9</sup>

The single most important analysis for determining if a specific incidental finding is actionable rests on the strength of evidence for disease causality of the gene/variant pair. Identifying a variant in a gene previously observed in multiple cases or families, including at times functional data confirming a damaging effect, can have substantial evidentiary strength, and such variants may be able to be classified as P or LP. Such evidence forms the basis of the ACMG recommendations and informs sections a, b, and c of this guideline. For HCM, where 80% of genetic cause, when found, is within 2 genes (*MYBPC3* and *MYH7*), a greater likelihood exists that previous case data may be available. However, in contrast to HCM, the gene ontology for DCM is much more extensive, because most genes contribute only a small fraction to the totality of known genetic causes, and many reported variants remain private. The number of genes considered to be relevant for ARVC is smaller than for either DCM or HCM, but because it is much less common than HCM or DCM, many ARVC variants will also remain private. Overall, it is likely that most cardiomyopathy variants identified as incidental findings, even those for HCM, will remain VUSs because of lack of previous data or lack of the requisite genetic data to assess segregation in large and well phenotyped families with multiple affected individuals.

Item c of this guideline suggests that thoughtful and cautiously implemented cascade clinical (phenotype) screening of putatively at-risk family members may be considered even if the clinical phenotype screening was negative in the individual (proband) who completed genetic analysis. This statement recognizes the possibility that the proband may be younger

than the usual age of onset of the cardiovascular phenotype. It also recognizes the utility and necessity of gathering clinical phenotype data in an extended family to help in interpreting the genetic information in cascade testing if phenotypes are encountered in the family members predicted by the gene/variant pair.

We also recognize that at times a novel variant will be identified in an established well curated<sup>131</sup> gene known to have other variants of high risk, and that the variant will be recognized as the type that is expected to be pathogenic, but because it is novel it may be appropriately adjudicated as a VUS. In select situations within the context of expert evaluation described above (guideline 3) and known limitations summing the integrated risk derived from molecular genetics and clinical knowledge of the gene/variant pair (guideline 4), a personal and family history, pedigree analysis, and phenotyping of the individual harboring such a VUS may be considered. The rationale for this comment results directly from the significant risk of morbidity and mortality noted above that may devolve from such cardiomyopathy genes and variants. If phenotype evidence is found to support a disease association in the individual, the remainder of these guidelines would become operative, including consideration of pedigree expansion to help establish or refute the pathogenicity of the variant and to better discern the overall risk incurred to the individual and the family.

A distinct limitation is that we are unaware of published outcomes data to support, validate, or refute the above guidance, which can be considered only as expert opinion. This emphasizes the need for well designed rigorous studies examining outcomes of phenotyping and family studies following secondary or incidental findings of variants relevant for the cardiomyopathies.

## Therapy Based on Genetic Evaluation and Cardiac Phenotype

The clinical characteristics associated with variants in some disease genes, when integrated with pedigree data, may directly influence the overall assessment and clinical recommendations for a patient or family.

One gene with substantial evidence fitting this situation is *LMNA*, which commonly presents with nonsyndromic cardiomyopathy in adult cardiology practice and is well known for progressive conduction system disease (1st-, 2nd-, or 3rd-degree heart block), usually with supraventricular and/or ventricular arrhythmias before, during, or soon thereafter. All of this may occur before or contemporaneously with early DCM. Because in the United States the use of ICDs is not recommended until the left ventricular ejection fraction (LVEF) falls to <35%, patients with *LMNA* cardiomyopathy may have inadequate protection from life-threatening ventricular arrhythmias if the LVEF remains >35%.<sup>78,132</sup> For this reason a specific guideline was created for the 2009 HFSA guideline<sup>1</sup> and has been preserved (guideline 9). Other DCM genes (eg, *DES* or *SCN5A*, *FLNC*, and other genes not yet identified) may also have prominent risk of lethal arrhythmia and may also benefit from earlier ICD use.<sup>133</sup> As noted above, arrhythmia or sudden cardiac death may precede the development of cardiomyopathy and may be the presenting feature.



Other genes with mutations causing syndromic diseases involving cardiomyopathy that have clear therapeutic indications include *GLA*, which encodes alpha-galactosidase A, and *GAA*, encoding alpha-glucosidase. Deficiencies of these enzymes cause Fabry and Pompe disease, respectively. Both have protein replacement treatments that have been shown to be efficacious.<sup>134,135</sup>

The rationale for conducting genetic evaluations for the cardiomyopathies rests on the concept that in most cases treatment interventions, once clinical disease has been recognized, can forestall progressive disease and/or anticipate and prevent complications of disease progression. Each cardiomyopathy type has its own considerations that exceed the scope of this genetics-oriented document. However, even surveillance for common complications (eg, sudden cardiac death from either brady- or tachyarrhythmias in progressive *LMNA* cardiomyopathy, atrial fibrillation in longstanding HCM, onset of heart failure in previously asymptomatic but progressive DCM) can trigger appropriate interventions with drugs and/or devices to prevent or ameliorate disease, as reviewed below.

Questions regarding the role and risks of exercise in cardiomyopathy, and exercise limitation, are frequently raised by patients and families. These have been addressed in other guideline statements.<sup>136</sup>

**Guideline 7 Medical therapy based on cardiac phenotype is recommended, as outlined in consensus guidelines. (Level of Evidence = A)**

Guidelines for the evaluation and management of patients with cardiomyopathy have been published for HCM,<sup>137,138</sup> DCM,<sup>6,139–141</sup> and ARVC.<sup>142</sup> These guidelines provide comprehensive guidance for care of those who are presymptomatic (stage B heart failure) or have had the onset of symptoms (stage C or D heart failure). Guidelines for the clinical care of patients with RCM are not yet available. Controversy continues whether LVNC represents an anatomic phenotype or a distinct cardiomyopathy, and even when observed, no specific treatment is indicated other than for associated cardiovascular phenotypes, as reviewed above. A multisociety (ACC/ AHA/HFSA) guideline update for management of patients with heart failure has recently been published.<sup>140</sup>

**Guideline 8 Device therapies for arrhythmia and conduction-system disease based on cardiac phenotype are recommended, as outlined in consensus guidelines. (Level of Evidence = B)**

In brief, ICDs are indicated for secondary prevention of ventricular tachycardia or ventricular fibrillation regardless of the type of cardiomyopathy or degree of ventricular dysfunction. The indications for ICDs for primary prevention of sudden cardiac death in patients with nonischemic cardiomyopathy with reduced LVEF of any etiology are summarized in guideline statements,<sup>6,139,143–145</sup> even though some ICD trials excluded individuals with familial cardiomyopathy associated with sudden death.<sup>146</sup> Device therapy for arrhythmia should not rely exclusively on the presence of a P or LP gene variant but must be integrated into overall attributable risk. For DCM, ICD therapy is indicated in patients who have an LVEF  $\geq$  35% and who are in New York Heart Association functional class II or

III (class I, level of evidence B). Additional class II and III guideline recommendations<sup>144</sup> are provided in Supplementary Table S3.

**Guideline 9 In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia, an ICD may be considered before the LVEF falls below 35%. (Level of Evidence = C)**

Electrophysiologic disease can be considered broadly as conduction system disease and arrhythmia (see the discussion above regarding *LMNA* cardiomyopathy), but this guideline applies to any genetic cardiomyopathy that presents or progresses to lethal arrhythmia or heart block before advanced LV dysfunction. Examples of other conditions include the myotonic dystrophies.<sup>58</sup> Conventional guidelines apply for symptomatic or presymptomatic conduction system disease regardless of other aspects of the patient's clinical situation.<sup>144</sup> Pacemakers are indicated for symptomatic bradycardia, high-grade AV block regardless of symptoms, and any other symptomatic conduction-system disease. Pacemakers may also be considered to allow for the institution of disease-modifying therapy (eg, beta-blockers) when limited by bradycardia or along with atrioventricular junction ablation to treat refractory atrial fibrillation with rapid ventricular response. In the setting of *LMNA* cardiomyopathy and other genetic conditions with similar risk profiles requiring pacemaker placement, the use of an ICD rather than a pacemaker has been previously recommended<sup>1</sup> and is supported by extensive literature documenting the risks of sudden cardiac death concurrent with conduction-system disease requiring pacemaker placement.<sup>76,78,99,100,147–150</sup> For a patient with reduced ejection fraction that is likely to require chronic ventricular pacing, placement of a cardiac resynchronization therapy device (eg, CRT-defibrillator) should be considered.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Appendix.

### Author Relationships with Industry and Other Entities

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ray Hershberger	Ohio State University College of Medicine and Wexner Medical Center, Columbus, OH	Array Biopharma	None	None	None	None	None
Michael M. Givertz	Brigham and Women's Hospital, Harvard Medical	None	None	None	None	None	None

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Carolyn Ho	School, Boston, MA Brigham and Women's Hospital, Harvard Medical School, Boston, MA	Myokardia	None	None	None	Myokardia	None
Daniel P. Judge	Johns Hopkins University School of Medicine	Array Biopharma, Eidos Therapeutics, Glaxo Smith Kline, Invitae, Myokardia, Pfizer	None	None	Pfizer	None	None
Paul F. Kantor	University of Alberta, Stollery Children's Hospital, Edmonton, AB, Canada	None	None	None	None	None	None
Kim L McBride	Nationwide Children's Hospital and College of Medicine, Ohio State University, Columbus, OH	None	None	None	None	None	None
Ana Morales	Ohio State University College of Medicine and Wexner Medical Center, Columbus, OH	None	None	None	None	None	None
Matt Taylor	University of Colorado Denver	Array Biopharma, Guidepoint Global, Wellpoint	GeneDx	None	None	None	None
Matteo Vatta	Indiana University, Indianapolis, IN; Invitae Corporation, San Francisco, CA	None	None	Invitae Corporation, San Francisco, CA	None	Invitae Corporation, San Francisco, CA	None
Stephanie M. Ware	Indiana University School of Medicine, Indianapolis, IN	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be possibly relevant to this document. These relationships were reviewed and updated in conjunction with meetings and/or conference calls of the writing committee during the document development process. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% of the voting stock or share of the business entity, or ownership of \$5,000 of the fair market value of the business entity, or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

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Table 1.

## Studies Recommended in Baseline Clinical Phenotyping

Study	DCM	HCM	ARVC	LVNC	RCM
CK-MM*	X			X	
ECG	X	X	X	X	X
ETT		X			X <sup>†</sup>
Holter monitoring		X	X		X
CMR <sup>‡</sup>	X	X	X	X	X
Metabolic disease screening <sup>§</sup>	X	X		X	X

ARVC, arrhythmic right ventricular cardiomyopathy; CK-MM, MM band (skeletal muscle) fraction of creatine kinase; CMR, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; ECG, electrocardiography; ETT, exercise treadmill testing; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompact; RCM, restrictive cardiomyopathy.

\* CK-MM should be completed if syndromic or neuromuscular disease is suspected.

<sup>†</sup> In children.

<sup>‡</sup> Cardiac magnetic resonance imaging (CMR) is recommended if echocardiography is insufficient to define the phenotype; this is relevant to assess the cardiac morphology and function for all of the cardiomyopathies, and the presence and degree of fibrosis inferred from gadolinium uptake.

<sup>§</sup> Additional screening tests are indicated for pediatric-onset and select adult-onset presentations; see guideline 3.

Suggested Clinical Phenotype Screening Intervals by Age and Cardiomyopathy for Unaffected First-Degree Family Members of Affected Individuals

Table 2.

Cardiomyopathy	0–5 Years <sup>†</sup>	6–12 Years	13–19 Years	20–50 Years	>50 Years
DCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 1–3 years	Every 2–3 years	Every 5 years
HCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 2–3 years	Every 5 years	Every 5 years
ARVC	Consider once with positive FDR*	Every 5 years	Every 1–3 years	Every 2–3 years	Every 3 years
RCM	Annually with positive FDR*	Every 1–2 years with positive FDR*	Every 2–3 years	Every 3 years	Every 5 years

FDR, first-degree relative; RCM, restrictive cardiomyopathy; other abbreviations as in Table 1.

\* Positive FDR means that the unaffected but at-risk family member has a first-degree relative with the phenotype of interest. These screening intervals apply to at-risk family members when genetic testing has not been performed or is uninformative in the proband, or when it has identified a likely pathogenic or pathogenic variant in the at-risk family member.

<sup>†</sup> Although most DCM is adult onset and most HCM is adolescent or adult onset, both occur in neonates and young children. ARVC is early adult to adult onset. Data are limited for RCM.

Table 3.

## Selected Genes in Association With Cardiomyopathy

Cardiomyopathy	Core Genes*	Estimates of Genetic Testing Diagnostic Yield	ACMG Secondary Findings Gene List	Metabolic Causes of Cardiomyopathy	Examples of Genetic Syndromes
HCM	<i>MYH7, MYBPC3, TNNT2, TNNC1, TNNT3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKAG2, LAMP2, GLA</i>	30%–60%	<i>MYBPC3, MYH7, TNNT2, TNNT3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA</i>	<i>GAA</i> (Pompe); Mitochondrial disease genes	RASopathies (eg, Noonan syndrome, others); Friedreich ataxia
DCM	<i>TTN</i> <sup>†</sup> , <i>LMNA, MYH7, TNNT2, BAG3, RBM20, TNNC1, TNNT3, TPM1, SCN5A, PLN</i> . For testing, all HCM and ARVC genes are recommended to be included.	10%–40%		Mitochondrial disease genes	Muscular dystrophies; Alström syndrome
ARVC	<i>DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TMEM43, TTN</i> <sup>†</sup> ; consider full DCM panel	10%–50%	<i>PKP2, DSP, DSC2, TMEM43, DSG2, RYR2, SCN5A</i>		Naxos syndrome; Carvajal syndrome
RCM	Consider HCM or DCM gene panel	10%–60%			
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown		Mitochondrial disease genes, including <i>TAZ</i> in Barth syndrome	1p36 deletion syndrome; RASopathies

Abbreviations as in Tables 1 and 2.

\* Core gene lists represent genes with the highest diagnostic yield and/or strongest evidence of the gene in association with the listed phenotype; the genes listed are not exhaustive and should be considered as illustrative for the type of cardiomyopathy. Considerable overlap of genes between cardiomyopathy phenotypes is well established. Genes known to cause metabolic disease or genetic syndromes are often included in testing panels, but that varies depending on the clinical laboratory. Gene lists therefore need to be reviewed carefully before ordering testing. Metabolic and genetic syndrome columns provide examples only and are not intended to be comprehensive.

<sup>†</sup> Only *TTN* truncating variants are thought to be relevant for cardiomyopathy.