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Understanding the genetics of adult-onset dilated cardiomyopathy: what a clinician needs to know

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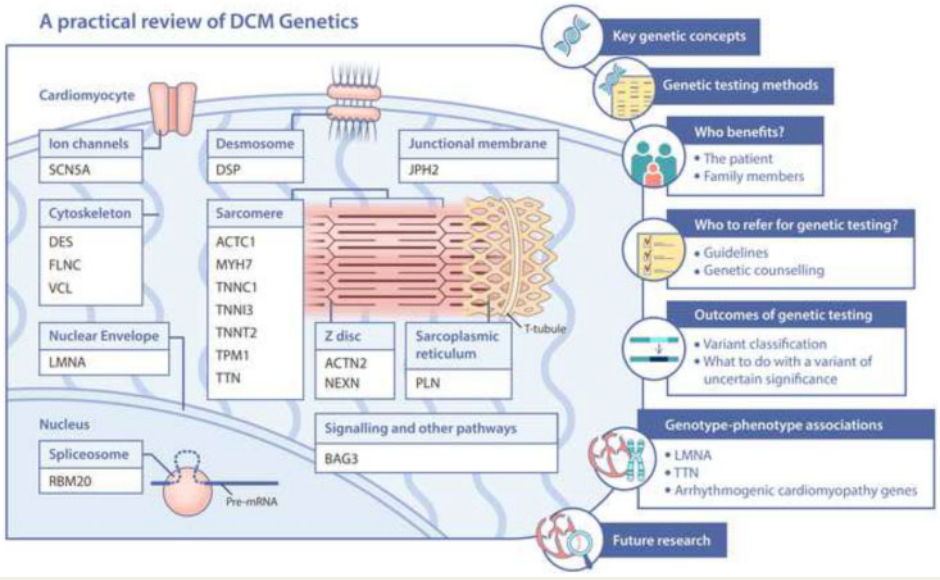
There is increasing understanding of the genetic basis to dilated cardiomyopathy and in this review, we offer a practical primer for the practising clinician. We aim to help all clinicians involved in the care of patients with dilated cardiomyopathy to understand the clinical relevance of the genetic basis of dilated cardiomyopathy, introduce key genetic concepts, explain which patients and families may benefit from genetic testing, which genetic tests are commonly performed, how to interpret genetic results, and the clinical applications of results. We conclude by reviewing areas for future research in this dynamic field.

Graphical Abstract



DCM genetics- what the practising clinician needs to know.

Keywords Genetics • Dilated cardiomyopathy • Heart

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Introduction

Dilated cardiomyopathy (DCM) affects up to 1 in 250 people and is the leading global indication for heart transplantation. It is characterized by left ventricular (LV) dilatation and systolic impairment. There is increasing understanding of the genetic basis to this disease and in this review, we offer a practical primer for the practising clinician. We aim to help all clinicians involved in the care of patients with DCM understand the clinical relevance of the genetic basis of DCM, which patients and families may benefit from genetic testing, which genetic tests are commonly performed, how to interpret genetic results, and the clinical applications of results (*Graphical abstract*).

Dilated cardiomyopathy definition

According to the revised 2016 European Society of Cardiology position statement, DCM is defined as LV or biventricular systolic dysfunction and dilatation that is not explained by abnormal loading conditions or coronary artery disease.[1] Systolic dysfunction is defined by abnormal LV ejection fraction (LVEF) measured using any modality, and LV dilatation is defined as LV end-diastolic volumes or diameters greater than two standard deviations from age, gender, and body surface area-adjusted nomograms.[1]

Dilated cardiomyopathy prevalence

Prevalence data for DCM are variable. Historic estimates from the Olmsted County cohort prior to the widespread availability of echocardiography suggested the disease affected 1 in 2700 individuals.[2] In the absence of large contemporary population studies, estimated DCM prevalence has more recently been revised based on triangulation of data from hypertrophic cardiomyopathy, heart failure, and asymptomatic LV dysfunction, yielding estimates of up to 1 in 250 individuals,[3] though this estimate likely represents an upper bound.

Genetic basis of dilated cardiomyopathy: key concepts

Dilated cardiomyopathy is recognized as familial in 20–30% of cases.[4] Approximately 40% of these families have an identifiable monogenic cause,[3] or at least a rare variant of large effect size as the primary determinant of risk. Higher estimates of sensitivity for genetic testing have been reported (from 46% to 73% in one study[5]) but these estimates are likely inflated by enrichment for familial cases, and likely confounded by false positives due to insufficient control for background population variation in the genes studied. In reality, the genetic contribution to DCM risk is not solely attributable to individual DNA variants of large effects, as in a Mendelian model; rather many variants with individually small effects on disease risk likely contribute to the observed heritability. There is also increasing recognition of wider genetic or environmental modifiers,[6] as discussed later in this article. Similarly, a seemingly identifiable aetiology for DCM (such as alcohol exposure) does not preclude a relevant genetic predisposition to disease that may influence management.[7]

In this review, we focus on DCM presenting to the adult cardiologist. The clinical and genetic evaluation of DCM presenting in early childhood, which is much rarer, is overlapping but distinct—representing a mixture of early presentations of those same entities that present in adults, alongside molecularly distinct entities. We direct the reader to other resources for comprehensive reviews of paediatric cardiomyopathies.[8–10]

We next review some key genetic concepts as relevant to DCM.

The continuum from monogenic to polygenic disease

Since variants with large effects on disease risk are under strong negative selection, they are depleted from the population. Genetic contributions to disease can therefore come from individually rare variants of potentially large effect size, from common variants each of small effect size, and from variants lying on the spectrum spanning those extremes. Variants may act alone or in combination to predispose to disease. Diseases with a genetic component may have various architectures, including monogenic, polygenic, oligogenic, and multifactorial (*Figure 1*). Dilated cardiomyopathy is genetically heterogeneous, with an important proportion behaving as monogenic diseases, but many cases are best understood by a more complex genetic model.

Modes of inheritance

Most monogenic forms of DCM follow an autosomal dominant inheritance pattern, although X-linked, autosomal recessive, and mitochondrial inheritance are observed, particularly in paediatric populations.[11]

Genetic architecture of monogenic dilated cardiomyopathy

The genetic architecture of presumed 'monogenic' DCM has emerged to be particularly complex, with more than 60 genes[12] purported to be associated with DCM and/or included in diagnostic test panels. However, not all implicated genetic loci are statistically robust. Some genes were reported in studies of candidate genes without adequate control populations.[13] Subsequently, many genes suggested on the basis of candidate gene studies do not show association with disease in larger case-control studies.[14] As a more critical evaluation of the genes linked to DCM continues,[15] we expect that many purported DCM genes will be refuted as has happened with hypertrophic cardiomyopathy.[16,17]

The genes reported to be associated with DCM and/or included on diagnostic test panels span diverse biological pathways, including components of the sarcomere, cytoskeletal and desmosomal proteins, and mitochondrial proteins amongst others (key examples given in *Figure 2*). This is more heterogeneous than the genetic aetiology of other cardiomyopathies such as hypertrophic cardiomyopathy and suggests that DCM may manifest as a final common pathway for a number of processes.

In addition to this locus heterogeneity, there is marked allelic heterogeneity, whereby different variants in the same gene can cause a similar phenotype. Of note, different variants in the same gene can also produce contrasting phenotypes (e.g. different variants in *MYH7*,

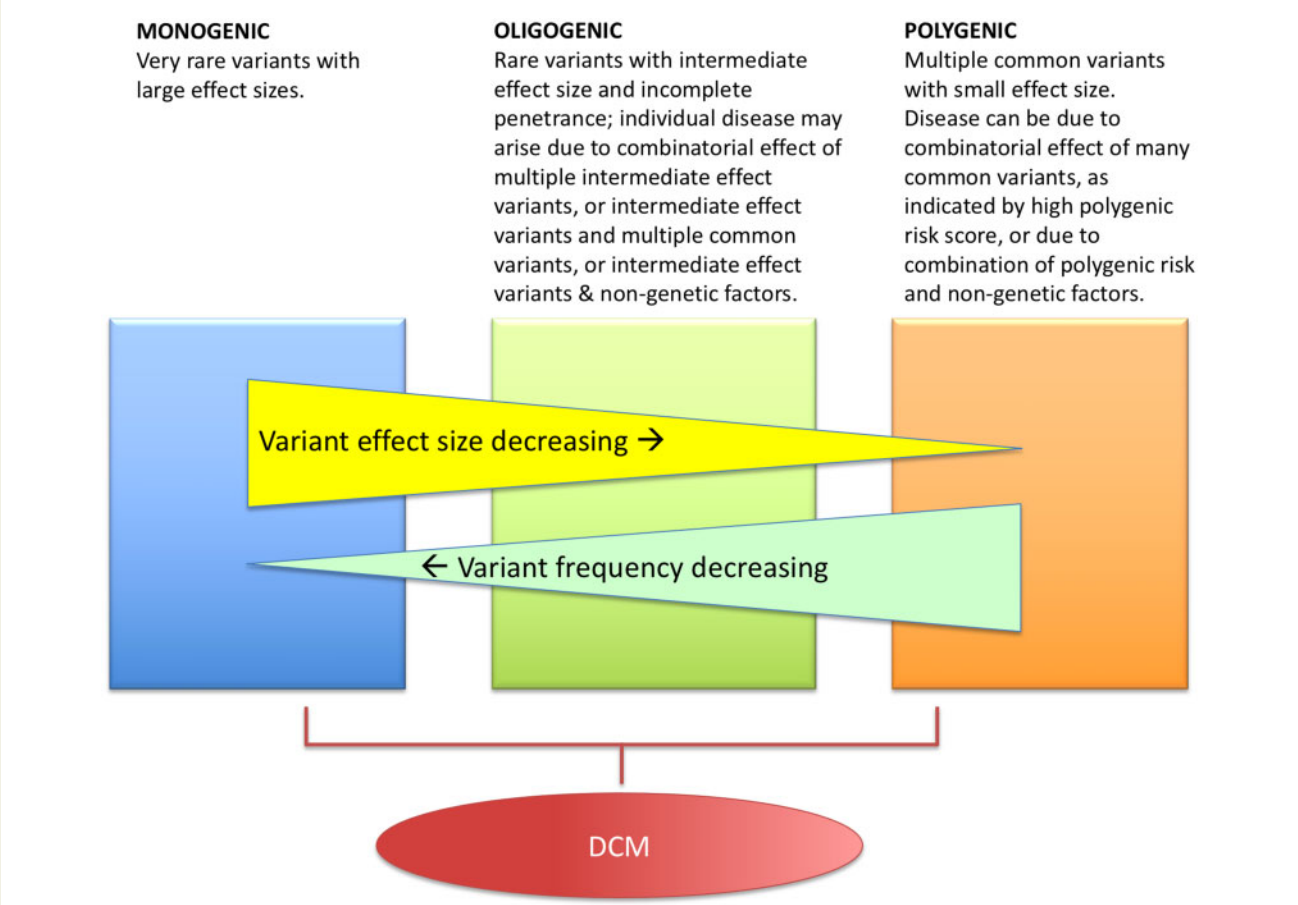


Figure 1 Genetic architectures. Diseases with a genetic component may have monogenic, oligogenic, or polygenic architectures, or a multifactorial process. Our current understanding of the genetic architecture of dilated cardiomyopathy (DCM) supports a likely monogenic and oligogenic basis, though this may be revised as our understanding of common genetic variants develops.

with distinct molecular effects, cause hypertrophic cardiomyopathy and DCM[18])

Penetrance and expressivity

Many genetic variants in DCM exhibit incomplete and age-related penetrance and variable expressivity. Penetrance is defined as the proportion of individuals carrying a variant who develop the disease phenotype, and incomplete penetrance means that not all individuals who carry a particular genetic variant will develop disease. Penetrance is typically age related in DCM—an individual carries the genetic variant from conception, but usually does not develop the DCM phenotype until middle age (>40 years old), or may not manifest at all. Penetrance is essentially unknown for many DCM variants and is an area of active research. Variable expressivity refers to heterogeneity in the severity and diversity of the resulting phenotype. For example, considering two individuals within a family carrying exactly the same genetic variant, one may have severe DCM with ventricular tachyarrhythmias and advanced heart failure requiring heart transplantation, while the other may be minimally symptomatic with only mildly impaired cardiac function. This raises the possibility that additional modifiers, either genetic, epigenetic, or environmental, contribute to the phenotype.

Unknowns in dilated cardiomyopathy genetics

There are a number of unanswered questions in our understanding of the genetics of DCM. One puzzle is the relatively low genetic diagnostic yield even in familial DCM. This most likely represents cases with genetic architectures that are harder to study—strongly genetic, but not monogenic. These include oligogenic and polygenic combinatorial models where genetic susceptibility may be determined by the cumulative effect of multiple common genetic variants,[19,20] as opposed to a near Mendelian inheritance driven by a strong monogenic component. These additional variants may produce additive effects (where a cumulative burden of these more common variants contributes to disease), or non-additive interactions (where more common variants modify the effect of a rare variant). Gene–environment interactions[21] likely also modify the effect of both rare and common variants.

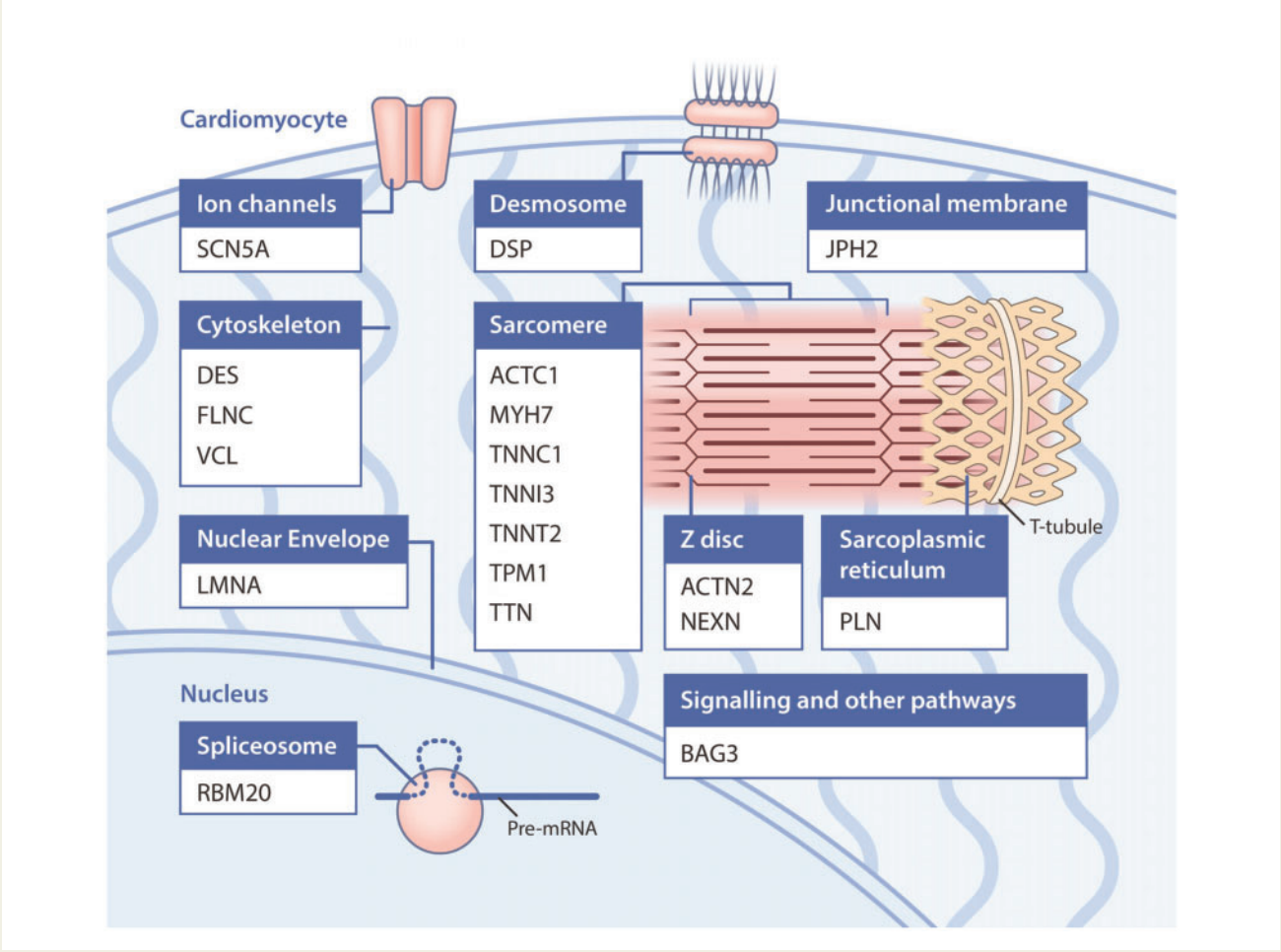


Figure 2 Genes most robustly associated with monogenic dilated cardiomyopathy, grouped by their location within the cardiomyocyte. For clarity, genes associated with syndromic forms of dilated cardiomyopathy have not been included. Graphics created by Elfy Chiang (elfylandstudios.com).

Genetic studies in DCM have largely focused on more interpretable variants that directly alter protein-coding sequence, but there is increasing evidence that variation in areas of the genome that are not assessed using current standard methods, such as non-coding regulatory variants and larger structural variants (e.g. copy number changes) may also contribute to genetic risk in DCM.[22–24] Studies of many complex traits have shown that common variants with small effect sizes are often non-coding variants, likely serving regulatory functions.

It is also likely that there are as yet undiscovered genes contributing to monogenic DCM, but these likely account for a relatively small proportion of genetically unexplained cases.

Updates on genetic testing

Genetic testing methodologies

A number of methodologies have been used to understand the genetics of human disease and their application as relevant to DCM is reviewed in detail in Supplementary material online (*Table 1*).

Confirmatory vs. predictive genetic testing

Currently, genetic testing is performed in DCM patients who have evidence of the disease. This is known as confirmatory or diagnostic testing. The results of this testing may direct management for the patient or be used to guide family (cascade) screening.

Predictive genetic testing is the use of a genetic test in an asymptomatic person to predict future risk of disease.[25] However, the presence of a single monogenic variant is not sufficiently indicative of developing disease so in practice this refers to cascade genetic testing. In the context of DCM, this is most useful in families where someone has genetically explained DCM (the identification of a pathogenic/likely pathogenic variant), where genetic testing can identify family members who do not carry the genetic predisposition and can therefore be safely discharged without ongoing surveillance. For unaffected relatives who do carry a familial variant the predictive value is less clear. These individuals are at risk and remain under surveillance, but it is not possible to precisely quantify the risk of developing overt disease given our current limited understanding of disease penetrance.

Table 1 Advantages and limitations of sequencing technologies used in clinical practice

	Sequencing of single gene or individual variant	Panel sequencing	Whole-exome sequencing	Whole-genome sequencing
Role	Confirmatory testing in a family member of variant detected in proband through other technique	Majority of diagnostic cardiomyopathy testing	Limited role in diagnostic testing in adult-onset DCM	Limited role in diagnostic testing in adult-onset DCM
Advantages	Focused testing of variant of interest—reduced cost and time	Good coverage of genes robustly linked to disease (i.e. genes most likely to yield clinically actionable data)	Is not limited to genes previously linked to disease—potential to identify novel variants in new genes of interest when applied in families or cohorts with sufficient power to establish a new gene–disease relationship (rare)	Captures structural variants and non-coding variants including deep intronic variants. Ability to interrogate rare and common variants. Unbiased approach to genome and therefore variants across the genome can be interpreted in light of new information as the evidence base evolves. Allows calculation of polygenic risk scores, and reporting of pharmacogenetic variants
Limitations	Not appropriate for diagnostic testing in the proband	Does not usually capture non-coding variants. Reduced sensitivity to identify larger structural variants	Potentially incomplete coverage of genes of interest. Challenge to interpret data. Increased likelihood of identifying a variant of uncertain significance	Higher cost. Challenge to interpret data. Limited incremental clinically actionable variants due to limited functional data on many newly identified variants. Increased likelihood of identifying a variant of uncertain significance

DCM, dilated cardiomyopathy.

Why is the genetic test result useful and who benefits?

A genetic test may have implications for the management of the individual tested, or their family members. Historically the main beneficiaries have been family members who can be stratified for ongoing surveillance, or reassured and confidently discharged, on the basis of predictive testing and this remains the major benefit of testing today. While only a proportion of test results have direct implications for management of the proband, this is likely to become increasingly informative.

Benefits for the patient

For the DCM patient, the diagnosis is largely made based on clinical and imaging data. However, in a limited number of patients, genetic testing may assist in confirming the diagnosis when there is diagnostic uncertainty. For example, if there is a dual pathology under consideration such as sarcoid disease, the presence of an alternate genetic diagnosis can inform a decision to desist with more extensive and lower yield diagnostic testing (e.g. endomyocardial biopsy for isolated cardiac sarcoid).[26] We would recommend this application of genetic testing in diagnostic uncertainty be limited to expert centres with multidisciplinary input, given the challenges in interpreting genetic variants in the absence of a confirmed phenotypic diagnosis.

There is great promise for the results of genetic testing to inform precision medicine through risk stratification and targeted therapies. At present, however, in DCM, there are only a few genes in which identified pathogenic variants may change management, reviewed in later sections. The most notable is *LMNA* (lamin), where variants are associated with high rates of conduction disease, atrial and ventricular arrhythmias, and sudden cardiac death. This may lower the threshold for primary prevention implantable cardioverter-defibrillator (ICD) implantation, and encourage enhanced rhythm surveillance.

With improved genotype-phenotype correlations studied in larger multicentre cohorts with long-term follow-up data, we expect the list of genes that will lead to a change in patient management to evolve, and these are discussed in more detail below.

Benefits for the family and cascade screening

The main benefit of cascade genetic screening is identification of family members *not* at risk who can be safely discharged from ongoing surveillance as previously described. Cascade genetic screening can also identify asymptomatic affected family members and pre-

symptomatic unaffected carriers of pathogenic variants that were identified in the proband. It is important that family members are appropriately counselled prior to undertaking genetic testing particularly with regard to reduced penetrance and variable expressivity, meaning that even if they carry a pathogenic variant, they may never develop the phenotype and if they do, the severity of that phenotype may vary. Unaffected carriers should be counselled regarding symptoms and signs of incipient DCM and they will undergo more regular clinical surveillance—every 1–3 years according to the European Society of Cardiology (ESC) guidelines[27] or every 3–5 years according to the American Heart Association guidelines.[28] Future remote monitoring devices able to exclude or detect a DCM phenotype early based upon machine learning analysis of combined clinical and electrocardiographic characteristics, used by the generalist or the family members themselves, may reduce this burden of cardiological surveillance.

Using genetic information to guide reproduction options

Providing information regarding recurrence or transmission risk of DCM is an important benefit of genetic testing for both the proband and their family members. The identification of a disease-causing variant in a prospective parent may also be used to inform prenatal genetics, such as pre-implantation genetic diagnosis, which involves *in vitro* fertilization with embryo selection or editing.[29,30] This is an invasive process with high attrition at each stage, requiring oocyte retrieval, *in vitro* fertilization, genetic testing of embryos, and implantation of pathogenic variant negative embryos. All patients with a robust diagnosis with a clear pathogenic/likely pathogenic variant should be aware of this option. Chorionic villus sampling and amniocentesis are other examples of prenatal genetic diagnosis methodologies. With all of these options, it is vital patients have adequate pre-test genetic counselling, to ensure they have sufficient information and support to make an informed decision. This includes being able to understand the potential implications of test results, exploring the decision-making in response to the results, and supporting communication to other at-risk relatives.

Which dilated cardiomyopathy patient should I refer for genetic testing?

What do the guidelines say?

At present, there is no consensus recommendation for genetic testing of all patients with DCM. The general principles are for genetic testing to be used when it may change management (of the patient or family members), and when it is cost-effective. International guidelines differ and it is worth noting that some have not been updated since pivotal discoveries were made (e.g. recognition of the important contribution of titin-truncating variants in 2012), and sequencing costs have fallen markedly, both leading to evolution of the cost-benefit ratio of genetic testing since some of these guidelines were written.

The American College of Medical Genetics and Genomics (ACMG) recommends genetic testing for patients with cardiomyopathy in two scenarios: (i) for a confirmed affected individual; if in a family then the most clearly affected family member and (ii) cascade testing of at-risk family members for pathogenic and likely pathogenic variants.[31] The ACMG recommend genetic testing at the time of a new cardiomyopathy diagnosis, but it can also be conducted any time following diagnosis. Genetic testing can also be thought of as a continual process, with testing being repeated years after an initial negative test, as new genetic discovery comes to light.

In slight contrast, the 2010 ESC position statement on genetic testing in cardiomyopathies states that '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'.[27] In practice, we interpret this to mean that genetic testing can be performed whenever there are relatives who might benefit from a family diagnosis—e.g. relatives who could be discharged from ongoing follow-up who would otherwise be under clinical surveillance.

The European guidelines do recommend genetic testing for the diagnosis of a particular cardiomyopathy in the presence of features suggesting a specific genetic aetiology that would influence management (e.g. conduction defects in suspicion of *LMNA* cardiomyopathy).

The US Heart Rhythm Society and the European Heart Rhythm Association issued a consensus statement in 2011 recommending DCM genetic testing only for patients with DCM and significant cardiac conduction disease and/or a family history of premature unexpected sudden death.[32] They did not explicitly recommend genetic testing for patients with familial DCM but suggested testing could be useful for these patients to confirm the diagnosis, recognize those at highest risk of arrhythmia, and to facilitate cascade screening.[32]

Genetic testing is not recommended for the diagnosis of a borderline cardiomyopathy. However, the prevalence and prognostic relevance of pathogenic genetic variants did not differ in isolated LV dysfunction compared with DCM in a recent cohort study,[33] suggesting that genetic testing should not depend on the degree of cardiac systolic dysfunction or dilatation.

The reticence to recommend universal genetic testing in DCM stems from a number of factors. The sensitivity for genetic testing in DCM has been variable (25–40% for familial DCM, 10–25% for isolated DCM[31,33]) and there have been limited genetic-prognostic associations that would directly change the management for the proband. However, we propose that genetic testing for DCM has a higher yield than many of the other screening investigations that are recommended for the work-up of a patient with a new diagnosis of DCM (e.g. checking thyroid function tests and ferritin levels). We also propose that genetic testing should be strongly considered in non-familial DCM as 10–25% may have pathogenic variants and that genetic testing should be considered in 'acquired' DCM such as exposure to alcohol or pregnancy as these conditions have been demonstrated to have a similar genetic basis to 'non-acquired' DCM.[7,34] Conversely, in patients with a proven genetic basis, other 'acquired' triggers, such as auto-immunity, alcohol, and chemotherapy, should be considered. We outline our suggested approach in *Figure 3*.

How should the patient be counselled before genetic testing?

It is very important that all individuals at risk of a genetic disease undergo genetic counselling, and certainly prior to genetic testing.

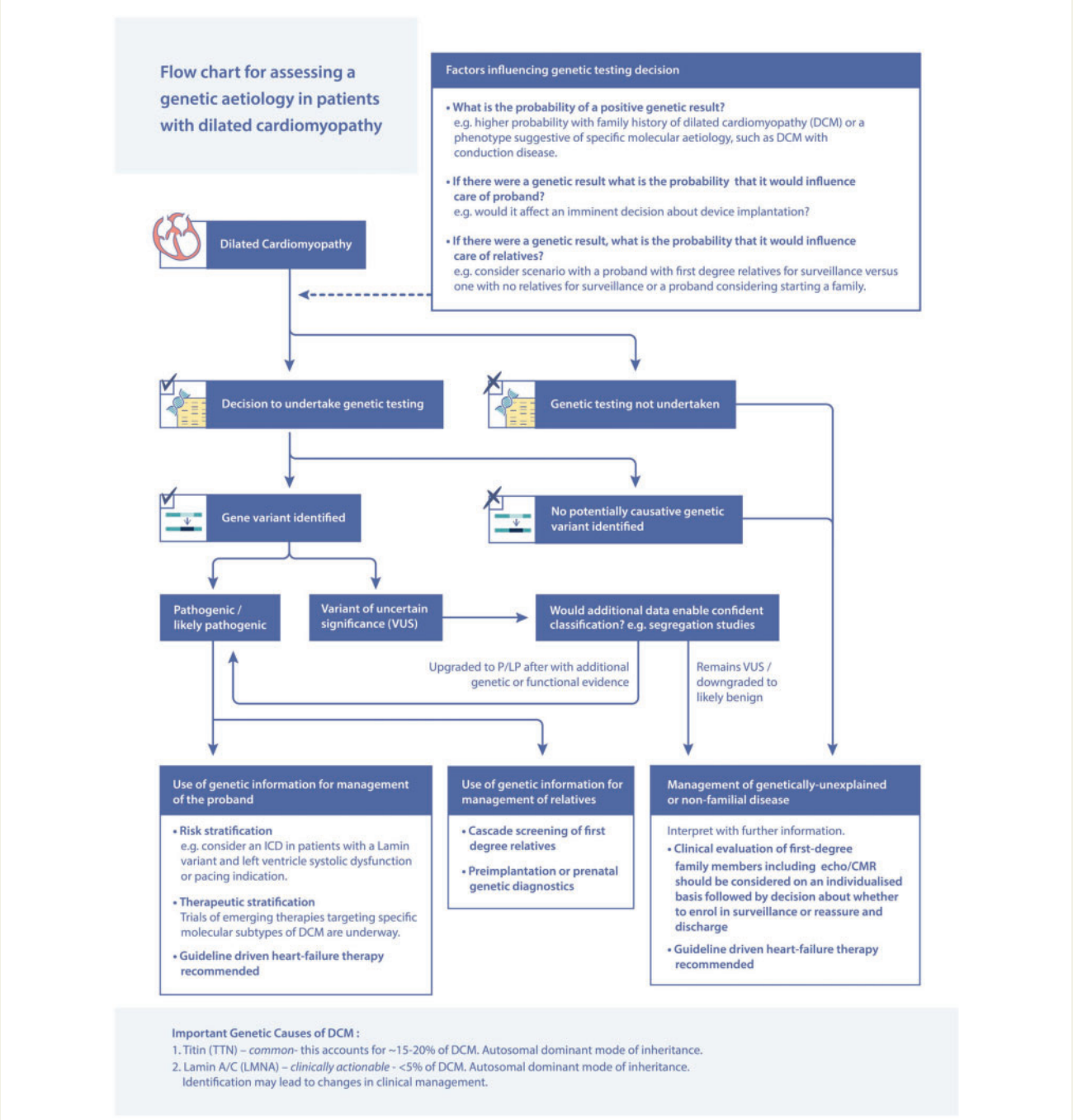


Figure 3 Approach to genetic testing in dilated cardiomyopathy. CMR, cardiac magnetic resonance; ICD, implantable cardioverter-defibrillator; LP, likely pathogenic; P, pathogenic.

This can be with a genetic counsellor or other clinician (doctor—cardiologist or geneticist, specialist nurse) with appropriate expertise, in line with local regulations and care systems. Genetic counselling is a communication process and requires both the provision of information as well as psychosocial support as the patient adjusts to their genetic status.[35] Genetic counselling will involve taking a detailed medical and family history, discussion of genetic testing, informed consent if genetic testing is performed, result disclosure, and psychosocial support. Key concepts to be discussed include the limitations of genetic testing, including the possibility of a negative test or the identification of a variant of uncertain significance (VUS; when a variant cannot be confidently reported as either pathogenic or benign, explained further in next section). In these scenarios, it does not mean that their disease does not have a genetic aetiology, rather than

a monogenic cause has not been identified on current testing of genes known to be linked to DCM. It is important to highlight that the results may change over time as other genes are identified or curated and that testing may need to be repeated. It should also be highlighted that genetic testing will not always change the patient's management but may be undertaken predominantly to benefit the patient's relatives in facilitating family screening (so that unaffected relatives who do not carry the pathogenic variant identified in the proband can be discharged from ongoing follow-up). Patients should be made aware of the EU charter of fundamental rights (Lisbon treaty), article 21, which prohibits discrimination on the basis of 'genetic features', and relevant national legislation or protections, e.g. pertaining to health insurance, life assurance, etc. Patients should also be aware that their rights may differ in different geographic regions if they travel or relocate and their rights may change in the future. For example, in the USA, under a federal law called the Genetic Information Nondiscrimination Act (GINA), it is illegal for health insurance providers to use genetic information to determine health insurance eligibility or coverage. However, life insurance is not covered under GINA; therefore, life insurance companies can use genetic testing results to determine eligibility and/or cost of life insurance. Therefore, in the USA, it is recommended that unaffected family members obtain life insurance prior to genetic testing.

Side Boxes 1 and 2—How to take a family history and how to draw a pedigree (see end of the article).

What are the possible outcomes from genetic testing?

Variant classification and the identification of an informative variant

Genetic variants are classified as pathogenic, likely pathogenic, of uncertain significance, likely benign, or benign.[36] Following a genetic test, there are two broad categories of result; an informative variant is identified (pathogenic or likely pathogenic), or no informative variant is identified (no variant, or benign, likely benign, or VUS). Laboratories should also indicate if a VUS is identified that may become informative with further investigation.

Variant classification is based on integration of data from multiple sources including population data (presence of the variant in people with and without disease), segregation data for variants previously found in families, computational annotations, and functional data from experimental systems. A detailed description of variant identification and classification is beyond the scope of this review but we refer the reader to other resources.[31,36]

What does no genetic variant mean?

The absence of an identifiable genetic variant does not necessarily mean that there is no genetic aetiology to the DCM. The possibilities include (i) gene linked to DCM not on tested gene panel—this could occur with recently reported disease genes; (ii) genetic aetiology of monogenic DCM not fully characterized, so gene not yet identified for inclusion on testing panel; or (iii) genuinely not monogenic aetiology of DCM (though polygenic disease may still cluster in families). However, there is emerging evidence from the study of hypertrophic cardiomyopathy that the absence of an identifiable causative variant substantially increases the likelihood that there is no underlying monogenic/Mendelian disease,[37] and that ongoing surveillance of family members may not be needed if initial evaluation is reassuring.

How to deal with a variant of uncertain significance?

A variant is defined a VUS when it cannot be confidently reported as either pathogenic or benign. A VUS can arise following the identification of a rare genetic variant in either a gene not known to be linked to DCM or if there is insufficient evidence to assign pathogenicity as per the criteria listed above (<90% chance of pathogenicity). It is also established that genetic testing can be less informative for the interpretation of variants in non-European ancestry populations, due to less complete understanding of background genetic variation in these populations.[38]

A VUS cannot be used for cascade screening and it is unlikely to change management for the proband. In clinical practice, the diagnostic laboratory should highlight if the variant might be interpretable with additional information and we may try to gain further evidence for possible pathogenicity including whether it segregates with disease in affected family members.

A VUS may be redefined as pathogenic or likely pathogenic in light of such segregation data or following the publication of reports confirming pathogenicity of that variant in another population/family. As such patients should be counselled about this possibility. Publicly available datasets can be used to revisit pathogenicity such as ClinVar (a free resource of variant-phenotype information, to enable ongoing re-evaluation of variants),[39,40] population datasets such as gnomAD,[41] or gene-specific resources, e.g. atlas of cardiac genetic variation (https://www.cardiodb.org/acgv/; last accessed 18 May 2021). As a community, we encourage data sharing of these rare variants and phenotypes so that we may better understand how to interpret genetic variation in cardiomyopathy genes, though we recognize that uncertainties around data protection have hindered routine sharing of these data.[42]

Genotype-phenotype associations and implications for clinical practice

As outlined, there are a limited number of genes in DCM that are informative for the direct management of the proband. We focus on lamin in this main text but refer the reader to the Supplementary material online, which provide a comprehensive review of titin, other sarcomere-encoding genes, and genes associated with arrhythmogenic cardiomyopathies. We highlight the genes in which variants are most likely to be encountered by a practising cardiologist looking after patients with DCM and genes in which identified variants may change clinical care of patients with DCM.

LMNA variants

The lamin A/C gene (*LMNA*) encodes the nuclear envelope proteins lamin A and lamin C. In addition to DCM, variants in *LMNA* cause a diverse range of phenotypes including Emery-Dreifuss muscular

Side Box 1 How to take a family history

- Always take at least a three-generation family history
- Ask about a family history of cardiomyopathy or heart muscle disease
- Establish if family members have undergone clinical screening and the outcome of the screening
- In affected living family members, ask if they have undergone genetic testing and if the results are available
- Ask about a family history of early pacemakers (<55 years old) or heart transplantation
- Ask about a family history of sudden cardiac death
- Ask about a history of unexplained deaths under the age of 50 years, unexplained accidents or drownings
- If there is a history of sudden death, ask if post-mortem reports are available or if they can be obtained
  - Cardiomyopathy specialists will want to (i) see the post-mortem report, (ii) establish whether a specialist cardiac exam was undertaken, and (iii) establish whether DNA has been retained.
- Many patients do not understand the difference between heart attack, stroke, and cardiac arrest, so spend some time asking what they mean by each term.

dystrophy, limb-girdle muscular dystrophy, lipodystrophy, progeria, and restrictive dermopathy.

LMNA protein-altering variants are found in ~4–6% of patients with DCM.[12,43–46]

LMNA-associated DCM is frequently associated with conduction disease or atrial and ventricular arrhythmias and is often associated with skeletal involvement, early-onset cardiomyopathy and a higher risk of sudden cardiac death.[47–49] *LMNA*-associated DCM is also typically highly penetrant, with development of the phenotype between 20 and 39 years of age in two-thirds of cases and complete penetrance by 60 years.[46,48]

LMNA variant carriers have a poor prognosis compared with the broader cohort of DCM patients, because of a high rate of progression to malignant arrhythmias (~20% over 5 years[50,51]) and pump failure (~19% heart transplantation, ~8% mortality over 8 years[45]). The clinician should be aware of the risk factors that are associated with a higher risk of adverse outcome in *LMNA*-associated DCM. In a landmark multicentre cohort of 269 *LMNA* variant carriers, non-sustained ventricular tachycardia, LVEF <45%, male sex, and non-missense variants, were independent and cumulative risk factors for malignant ventricular arrythmias.[49] Separating predictors of adverse arrhythmic and non-arrhythmic outcomes, in a study of 122 *LMNA* variant carriers, male sex, non-missense variants, and LV dysfunction at index presentation were associated with the development of ventricular arrhythmias, whereas LV dysfunction at presentation was associated with end-stage heart failure or death.[51] Index presentation LVEF is a key predictor of end-stage heart failure.[45] Patients should be referred to a specialized heart failure centre once clinical heart failure or recurrent ventricular tachycardia are present.

The key implication for clinical care in light of these adverse outcomes is a lower threshold for implantation of an ICD. Guidelines recommend that an ICD is considered in patients with *LMNA*-associated DCM where a pacemaker is indicated.[32] As yet, there is no absolute recommendation for a primary prevention ICD in *LMNA*-associated DCM patients without an indication for pacing or a conventional ICD indication. However, in a multicentre cohort of 589 *LMNA* variant carriers, a risk score has been developed and validated for the prediction of life-threatening ventricular arrhythmias (https://lmna-risk-vta.fr).[50] Predictor variables were male sex, non-missense *LMNA* variant, first-degree and higher atrioventricular block, non-sustained ventricular tachycardia, and reduced LVEF. A 5-year estimated risk threshold ≥7% predicted 96.2% of ventricular arrhythmias and led to the net reclassification of 29% of patients with ventricular arrhythmias compared with guideline-based management. These data support broader criteria for placement of a primary prevention ICD in *LMNA* variant carriers, though there is no randomized controlled trial evidence to support this recommendation. At present, according to the 2019 Heart Rhythm Society recommendations, in individuals with lamin A/C arrhythmogenic cardiomyopathy and two or more risk factors (LVEF <45%, non-sustained ventricular tachycardia, or male sex) an ICD is reasonable (class IIa recommendation).[52] Due to the high rates of heart block and need for pacing, a transvenous ICD, not a subcutaneous device, is recommended for patients with *LMNA* cardiomyopathy.

The adverse prognosis also has implications for the management of asymptomatic variant carriers. In a Norwegian series of *LMNA* carriers, asymptomatic gene-positive family members had a 9% annual incidence of a newly documented cardiac phenotype and a 61% cardiac penetrance during 4.4 years of follow-up.[45]

As yet, gene-specific targeted therapies for *LMNA*-associated DCM are lacking, but a Phase 3 randomized double-blind clinical trial is currently underway evaluating ARRY-371797, an oral, selective p38 mitogen-activated protein kinase inhibitor (ClinicalTrials.gov Identifier: NCT03439514). This has been shown to prevent LV dilatation and deterioration in a mouse model of *LMNA* cardiomyopathy[53] and was associated with improved functional capacity in patients in a Phase 2 clinical study.[54]

Areas for future research

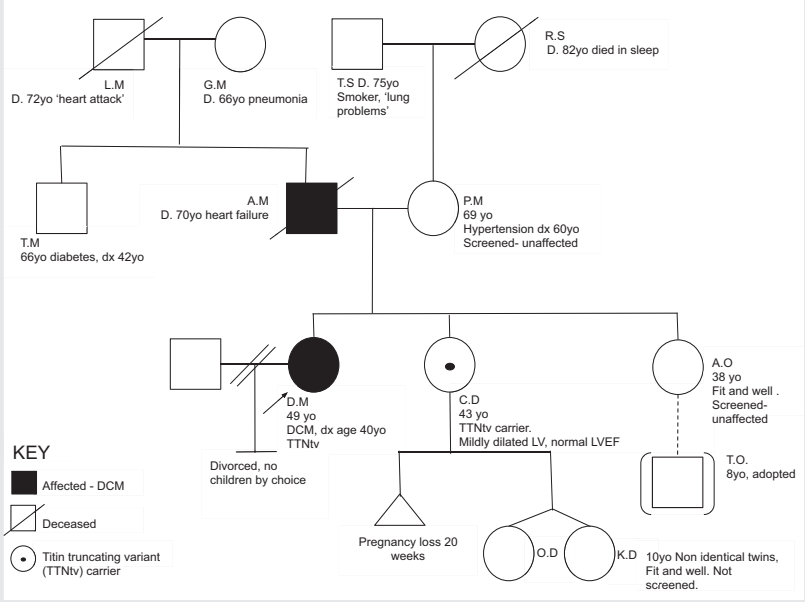
The last 10 years have seen strong progress in the characterization and refinement of the genetic basis of DCM. Harnessing this knowledge to provide targeted therapies should be the goal for the next 10 years.

Understand biological basis of disease and identify therapeutic targets

Discovery of disease associated molecular pathways and targeted molecular therapies, such as the p53-mediated fibrosis in lamin A/C DCM, will be facilitated through RNA and protein profiling of cardiac samples, preferably of diagnostic and not end-stage ventricular samples. Titin-truncating variant (TTNtv) in DCM is characterized by pronounced alterations in mitochondrial energetics, with up-

Side Box 2 How to draw a pedigree

- Example pedigree:



- Start with a solid square (male) or circle (female) for the first person with disease who presented to medical attention (the proband). Indicate that they are the proband with an arrow in the lower-left corner.
- Draw a key on your pedigree to indicate what the shading means. This is particularly helpful if you are attempting to indicate multiple pathologies.
- Add the person's name/initials, current age or date of birth, disease, and age at disease onset below the symbol.
- Then draw the proband's parents. Consanguinity (reproductive relationship between related individuals) is indicated by a double horizontal line instead of a single horizontal line between parents. Annotate the parents' names, current age or age at death, and any medical diagnoses.
- If an individual is deceased, put a line through their symbol.
- Add siblings on the same line as the proband and connect using lines as illustrated. Annotate age and medical information as before.
- Continue for children, aunts, uncles, and grandparents for at least a three-generation pedigree.

regulation of all components of the metabolic mitochondrial electron transport chain in human and experimental TTNtv hearts[55,56] and this opens the path for metabolic interventions.

Improving diagnostic yield

With regard to genetic testing itself, there is potential for the refinement of potential DCM disease-gene associations to improve diagnosis and cascade screening. New gene discovery will increase the sensitivity of genetic testing in DCM but as previously outlined, the incremental gain in Mendelian gene discovery is likely to be limited for DCM. In our opinion, the greatest opportunity is likely through investment to improve variant interpretation—that is to improve discrimination of pathogenic variants from rare but benign bystanders. This is likely to arise from a combination of *in silico* methods and high-throughput *in vitro* functional perturbation assays, though defining high-throughput assay endpoints for many DCM genes is far from trivial.

Many DCM genes show variable penetrance but we still need to better define penetrance for many of these genes in order to be able to counsel gene carriers effectively. Understanding the reasons for the variable penetrance will also be a major focus of future research. One of the most promising avenues will be exploring the collective additive or interactive contributions of common variants with individually smaller effects as contributors to polygenic disease and modifiers of penetrance and expressivity. Polygenic risk scores will capture some of the common variant contribution to disease risk and may improve our ability to discriminate which family members will manifest disease.[57,58] Polygenic risk scores for incident disease as well as risk stratification/outcomes have been developed for many

common diseases[59,60] and often the risk of disease cannot be predicted from conventional (non-genetic) risk factors; the same principles may apply to cardiomyopathy.

Risk and therapeutic stratification

Precision risk stratification and therapeutic stratification to improve clinical outcomes will also be a key focus of future research. More pressingly, both rare variants and genomic risk scores need to be placed in the context of conventional DCM risk markers such as age, New York Heart Association class, biomarkers, and phenotypic variables including LVEF and mid-wall fibrosis to provide multi-modality risk stratification. Regarding therapeutic stratification, much of the evidence base surrounding device implantation in genetic DCM comes from registry and observational data. We would welcome the development of trials stratified by genetic status to evaluate medical and device therapy further.

Targeted therapies

In the last decade, several strategies have been developed to remove, correct, or silence genetic defects, including genome editing, exon skipping, allele-specific silencing, spliceosome-mediated RNA trans-splicing, and gene replacement. Most of these technologies have already been tested for efficacy and efficiency in animal- or human-induced pluripotent stem cell models of hypertrophic cardiomyopathy, DCM or other cardiomyopathy with promising results[61–63] and some have been tested in humans for other conditions.[64] For example, nonsense variants in *LMNA* are anticipated to cause disease through haploinsufficiency. Therapies that target read-through of the premature stop codon may allow normal expression and cellular function. Application of genetic therapy will require extensive efficacy and safety studies.

Conclusion

We have outlined the genetic basis of DCM as relevant to clinical practice, highlighting genes which are informative for management and how genetic testing can underpin evaluation of family members, and increasingly inform the management of affected individuals. We have also addressed some of the challenges in interpreting genetic testing in DCM patients which we hope will be useful for the practicing clinician. The landscape of genetic DCM is continuously evolving and we expect the next 10 years to be characterized by greater understanding of disease beyond the monogenic model, refinement of variant interpretation, further target identification, and the application of genetic biomarkers to patient stratification for improved outcomes in DCM.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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