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CURRENT OPINION

Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

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Advances in molecular genetics present new opportunities and challenges for cardiologists who manage patients and families with cardiomyopathies. The aims of this position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases are to review the general issues related to genetic counselling, family screening and genetic testing in families with a cardiomyopathy, and to provide key messages and suggestions for clinicians involved in their management.

Keywords Cardiomyopathy • Genetic counselling • Genetic testing • Predictive diagnosis • Prenatal diagnosis

Introduction

Recent advances in the understanding of the molecular genetics of cardiomyopathies[1–7] present new challenges for clinicians who manage patients with all types of heart muscle disease. Cardiologists, in particular, have to learn how to integrate this new knowledge into diagnostic and treatment protocols in order to improve the management of families with inherited cardiomyopathies. Specific clinical objectives include: informing patients and families about the genetic aspects of their disease, including the risk of transmitting the disease within the family; organization of appropriate cardiac evaluation and follow-up of relatives; and discussion of genetic testing, which may improve the medical management in various situations. Achievement of these goals requires at least a basic understanding of the principles of genetic counselling, conventionally defined as 'a communication process which deals with the human and psychological problems associated with the occurrence or the risk of occurrence of a genetic disorder in a family',[8–10] in order to help individuals deal with the psychological, social, professional, ethical, and legal implications of a genetic disease. Therefore, provision of genetic counselling and genetic testing requires a wide range of competencies usually achieved through trained health-care providers working within multidisciplinary teams.

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Box 1. Glossary of terms and acronyms

Allele: One of several alternative versions of a particular gene.
Cardiomyopathy: A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality.
Heterozygote: An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation).
Homozygote: An individual who has the same allele at a particular gene locus on homologous chromosomes (carrier of a double copy of the mutation).
Mutation: Any alteration in the inherited nucleic acid sequence of the genotype of an organism. A mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease, whereas a genetic polymorphism refers to a common genetic variation observed in the general population.
Missense mutation: A point mutation that results in the substitution of one amino acid by another.
Penetrance: The proportion of individuals carrying a mutation who also express the associated phenotype (applied to cardiomyopathies, it is related to the percentage of mutation carriers who exhibit the cardiomyopathy on cardiac examination such as echocardiography).
Proband or index case or propositus: The first affected family member who seeks medical attention for a genetic disease.
Variable expressivity: Variation of the phenotype (cardiac and/or extra-cardiac abnormalities) among carriers of a particular mutation.
ARVC: Arrhythmogenic right ventricular cardiomyopathy
DCM: Dilated cardiomyopathy
HCM: Hypertrophic cardiomyopathy
LVNC: Left-ventricular non-compaction
RCM: Restrictive cardiomyopathy
Name of genes and related acronyms are listed in *Table 5*.

The aim of this Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases is to describe the various situations the clinician may face when dealing with cardiomyopathies and to make specific suggestions on how to improve the management of these diseases in daily practice. The statement applies only to common forms of cardiomyopathies[1] and does not consider detail syndromic diseases or paediatric cardiomyopathies or channelopathies.[11]

A development group was selected by the ESC Working Group in April 2008. The group conducted a systematic review of evidence in the English language literature on the role of clinical and genetic testing in cardiomyopathies (Medline Review, years 1995 to January 2010). A preliminary discussion document was circulated to all development group members and a draft position statement was produced by the group's chairman. This was discussed and agreed by all members and was then sent to external expert reviewers for comment. The final revised document is reported here. It is important to note that this paper does not aim to provide formal recommendations as the available data in this field are restricted to observational and epidemiological studies. In the absence of randomized trials, the group's suggestions are based on expert opinion in most cases.

General genetic concepts in cardiomyopathies

What the cardiologist should know?

(i) Mode of inheritance and risk of recurrence

Cardiomyopathies have a variable probability of arising from a monogenic origin (i.e. a gene defect that is sufficient by itself to cause the trait) and different patterns of inheritance may be observed (*Figure 1*).[1–7] For most cardiomyopathies autosomal dominant transmission is the most frequent mode of inheritance (*Table 1*), with the exception of those caused by metabolic disorders, which are usually autosomal recessive or X-linked. Clues to the mode of inheritance from the family pedigree include: the presence of male-to-male transmission, which affirms autosomal dominant inheritance; female-to-male transmission with affected males and healthy mothers, which is highly suggestive of X-linked recessive disease; and female to male and female transmission without male-to-offspring transmission, which suggests mitochondrial disease (matrilinear inheritance). Common pitfalls in pedigree interpretation include X-linked disorders (such as Fabry disease or Duchenne/Becker dystrophies) in which female 'carriers' develop the same disease as affected males (although usually in later life) and autosomal dominant disorders that appear to be sporadic (in the presence of a normal cardiac examination in the parents and siblings). This latter situation can be caused by a mutation transmitted by one parent who did not express the disease (this is increasingly recognized in ARVC for example) or by a *de novo* mutation (multiple reports in HCM), i.e. the genetic defect has occurred in the proband for the first time within the family (in fact at the germinal level in one of the parents).

(ii) Molecular genetics

One of the major challenges in making a genetic diagnosis in patients with cardiomyopathies is the considerable genetic heterogeneity of most disease subtypes (*Table 1*), all of which are associated with many mutations in different genes. For example, HCM is associated with over 400 mutations in more than 15 genes. The nature of individual mutations is also highly variable, including missense, frameshift and nonsense mutations, as well as a few small in-frame deletions or insertions and very rare large deletions. Mutations are usually located along the full length of a gene with no predominant location. Mutations are often 'private' (i.e. are family-specific, with a very low rate of recurrence of the same mutation in other families). The distribution and frequency of genetic mutations in a general population may vary according to the geographic area, often because of 'founder' mutations.[12] Nevertheless, when considering molecular genetic analysis in cohorts of patients with cardiomyopathies, the prevalence of detectable mutations is sufficiently high and consistent to justify routine targeted genetic screening for some subtypes of cardiomyopathy (*Table 1*). When detailed clinical and

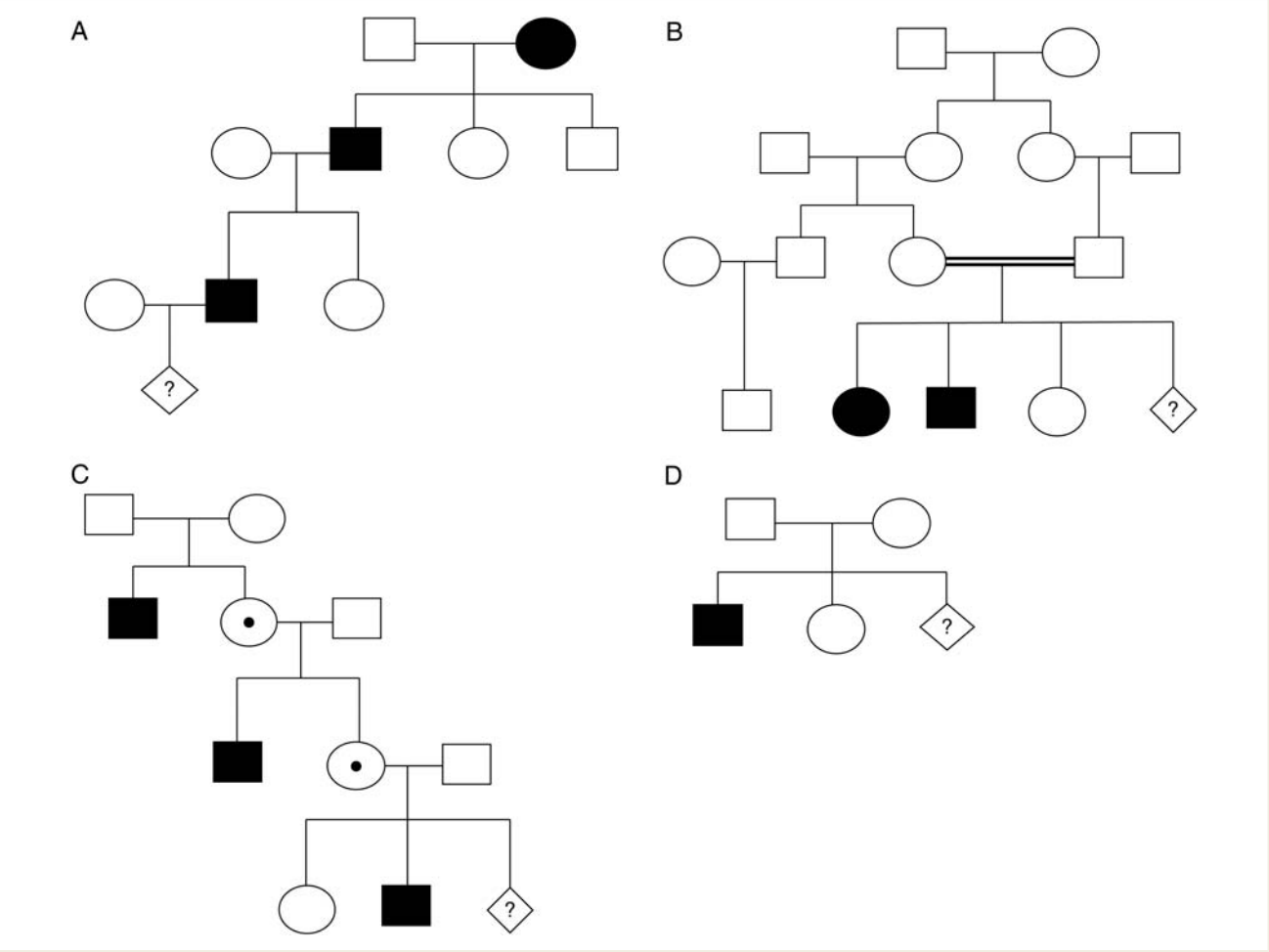

Figure 1 Pedigrees, mode of inheritance, and risk of recurrence within the family. (*A*) The risk is 50% (for all first-degree relatives) in this pedigree with an autosomal dominant inheritance. (*B*) The risk is 25% (within the siblings) when the inheritance is autosomal recessive. (*C*) The risk is 50% for future boys (and 50% for being carrier in future girls) in this pedigree with an X-linked inheritance. (*D*) The contribution of heredity and mode of inheritance is difficult to determine from the pedigree analysis only. If the male patient carries a heterozygous mutation (autosomal dominant inheritance), then the risk of inheriting the mutation to offspring is 50%, whereas the risk for sibling depends on the situation. If the mutation is transmitted from one of the two parents (without cardiac expression because of delayed or incomplete penetrance), the risk for siblings is 50%. If the mutation is *de novo* mutation (no mutation in the parents), then the risk for siblings is nearly zero (not exactly 0% because of the exceptional possibility of germline mosaicism: the mutation is present in a small percentage of germinal cells of one of the parents). Filled symbol: phenotypically affected subject; empty symbol: unaffected subject; circle: woman, square: man. Question mark ('?') is related to the risk of being the carrier of the mutation for a future child.

family assessment identifies phenotypic features suggestive of a specific underlying aetiology, the initial molecular genetic strategy can be more focused (for example DCM and conduction defects related to a lamin A/C gene mutation).

(iii) Penetrance and natural history

The penetrance of a mutation is defined as the percentage of mutation carriers who express a phenotype (in this context, the proportion of patients who have an abnormality on cardiac examination such as electrocardiography or echocardiography). Importantly, this concept refers to the *life-time* risk of developing the disease for an individual who carries a mutation. Thus, penetrance can be complete (100%) if all mutation carriers eventually develop the disease or incomplete if some mutation carriers never develop the disease (*Table 1*). The majority of autosomal recessive cardiomyopathies (e.g. cardiocutaneous forms of ARVC or some metabolic causes of HCM) are associated with complete penetrance before adulthood, whereas most autosomal dominant cardiomyopathies are characterized by incomplete penetrance or more accurately age-related penetrance.[13–18] Thus, during the first phase of disease, which can continue until adolescence or adulthood, mutation carriers exhibit no symptoms and have no detectable cardiac abnormalities. During the second phase, that can continue for several years, there are no symptoms but cardiac expression can be diagnosed. During the third phase, the patients become symptomatic or complications may occur. As a consequence of the age-related penetrance of most cardiomyopathies, clinical evaluation of families takes a

Table 1 General clinical and genetic features of most frequent cardiomyopathies

	HCM	DCM (common phenotype[a])	DCM with another phenotype	RCM	ARVC	Unclassified CMPs: isolated LVNC
Genetic origin (Mendelian)	Nearly certain	Possible (20–35%)	High probability	Possible	Nearly certain	Possible
Mode of inheritance	AD (usually) AR, mitochondrial and X-linked (rare forms)	AD (usually) AR, X-linked (infrequent)	AD (conduction defect) X-linked (high CK) AR (myopathy) mitochondrial	AD (usually)	AD (usually) AR (syndromic)	AD X-linked
Penetrance	Age-related Nearly complete at 50–60 years	Age-related Nearly complete at 60 y	Age-related	Probably age related	Age-related Incomplete (not rare)	Unknown
Genetic heterogeneity[b]	High (>15 genes; >400 mutations)	High (>20 genes; >40 mutations)	Quite low	High (not well evaluated)	High (>8 genes; >70 mutations)	High (>7 genes; >20 mutations)
Mutation screening efficiency (proband)	High (40–70%)	Low (≤20%)	High (>50%?)	Unknown	High (30–60%)	Low (15–25%?)
Phenotype/genotype correlations	Yes but few (high risk vs. low risk or delayed onset)	Unknown	Yes but few (high risk for LMNA gene)	Unknown	Unknown	Unknown

AD: autosomal dominant; AR: autosomal recessive; X: X-linked inheritance; CK: creatine phospho-kinase elevation.
[a]Phenotype with isolated DCM, without associated features such as myopathy of conduction defect.
[b]Number of published mutations, namely from the Human gene mutation data base in Cardiff (http://www.hgmd.cf.ac.uk/ac/index.php).

picture at a given moment or phase of the disease, and children or young adults who are clinically healthy may subsequently develop the disease.

(iv) Variable expressivity

Most cardiomyopathies with autosomal dominant inheritance are characterized by variable expression of the disease with respect to the age at onset, the severity of symptoms, and the risk of complications. Inter-familial variation in expressivity can be partly explained by differences in the affected gene and type of mutation. However, there are few data available on specific genotype–phenotype correlations[17–25] and those that have been reported are mostly based on small, and highly selected cohorts. There can also be large differences between relatives of the same family (intra-familial variability) who carry the same mutation.[26,27] This suggests that additional genetic and possibly environmental mechanisms modulate the phenotype of the disease. Such disease modifiers are not well understood, but some studies report an effect of specific genetic polymorphisms.[28,29] In other cases, intrafamilial differences are explained by the presence of a second causal mutation in the family. This situation is reported in about 5% of patients with HCM (double or compound heterozygotes, or homozygotes) and a gene–dose effect is usually observed (a more severe or early phenotype in patients with several mutations when compared with single heterozygotes).[30,31]

What information should the cardiologist give to a patient or a family with cardiomyopathy?

The assessment of familial cardiomyopathies requires expertise in clinical phenotyping and understanding of the implications of a genetic diagnosis for individuals, families, and society as a whole. Transmission of information to families can be performed by different individuals and in various clinical settings, provided that the necessary skills and safeguards are in place.

KEY MESSAGE 1: Information to give during genetic counselling in families with cardiomyopathies.

- *The genetic origin of the cardiomyopathy*. Indicate if this is certain or if there is a high probability or low probability of a monogenic origin. NB: In some cardiomyopathies, the probability of a monogenic origin can be nearly certain, whatever may be the familial context.
- *The mode of inheritance, and therefore the risk of transmission within the family* (including offspring). This is usually possible after careful review of the pedigree and phenotypic data. NB: An apparently sporadic case might be of monogenic origin (autosomal inheritance), because of incomplete penetrance in the transmitting parent, or because of a *de novo* mutation.
- *The clinical manifestations of the disease and its natural history (including possible delayed cardiac expression)*. NB: A normal first cardiac examination in a relative does not exclude the possibility that the relative carries the mutation and might express the disease at a later date.
- *Benefits of a cardiac screening within the family* (give specific written information to the patient for transmitting the information to the relatives, when possible). NB: Inform also about possible adverse implications (insurance, employment) of the disease recognition in asymptomatic relatives.
- *Risk of occurrence or worsening of the disease during pregnancy*. This risk, along with the risk of transmitting the disease, should be explained in advance and a specific medical follow-up planned during pregnancy and after birth.
- *Availability and scope of molecular analyses/genetic testing*.
- *Appropriate patient organizations/associations*.
- *Medical sources of information* (such as websites, including orphanet, give written information support when possible).
- *When appropriate, give the address of a referral centre* for the management of cardiomyopathies. NB: Dedicated reference centres for cardiac hereditary diseases are currently designated at National or European level.

Clinical screening in relatives

Rationale of clinical family screening

The major goal of clinical (cardiac) family screening in cardiomyopathies is to identify relatives who have the same disease as the proband. The justification is the high probability of the disease in first-degree relatives (50% in autosomal dominant-inherited cardiomyopathies) and the potential benefit of an early clinical diagnosis. A secondary goal of family screening is to obtain information required to refine the initial diagnosis of the proband, by observing the disease at different phases. This aspect is especially relevant in family with mixed phenotypes or a variable expressivity.

In contrast, with many genetic disorders such as neurodegenerative diseases, early identification of clinically affected relatives, even without any symptoms, can result in measures designed to delay the development of the disease and/or prevent complications. These therapeutic interventions vary according to the type of cardiomyopathy and the stage of the disease but include lifestyle modifications (avoidance of intensive and strenuous physical training or competitive sports, avoidance of alcohol), drug therapy (e.g. angiotensin-converting enzyme-inhibitors in individuals with DCM), and prophylactic implantation of an internal cardioverter defibrillator.[32–35] In addition, in the case of a pregnancy in a relative with asymptomatic disease, it is important to plan a specific cardiac follow-up as there is a possibility of deterioration.[36–38] It is important to note, however, that prospective randomized clinical trials on the cost–benefit ratio and clinical efficacy of family screening are lacking.

There are two common scenarios in family screening (*Figure 2*). The first occurs when molecular genetic data are not available because genetic testing could not be performed (e.g. no local molecular resources or premature death of the proband), genetic test results are pending in the proband (which usually takes several months), extensive molecular screening has failed to identify a mutation in the proband or when a genetic variant of uncertain significance is identified. The following discussion focuses on these situations. The second scenario occurs after the identification of a causative mutation in the proband of the family. This scenario is discussed elsewhere (see 'predictive diagnosis' in the section 'Genetic testing').

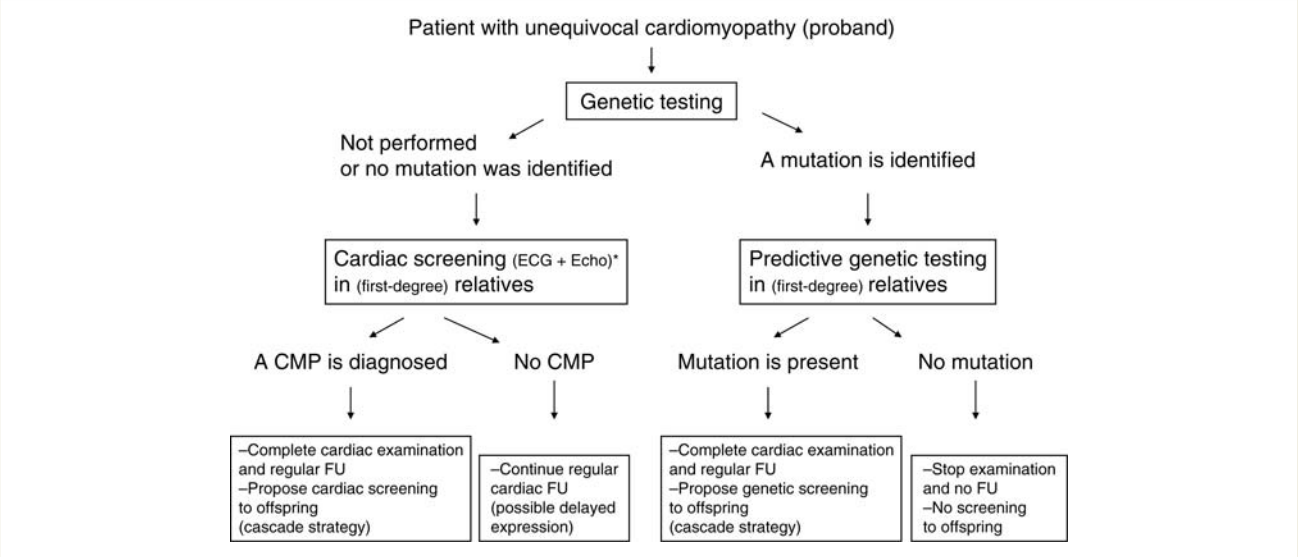

Figure 2 Organization of family screening. Asterisk (*) indicates additional cardiac examination in selected cardiomyopathies (i.e. Holter-ECG, SAECG, MRI, etc.). FU, follow-up.

General screening technique in families with no genetic data

Simple non-invasive cardiac examination should be considered in relatives at high risk of inheriting the cardiomyopathy, namely the first-degree relatives of an affected patient (or of a suspected patient with premature cardiac death) within the family.[5,34,35,39–43] In many European countries, the clinician in-charge of the proband is not authorized to contact the relatives directly. It is, therefore, important to advise the proband on the process of notification of family members. Strategies include the provision of a written support such as a family information letter (about the presence of an inherited cardiomyopathy in the family, the benefit of a clinical familial evaluation, and the appropriate modalities for cardiac screening) that is given by the clinician to the proband, for dissemination to his/her relatives. Adoption of this strategy recently resulted in a higher uptake of familial screening.[44]

The scope of the cardiac examination varies according to the type of the cardiomyopathy, and inevitably will evolve with accumulating knowledge. Nevertheless, standard 12-lead ECG and echocardiography are sufficient for most cardiomyopathies if performed by cardiologists with expertise in the diagnosis and management of inherited cardiac diseases. A notable exception is ARVC where additional testing including signal-averaged ECG, exercise testing, and cardiac magnetic resonance imaging may be necessary.

Stepwise (cascade) screening

If a family member has abnormal cardiac screening, evaluation is then recommended in all first-degree relatives of this newly diagnosed patient. This stepwise (also called 'cascade') screening should be continued until all consenting first-degree relatives of clinically affected individuals (or highly suspected affected individuals in the case of premature cardiac death) have been evaluated. If the index case is a sudden death case and the diagnosis of cardiomyopathy has been reached at autopsy, the clinician should try to obtain all the available data to assess whether the final diagnosis is in keeping with the morphological findings. Family members with a clear positive diagnosis, even if they are asymptomatic, should have a similar clinical work-up (including stratification for sudden death risk) as the index patient. This usually requires additional tests including ambulatory ECG monitoring, exercise testing, and in some cases cardiac magnetic resonance imaging, cardiac catheterization, skeletal muscle, or endomyocardial biopsy.

Serial screening

Because of the wide range of age-at-onset of most inherited cardiomyopathies (owing to age-related penetrance), normal findings on initial clinical screening do not exclude the possibility of future cardiac expression, except in some rare cardiomyopathies such as those associated with inborn errors of metabolism, which are limited to the paediatric age group.

The age at which cardiac screening begins should be guided by the age at which cardiac expression and cardiac complications are relevant to medical management. In most cases the phenotype starts to manifest during or after puberty. Screening should be conducted at regular intervals during adolescence and continued into adulthood (with reduced frequency) until penetrance is estimated to be complete (*Table 2*). Penetrance is usually complete by the age of 50–60 years in most forms of DCM and HCM, but may remain incomplete in ARVC and is still unknown in RCM and LVNC.[13–18]

KEY MESSAGE 2: Protocol for clinical family screening when genetics is not available.

(i) Clinical screening is indicated in first-degree relatives of a proband with a cardiomyopathy, unless an acquired cause of the cardiomyopathy is demonstrated.
(ii) Cardiac screening in first-degree relatives should in most diseases start at the age of 10–12 years.

Table 2 Clinical family screening indicated in first-degree relatives of a patient with cardiomyopathy (situation in which genetic results are not available within the family)

	HCM	DCM	ARVC	RCM	LVNC
Cardiac evaluation	ECG, echocardiography	ECG, echocardiography (*and Holter-ECG if CD in the proband*)	ECG, echography, Holter-ECG, signal-averaged ECG	ECG, echocardiography (*and Holter-ECG if CD in the proband*)	ECG, echocardiography
Start of the cardiac evaluation	10–12 years	Childhood (*except laminopathies: 10–12 years*)	10–12 years	10–12 years	New-born
Repeated cardiac evaluation	[Every 3–5 years if performed before 10 years]	Every 1–3 years before 10 years[a]	[Every 3–5 years if performed before 10 years][b]	[Every 3–5 years if performed before 10 years]	Every 1–3 years before 20 years[a,c]
	Every 1–2 years between 10 and 20 years	Every 1–2 years between 10 and 20 years[a]	Every 1–2 years between 10 and 20 years	Every 1–2 years between 10 and 20 years	Every 2–5 years after 20 years[a,c]
	Every 2–5 years after 20 years	Every 2–5 years after 20 years[a]	Every 2–5 years after 20 years	Every 2–5 years after 20 years	
Screening can be stopped at:[d]	50–60 years	50–60 years	50–60 years	50–60 years	50–60 years[c]

CD, conduction defect. NB: The start and frequency of screening can be modulated by several factors including the precise type of cardiomyopathy, the age at onset within the family, the age and severity of complications within the family, practice of strenuous physical training or competitive sports, pregnancy, presence of symptoms or other clinical suspicion.

[a]Repeated cardiac evaluation is mandatory in the context of a familial form (at least two affected patients) of DCM or LVNC but is questionable and cannot be recommended in the context of a sporadic form in the proband. In the latter situation, a unique cardiac evaluation of relatives during puberty or adulthood might be sufficient.

[b]Only ECG and echocardiography.

[c]To be continued until 50–60 years because possible overlap with other cardiomyopathies within the family.

[d]But cardiac examination to be performed if symptoms.

(iii) Repeated cardiac evaluation should be performed every 1–2 years until the age of 20.
(iv) Repeated cardiac evaluation should then be performed (after 20 years of age) every 2–5 years until the age of 50–60.
(v) Refined recommendations according to the type of cardiomyopathy are indicated in *Table 2*.
(vi) The timing and frequency of screening can be modulated by several factors including the age-at-onset within the family, the age and severity of complications within the family, lifestyle including physical training/competitive sports, presence of symptoms or minor non-diagnostic clinical features, and the precise type of cardiomyopathy.

KEY MESSAGE 3: Protocol for clinical screening in asymptomatic relatives who carry a disease-causing mutation.

(i) Asymptomatic relatives who carry the disease-causing mutation might benefit from an initial detailed cardiac examination, including not only ECG and echocardiography but also exercise test, Holter-ECG, and additional examination according to the disorder.
(ii) Repeated cardiac evaluation (including at least ECG and echocardiography) should be performed every year between the age of 10 and 20, and then every 1–3 years.

Genetic testing in patients and relatives

Until recently, molecular genetic testing was predominantly a research tool. However, genetic testing has now entered the clinical arena because of its potential to provide more individualized and informative counselling in families with cardiomyopathies.[2–5,7,45,46] In any discussion on genetic testing, three main points require consideration: the expected medical impact of the genetic test; the correct interpretation of the genetic results; and the appropriate genetic counselling that should be provided.

Reasons for performing genetic testing

There are several reasons to consider genetic testing in patients with cardiomyopathy and their relatives including diagnosis, prognostic evaluation, and therapeutic decision-making. The indications for genetic testing may vary according to the type of cardiomyopathy as the discussion has to take into account (i) the efficiency of a mutation gene screening, based on the current knowledge of the responsible genes (*Table 1*), (ii) the complexity and cost of the molecular analyses, and (iii) the specific impact of genetic testing on the medical management of the individual and their family. At present, the indications for genetic testing in cardiomyopathies should be conservative because of the considerable genetic heterogeneity which results in complex and time-consuming molecular analyses, and because studies documenting the impact of genetic testing are still lacking. However, genetic testing can be considered as reasonable in the following situations.

Positive diagnosis in a patient with a definite or suspected cardiomyopathy

In most patients with a definite clinical diagnosis, there is no confirmatory role for routine genetic testing. The main role of genetic testing in this context is to provide predictive diagnosis in first-degree relatives (see corresponding section).

In some situations, the phenotype of a patient with an obvious cardiomyopathy presents atypical features (phenotypic red flags) suggestive of a rare or particular cardiomyopathy that can be confirmed or ruled out through genetic testing. Correct diagnosis can result in the recommendation of a specific therapy (for example, enzyme replacement therapy in Anderson-Fabry disease or liver transplantation in transthyretin-related amyloidosis)[47] or early prophylactic defibrillator implantation owing to a high risk of sudden death (for example, in DCM related to a lamin A/C gene mutation),[48,49] early heart transplantation (for example in Danon disease),[50] modification of genetic counselling (for example, X-linked inheritance in LVNC related to TAZ gene mutation),[51] a specific follow-up (search for conduction defect and indication for pacemaker in RCM with a desmin gene mutation or in HCM with a PRKAG2 gene mutation).[52]

Genetic testing can also be useful in selected cases to make the correct diagnosis in the presence of a borderline or doubtful cardiomyopathy and distinguish a cardiomyopathy from a phenocopy or physiological heart adaptation, especially to differentiate a mild form of HCM from hypertrophy secondary to athlete's heart.[53] In the latter situation, it should be borne in mind that only a positive result (identification of a mutation) is meaningful, whereas a negative result (no mutation is identified) usually does not lead to a useful conclusion. In addition, the efficiency of the mutation screening is quite low in this situation (as the probability of a cardiomyopathy is usually low), and the cost–efficiency ratio is high. In this setting, genetic testing should therefore be restricted to expert teams.

KEY MESSAGE 4: Genetic testing and positive diagnosis (as a complete analysis of potential genes of interest in the proband of a family)

- Genetic testing is appropriate for the diagnosis of a rare or particular cardiomyopathy, especially in the presence of atypical phenotypic features, in the setting of expert teams after detailed clinical and family assessment.
- Genetic testing is not indicated for the diagnosis of a borderline or doubtful cardiomyopathy, except selected cases in the setting of expert teams after detailed clinical and family assessment.

Predictive diagnosis in asymptomatic relatives

When the disease-causing mutation is identified in the index patient of a given family (sometimes through postmortem analyses as recently underlined by the Association for European Cardiovascular Pathology),[54] then genetic testing can be offered to the apparently healthy relatives within the family in order to determine if they carry the same mutation and therefore are at risk of developing the disease in the future.[2,4,5,12,55–57] If the relatives do not carry the mutation, then they can be reassured and cardiological follow-up including serial echocardiography is no longer required (this strategy is probably highly cost-effective but has not yet been evaluated). Moreover, there is no risk of transmitting the disease to offspring. If the relative carries the mutation, then regular medical follow-up is required in order to detect cardiac expression early, and thereby improve their management. Restriction of physical activity (especially competitive sport) is recommended once cardiac expression has occurred.[34,35] This may also be considered in apparently healthy mutation carriers from

Table 3 Main outcomes associated with predictive diagnosis in cardiomyopathies

	If the mutation is present	If the mutation is absent
Positive outcome	Removal of uncertainty	Removal of uncertainty, and relief
	Regular medical follow-up is organized which will improve the prognosis	No future development of the disease, and medical follow-up is no more required No risk of transmission to offspring
Negative outcome	Anxiety because of future cardiac expression (risk of premature death)	Possible 'survivor' guilt
	No treatment to begin at this stage in most disorders	
	Risk of transmission to offspring	
Uncertainties remaining	Recommend environmental modifications? (exercise or alcohol restriction)	Not always easy to affirm that the mutation identified in the proband is the cause of the disorder in the family, especially if missense mutation
	Medical costs?	
	Insurability or professional concerns?	

Table 4 Main principles of genetic counselling when genetic testing is discussed (especially predictive testing). Adapted from Cassiman.[69]

Autonomy: decision to make genetic testing is solely the choice of the counsellee. No pressure can be put on the counsellee and every decision should be equally accepted
Non-directiveness: information should be appropriate and honest
Written informed consent: must be provided before blood sampling
Right to know and not to know the genetic result: both should be respected
Confidentiality: should be respected so that the counsellee cannot be discriminated against in any way

families with a history of multiple sudden cardiac deaths or in families with a mutation related to a high-risk of sudden death, as rare cases of sudden death before the occurrence of typical HCM or ARVC have been reported.[22,58,59]

Several limitations of predictive testing should be emphasized: (i) at present no therapy can be proposed in mutation carriers before the occurrence of the cardiac expression to prevent its development; (ii) the expression of the disease is highly variable and cannot be predicted (age at onset, severity); (iii) the identification of the mutation may result in adverse psychological consequences as the previous psychological burden related to uncertainty might be replaced by the near-certainty of developing the disease and the risk of transmitting the disease to the offspring (*Table 3*).[5,12,55–57,60,61] A preliminary study suggests, however, that these psychological sequelae can be minimized when individuals are counselled appropriately.[62]

Predictive testing in children is still a matter of debate[5,56,57,63–66] as ethical, legal, and psychosocial issues are more complex.[67,68] These issues are shared by many delayed-onset inherited diseases and relate mainly to the fact that children cannot provide autonomous informed consent, do not usually have the capability to understand the potential benefits and drawbacks of the screening process, and are at risk of serious psychological stress. The medical case for screening is also weakened by a very low death rate in asymptomatic children with most disease-causing mutations. In general, the age at which predictive testing is conducted is determined by the likely age of onset of the cardiomyopathy and the risk of cardiac complications. These general considerations are then modified according to the pattern of disease in the family, the practice of strenuous physical training or competitive sports, and the presence of symptoms or other clinical suspicion.

Irrespective of the age at which predictive testing is performed, its complex medical and psychological implications (*Table 3*) mean that predictive diagnoses should be performed very carefully, guided by the 'best interest of the child', according to a standardized procedure, a multidisciplinary approach, and good practice in medical genetics (*Table 4*).[69,70]

KEY MESSAGE 5: Genetic testing and predictive diagnosis.

(i) Genetic testing is appropriate for predictive diagnosis in asymptomatic relatives of a patient with a cardiomyopathy when the disease-causing mutation has been previously characterized in the family.

(ii) Genetic testing is therefore indicated in the proband of a family (the first or most clearly affected patient with a cardiomyopathy) as a first condition for the proposal of predictive diagnosis within the family. NB1: Post-mortem (necropsy) molecular analyses can be considered in the proband if he/she is the only patient with the cardiomyopathy within the family. NB2: This is appropriate, whatever may be the 'familial' or 'sporadic' context, in HCM and ARVC, but questionable in sporadic DCM and sporadic RCM (except in the presence of atypical associated phenotype or red-flags).

(iii) Predictive diagnosis in children can be considered at the age at which cardiac examination is useful (10–12 years of age for most cardiomyopathies).

Prognostic testing in a patient with an obvious cardiomyopathy

In the context of a disease with clear phenotype–genotype correlations (correlation between the evolution of a disease and the

Table 5 Main genes of interest in cardiomyopathies for mutation screening in routine practice

Cardiomyopathies	Genes
HCM	*MYBPC3* (myosin-binding protein C), *MYH7* (bêta myosin heavy chain), *TNNT2* (troponin T), *TNNI3* (troponin I), *MYL2* (regulatory myosin light chain) ± *TPM1* (alpha tropomyosin), *MYL3* (essential myosin light chain), *ACTC* (actin)
With particular phenotype	*PRKAG2* (AMP-activated protein kinase), *LAMP2* (lysosome-associated membrane protein2), *GLA* (alpha galactosidase), mitochondrial DNA
DCM	*MYH7*(bêta myosin heavy chain), *TNNT2* (troponin T) ± other sarcomeric genes
With particular phenotype	*LMNA* (lamin A/C), *TAZ* (tafazzin), *DES* (desmin), *DMD* (dystrophin), mitochondrial DNA
RCM	*TNNI3* (troponin I) ± other sarcomeric genes
With particular phenotype	*DES* (desmin), *TTR* (transthyretin), *HFE* (haemochromatosis)
ARVC	*PKP2* (plakophilin2), *DSP* (desmoplakin), *DSG2* (desmoglein2), *DSC2* (desmocollin2)
LVNC	*MYH7* (bêta myosin heavy chain) ± other sarcomeric genes

underlying gene or mutation), genetic testing might be useful in stratifying the prognosis of a patient with the disease, through the better identification of patients at high or low risk of cardiac death. This would have a medical impact with a more accurate choice in the therapeutic strategy. However, only few correlations have been described until now in the cardiomyopathies and, even in these examples, data are based on small and usually retrospective cohorts with selected mutations. For example, in HCM patients, a high risk of sudden death mutation has been associated with mutation in the *TNNT2* gene.[16,17,20,21] In DCM patients, a high risk of cardiac death is associated with mutations in lamin A/C gene.[19,48] Another promising situation is the case of patients with multiple mutations (especially in HCM and ARVC) who appear associated with a more severe phenotype when compared with single heterozygotes.[30,31,71]

KEY MESSAGE 6: Genetic testing and prognostic testing.

- Genetic testing cannot be systematically recommended for prognostic stratification of a patient with a cardiomyopathy, but should be considered in selected patients or for selected types of cardiomyopathies, in the setting of expert teams after detailed clinical and family assessment.

NB: Indirect prognostic information might be provided through diagnostic testing (see related section).

Prenatal diagnosis and other options to prevent the transmission of the disease

Some couples may request prenatal diagnosis through chorionic villus sampling or amniocentesis at the beginning of pregnancy to determine the genetic status of the foetus and to consider pregnancy termination if the mutation is present.[72,73] Ethical and legal issues are of outstanding relevance in this setting. Legal rules vary considerably across Europe as prenatal diagnosis is not authorized in some countries or can be considered only when there is a possibility of significant disability associated with the transmitted disease in others. No universally relevant consensus can therefore be determined, especially when considering the complexity of the various subtypes of cardiomyopathies, the personal view of the clinician and the personal view of the parents. However, prenatal diagnosis might be theoretically possible when the mutation is characterized in the parent(s) and it can be medically supported when the risk of developing the disease is certain, the risk of premature death or severe disability is very high, and there is no curative treatment. Very few cardiomyopathies meet these conditions,[51,74,75] as most diseases are characterized by age-related penetrance, the risk of premature death or severe disability is usually low, and in some cases treatment and lifestyle modification may delay the evolution of the disease. The decision to perform prenatal diagnosis is particularly difficult and should be made on a case-by-case basis, with involvement of a multidisciplinary team.[75] Other options should also be discussed, such as adoption, artificial insemination using donated gametes, and pre-implantation genetic diagnosis. The latter option uses *in vitro* fertilization to conceive embryos that can be tested for the familial mutation before being implanted in the mother.[76] This is a long procedure restricted to severe and untreatable diseases and is still not authorized in some European countries.

KEY MESSAGE 7: Genetic testing and prenatal diagnosis.

- Legal rules for prenatal diagnosis vary from one country to other and indications can therefore not be standardized.
- Based on medical considerations, genetic testing is not appropriate for prenatal diagnosis in most cardiomyopathies, except for selected disorders or high-risk situations in the setting of expert teams after detailed clinical and family assessment.

Interpretation of the results of genetic testing

Genetic testing has been defined as the use of specific tests for the analysis of a gene, its product or function, in individuals who are at increased risk of having a genetic disorder because of their family history or own symptoms.[77,78] Genetic testing not only refers to investigations of DNA or chromosomes but also to the analysis of proteins, certain metabolites, or even of the ECG or the echocardiogram, assuming that these investigations may reveal a genetic predisposition. This section focuses on DNA/RNA analysis only.

A clear understanding of the purpose of the test and a detailed clinical family assessment (including the precise phenotype and the pedigree) are important pre-requisites for appropriate molecular analyses and their correct interpretation.

The molecular diagnostic strategy typically begins with the analysis of blood samples taken from a patient with unequivocal disease (the proband). At present, the most frequent genes of interest are screened for a mutation using various direct (such as sequencing) or indirect (such as dHPLC, HRM) methods (*Table 5*). The analysis usually includes all the coding sequences of the genes in question and the exon–intron boundaries. This process is time-consuming and results are usually given within several months.[2–5,46]

The identification of a genetic variant should lead to a specific procedure to distinguish a causal mutation from a genetic polymorphism, but is not always an easy task in cardiomyopathies, especially when the abnormality is a missense mutation (a single nucleotide substitution). A genetic variant is usually considered as a causal mutation on the basis of the absence of the variant in a control population matched for ethnic origin (and in single nucleotide polymorphisms databases) and a functionally important effect occurs in the encoded protein (nonsense mutation, frameshift mutation). In the presence of a missense mutation, the mutated residue should be highly conserved among species/isoforms and a damaging effect of the mutation should be predicted by appropriate softwares. The co-segregation of the variant with the phenotype within the family provides important additional information but is usually lacking in the context of routine clinical practice (as only the proband is usually available for molecular analyses). Some genetic variants may remain to be of uncertain significance, even after careful analyses, and should not be considered as causal mutation and not taken into account for genetic counselling.

To ensure safe and acceptable standards of performance, it has been recommended that clinical genetic testing should be provided by a laboratory under quality control assessment.[79–82] Several detailed standards and guidelines for quality assurance in molecular genetic testing have been published that cover technical issues as well as ethical and legal issues. Clinical laboratories are expected to have plans for quality control, quality assurance, and quality improvement.

The efficiency (ability to identify a mutation in a patient with an obvious form of the disease) of conventional mutation screening varies according to the type of cardiomyopathy (*Table 1*), the number, size, and complexity of the genes being tested, the sensitivity of the screening method, the expertise and facilities of the laboratory, and the quality of the clinical data provided. The efficiency of mutation screening in a proband with a clear cardiomyopathy can be high (40–70% in HCM, 30–60% in ARVC) or low (<20% in conventional DCM). It is always less than 100% as the reported disease genes account for less than 100% of families.[4,31,83–85] Importantly, when no mutation is identified in the proband, a genetic origin still cannot be ruled out.

In contrast, when the causal mutation is identified in the proband, then it is very efficient (100%), easy (usually one polymerase chain reaction reaction and sequence), and quick (within few days or weeks) to determine the genetic status of relatives (predictive diagnosis).

KEY MESSAGE 8: Molecular analyses and appropriate interpretation.

(i) Genetic testing should be performed in certified diagnostic laboratories, whose connections with expert multidisciplinary centres in cardiomyopathies result in appropriate molecular analyses and correct interpretation.
(ii) Detailed phenotypic and family assessment should be available to permit appropriate molecular analyses and correct interpretation.

Organization of genetic counselling

The process of genetic counselling comprises several steps that have been previously described in general guidelines and policy statements.[9,67,69,70,86] Briefly, genetic counselling begins with the *diagnosis step* or collection of necessary information to characterize the disease in the family, through a detailed family history, construction of a pedigree, collection of medical and autopsy reports, information about prior genetic testing within the family when available, and cardiologic assessment of the counsellee when appropriate. Construction and presentation of the pedigree should be performed in accordance with standardized methods.[87] Pedigrees should ideally span at least three generations and should document individuals that have the same diagnosis as the proband, or have other phenotypes (including unexplained sudden cardiac death and non-cardiac features) that could represent expression of the same underlying genetic abnormality. The second phase is the *information step or pre-test counselling*. When genetic testing is being considered, individuals should be informed about the purpose of the test, about the disease (including the symptoms, natural history, and treatment of the cardiomyopathy), the likely mode of inheritance and genetic risk figure for the counsellee's situation, the reliability and limitations of genetic test, the possible psychological impact of the test-result on the counsellee and their family. Privacy and confidentiality of the result, especially in relation to insurance companies and employers, should be anticipated and discussed. Psychological support should be proposed when necessary to adjust individuals to their situation, to help them cope with stress and to assist their individual decision-making. In the third phase of *decision-making and consent*, an individual that has made the decision to proceed with genetic testing is asked to provide written informed consent before blood sampling and testing. In the final stage of *disclosure of test–result and post-test counselling*, the individual should be informed about the interpretation of the result, the significance for their medical management, and the implications for their offspring and other relatives. Psychological support may also be necessary at this stage (preferably in a separate session). The proband/counsellee is encouraged to inform the relatives (with written support when possible) about genetic risk, the possibility of cardiac evaluation or genetic testing (cascade screening).

Genetic counselling should be regarded as an integral part of the genetic testing process. It should be provided or supervised by health-care professionals appropriately trained in genetic counselling, which in most health-care systems will be a medical geneticist, genetic counsellor, or genetic nurse.[10,69,88,89] However, the complexity of most cardiomyopathies means that health-care

professionals who provide counselling must also have an understanding of the spectrum and clinical implications of the different clinical phenotypes. In a recent survey on HCM in the Netherlands, cardiologists expressed their wish to inform patients themselves and requested DNA testing to be their sole responsibility for *symptomatic patients*, whereas most geneticists considered a request for DNA testing in *asymptomatic relatives* as their exclusive responsibility.[90] In fact, the discussion about genetic testing requires careful consideration as various medical, psychological, ethical, social, and legal aspects must be taken into account. For this reason, we believe that genetic counselling is best provided by multidisciplinary teams that have all the competencies required to advise and manage patients with familial cardiomyopathies. Some multidisciplinary teams have been already designated as referral or reference centres for inherited cardiac diseases in some European countries, usually as part of a Health program set up at a National or European level.[69,91]

KEY MESSAGE 9: Organization of genetic counselling.

(i) Genetic counselling is recommended for all patients with a cardiomyopathy, unless an acquired cause of the cardiomyopathy is demonstrated. Genetic counselling is also appropriate in the family of those patients.
(ii) Genetic counselling should be performed by professionals trained for this specific task.
(iii) Genetic counselling should take place in the context of multidisciplinary management, ideally in a centre specialized in inherited cardiomyopathies, especially when genetic testing is discussed in complex situations such as predictive or prenatal testing.

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