Precision Medicine in Cardiovascular Disease

Part 3 of a 5-part review series:

Contemporary and Future Approaches to Precision Medicine in Inherited Cardiomyopathies

Running title: Precision medicine in CVD, Part 3 – Cardiomyopathies

Diane Fatkin, MD,[a,b,c] Hugh Calkins, MD,[d] Perry Elliott, MBBS, MD,[e,f] Cynthia A. James, PhD,[d] CGC, Stacey Peters, MBBS,[g,h] Jason C. Kovacic, MD, PhD[a,b,c,i]

[a] Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia.
[b] St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, Kensington, New South Wales, Australia.
[c] Cardiology Department, St. Vincent's Hospital, Darlinghurst, New South Wales, Australia.
[d] Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, MD.
[e] Institute of Cardiovascular Sciences, University College London, London, United Kingdom.
[f] Barts Heart Centre, St Bartholomew's Hospital, London, United Kingdom.
[g] Departments of Cardiology and Genomic Medicine, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[h] Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
[i] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Address for correspondence regarding this article:
Professor Diane Fatkin,
Victor Chang Cardiac Research Institute,
405 Liverpool St, Darlinghurst NSW 2010, Australia.
PH : +61 2 9295 8618 ; FAX : +61 2 9295 8770;
Email: d.fatkin@victorchang.edu.au
Twitter: @FatkinLab

Address for correspondence regarding review series:
Professor Jason Kovacic
Victor Chang Cardiac Research Institute
Lowy Packer Building
405 Liverpool St
Darlinghurst NSW 2010
Australia
Tel: +61 2 9295 8602
Fax: +61 2 9295 8601
E: j.kovacic@victorchang.edu.au

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UNSTRUCTURED ABSTRACT

Inherited cardiomyopathies are commonly occurring myocardial disorders that are associated with substantial morbidity and mortality. Clinical management strategies have focussed on treatment of heart failure and arrhythmic complications in symptomatic patients according to standardized guidelines. Clinicians are now being urged to implement precision medicine, but what does this involve? Advances in understanding of the genetic underpinnings of inherited cardiomyopathies have brought new possibilities for interventions that are tailored to genes, specific variants, or downstream mechanisms. However, the phenotypic variability that can occur with any given pathogenic variant suggests that factors other than single driver gene mutations are often involved. This is propelling a new imperative to elucidate the nuanced ways in which individual combinations of genetic variation, co-morbidities and lifestyle may influence cardiomyopathy phenotypes. Here in this third of a 5-part precision medicine seminar series we review the current status and future opportunities for precision medicine in the inherited cardiomyopathies.

CONDENSED ABSTRACT

To date, the clinical management of individuals with cardiomyopathy has been based on consensus practice guidelines that are largely genotype agnostic. Expanded cohorts of genotyped patients and new functional genomics tools are now providing a wealth of knowledge about the effects of genotype on disease outcomes and mechanisms. In parallel, there is increasing awareness of patient-related factors as phenotype modifiers and increasing sophistication of cardiac phenotyping tools. In this third of a 5-part seminar series on precision medicine, we review how these advances are providing a framework for novel precision approaches to the management of cardiomyopathy patients and their families.

ABBREVIATIONS

ACM	Arrhythmogenic cardiomyopathy
ARVC	Arrhythmogenic right ventricular cardiomyopathy
CMR	Cardiac magnetic resonance imaging
DCM	Dilated cardiomyopathy
GWAS	Genome-wide association studies
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
PRS	Polygenic risk score
*TTN*tv	Truncating *TTN* variant
VUS	Variant of uncertain significance

The past three decades have witnessed an incredible journey for the field of inherited cardiomyopathies that began with the discovery of the first disease-causing gene mutation in 1990 (1). Advances in sequencing techniques have expedited mutation detection and now allow a person's entire genome to be evaluated in a single test. Variants in hundreds of genes have been identified and genetic testing has moved from research laboratories into routine clinical care. In parallel with this technological revolution, there has been a conceptual evolution in our understanding of cardiomyopathy disease pathogenesis. New insights have been gained not only into the genetic triggers of disease but also in the downstream responses that accelerate or compensate for myocardial dysfunction. These findings have led to a new generation of clinical trials of small molecules and pharmacological agents devised to directly target causative disease mechanisms. Although inherited cardiomyopathies are fundamentally monogenic disorders, there is increasing appreciation that the effects of single driver rare variants may be modified in different ways within the context of each individual's genetic background, co-morbidities, and lifestyle. Here in this third of a 5-part seminar series we review the state-of-the-art for diagnosis and management of adult patients with inherited cardiomyopathies, with a specific view toward emerging and future precision medicine approaches. Our focus is on the three major cardiomyopathy sub-types: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmic right ventricular cardiomyopathy (ARVC). The pathogenesis and clinical course of pediatric-onset cardiomyopathies differ in many important ways to those of adults and are reviewed elsewhere (2).

ESSENTIAL FACTS ABOUT DISEASE PATHOGENESIS

Inherited cardiomyopathies are Mendelian disorders that are usually transmitted as autosomal dominant traits. Studies to identify causative rare variants have resulted in numerous

suspected disease genes for HCM, DCM, and ARVC (see Online Table 1 for full gene lists). In recent years, critical reappraisal of these data has revealed that the weight of evidence for roles in disease pathogenesis is quite variable (3,4). Genes for which there is moderate to high levels of confidence are shown in Table 1. It is important to note that gene classification is an iterative process responsive to emerging clinical and functional data. High-confidence genes are those in which there are multiple examples of variants that co-segregate with disease or *de novo* cases and there is usually robust support from cell or animal models that gene dysfunction is relevant to the phenotype in question. Within the moderate- and low-confidence genes, some will be *bona fide* disease genes that have few published reports while in others, disease associations may be spurious. Gene curation efforts have facilitated interpretation of genetic testing results and provided clarification of the principal underlying myocardial defects.

The high-confidence genes for typical adult-onset HCM encode proteins in the thick filaments (*MYH7*), thin filaments (*ACTC1, TNNT2, TNNI3, TPM1*) and interacting components (*FHOD3, MYBPC3, MYL2, MYL3*) and this has given rise to the notion that HCM is mainly a disease of the sarcomere (Figure 1). For some mutations, myocardial dysfunction is characterized at the single molecule level by increased force generation, ATP hydrolysis and actin-myosin sliding velocities (5-7). Elegant modeling studies have revealed that the fundamental cause of contractility and relaxation defects in HCM is an imbalance of the proportion of myosin heads that are in a disordered or super relaxed state (8). These sarcomeric defects are energy requiring and result in increased energy consumption and metabolic demands (9). Functional analyses of HCM mutations have also demonstrated abnormalities of myocardial calcium homeostasis (10). Collectively, these mechanical and calcium-induced changes activate signaling cascades that culminate in myocardial remodeling with the development of pathological hypertrophy and fibrosis (5).

Genetic studies of ARVC show this to be primarily a disease of the desmosome with five of the seven high-confidence disease genes encoding the desmosomal proteins desmocollin (*DSC2*), desmoglein (*DSG2*), desmoplakin (*DSP*), plakoglobin (*JUP*), and plakophilin (*PKP2*) (Figure 1). These proteins form a lattice that links the sarcolemma to cytoskeletal intermediate filaments. When the structural stability of this lattice is compromised by abnormal mutant protein, there is disruption of intercellular junctions and cardiomyocyte detachment (11). This is particularly likely to occur under conditions of increased mechanical stress such as vigorous exercise (11). A further consequence of desmosomal dysfunction is the translocation of plakoglobin from intercellular junctions into the cytosol and nucleus (12,13). This pattern is also seen with ARVC-associated variants in the cell membrane protein, *TMEM43*, and the sarcoplasmic reticulum protein phospholamban (*PLN)* (13). Once in the nucleus, plakophilin alters activation of canonical Wnt-β-catenin and Hippo signaling pathways, resulting in a transcriptional switch from myogenesis to adipogenesis and fibrosis (13). Other factors that have been implicated in ARVC pathogenesis include altered connexin 43 expression and gap junction remodeling, and abnormalities of cardiac sodium channel activity and calcium handling (13). There is also emerging evidence that auto-immunity and myocardial inflammation may contribute to disease progression (13).

Unlike HCM and ARVC, there is no single disease paradigm for DCM (Figure 1). Variants in sarcomere protein genes are a frequent cause of DCM (*TTN*, *MYH7*, *TNNT2*, *TNNC1*, *TPM1*), however in contrast to HCM, these result in depression of ventricular systolic contraction and impaired force generation. DCM-causing variants can perturb diverse additional aspects of cardiomyocyte function including force transmission, mechanical stress sensing and signaling (*DES, DMD, DSP, FLNC, LDB3*), nuclear structure and function (*LMNA, RBM20*), ion channel activity (*SCN5A*), protein turnover (*BAG3*), and calcium

homeostasis (*PLN*) (14,15). The extent to which these pleiotropic defects might converge on common downstream pathophysiological processes remains to be determined.

ESTABLISHING A CLINICAL DIAGNOSIS

Patients with inherited cardiomyopathies can present with a range of cardiac symptoms that are often associated with heart failure or arrhythmias. The basic work-up includes a detailed medical history, physical examination, laboratory tests (hematological and biochemical screens), 12-lead ECG, and assessment of ventricular size and function with either transthoracic echocardiography or cardiac magnetic resonance imaging (CMR), depending on availability and local expertise (Figure 2 & Central Illustration). Construction of a three-generation family history is essential, with attention paid to cardiomyopathy diagnoses, arrhythmias, conduction abnormalities, procedures (arrhythmia ablation, cardioversion, pacemaker or defibrillator implantation, valve surgery, heart transplantation), extra-cardiac syndromic features, or unexplained sudden deaths (16).

Left ventricular hypertrophy

HCM is defined by the presence of left ventricular hypertrophy in one or more myocardial segments that is not attributable to abnormal loading conditions. The phenotype is most commonly caused by mutations in sarcomeric protein genes, but phenocopies caused by rarer genetic variants in non-sarcomere genes as well as acquired disease mimics such as amyloidosis are not infrequent (17,18). Sarcomere protein gene variants typically have characteristic echocardiographic features such as marked asymmetric hypertrophy of the interventricular septum that is often associated with left ventricular outflow tract obstruction and mitral valve abnormalities. However, the extent and pattern of hypertrophy can be quite variable and the diagnosis is not always straightforward (19). In these situations, the

presence of other cardiac or extra-cardiac traits and an integrated approach to the assessment of ECG, cardiac imaging and biochemical data often points towards specific disease phenocopies (Figures 2 & 3). The age of the patient may provide clues, with conditions such as congenital heart abnormalities and myocardial storage disorders being relatively more common causes of ventricular hypertrophy in the young and amyloidosis or hypertension in the elderly (18). Obesity is associated with both hypertension and left ventricular hypertrophy (20). In individuals who have a history of competitive sports activity, ventricular hypertrophy may be part of a spectrum of athletic-induced myocardial remodeling but is usually distinguishable from pathological hypertrophy by careful assessment of the type of athletic participation, family and personal history, and imaging data (21). In the clinical examination, a number of diagnostic clues or "red flags" may point to specific multi-system disorders that require targeted investigation and treatment (18). These include intellectual disability, sensorineural deafness, visual impairment, palpebral ptosis, skeletal myopathy, gait disorders or skin changes that may be indicative of metabolic disorders (eg. Anderson Fabry disease, Danon disease), mitochondrial diseases, neuromuscular disorders (eg. myotonic dystrophy, Friedreich's ataxia, myotonic dystrophy), or malformation syndromes (eg. Noonan/LEOPARD syndrome). Cardiac amyloidosis caused by deposition of transthyretin or immunoglobulin light chains is important to recognize as effective therapies that impact on prognosis are available. Cardiac amyloidosis may be suspected from the history (e.g. bilateral carpal tunnel syndrome, lumbar spinal stenosis, vitreous opacities, or spontaneous biceps tendon rupture) or from ECG and imaging features on echocardiography, CMR or bone scintigraphy (the latter highly sensitive for transthyretin-related cardiac amyloidosis) (22).

Dilated cardiomyopathy

There are numerous causes of DCM and newly diagnosed patients need to be thoroughly evaluated for acute or chronic exposure to factors that promote ventricular chamber dilatation and/or systolic dysfunction (Figure 2). These include common cardiac pathologies such as myocardial ischemia, valve dysfunction, myocarditis, arrhythmias, multi-system pathologies (eg. anemia and endocrine), drug exposure (eg. anthracyclines), and toxins (eg. alcohol, iron overload, cocaine). Many of these conditions are potentially treatable and reversible (23-25).

It has been estimated that ~50% of patients have an identifiable cause and in the remaining 50%, DCM is often called "idiopathic" (IDCM) (26). This term is somewhat misleading since at least 25% of these individuals have a positive family history and an expected genetic cause of disease ("familial" DCM [FDCM]) (27). The extent to which genetic factors are involved in apparent sporadic IDCM is not fully understood but is likely to be ~ 25%. By definition, probands are the first individuals to present with DCM in a family and a potential genetic cause may not be suspected until additional relatives become affected. A positive family history might also be unrecognized if relatives have clinical features other than DCM, such as arrhythmias, conduction abnormalities, sudden death, or extra-cardiac defects. Some sporadic cases are likely to be explained by *de novo* gene mutations but another possible scenario is that potentially deleterious rare genetic variants remain silent until unmasked by interactions with other genetic and acquired factors. Unlike HCM and ARVC, "DCM" is not specific for a primary genetic cardiomyopathy. In this review, we have used the term "genetically-mediated DCM" (G-DCM) to refer to this DCM subtype. In these individuals, CMR imaging and 24-hour ambulatory Holter monitoring are useful to clarify the phenotype and to improve prognostic stratification of arrhythmias.

Uni/biventricular dilation with contractile dysfunction and arrhythmias

Classical ARVC is characterized by global or regional right ventricular dysfunction and dilation in association with ventricular arrhythmias (Figure 4) (11). Advances in the understanding of the clinical, pathological, and genetic architecture of ARVC have informed consensus diagnostic criteria which have proved to be sensitive but not entirely specific for the disease (28). More recently, clinical and genetic data from families and the recognition of a much broader spectrum of structural disorders affecting both ventricles, has led to the use of the term *arrhythmogenic cardiomyopathy* (ACM) to describe a family of diseases (29). While precise definition for ACM is challenging, the concept includes the following: heritable ventricular arrhythmia in the form of frequent ventricular ectopy from either ventricle, sustained or nonsustained ventricular tachycardia, or unexplained cardiac arrest, and abnormalities of myocardial structure and function. In all cases of ACM, it is important to exclude mimics of the ACM phenotype such as congenital defects, pulmonary hypertension, sarcoidosis and myocarditis. One consequence of this definition is an overlap between ACM and DCM, some forms of which are highly arrhythmogenic.

Phenotype plasticity

All cardiomyopathy phenotypes are dynamic, in that they evolve over time. As an example, individuals with *LMNA* mutations may initially present with cardiac conduction abnormalities or arrhythmias (atrial and ventricular) that precede overt DCM by several decades (30). Once DCM is established, ventricular dysfunction may be exacerbated by a variety of factors including paroxysmal tachyarrhythmias, myocardial ischemia and alcohol excess, or, it may be normalized by effective medical therapy (25). In patients with HCM, systolic left ventricular dysfunction may develop and dominate the later stages of the disease (31). Dissecting out the effects of the main driver gene mutation from other factors that contribute to the phenotypic manifestations of disease in individual patients is both the

challenge and goal of precision medicine. These issues are discussed further in subsequent sections.

FINDING THE GENETIC CAUSE OF DISEASE

Genetic testing is used to define the underlying *cause* of inherited cardiomyopathy, but the *diagnosis* of these disorders is primarily based on the clinical presentation. As shown in Table 1, variants in the same gene can give rise to different disorders and thus a positive genetic test result alone cannot be used to infer either the presence or type of cardiomyopathy. Genetic testing does not replace careful clinical evaluation and is generally undertaken only once this has been performed (Figure 2). ARVC is an exception in that genetic testing is considered a diagnostic criterion in the family history component of the Task Force recommendations (28). A positive genetic test result allows patients to understand why their disease developed. This has immediate psychosocial benefits and can inform reproductive choices. A positive test result also enables predictive cascade testing and genetics counselling to family members.

Who needs genetic testing?

Genetic testing is recommended for all patients with HCM and for those with suspected ARVC/ACM (Figure 2) (18,29). In patients with DCM, genetic testing is recommended for those with a positive family history and should be considered in sporadic cases if there is a young onset of DCM or if there are clinical features such as conduction defects or skeletal myopathy that suggest specific genetic etiologies (32). As a general rule, the individual who has the youngest onset and/or most severe phenotype in the family is selected for comprehensive genetic testing. If a clinically actionable pathogenic or likely-pathogenic variant is found in the index case, then adult family members can be tested to determine

whether or not they carry this specific variant. This can be done using targeted Sanger sequencing and repeating the full panel testing is not needed. Variants that are annotated to have uncertain significance (VUS) are not clinically actionable and cascade testing of these variants in family members is not recommended. In the research context, family genotyping may be undertaken in order to further investigate the potential effects of VUS. The age threshold for genetic testing of children and adolescents depends on a number of factors including the typical age of disease onset in the family and the impact that a positive result might have on medical surveillance and lifestyle choices. Recent data in families with HCM suggest that phenotype expression may occur in preadolescent children that carry pathogenic sarcomeric protein gene mutations (33).

Which test to use?

There are a number of genetic testing options for family probands, including gene panel sequencing, exome sequencing and genome sequencing. Each of these methods has its advantages and disadvantages and the choice depends on factors such as local expertise and cost. Gene panel sequencing is widely used for clinical genetic testing and even with exome and genome sequencing, data interpretation is usually based on the same sets of disease-specific genes that are included on panels. Whether gene panels should be inclusive of all disease-associated genes or restricted to the small number of genes that have been shown to be definitively causal is debated, but the latter may be preferable in the clinical setting to reduce the chance of false-positive results.

Interpretation of genetic test results

The aim of genetic testing is to identity the single rare variant that is likely to be the cause of disease in each family. This is not always straightforward and prioritizing the hundreds of

variants that arise in every test is a major challenge. To facilitate variant interpretation, the American College of Medical Genetics and Genomics has devised a scoring matrix that utilizes variant-based and gene-based parameters to rank potential effects (34). Variants have a greater chance of being classified pathogenic/likely pathogenic if they have been previously seen in affected patients, occur in genes in which pathogenic/likely pathogenic variants have been found in multiple families, and if animal models recapitulate the same disease. These stringent criteria reduce the chance of false-positive findings and delivery of potentially harmful incorrect results to patients and their families. Many variants fail to meet the threshold for pathogenicity because of lack of evidence upon which to make a decision, and it can be expected that at least some variants in the gray zone of "uncertain significance" may in fact be deleterious. Periodic re-annotation of variant classification is needed, as this may change over time as new family members become affected, clinical databases expand, or functional genomics data are generated. Thorough and repeated clinical phenotyping of patients and families is essential in the process of ascribing pathogenicity to variants of unknown significance.

RARE VARIANTS, COMMON VARIANTS, CO-MORBIDITIES AND LIFESTYLE FACTORS: PUTTING ALL THE PIECES OF THE PUZZLE TOGETHER

The clinical manifestations of inherited cardiomyopathies can differ from gene to gene, and for any single gene, there is often variability between families and within members of the same family. Variable expressivity (i.e. the range of clinical features) and penetrance (i.e. the proportion of variant carriers who show signs of disease) have been considered as characteristics of the genes in which the main driver rare variants are found. As precision medicine dictates a focus on the whole patient, there has been increased interest in looking at how the effects of a gene mutation might be uniquely modified by personal milieu (Figure 5).

The relative contributions of background genetic and environmental factors will differ in every patient and the overall impact on the cardiac phenotype will depend on the balance of exacerbating and protective effects (Figure 6).

Additional rare variants

As the numbers of genes on testing panels has expanded, it is not uncommon to find families in which there are two or more deleterious rare variants (4,35-41). These result in a number of potential scenarios, including (i) only one of the identified variants is the *bona fide* cause of disease; (ii) several rare variants may collectively be required for disease to be manifest; or (iii) disease severity may differ according to the total number of variants carried by each family member. There are now accumulating reports of patients with multiple mutations who have earlier onset and more severe disease than those with single gene mutations, suggesting that deleterious variants can have additive effects (36-40). With this in mind, it is important that genetic test results are comprehensively evaluated and not prematurely terminated once one candidate variant is found. “Rare” variants are defined by the frequency in which the minor allele is seen in the general population, with threshold levels of <1% often used. In recent years, there has been increasing interest in also looking at “low frequency” variants (minor allele frequencies ranging from 1% to 5%) as potential disease modifiers in families.

Common variants

Variants that are commonly occurring (minor allele frequency >5%) in the general population) can affect susceptibility to many human disorders. Relevant variants are typically identified by genome-wide association studies (GWAS) in large cohorts of affected cases and control subjects. To date, very little is known about the role of common variants as possible disease modifiers in the inherited cardiomyopathies, although there are emerging data linking

GWAS loci with echocardiographic traits such as ventricular hypertrophy, diameter, and contractile function, and with clinical endpoints such as heart failure (Table 1, Online Table 2) (42-53). Significant GWAS loci are often located in non-coding regions that are thought to harbor regulatory sequences that influence gene expression. The target genes are often presumed to be in close proximity to the GWAS loci but may also be located more distantly or on other chromosomes. It is notable that many of the genes implicated in GWAS loci for heart failure have also been shown to carry rare cardiomyopathy-causing variants (Table 1). These findings raise the possibility that at least some of the common variants identified by GWAS could be phenotype modifiers in cardiomyopathy patients. To better define high (and low) risk subgroups of patients, polygenic risk scores (PRS) have been derived using suites of top-scoring GWAS variants. PRS for cardiovascular disorders such as coronary artery disease and atrial fibrillation have been extensively studied and shown to provide incremental information over clinical factors for risk stratification (54-57). At present, PRS have mainly been used in genetic epidemiological studies and have not yet entered the clinical setting.

Co-morbidities and lifestyle factors

Many patients with cardiomyopathy have *both* an inherited cardiomyopathy *and* commonly occurring clinical conditions such as hypertension or coronary artery disease that could influence the disease phenotype (Figure 2). Furthermore, there is emerging evidence that lifestyle factors are also potential disease modifiers (Figure 2). Obesity is one example. In a recent analysis of 3282 patients with HCM in the Sarcomeric Human Cardiomyopathy Registry (SHaRe), almost one third of participants were obese (58). These individuals were more symptomatic, more often had left ventricular outflow obstruction, and were more likely to develop heart failure or atrial fibrillation when compared to normal-weight and pre-obese participants. In general, obesity promotes heart failure, but once heart failure develops, obese

patients have better survival than those who are underweight (the obesity paradox) (20). There are few data on the effects of obesity in ARVC but myocardial fat replacement in obese subjects may confound interpretation of CMR imaging (59). In all patients with inherited cardiomyopathies, there may be a vicious circle with restriction of physical activity offset by increased obesity.

Patients with cardiomyopathy gene mutations might be more susceptible to myocardial depressant effects of cardiotoxins, such as alcohol and anthracycline chemotherapy (60-62). Both of these agents are independent causes of DCM and this is typically dose-dependent (63-65). However, the development of cardiotoxicity at lower doses has suggested that some patients could have a genetic predisposition. This is particularly the case for truncating *TTN* variants (*TTN*tv), that have been found in 10% and 7.5% of patients with alcoholic cardiomyopathy and anthracycline-induced cardiomyopathy, respectively (60, 62). These prevalence rates are similar to those for *TTN*tv in sporadic DCM cohorts (66) and therefore it is uncertain whether there is a true gene-environment interaction. It seems likely however, that the addition of an environmental stressor such as excessive alcohol, might bring forward the age of onset of DCM, or worsen its severity, in *TTN*tv carriers.

In general, competitive sports are contra-indicated in patients with definitive HCM, DCM and ARVC (67,68) but the pendulum is swinging to some extent in HCM, with several studies suggesting that moderate and even vigorous exercise can be both safe and beneficial (69-71). In ARVC, disruption of intercellular junctions between adjacent myocytes is a key pathophysiological feature and this can be exacerbated by hemodynamic stress (11). There is some evidence that participation in competitive sport and endurance sports accelerates disease progression, with a higher penetrance of clinical manifestations, earlier onset of symptoms, and increased risk of ventricular arrhythmias, heart failure, and need for cardiac transplantation (72-75). In one large study of ARVC patients, competitive sport was

associated with a two-fold increase in ventricular tachycardia or death, while the outcomes of patients who participated in recreational sport were similar to those of inactive patients (74). Exercise appears to be a particularly important modifier in genotype-negative patients with ARVC who lack a family history (75). Although there are concerns about adverse effects of exercise in cardiomyopathy patients, these need to be balanced with the potential cardiac and overall health benefits of improved cardiorespiratory fitness.

Ethnicity

Ethnicity may also have an effect on disease expression and clinical outcomes in cardiomyopathy. A recent study of 2467 patients with HCM highlights several important points (76). In that series, black patients were younger and more symptomatic than white patients at the time of diagnosis and had more heart failure episodes. At least some of these differences can be attributed to genetic factors, since the black patients had a lower prevalence of disease-causing sarcomeric gene mutations, and profiles of background genetic variation vary from those of white patients. However, black patients were also found to have lower rates of genetic testing and septal reduction procedures, suggesting that differential access to healthcare services and clinical management strategies might be contributing factors. Much of what is currently known about the genetic architecture and natural history of inherited cardiomyopathies is based on studies of white-predominant cohorts and interpretation of existing data is confounded by the paucity of ethnic diversity in genetic testing repositories and reference cohorts. Expanding these types of studies to patients with a broader range of ethnic backgrounds is a research priority.

PRECISION APPROACHES TO HCM, DCM and ARVC

In general, patients with HCM, DCM and ARVC, are treated according to the severity of symptoms, the predicted risk of a sustained ventricular arrhythmia (77-79), and the extent of myocardial dysfunction (Table 2). Comprehensive clinical practice guidelines are provided elsewhere but therapy involves pharmacologic agents (eg. β-blockers, angiotensin II receptors blockers, anti-arrhythmic drugs), devices (eg. implantable cardioverter-defibrillators [ICD], pacemakers and resynchronization therapy, left ventricular assist devices), catheter ablation of ventricular tachycardia, or surgery (myectomy, heart transplantation) (17,18,23,24,29). Most therapies are based on an implicit assumption that all patients have the same or similar phenotype, often defined by a single variable of interest (e.g. left ventricular ejection fraction or wall thickness). This simplification is useful for trial design and in the creation of general management frameworks that assist in the translation of evidence-based medicine into clinical practice. However, a goal of precision medicine is to refine or sometimes redefine clinical presentations into new endophenotypes that link more closely with mechanisms of disease and as a consequence, more precise therapeutic strategies. Scientists and clinicians are pursuing this goal through the application of new tools in genomics and proteomics, and novel analytics such as artificial intelligence. However, clinicians can already make more precise "multiparametric" diagnoses based on routine clinical methods that influence disease management.

Genotype-positive affected index patients and relatives

To date, genotype information has had a limited role in drug treatment choices for symptomatic patients. One example where medical therapy has directly changed as a result of insights in the functional effects of a specific variant is the p.R222Q missense variant in the *SCN5A* gene. This variant has been identified in several families and gives rise to a distinctive phenotype with multifocal ventricular ± atrial ectopy and DCM that are caused by

gain-of-function effects on cardiac sodium channel activity (80-85). Affected variant carriers are effectively treated by drugs that have sodium channel-blocking effects, such as flecainide, amiodarone, and quinidine (80,84,85). Although variant-directed therapies like this are extremely useful for selected families, the need for experimental evaluation of each variant limits the scalability of this approach (86). Targeted genome editing approaches to correct primary disease-causing variants are under investigation in animal and cell models and may be feasible for clinical applications in the future (86).

An alternative option is to target key, common pathophysiological processes that are perturbed by defects in one or more genes (86). Examples of this include mitogen-activated protein kinase inhibitors in patients with severe DCM due to *LMNA* mutations (87,88; NCT02057341/NCT02351856, results pending), and myosin inhibitors (or activators) for patients with HCM (or DCM) due to sarcomere gene mutations (89-91). For the most part, these agents are still in early phase investigation. However, data from clinical trials published this year (EXPLORER-HCM, MAVERICK-HCM) have shown highly promising results for mavacamten, a selective allosteric inhibitor of cardiac myosin ATPase, which reduces actin-myosin crossbridge formation, in patients with symptomatic obstructive and non-obstructive HCM (92,93). Whether this therapy might preferentially benefit patients with sarcomere gene mutations or have more universal application in patients with HCM due to any cause remains to be determined.

Arrhythmic risk stratification and indications for ICD implantation are mainly based on history (especially recent cardiac syncope), ECG, electrocardiographic monitor results (frequency of ventricular ectopy, nonsustained ventricular tachycardia) and imaging parameters (Table 2) (77-79,94). CMR may enable risk predictions in HCM, DCM, and ARVC to be refined, with strong correlations seen between the extent of late gadolinium enhancement and adverse outcomes such as ventricular tachycardia and sudden cardiac death

(95,96). There is increasing evidence that some genes are associated with a high arrhythmia propensity and this may influence ICD decision-making (Table 2). A meta-analysis of >7000 HCM patients showed that sarcomere gene mutation carriers had an earlier onset of disease and higher rates of sudden cardiac death than non-carriers (97). CMR studies have shown that sarcomere gene mutation carriers are more likely than non-carriers to have late gadolinium enhancement, which may contribute to differences in arrhythmic outcomes (98). Similarly, a study of 1001 ARVC patients and at-risk relatives showed patients with pathogenic desmosomal variants had earlier onset disease and ventricular arrhythmias than those in which a pathogenic variant could not be identified (41). Genes such as *LMNA*, *SCN5A*, *FLNC*, *RBM20*, *PLN*, *DSP*, *DES*, and *TMEM43* can be associated with arrhythmic forms of DCM or ARVC/ACM and the threshold for ICD implantation may be lower than for routine primary prevention (30,79-85,99-107). Genotype-phenotype studies may help to further stratify risk within these patient subgroups. As an example, a recent CMR study in 89 patients with G-DCM found that a distinctive ring-like pattern of subepicardial late gadolinium enhancement was present in 78% of *DSP* or *FLNC* mutation carriers and in none of the patients with other genetic causes of DCM (108) (Figure 7). The *DSP* and *FLNC* mutation carriers had a greater prevalence of regional wall motion abnormalities than the other genotype groups, although the latter had overall lower left ventricular ejection fraction and more impaired global longitudinal strain. These findings point to different mechanisms for ventricular arrhythmias and contractile dysfunction between these mutation types. It is important to note that not all variants in these arrhythmic genes will be equally deleterious and that for any single variant, the phenotype severity may differ within families. Families with *TTN*tv demonstrate this point, with some individuals showing severe DCM and early-onset arrhythmias, while others have normal cardiac function until late in life (109,110). As longitudinal studies in large cohorts of genotyped patients become available, further insights

will be gained into the natural history and penetrance of disease associated with different cardiomyopathy genes and this will help to further define high- and low-risk subgroups.

Genotype-positive unaffected relatives

A major goal of genetic testing is identification of genotype-positive, phenotype-negative family members in whom pre-emptive strategies to delay or prevent disease onset might be possible. These individuals need regular cardiac monitoring with ECG (± electrocardiographic monitor) and echocardiography (Table 2). The age at which monitoring should commence is not clearly defined, and factors such as the type of gene mutation and the typical age at diagnosis (and onset of complications including death) in other family members need to be taken into consideration. The frequency of follow-up is also variable and depends on cardiomyopathy type, patient age, appearance of new symptoms, or borderline echocardiographic findings.

Ideally, periodic monitoring allows detection of preclinical disease and many efforts have been made to leverage novel imaging techniques to inform early detection of phenotypic expression. In G-DCM, left ventricular dilation has been investigated as a marker of early disease, but the lack of specificity limits its prognostic utility (111,112). Echocardiographic deformation studies suggest that abnormalities of myocardial strain precede overt evidence of ventricular hypertrophy or contractile dysfunction in HCM, G-DCM and ARVC (113-120). A range of CMR-based methods that evaluate deformation characteristics and fibrosis have also been proposed as sensitive ways to identify diseased myocardium (33,121-125). Although these imaging studies can show differences between groups of affected family members, unaffected family members and control subjects for various parameters, the threshold levels for transition to pathogenicity in individual patients remain to be clearly defined. Apart from imaging, clinical indices and biomarkers have also been used to evaluate preclinical disease.

In a recent study of asymptomatic sarcomere gene mutation carriers, male sex and baseline ECG abnormalities were associated with a higher risk of HCM development over a 15-year period (33). Biomarkers such as N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin I, or pro-fibrotic peptides have been shown to detect mechanical stress and myocardial injury in patients with established disease but have variable efficacy in predicting early disease (98,112,126,127). Other biomarkers such as circulating microRNAs and autoantibodies remain under investigation (128-131). At present, there are no definitive guidelines for when, and how to initiate preventative interventions in genetically-predisposed individuals beyond limiting exercise in pathogenic desmosomal mutation carriers (132).

Genotype-negative relatives in families with an identified gene mutation

For autosomal dominant forms of HCM, DCM and ARVC, 50% of relatives on average will not carry the family gene mutation. Current guidelines indicate that these individuals can be released from ongoing clinical screening. Caution is needed however, if there are multiple potentially deleterious variants or other causes of cardiomyopathy in the family that may give rise to apparent lack of cosegregation or incompatible phenotypes in relatives.

Families without an identified gene mutation

The yield of genetic testing differs according to cardiomyopathy type, with estimates ranging from 30-60% for HCM, 10-40% for DCM and 40-65% for ARVC (13,16). This means that many families will not get a positive result in the initial test report. When one or more VUS has been identified, re-interpretation of these variants is warranted from time to time and this may enable some variants to be upgraded to pathogenic or likely pathogenic. Symptomatic individuals in families with no identified gene mutation should be treated according to

standard guidelines and all unaffected individuals need serial monitoring (similar to unaffected genotype-positive individuals).

Managing modifiers

Reversible co-morbidities and lifestyle factors that might accelerate progression should be identified and treated promptly, especially in patients with HCM and DCM (Table 2). Exercise is an important component of patient management, but optimal exercise doses for patients with inherited cardiomyopathies, and in ARVC for genotype-positive relatives, are still evolving (132,133). Current knowledge suggests that exercise prescriptions should be individually tailored according to patient-related factors (such as cardiomyopathy type, symptoms and severity of cardiac dysfunction, presence/absence and type of arrhythmic gene mutation, age, and general health) and exercise-related factors (such as sports type, intensity, and duration) (Figure 8).

FUTURE DIRECTIONS

In coming years as more people undergo genome sequencing, increasing numbers of cardiomyopathy gene variants will be identified in patients and the general population, and classification of variant pathogenicity will be an ongoing challenge. Patient genomes will also be mined for clinically useful information in addition to causative rare variants, including assessment of genetic risk of co-morbidities and cardiac complications by PRS, and identification of variants that may be amenable to specific pharmacologic or other therapies (134). Expanded opportunities will arise for genotype-phenotype studies at the whole heart, cellular and molecular levels and much will be learned about the basic mechanisms of disease, using patient-derived cell systems, animal models, and multi-omics analyses of human heart tissues, paving the way for development of novel biomarkers, new disease-

modifying therapies and clinical trials. New methods for cardiac phenotype assessment and monitoring are expected to emerge from machine learning analyses and ongoing refinement of imaging tools. Clinical management is likely to increasingly involve patient-derived measures, with arrhythmia detection and therapeutic monitoring informed by dynamic input of biological data from wearable devices. As a collective result of these changes, we will also see a progressive reappraisal and refinement of our disease classification systems, such that these systems also take into account specific genes and disease pathways, rather than merely grouping together patients because they have a superficially similar clinical phenotype (i.e. reduced left ventricular ejection fraction in DCM). This theme of the refinement of disease classification as we progressively implement precision medicine approaches is covered in depth in the final article in this JACC series (ref xx).

CONCLUSIONS

Advances in genome sequencing, cardiac imaging techniques, and experimental model systems are laying the groundwork for a new era of precision medicine in the inherited cardiomyopathies. This should not only have health benefits for adult cardiomyopathy patients and their families but also for subsequent generations of children at risk. While valuable information can be gained by these approaches, precision medicine dictates a shift in focus back to the individual patient, and for clinical practice to move away from a ‘one-size-fits-all’ approach. It relies on a comprehensive evaluation of every cardiomyopathy patient to identify factors that contribute to disease causation and to assess the impact that these factors have on myocardial structure and function. Accordingly, individualized approaches to clinical management may encompass targeted disease-modifying interventions or the more directed use of established heart failure and anti-arrhythmic therapies. These factors appear likely to shape the way medicine and cardiology are practiced, as it appears unlikely that the

existing workforce of cardiologists in the USA and globally will be able to take on the significant increase in time commitment that will be required to investigate, understand and treat each individual patient and their families. However, the prospect of tailored, more effective precision medicine therapies based on a comprehensive evaluation of cardiomyopathy phenotype, genotype and environmental factors is driving the field forward at an unprecedented pace, and we eagerly await the clinical revolution that will ensue.

HIGHLIGHTS:

- Much has been learned about genetic causes of inherited cardiomyopathy.

- However, translation of this knowledge into patient management has been limited.

- Comprehensive patient evaluation is needed to identify relevant genetic and environmental factors and provide detailed phenotype assessment.

- Precision medicine promises to leverage data on the individual patient to implement personalized approaches to disease management

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FIGURE LEGENDS

Central Illustration. Key steps for implementing precision medicine in cardiomyopathies. For patients with suspected inherited cardiomyopathies, it is important to first establish a clinical diagnosis. Patients need to undergo comprehensive assessment to identify all the factors that may be contributing to disease and to evaluate the cardiac phenotype. Risk stratification and precision management will increasingly involve therapies targeted towards the causes of disease as well as alleviation of symptoms.

Figure 1. Location of cardiomyopathy disease genes. Schematic showing cardiomyocyte subcellular architecture and location of key disease genes. For HCM and ARVC, these genes are clustered in the sarcomere (central inset) and desmosomes (right inset), respectively. DCM disease genes are found in these regions and also along an axis of force transmission that links the sarcolemma and extracellular matrix to cytoskeletal components and the nucleus (left inset).

Figure 2. Pipeline for establishing a clinical diagnosis for patients with suspected cardiomyopathies. ACM = arrhythmogenic cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; AS = aortic stenosis; CMR = cardiac magnetic resonance imaging; DCM = dilated cardiomyopathy; G-DCM = genetically-mediated DCM; HT = hypertension; LV = left ventricle; LVH = left ventricular hypertrophy; RV = right ventricle.

Figure 3. Three cases with a hypertrophic phenotype and different diagnosis. Transthyretin (TTR) cardiac amyloidosis: ECG shows first degree AV block and left bundle branch block, (**A**), with concentric hypertrophy (**B**), widespread non-ischemic late gadolinium enhancement (**C**) and markedly increased native T1 (MOLLI 1206ms @ 1.5T, **D**) seen on CMR.

Sarcomeric HCM: ECG shows left ventricular hypertrophy (**E)**, and CMR shows asymmetric hypertrophy (**F**), non-ischemic late enhancement in the hypertrophied septum, particularly at the right ventricular insertion points (**G**) and native T1 is mildly raised (MOLLI 1098ms @ 1.5T, **H**). Anderson-Fabry disease: ECG shows borderline PR duration, broad left bundle branch block, and left ventricular hypertrophy (**I**), CMR shows asymmetric hypertrophy (**J**), basal infero-lateral non-ischemic late enhancement (**K**) and reduced native T1 (MOLLI 893ms @ 1.5T, **L**).

Figure 4. Characteristic CMR features of ARVC. **(A)** Right ventricular (RV) dilation seen on short axis images. Diastolic (**B**) and systolic (**C**) images in the RV outflow plane showing RV anterior wall akinesis (arrows) and inferior wall dyskinesis (arrowheads). (**D**) Focal areas of dykinesis (microaneuryms; arrowheads) in the RV free wall seen on axial cine image. (**E**,**F**) Foci of late gadolinium enhancement (arrowheads) in a non-vascular distribution. (**G**) RV free wall longitudinal strain assessed using feature tracking CMR software. When compared to a normal study (**H**), there is a reduced magnitude of global strain (-20 vs -33) and increased dispersion (arrowheads), with widening and reduced coordination of the segmental peak strains in a patient with ARVC (**I**).

Figure 5. Factors that contribute to cardiomyopathy phenotypes. The clinical manifestations of any given deleterious rare variant will be determined by the effects of the variant itself and the patient context.

Figure 6. Myocardial phenotype “wheel of fortune”. Cardiomyopathy phenotypes (P) such as left ventricular ejection fraction or wall thickness are continuous variables (outer colored circle). Inner circles represent variable effects (gradations of color) of background rare

variants (Rv), common variants (Cv), co-morbidities (Co), lifestyle factors (L) and ethnicity (Eth). For any given value of P (arrow), the relative contributions of a primary gene mutation and modifying factors will differ in individual patients.

Figure 7. Distribution of left ventricular scar using contrast enhanced CMR for different genetic subtypes of arrhythmogenic left ventricular cardiomyopathy (ALVC) versus DCM. *DSP* and *FLNC* genotypes show a characteristic subepicardial, ring-like scar pattern (yellow arrowhead) whereas non-*DSP*/*FLNC* genotypes are more heterogeneous, but with overall less scar and lower left ventricular ejection fraction. *DSP*/*FLNC* genotypes have more regionality in LV impairment. Adapted from (107). LGE = late gadolinium enhancement; RV = right ventricle.

Figure 8. Exercise recommendations for patients with inherited cardiomyopathies. Exercise prescriptions will ideally be individually tailored and take patient-related and exercise-related factors into account.

TABLE 1. Moderate- and high-confidence cardiomyopathy disease genes and phenocopies

Gene	Protein	Rare variants*			Common variants† (trait)	Notes
		HCM	G-DCM	ARVC /ACM		
ACTC1	Actin alpha cardiac muscle	+++	++			Sarcomeric protein. Strongly associated with HCM. DCM/LVNC often co-occur. Also associated with RCM and CHD.
ACTN2	Actin alpha 2	++	++			Skeletal sarcomeric protein. Mixed phenotypes described within families including HCM, DCM, LVNC and arrhythmias.
ALPK3	Alpha kinase 3	+++	++		Y (DCM)	Nuclear kinase protein. Biallelic variants cause pediatric DCM transitioning to HCM in adulthood with dysmorphic features. Heterozygous rare variants may cause mild cardiomyopathy.
BAG3	BAG cochaperone 3		+++		Y (DCM, LV EF/EDV/ ESV, HF)	Chaperone protein. Strongly associated with DCM. Also associated with AD myofibrillar myopathy which can present with concomitant HCM/RCM.
CSRP3	Cysteine and glycine rich protein 3	++	+		Y (LV EF/ESV)	Cytoskeletal regulatory protein. Moderate association with HCM. Weakly associated with DCM.
DES	Desmin		+++	++		Cytoskeletal protein. Associated with DCM and ACM overlap phenotypes that can co-occur with variable CD and myopathy. Rarely associated with RCM.
DMD	Dystrophin		+++			Cytoskeletal protein. Associated Duchenne and Becker muscular dystrophy (skeletal ± cardiac involvement), can present as isolated X-linked DCM.

DSC2	Desmocollin		+	+++		Desmosomal protein. Strongly associated with ARVC. Rare cases of isolated DCM.
DSG2	Desmoglein		+	+++		Desmosomal protein. Strongly associated with ARVC. Rare cases of isolated DCM.
DSP	Desmoplakin		+++	+++		Desmosomal protein. Strongly associated with ACM with dominant right or left ventricular presentations. Can present as DCM. Flares of inflammation can present like myocarditis. Rarely associated with LVNC. Autosomal recessive disease causes cardio-cutaneous syndrome.
FBXO32	F-box only protein 32		++			Autophagy protein. Associated with severe autosomal recessive DCM.
FHOD3	Formin homology 2 domain containing 3	+++	+		Y (DCM, LV EF)	Sarcomeric function protein. Emerging strong evidence for association with HCM. Rare reports in DCM.
FLNC	Filamin C	++	+++	++	Y (DCM, LV EF/ESV)	Cytoskeletal protein. Primary association is with arrhythmic DCM. Moderate association with HCM and ARVC. Also associated with RCM, LVNC, CHD, arrhythmias and myofibrillar myopathy.
GLA	Galactosidase alpha	+++				Galactosidase protein. Associated with Fabry's disease. HCM phenocopy.
JPH2	Junctophilin 2	++	+			Cytoskeletal protein. Primary association is with HCM. Isolated cases of AR/AD DCM. Also associated with atrial fibrillation.
JUP	Junction plakoglobin			+++		Junctional plaque protein. Strong association with ARVC.
LAMP2	Lysosome associated membrane protein 2	+++	++			Membrane glycoprotein. Associated with X-linked Danon disease. Female carriers can present with isolated DCM or LVH. HCM phenocopy.

LDB3	Lim domain binding 3	+	++			Sarcomeric stabilization protein. Moderate association with DCM. Weak association with HCM and LVNC. Also associated with late onset myofibrillar myopathy.
LMNA	Lamin A/C		+++	+		Nuclear lamina protein. Strong association with DCM which co-occurs with CD and atrial and ventricular arrhythmias. Weakly associated with ARVC and LVNC. Also associated with AD Emery-Dreifuss muscular dystrophy.
MYBPC3	Myosin binding protein C	+++	+	+		Sarcomeric protein. Strongly associated with HCM. Weakly associated with DCM, LVNC and ACM.
MYH7	β-myosin heavy chain	+++	+++	+		Sarcomeric protein. Strongly associated with HCM. Less common association with DCM/LVNC, ACM and CHD. Also associated with Laing distal myopathy.
MYL2	Myosin light chain 2	+++	+			Sarcomeric protein. Strong association with HCM. Rare cases of isolated DCM.
MYL3	Myosin light chain 3	+++	+	+		Sarcomeric protein. Strong association with HCM. Rare cases of isolated DCM or ACM.
NEXN	Nexilin	+	++			Actin binding protein. Moderate association with DCM. Rarely associated with HCM and CHD.
NKX2.5	NK2 homeobox 5		++		Y (DCM/SV)	Transcription factor. Associated with DCM with variable AVB and CHD (ASD).
PKP2	Plakophilin		+	+++		Desmosomal protein. Strongly associated with ARVC. Rarely reports of isolated DCM.
PLN	Phospholamban	+	+++	+++	Y (LV EDV/ESV /SV)	Regulates sarcoplasmic reticulum Ca^{2+}/ATPase. Strongly associated with DCM with arrhythmias, ARVC and overlap phenotypes.

PPP131RL	Protein phosphatase 1, regulatory subunit 13 like		++			Desmosomal protein. Associated with severe pediatric AR DCM.
PRKAG2	Protein kinase AMP-activated non-catalytic subunit gamma 2	+++				Protein kinase. Associated with glycogen storage disease. Often co-occurs with ventricular pre-excitation, conduction block and atrial arrhythmias. HCM phenocopy.
RBM20	RNA binding protein		+++		Y (LV EF/ESV)	RNA binding protein. Strongly associated with severe arrhythmic DCM.
SCN5A	Voltage gated sodium channel 5A		+++	+		Voltage gated sodium channel subunit. Strongly associated with DCM with either tachy- or brady-arrhythmias or arrhythmias without DCM. Also associated with Brugada syndrome and Long QT syndrome.
TAZ	Tafazzin	+	+++			Mitochondrial protein. Associated with DCM/LVNC in Barth syndrome. Also reported in isolated infantile DCM/LVNC.
TMEM43	Transmembrane protein 70		++	+++		Nuclear membrane protein. Newfoundland founder mutation causing ACM with right or left dominant subtypes. 10-15% of cases meet criteria for DCM.
TNNC1	Troponin C1	++	++			Sarcomeric protein. Moderate association with both DCM and HCM.
TNNI3	Troponin I3	+++	++			Sarcomeric protein. Strong association with HCM and RCM overlap phenotypes. Also associated with DCM.
TNNI3K	Troponin I3 interacting kinase		++			Protein kinase. Several reports of families with DCM co-occurring with CD and ventricular arrhythmias.
TNNT2	Troponin T2	+++	+++			Sarcomeric protein. Strongly associated with both HCM and DCM. Also associated with LVNC and RCM.

TPM1	Alpha tropomyosin	+++	+++			Sarcomeric protein. Strongly associated with both HCM and DCM. Also associated with LVNC and RCM.
TTN	Titin	+	+++	+	Y (DCM, LV EF/EDV/ ESV/mass)	Sarcomeric protein. Strongly associated with DCM. Weakly associated with HCM and ACM. Also associated with AR myopathy.
TTR	Transthyretin	+++	+			Transport protein. Associated with systemic amyloidosis. HCM phenocopy.
VCL	Vinculin	+	++			Cytoskeletal protein. Moderate association with DCM. Weakly associated with HCM.

*Classification of genes according to level of human genetic evidence for roles in disease causation: +++ Gene has been associated with primary presentation of cardiomyopathy in multiple cases in the literature, with at least 5 instances of family segregation or de novo mutations; ++ Primary cardiomyopathy phenotypes reported in more than 10 individual cases, or 3-5 instances of family segregation or de novo cases (or 2-3 instances if recessive inheritance); + Gene of uncertain significance; primary cardiomyopathy phenotypes reported in up to 10 individual cases, 1-3 instances of family segregation or do novo cases, OR cardiomyopathy is reported primarily in cases with syndromic features or skeletal myopathy.
†Target genes implicated in genome-wide association studies (GWAS) of heart failure, DCM, or echocardiographic/CMR parameters of cardiac structure and function.
ACM = arrhythmogenic cardiomyopathy; AD = autosomal dominant; AR = autosomal recessive (includes biallelic inheritance); ARVC = arrhythmogenic right ventricular cardiomyopathy; AD = atrial septal defect; AVB = atrioventricular conduction block; CD = conduction disease; CHD = congenital heart disease; DCM = dilated cardiomyopathy; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HCM = hypertrophic cardiomyopathy; LV = left ventricular ; LVNC = LV non-compaction; RCM = restrictive cardiomyopathy; SV = stroke volume; Y = yes.

TABLE 2. Key aspects of clinical management in gene mutation carriers

	HCM	G-DCM	ARVC/ACM
Affected (phenotype-positive) individuals			
Pharmacological therapy	β-blockers, non-dihydropyridine calcium antagonists, and disopyramide for LVOT obstruction. Avoidance of excess diuresis, vasodilators, digoxin. Prophylactic anticoagulation with VKA or DOAC in patients with AF or atrial flutter.	β-blockers +ACE/ARB. Consider sacubutril/valsartan, aldosterone antagonists, SGLT2 inhibitors, ivabradine, diuretics. Prophylactic anticoagulation with VKA or DOAC in patients with AF or atrial flutter.	β-blockers for all. ACE/ARB if reduced RV or LV function. Sotolol or flecainide is symptomatic PVCs / NSVT or sustained VT. Amiodarone if sotolol and flecainide fail and catheter ablation not preferred.
SCD risk prediction/ICD indications	For primary prevention, risk markers include age, LV wall thickness, NSVT, LA diameter, LVOT gradient, family history of SCD, unexplained syncope. Patients with LV systolic dysfunction also at higher risk of SCD.	Personal history of cardiac arrest/VF or sustained VT. For primary prevention if LV EF <35% with NYHA II-III and expected survival >1 year. Consider lower threshold for ICD with highly arrhythmic gene mutations eg. *LMNA*, *SCN5A*, *FLNC*, *RBM20*, *PLN*, *DSP*, *DES*, *DSG2*, *TMEM43* variants.	Personal history of cardiac arrest/VF or sustained VT. For primary prevention risk markers include extent of RV ± LV dysfunction, PVC burden, male gender, extent of T wave inversion, exercise plans. Consider lower threshold for ICD with multiple desmosomal gene mutations or *TMEM43* Newfoundland founder mutation (ARVC) or highly arrhythmic gene mutations eg. *LMNA*, *FLNC*, *RBM20*, *PLN*, *DSP*, *DES*, variants (ACM).
Invasive procedures	Alcohol septal ablation for reduction of LVOT obstruction. Dual chamber RV pacing in	Cardiac re-synchronization therapy if LV EF <35%,	EPS can play a role in risk stratification.

	selected patients with LVOT obstruction. Catheter ablation in selected patients with AF or sustained ventricular arrhythmia.	NYHA >II and LBBB (QRS>120ms)	VT ablation is recommended if recurrent VT or ICD shocks despite antiarrhythmic therapy.
Treat key co-morbidities and lifestyle risk factors	Treat hypertension. Avoid obesity. Patients with LVOT obstruction should avoid excess alcohol, stimulants, dehydration, temperature extremes.	Restrict alcohol. Promptly treat arrhythmias. Monitor during anthracycline chemotherapy. Carefully manage other cardiovascular risk factors.	
Exercise recommendations	Athletes: competitive sports contraindicated if symptoms, history of cardiac arrest, exercise-induced VT, LVOT gradient >50 mmHg, abnormal blood pressure response to exercise. Recreational sports: permitted but only after careful assessment in expert centers.	Athletes: competitive and endurance sports not advisable if symptoms, unexplained syncope, LV EF <40%, extensive LGE on CMR, frequent/complex VA, family history of SCD, arrhythmic gene mutation (eg. *LMNA*, *FLNC*). Recreational sports: permitted	Athletes: avoid competitive and endurance sports. Recreational sports: permitted at low levels.
Unaffected (phenotype-negative) individuals			
Monitoring method	ECG, echo.	ECG, echo.	ECG, Holter, echo or CMR.
Frequency of monitoring	From mid-adolescence, 1-5 yearly.	From mid-adolescence (if adult onset DCM in other family members), 1 to 5-yearly	From 10-12 years age, ECG/Holter - yearly, imaging 2- to 3-yearly.
Treat key co-morbidities and lifestyle risk factors	Treat hypertension. Avoid obesity.	Advise limits to alcohol. Promptly treat arrhythmias. Monitor during anthracycline chemotherapy. Carefully manage cardiovascular risk factors.	

Exercise recommendations	Competitive sports: permitted. Recreational sports: permitted.	Competitive sports: permitted, needs annual review. Recreational sports: permitted	Athletes: avoid competitive sports. Recreational sports: permitted at low levels.

ACE/ARB = angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF = atrial fibrillation; CMR = cardiac magnetic resonance imaging; DCM = dilated cardiomyopathy; DOAC = direct-acting oral anticoagulants; EF = ejection fraction; EPS = electrophysiological studies; ICD = implantable cardioverter-defibrillator; LA = left atrial; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV= left ventricular; LVOT = outflow tract; NSVT = non-sustained ventricular tachycardia; NYHA = New York Heart Association; PVC = premature ventricular contractions; RV = right ventricular; SCD = sudden cardiac death; SGLT2 = sodium-glucose transport protein 2; VA = ventricular arrhythmias; VF = ventricular fibrillation; VKA = vitamin K antagonist; VT = ventricular tachycardia.