Dilated cardiomyopathy in the era of precision medicine: latest concepts and developments

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Abstract

Dilated cardiomyopathy (DCM) is an umbrella term entailing a wide variety of genetic and non-genetic etiologies, leading to left ventricular systolic dysfunction and dilatation, not explained by abnormal loading conditions or coronary artery disease. The clinical presentation can vary from asymptomatic to heart failure symptoms or sudden cardiac death (SCD) even in previously asymptomatic individuals. In the last 2 decades, there has been striking progress in the understanding of the complex genetic basis of DCM, with the discovery of additional genes and genotype–phenotype correlation studies. Rigorous clinical work-up of DCM patients, meticulous family screening, and the implementation of advanced imaging techniques pave the way for a more efficient and earlier diagnosis as well as more precise indications for implantable cardioverter defibrillator implantation and prevention of SCD. In the era of precision medicine, genotype-directed therapies have started to emerge. In this review, we focus on updates of the genetic background of DCM, characteristic phenotypes caused by recently described pathogenic variants, specific indications for prevention of SCD in those individuals and genotype-directed treatments under development. Finally, the latest developments in distinguishing athletic heart syndrome from subclinical DCM are described.

Keywords Dilated cardiomyopathy · DCM · Cardiomyopathies · Precision medicine · Inherited cardiac diseases · ARVC · LMNA · FLNC · BAG3 · TMEM43 · PLN · DSP · Athletic heart syndrome · Hypokinetic non-dilated cardiomyopathy · Molecular cardiology · Heart failure

Introduction

Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) systolic dysfunction and LV enlargement, in the absence of abnormal loading conditions such as hypertension, valvular disease, or coronary artery disease (CAD) that could explain the myocardial abnormality [1–3]. The presence of the disorder is defined by an LV end-diastolic diameter (LVEDD) greater than 2 standard deviations (SD) of the predicted values and LV fractional shortening $< 25\%$ or an LV ejection fraction (EF) $< 45\%$ [2]. Predicted values are calculated according to the formula of Henry, corrected for age and body surface area, and are expressed as a percentage of the predicted diameter as follows: Predicted

$$LVEDD = (45.3 \times \text{body surface area}^{0.3}) - (0.03 \times \text{age}) - 7.2$$

[4]. A value of LVEDD $> 112\%$ (> 2SD) is a diagnostic criterion for DCM while a value $> 117\%$ (2SD $+ 5\%$) increases specificity. Until recently, the management of DCM patients has involved traditional heart failure management approaches including drugs, devices, and heart transplantation when indicated. The prognosis of DCM patients has significantly improved over the last decades due to pharmacological and non-pharmacological advances, earlier diagnosis due to familial screening, and pre-participation cardiac evaluation and individualized long-term follow-up. In the past few decades the prognosis of DCM has significantly improved, and survival along with no need for heart transplantation has risen to $> 80\%$ at 8-year follow-up [5].

Classification of cardiomyopathies

Over the years there have been several attempts to classify cardiomyopathies. The American Heart Association (AHA) has adopted a different approach from the European Society

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of Cardiology (ESC). The AHA firstly differentiates primary cardiomyopathies (i.e., those predominantly affecting the heart) which are further subdivided to genetic, acquired, or mixed according to their etiology [6]. In 2007 the ESC proposed a classification of cardiomyopathies based on their phenotypic and morphological characteristics, further subdividing them to familial and non-familial (secondary) forms [1]. However, due to overlapping phenotypic expression and variable penetrance, cardiomyopathies often cannot be clearly assigned to a specific category [1, 3, 6, 7].

Classification concepts of dilated cardiomyopathy

Over the past few decades, the etiology and natural history of DCM have been further elucidated [1, 8–11]. It has been demonstrated that various etiologies, causing LV dysfunction may manifest with the same clinical phenotype as DCM [12–14]. According to the ESC classification of cardiomyopathies, DCM can be further subdivided into two main groups, genetic or acquired. There are, however, several cases in which the phenotypic expression is strongly affected by the environmental stressors of the individual. The final phenotypic expression seems to be an amalgam of the genotype along with the environmental factors. In 2016. Pinto et al. published a position paper for a revised definition of DCM, introducing a new clinical phenotype and diagnostic criteria for relatives, allowing for better recognition of relatives at risk, while simultaneously emphasizing that DCM may develop after gradual escalation through a continuous spectrum of milder clinical expressions [2].

Epidemiology

DCM is the commonest indication for heart transplantation and the third most common cause of heart failure [6]. The continuous reclassification and definition amendments of DCM throughout the past decades led to ambiguous data regarding its epidemiology [15]. In 2007, the ESC Working Group on Myocardial and Pericardial Diseases published a position statement that defined cardiomyopathies, segregated them into morphological groups and set diagnostic criteria for each group for both, the probands and their relatives [1]. The prevalence of DCM is estimated to be about 1:2500 in the general population, but this ratio may be an underestimation [16, 17]. Familial DCM has been reported to have a prevalence of 30–50% of the total DCM cases, while a gene is identified in 20–40% of those [18–20]. The prevalence seems to be slightly higher in men, with a female to male ratio between 1:1.3 and 1:1.5 [21–23]. DCM has an annual incidence of sudden cardiac death (SCD) between 2 and 4%

[24]. In a registry of survivors of aborted SCD, DCM was found to be the underlying etiology in 10–19% [25]. SCD may occasionally be the initial manifestation of DCM [24, 26, 27] including victims with no abnormal autopsy findings [27, 28].

Etiology

DCM entails a broad group of diseases, acquired or genetic, which result in a similar phenotype. The clinician should always exclude secondary causes before giving the diagnosis of "idiopathic DCM" since some causes may be reversible [29]. The causes of DCM can be classified into genetic and acquired, though the two are not mutually exclusive. Sometimes a genetic predisposition along with the additional effect of environmental factors is what leads to the appearance of the phenotype of the disorder [30, 31].

Acquired DCM

Drugs and toxins

Several drugs and toxins, the most common being excess ethanol consumption, cocaine, chloroquine, psychiatric drugs (clozapine, olanzapine), and antineoplastic drugs such as anthracyclines, may directly damage the myocardium causing an acquired form of DCM. Some drugs or toxins can cause acute LV dysfunction, while exposure in toxins such as anthracyclines may lead to LV dysfunction several years after treatment (late-onset cardiotoxicity) [32]. Alcoholic cardiomyopathy accounts for up to 32% of cases of DCM [33]. Alcohol affects the heart in a dose-dependent manner, while abstinence has the potential for LV systolic dysfunction reversal. On the other hand, anthracycline treatment has typically irreversible cardiotoxic effects [32].

Inflammatory dilated cardiomyopathy

Myocardial injury caused by infectious agents (viral or bacterial myocarditis), autoimmune disorders (i.e., sarcoidosis), toxic agents (i.e., cocaine), or other factors [34] may trigger an inflammatory response starting with the activation of a proinflammatory cascade of cytokines, followed by an immune response and eventually leading to LV dysfunction and dilatation [35]. Myocarditis progresses to DCM in up to 30% of cases [34]. Almost half of DMC cases show evidence of inflammation in the myocardium [36].

The entity of autoimmune myocardial inflammation has also been recognized. Patients presenting with infection-negative myocarditis may progress to DCM [37]. These cases often occur with a familial inheritance pattern. Serum organ-specific anti-heart antibodies may be found

in symptom-free relatives of DCM patients and are associated with mild LV dysfunction as well as potential progression to DCM [37–39].

COVID-19 and myocardial damage

Myocardial damage, as indicated by elevated cardiac troponin (cTn) levels and evidence of myocardial edema, and myocardial fibrosis in cardiac magnetic resonance (CMR), are well-recognized cardiac complications of the novel coronavirus, Sars-CoV-2. These abnormalities may occur independently of illness severity, time from the original diagnosis, and preexisting conditions [40]. Elevated cTn is associated with adverse outcomes and may dictate decisions for hospitalization and further imaging tests in COVID-19 patients [41]. It is suggested that inflammation due to COVID-19 may increase the risk for the development of heart failure with preserved LVEF or DCM. In a case series of 21 COVID-19 patients, 33% developed cardiomyopathy [42]. Prospective evaluation of COVID-19 patients is required to evaluate this hypothesis.

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a rare and potentially life-threatening entity in which heart failure develops during the last trimester of pregnancy or in the first few months after delivery [43]. It has been associated with older age, multiparity, presence of hypertension with or without pre-eclampsia, and Afro-Caribbean ethnicity [44]. The conversion of prolactin to an angiostatic factor mediated by oxidative stress is a critical step in the pathogenesis of the disease [45]. Pathogenic variants in genes associated with typical DCM (TTN, MYBPC3) have been detected in cases of PPCM, reinforcing the notion that the combination of genetic predisposition and environmental stressors may decrease the threshold for the expression of the DCM phenotype [44–46].

Combined factors

All the abovementioned etiologies are not mutually exclusive and may occur in combination [2]. For instance, patients who are carriers of pathogenic variants may also suffer episodes of myocarditis or report excessive ethanol intake, which may sequentially aggravate their overall clinical picture. It is thus required to recognize and remove any environmental risk factors that may worsen the phenotype of someone already at risk of the disease.

Genetic causes of DCM

Genetic background and inheritance patterns

Various patterns of inheritance have been recognized, including autosomal dominant, X-linked, autosomal recessive and matrilinear transmission [1, 8, 9, 16, 47, 48]. The genetic yield of DCM is estimated to be about 20–37% [16, 49, 50]. Until now, more than 50 DCM related genes have been reported [46, 51]. With the development and advances of sequencing technologies, the analysis and discovery of more genes involved in DCM has become feasible, decreasing the frequency of "idiopathic DCM". Studies using next-generation sequencing have identified the presence of two or more variants in more than 38% of affected cases of DCM [52] suggesting a pattern of oligogenic rather than monogenic inheritance in some patients. Of note, there is a considerable overlap of genes involved in the pathogenesis of DCM and other forms of cardiomyopathy, or channelopathies such as Brugada syndrome [2, 7]. The presence of more than one pathogenic or likely pathogenic variants in an individual, as well as variants that cause an overlapping cardiomyopathy phenotype, may explain the variable penetration and phenotypic expression, even within the same family.

Most common genes involved in DCM

A vast array of DCM causative variants have been described so far. These can be classified according to the functional disruption caused at the cellular level. Some of the most studied groups include:

- **Sarcomeric DCM — deficit in force generation** This group represents the most frequent genetic cause of DCM and consists of genes encoding sarcomeric proteins: titin, myosin, actin, troponin, and tropomyosin. Titin (*TTN*) is the largest sarcomeric protein within the myocardium. Truncating-*TTN* variants result in abnormally truncated proteins and are present in 25% of end-stage disease [30, 53], 20–25% of familial cases of DCM and in 18% of sporadic cases, following an autosomal dominant inheritance pattern [53, 54]. Further research is required to establish whether all truncating *TTN* variants are pathogenic.
- **Nuclear envelope defects (laminopathies)** Variants in the Lamin A/C gene (*LMNA*) are found in up to 6% of DCM cases [25, 55]. They are inherited in an autosomal dominant pattern and are characterized by an aggressive phenotype with conduction abnormalities and malignant ventricular arrhythmias (VAs). A high incidence of SCD often occurring before the development of significant LV dysfunction [56–58], with a mortality rate of 30%

at 12 years of follow-up has been reported [59]. The median age of onset is between 30 and 40 years while the penetrance is almost complete by the age of 70 [59]. The detection of a pathogenic *LMNA* variant lowers the threshold for an implantable cardioverter defibrillator (ICD) for primary prevention of SCD regardless of the LVEF [60].

- **Force transmission deficit (cytoskeletal cardiomyopathy)** This group involves genes encoding proteins comprising the cytoskeleton like filamins, dystrophin, and desmin. Pathogenic variants in these genes can lead to muscular dystrophies that are very often associated with DCM. Desmin (*DES*) encodes a cytoskeletal protein, a muscle-specific intermediate filament, that helps integrate the sarcolemma, parts of the nuclear membrane, and the Z-disk. Variants in *DES* may cause a wide phenotypic spectrum of different or overlapping cardiomyopathies, skeletal myopathies, or mixed myopathies (skeletal and cardiac). Cardiac manifestations may be expressed in the form of restrictive cardiomyopathy, DCM, conduction system disorders, Vas, or SCD [61]. Dystrophin (*DMD*) is located in the X chromosome, showing an X-linked pattern of inheritance. It has an important role in the formation of a mechanical link between the intracellular cytoskeleton and the extracellular matrix. Heart involvement is found in 90% and 70% of the cases of Duchenne's and Becker's muscular dystrophies respectively [62, 63]. Filamins are large proteins that are responsible for the stabilization of actin filaments and their linkage to the cell membrane. Filamin C truncation variants are associated with a severe arrhythmogenic DCM phenotype, without the presence of overt skeletal muscle disorder [64].

- **Deficits of intercellular adhesion (desmosomal cardiomyopathies)** Pathogenic variants in genes encoding desmosomes have been described in both arrhythmogenic right ventricular cardiomyopathy (ARVC) and DCM. Up to 13% of DCM cases have been associated with desmosomal mutations [65].

Other Variants in the *RBM20 gene*, involved in the regulation of titin splicing, cause a DCM phenotype with frequent malignant VAs [7, 66]. *BAG3*, a gene encoding an antiapoptotic protein has also been implicated in the development of LV dysfunction and DCM phenotype [7, 67].
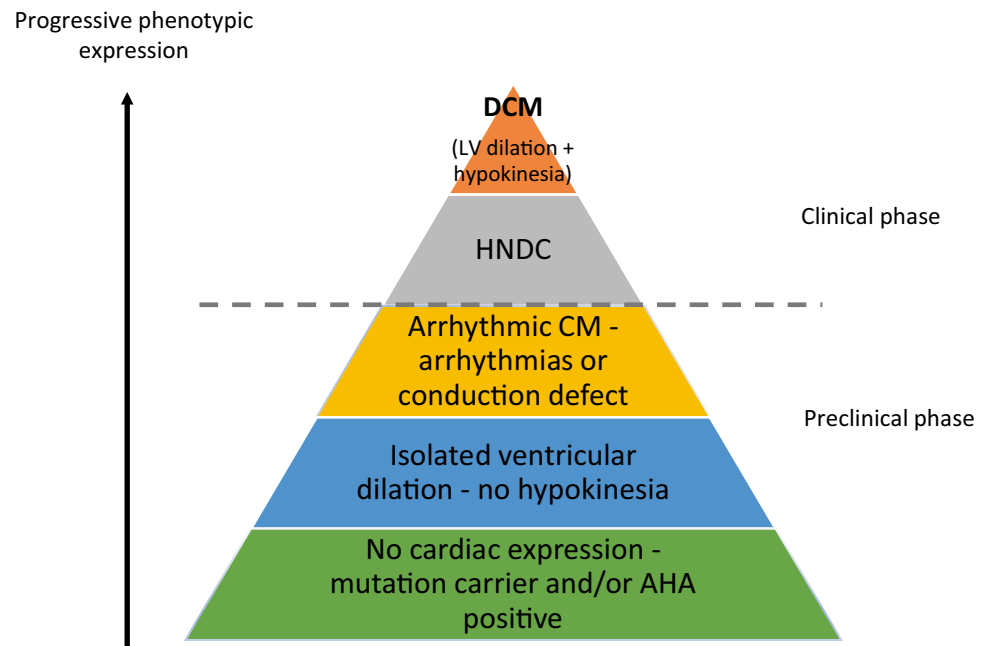
Diagnosis

DCM patients often show intermediate phenotypes not fulfilling the standard diagnostic criteria due to variable phenotypic expression and age-dependent penetrance [68, 69].

Advanced imaging techniques such as CMR are able to identify subtle or even extensive myocardial scar in patients with normal LV dimensions and function. Significant VAs and SCD may precede any evident structural or morphological changes. Pinto et al. attempted to overcome these limitations, by proposing a revised definition for DCM in 2016 and updating the diagnostic criteria for relatives of DCM patients. Three intermediate categories were proposed: isolated ventricular dilation, arrhythmic cardiomyopathy, and hypokinetic non-dilated cardiomyopathy (HNDC) [2] which filled the gap between no phenotypic expression and fully expressed DCM. HNDC was defined as "left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF < 45%), not explained by abnormal loading conditions or CAD." Furthermore, the concepts of variable penetrance and gradual progression of the disease from the preclinical to the clinical phase were emphasized, as well as the need for reclassification of the relatives after each follow-up. A preclinical phase with no or mild cardiac abnormalities such as the expression of anti-heart antibodies or mild LV dilatation was recognized in carriers of DCM-causing variants who were identified through family screening [37–39]. The spectrum of DCM was therefore segregated into different stages, some belonging in the preclinical, early phase with no clear phenotypic expression and others belonging to the clinical phase, as shown in Fig. 1. In 2019, Towbin et al. introduced the term "arrhythmogenic cardiomyopathy" via the HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy (ACM). ACM was described as a primary arrhythmogenic disorder of the myocardium incorporating genetic, systemic, infectious, and inflammatory disorders [70]. There is a significant overlap of the ACM phenotype with other cardiomyopathies, particularly DCM and should not be confused with the arrhythmic cardiomyopathy described as the preclinical phase of DCM by Pinto et al.

Diagnostic criteria of DCM in relatives

Family screening is essential in relatives of patients with DCM or HNDC, as it allows early detection of the disease and early treatment that may help improve prognosis and delay progression [34, 68]. Pinto et al. described diagnostic criteria in DCM relatives and defined what is considered familial DCM. Major and minor diagnostic criteria were proposed in DCM relatives (see Table 1). According to the findings, relatives are placed into the following 3 categories: definite disease, probable disease, or possible disease. This helps overcome the limitation of having several non-diagnostic abnormalities overlapping with normal phenotypes or may be seen in very common diseases such as hypertension. As the clinical picture is often dynamic, relatives should be recategorized if more criteria are met after each follow-up visit.

Fig. 1 Clinical spectrum of dilated cardiomyopathy. DCM, dilated cardiomyopathy; HNDC, hypokinetic non-dilated cardiomyopathy; CM, cardiomyopathy; AHA, anti-heart antibodies

In the absence of a definite pathogenic variant in a family, familial disease is defined as the presence of: (i) 2 or more individuals (first- or second-degree relatives) with definite DCM or HNDC or (ii) 1 patient fulfilling the diagnostic criteria for DCM or HNDC and a first-degree relative who suffered SCD < 50 years of age and autopsy-proven DCM [2].

Table 1 Diagnostic criteria for DCM relatives

Major criteria
1. LVEF > 45% and ≤ 50%, unexplained by other causes
OR
2. Unexplained LVED dilatation according to normograms (> 2SD + 5%)
Minor criteria
1. Complete LBBB, or AV block (1st degree or higher)
2. Unexplained ventricular arrhythmia (> 100 VPBs/24 h or NSVT at ≥ 120 bpm
3. RWMA in the LV without an intraventricular conduction defect
4. Late gadolinium enhancement of non-ischemic origin in CMR
5. Non-ischemic myocardial abnormalities (inflammation, necrosis ± fibrosis) on EMB
6. Serum organ-specific and disease-specific anti-heart antibody by ≥ 1 autoantibody tests
Disease probability
Definite disease:
Criteria for DCM or HNDC are met
Probable disease:
1 major + ≥ 1 minor criterion
OR
1 major + causative mutation identified in the proband
Possible disease:
2 minor criteria
OR
1 minor + causative mutation identified in the proband
OR
1 major (no major or genetic data in family)

CMR cardiac magnetic resonance, *EMB* endomyocardial biopsy, *LGE* late-gadolinium enhancement, *LVED* left ventricular end-diastolic, *LVEF* left ventricular ejection fraction, *NSVT* non-sustained ventricular tachycardia, *RWMA* regional wall motion abnormalities, *VPB* ventricular premature beats
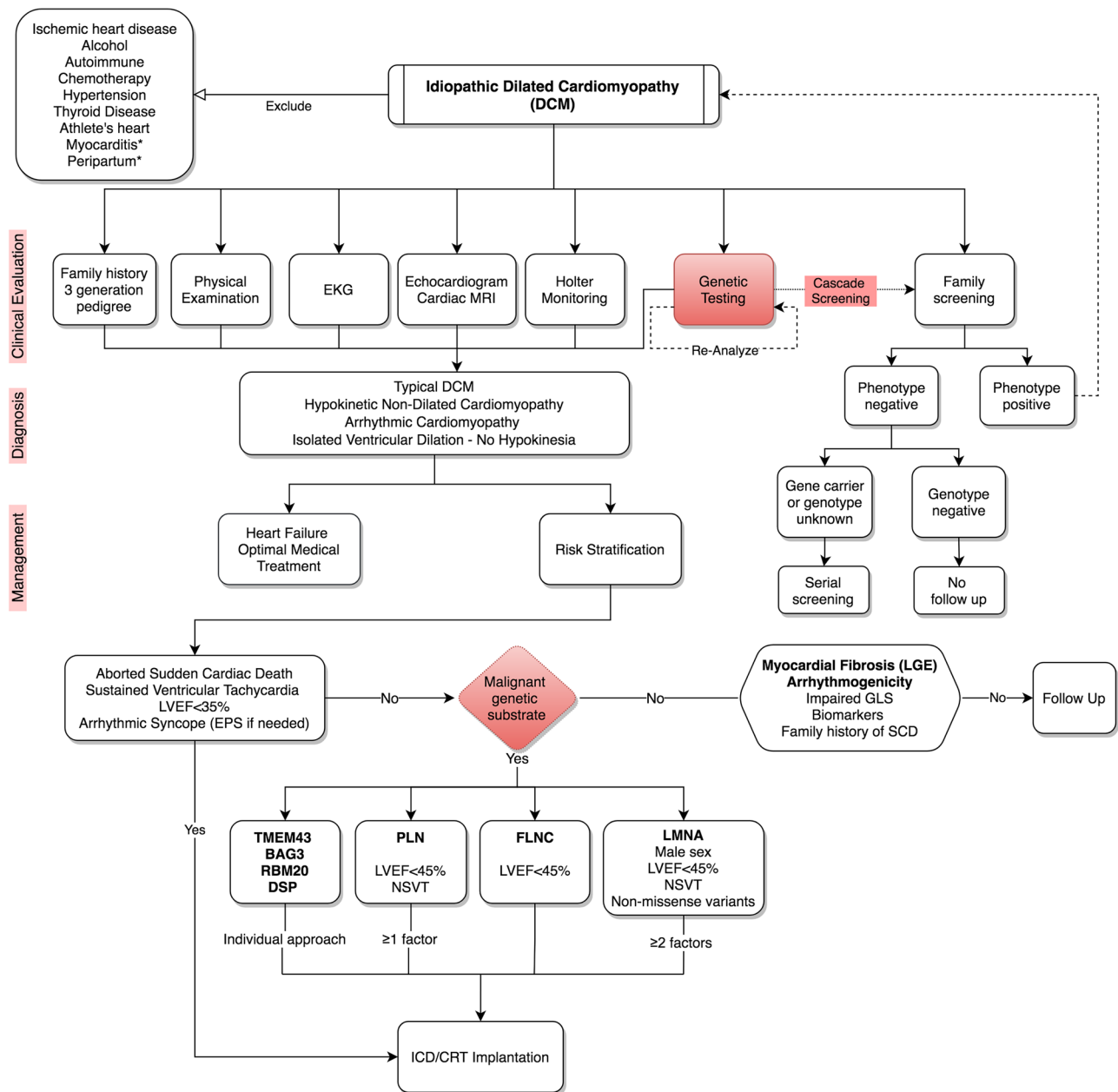
Fig. 2 A clinical management algorithm for DCM. CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; EPS, electrophysiological study; hs-Tn, high-sensitivity troponin; ICD, implanted cardioverted defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death. * A diagnosis of myocarditis or peripartum cardiomyopathy does not exclude the possibility of familial disease. # Genetic testing should be considered in all cases of DCM, including sporadic cases. An implanted cardioverted defibrillator may be still considered for patients not fulfilling established criteria of high risk of extensive myocardial fibrosis, ventricular arrhythmogenicity, elevated biomarkers

Diagnostic workup in patients and relatives

The broad spectrum of disorders leading to DCM mandates a systematic approach to facilitate the identification and management of rarer but specific forms of DCM. It should be emphasized that the diagnostic workup, management, and follow-up of DCM patients are a multifactorial process. Figure 2

depicts a management algorithm including the indications for ICD implantation according to the genetic substrate of DCM.

Basic evaluation should include personal and family history, physical examination, electrocardiogram (ECG), cardiac imaging and lab testing. The identification of disease-specific diagnostic clues (red flags) is critical *and should* guide further diagnostic workup [68]. This may include

CMR, endomyocardial biopsy (EMB), and genetic testing. If myocarditis is clinically suspected, EMB for detecting infectious agents via histology, immunohistology, and polymerase chain reaction is recommended [2]. When storage or metabolic diseases are suspected and cannot be confirmed otherwise, EMB may also be considered. Secondary etiologies leading to DCM, especially CAD should always be excluded. Exclusion of CAD in patients older than 35 years of age or younger patients with family history of early CAD or with significant CAD risk factors is recommended [2].

Laboratory testing should include hemoglobin and complete blood cell count, liver and kidney function tests, thyroid-stimulating hormone, serum iron, ferritin, calcium, phosphate, natriuretic peptides, Troponin, anti-heart antibodies, and urine analysis for detection of proteinuria [68]. Further testing may be required according to the yield of first-line testing if suspicion of a specific etiology arises.

Dysfunctional hearts are often metabolically deranged. However, the extent to which this might be detectable before the appearance of DCM phenotype is currently unknown. Different *biomarkers* may be released according to the pathophysiological process, such as strain, myocyte injury, and oxidative stress. The most commonly used biomarkers for heart failure patients are natriuretic peptides, brain natriuretic peptide (BNP) and NT-proBNP that are released during myocardial stretching. Galectin-3 (Gal-3) is an inflammatory component involved in the pathogenetic mechanisms of myocardial fibrosis and has been described as a prognostic marker since the presence of myocardial fibrosis poses a worse prognosis in DCM. The higher the Gal-3 levels the more intense the myocardial fibrosis and LV remodeling [71–73]. Interleukin-33/ST2, belonging to the family of Interleukin-1 (IL-1), is another biomarker reflecting inflammation and myocardial fibrosis [74] that may be used for risk stratification and prognosis in DCM. As a biomarker, it is considered superior to others such as BNP, troponins, and Gal-3 because it is not affected by age, sex, renal function, heart failure history, and body mass index (BMI) [75]. Other more common biomarkers or conditions reflecting a worse prognosis are increased troponins, anemia, and renal failure.

Electrocardiogram (ECG) abnormalities are reported in up to 80% of patients with DCM [76–78]. A distinct ECG phenotype seems to be related to specific genetic or acquired forms of DCM. Sinus node disease, AV conduction defects, and marked bradycardia are common in *LMNA* and *SCN5A* variants. Conduction abnormalities are characteristic of *DMD* and *DES*. Low voltage on the ECG, especially in the limb leads, are characteristic of *FLNC*, *PLN*, and *DSP* and may precede any echocardiographic changes. T wave inversion is found in *FLNC* and *DSP*. VAs are frequently observed before overt LV dysfunction in *LMNA*, *FLNC*, *DES*, *DSP*, and *SCN5A* carriers. The combination of conduction abnormalities and complex VAs is highly suggestive of

an *LMNA* variant. A "posterolateral infarction" pattern with pathologic Q waves (pseudonecrosis) in the inferior and lateral leads should raise suspicion of muscular dystrophy [79].

Specific ECG characteristics have been recognized as prognosticators in DCM. A meta-analysis suggested the potential use of QRS fragmentation and T wave alternans as prognostic markers for VAs [24]. Atrial fibrillation (AF) has been associated with a worse outcome and need for heart transplantation in DCM [80]. Left bundle branch block (LBBB), present in about a third of patients with DCM, may precede the development of structural changes in the heart and may serve as a poor prognostic indicator [81].

Current criteria for the diagnostic workup of DCM relatives include LBBB, AV block (PR > 200 ms or higher degree AV block), or unexplained VAs (> 100 ventricular premature beats in 24 h or NSVT at a rate of > 120 bpm [2]. In athletes, LBBB, QRS duration > 140 ms, frequent or complex ventricular arrhythmias, T wave inversion, and pathological Q waves are considered pathological and should prompt further investigation [82, 83].

Echocardiography

Echocardiography is vital in the diagnosis, follow-up, and family screening of DCM. LVEF is a vital parameter and an independent predictor of outcome, since low LVEF values and NYHA functional classes III–IV at baseline have been associated with a higher incidence of death or heart transplantation, in both adults and children [84]. LV dilatation has been described as a predictor of early VAs [29, 85]. Diffuse LV hypokinesia is usually seen but regional wall motion abnormalities may also be present. It is important to distinguish these from wall motion abnormalities due to CAD, especially if the abnormalities correspond to the anatomic perfusion of a coronary artery. Usually, LV eccentric hypertrophy is present in DCM, along with LV diastolic dysfunction. A restrictive LV filling pattern is independently associated with a poor outcome and heart transplantation [86]. Functional mitral regurgitation, if present, is independently associated with poor prognosis [87]. One of the strongest prognostic indicators in DCM is left ventricular reverse remodeling (LVRR), defined as an LVEF increase of > 10% or an LVEF > 50% and a decrease in indexed LVEDD of > 10% or indexed LVEDD of > 33 mm/m^2 at 24 months [88]. Right ventricular dilatation and dysfunction have prognostic significance and are correlated with a worse functional status and advanced LV failure [89].

Newer echocardiographic techniques, including assessment of myocardial strain and speckle-tracking deformation analysis have been used to detect early phase DCM in relatives with normal LVEF [90]. Global-longitudinal strain is currently being used as a predictor of mortality in

symptomatic DCM patients but also seems promising in identifying early ventricular dysfunction in asymptomatic variant carriers [90, 91].

Cardiac magnetic resonance

CMR is very helpful in assessing ventricular size and function along with tissue characterization, especially through the detection of fibrosis via late-gadolinium enhancement (LGE) [34].

In patients with desmoplakin disease who have a normal ECG and VAs of LV origin, the only abnormality detected has been LGE in LV [92]. Sepehrkhouv et al. demonstrated a distinct LGE pattern in patients with pathogenic *PLN* R14del variants in relation to the pattern seen in other hereditary cardiomyopathies [93]. Both of the aforementioned cardiomyopathies demonstrated fibrosis in the posterolateral wall of the LV, while *PLN* R14del also showed significantly more fibrosis in the free wall of the LV than the desmosomal variants.

Exercise stress imaging

Exercise stress imaging has shown some promising results as a potential tool in the diagnosis and prognosis of DCM. The distinction between individuals with DCM and otherwise healthy, athletic individuals is frequently challenging since the two may share an overlapping phenotype due to cardiac remodeling. Millar et al. indicated that an LVEF increase of > 11% during exercise echocardiography, may distinguish athlete's heart from early DCM [94]. Another study showed the utility of exercise stress CMR in distinguishing asymptomatic patients with suspected DCM from healthy individuals with exercise-induced cardiac remodeling. Patients who had genotype-positive and phenotype-positive DCM had a peak exercise cardiac index below the 35th percentile specific for their age and sex in contrast to healthy individuals [95]. The availability of tools that enable clinicians in distinguishing athlete's heart from DCM is vital for the prevention of SCD since athletes with a clinical diagnosis of DCM should be excluded from most competitive sports [96].

Familial screening

Familial evaluation is critical in the diagnostic workup of patients with DCM as it allows the identification of relatives with clinical or subclinical DCM in familial cases and provides critical information regarding the phenotypic expression of the condition [26]. Thus, families with an aggressive arrhythmic profile, high ventricular arrhythmia burden, or extensive myocardial fibrosis may be identified. Importantly, a negative family history of DCM does not exclude

familial disease, since systematic clinical screening may reveal asymptomatic or subclinical DCM cases [97].

All first-degree relatives should be screened with ECG and echocardiogram. Ambulatory Holter monitoring should be considered if there is evidence of an arrhythmic familial phenotype or symptoms suggestive of arrhythmia. Family screening should begin in childhood and repeated annually through adolescence and every 2–3 years in adulthood if no abnormalities are detected.

Genetic testing

According to the latest HRS expert consensus statement on arrhythmogenic cardiomyopathy, genetic testing should be performed in all individuals with a clinical diagnosis of cardiomyopathy or in decedents who were diagnosed with cardiomyopathy at necropsy [70]. The initially selected gene panel and subsequent interpretation should both be based on the phenotype of the patient. Cascade genetic screening and genetic counseling should be offered to first degree relatives if a pathogenic or likely pathogenic variant has been detected in the family [2].

Practice until today suggested that genotype and phenotype negative family members were assured that they carry no risk for developing DCM, and their follow-up was ceased. However, non-monogenic DCM cases have been described [98], and numerous variants that may potentially affect the phenotypic expression are still classified as variants of unknown significance [99, 100]. At the same time, environmental factors play a vital role in the expression of DCM. It is therefore plausible to say that genotype-negative relatives have a lower risk of developing DCM rather than no risk at all. Continuous surveillance but at more sparse intervals, possibly excluding genes with high penetrance such as *LMNA*, is an alternative strategy for these individuals.

Risk stratification

For years, risk stratification of DCM patients was based on the degree of LV dysfunction and the presence of symptoms. In symptomatic patients with LVEF < 35% and a predicted survival of more than 1 year, ICD implantation for primary prevention of SCD is indicated [60, 70, 101]. However, a considerable fraction of patients who experience SCD have an LVEF > 35% [102, 103]. An increasing amount of research supports the utilization of late gadolinium enhancement (LGE) in the risk stratification of DCM patients. LGE is an effective predictor of mortality, hospitalization, and SCD [104, 105]. The presence, extent, and patterns of LGE may also provide predictive data for malignant VAs or LV reverse remodeling [71, 105, 106]. In a meta-analysis by di

Marco et al., no significant correlation was found between LVEF (above or below 35%) and malignant VAs [105]. Instead, there was a significant correlation between VAs and the presence and extent of LGE. The correlation between LGE and VAs was maximal in studies that included only patients with primary prevention ICDs.

Due to systematic familial and preparticipation sports screening, DCM patients are commonly detected at an earlier and asymptomatic stage. The risk of heart failure-related events in these patients is low while the risk of life-threatening VAs and SCD may be high. Myocardial fibrosis and specific genetic substrate related to an arrhythmic phenotype have emerged as additional risk stratification markers.

Genotype–phenotype studies have led to the realization that patients with specific genotypes benefit from an ICD for primary prevention even in the absence of severe LV dysfunction. Patients carrying malignant LMNA variants were firstly recognized as a distinct group with a higher SCD risk [101]. In a recent HRS expert consensus document, recommendations for ICD placement in 4 more genes associated with an increased arrhythmic risk in moderately reduced LVEF (*BAG3*, *PLN*, *FLNC*, and *TMEM43)* were provided [107–111].

More specifically:

– **LMNA** In a cohort comprising 269 *LMNA* carriers, the presence of 2 or more of the following risk factors were associated with malignant VAs and SCD: non-sustained ventricular tachycardia (NSVT), LVEF < 45% at first evaluation, male sex, and non-missense mutations [59]. An ICD implantation is a class IIa indication for *LMNA* carriers and ≥ 2 of these risk factors [60, 70, 101].

– **BAG3** Various pathogenic BAG3 variants have been associated with DCM, characterized by high penetrance > 40 years and a high risk of progressive heart failure (HF) [67] (p. 3), [112–114]. A point mutation in *BAG3* gene is already known for causing myofibrillar myopathies with HCM or restrictive cardiomyopathy [67] (p. 3), [110] [113]. There was large phenotypic variability, with 8 out of 18 mutation carriers with DCM undergoing heart transplantation or dying of advanced heart failure, while 3 other carriers showed no penetrance [67]. Risk factors for adverse outcomes in patients with *BAG3* pathogenic variants include: male sex, decreased LVEF, and enlarged LVEDD [112].

– **PLN** A large multicenter cohort study found that carriers of the founder pathogenic R14del *PLN* variant were at high risk for malignant VAs or end-stage HF. Sustained or NSVT and LVEF < 45% were independent risk factors for the aforementioned outcomes [111]. High mortality and a poor prognosis were noted from late adolescence. Of note, R14del may cause both, DCM, and ARVC.

Therefore, in patients with phospholamban cardiomyopathy and LVEF < 45% or NSVT, an ICD should be considered (class IIa indication) [7].

– **FLNC** Filamin C plays an essential role in the attachment of sarcomeres to the plasmatic membrane. Truncating-*FLNC* variants have been associated with skeletal and cardiac myofibrillar myopathies [115] and an overlapping phenotype of left-dominant arrhythmogenic cardiomyopathy and DCM with high risk of malignant VAs and premature SCD. An autosomal dominant inheritance pattern was indicated with very high penetrance above 40 years old (97%). The phenotype comprised LV dilation and LV dysfunction, myocardial fibrosis, inferolateral negative T waves, and low QRS voltages on ECG. VAs were observed in 82% of the patients with a frequent family history of SCD (40 cases in 21 out of 28 families) [64]. Twelve carriers experienced sudden cardiac arrest with a mean LVEF of 39.6% ± 12% (range 21 to 54%). Accordingly, in individuals with FLNC mutation and LVEF < 45% an ICD is a class IIa indication [7].

– **TMEM43** A study in carriers of a transmembrane protein 43 variant (p.S358L-TMEM43) found better survival in those treated with an ICD rather than those under the conventional non-ICD management [110]. Males seem to have a worse prognosis than female carriers since affected males were hospitalized 4 times more often than affected females and died younger [116]. The most frequent ECG abnormality was poor R wave progression and was mostly seen in males [110].

– **DSP** Desmoplakin has been implicated in the development of LV dysfunction and may be involved in DCM and left dominant ARVC [117]. LGE in the LV may be the only abnormality found in patients carrying pathogenic variants of DSP with a normal ECG and arrhythmias of LV origin [92]. The mutation follows an autosomal dominant inheritance pattern.

Non-invasive parameters that have been used in ischemic cardiomyopathy such as premature ventricular complexes, NSVT, late potentials, and prolonged QTc [118] may also be relevant in DCM [119], though further studies are warranted.

Mild DCM in athletes vs. athletic heart syndrome

Left ventricular dilatation and low-normal left ventricular function (LVEF < 55%) occurs in 10–15% of competitive athletes, especially those engaging in intense endurance training. We demonstrate a practical diagram (Fig. 3) for differentiating between physiological left ventricular enlargement and subclinical DCM in athletes, adapted from Millar et al. [94].The combination of ECG, BNP, 24 h-Holter monitoring, and CMR failed to diagnose more than 30% of athletic individuals with mild DCM. Exercise

echocardiography has a much better diagnostic ability. The inability of an individual to increase LVEF by > 11% or an increase of peak LVEF > 63% has more than 80% sensitivity and 90% specificity for DCM [94].

Genotype dictates sports participation eligibility

In the 2020 ESC Guidelines on Sports Cardiology, specific recommendations have been described for sports participation in individuals with DCM. In the absence of limiting symptoms or exercise-induced VAs, participation in low to moderate-intensity recreational exercise should be considered in all DCM patients regardless of the LVEF [120]. In the presence of *LMNA* or *FLNC* genotype, high intensity exercise is prohibited, even in phenotype-negative individuals [120]. In contrast, participation in high- or very high-intensity exercise including competitive sports may be considered in asymptomatic individuals with the following: LVEF 45–50%, no frequent or complex VAs on Holter monitoring or during exercise testing, absence of LGE on CMR, ability to increase LVEF by 10–15% during exercise, and no high-risk genotype (*LMNA* or *FLNC).*

Genetics: the key to the future of DCM

Genetics have a promising potential to unlock and demystify many of the "blind spots" of the current management of DCM. The rapid expansion and advancements in genetics have come with its own challenges. The interpretation of genetic test results and accurate categorization of variants is a laborious and complicated process and should ideally be performed by multidisciplinary teams of molecular cardiologists, molecular pathologists, clinical geneticists, and genetic counselors.

Genotype-directed treatment

With the development of genetics, the concept of directing the treatment according to the genotype seems promising [121]. The understanding of gene-specific pathogenetic mechanisms and the unraveling of the functional effects of each variant should dictate different therapeutic strategies. The first attempts towards personalized management of DCM patients based on precision medicine have been made:

- The gain-of-function variant pR222Q in the *SCN5A* gene is associated with a severe form of arrhythmic DCM [122–124]. Standard heart failure therapies are relatively ineffective in these patients while a dramatic improvement was seen after administration of sodium-channel blocking drugs [123, 125, 126].
- The study of molecular changes involved in *LMNA*-mutated mice revealed increased cardiac activity of the
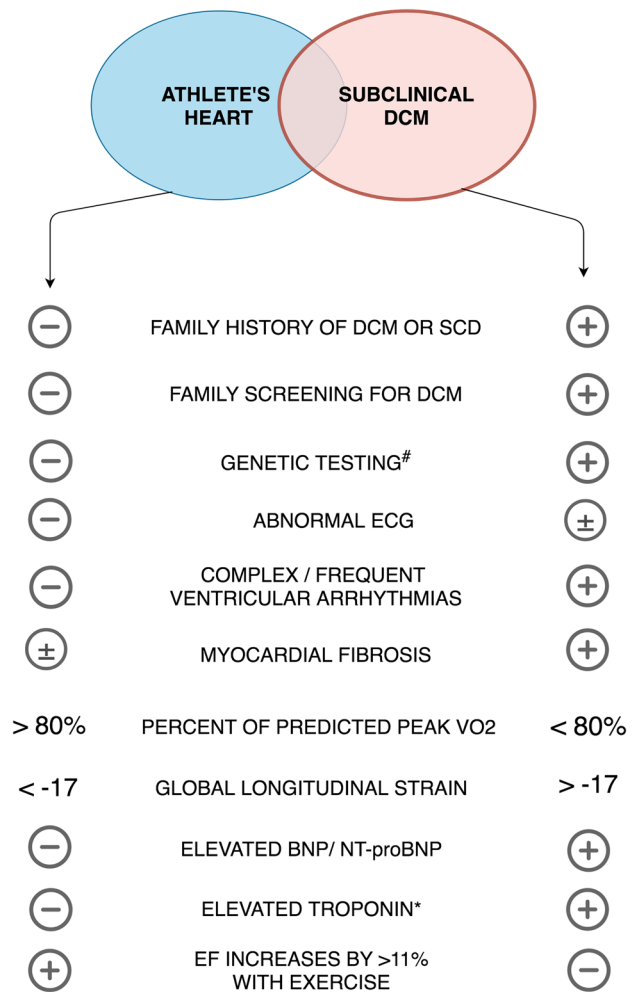

Fig. 3 Diagram for distinguishing between subclinical DCM and athletic heart syndrome. BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; NT-proBNP, N-terminal pro hormone BNP; SCD, sudden cardiac death; VO₂, oxygen consumption. # For a pathogenic or likely pathogenic variant in a gene associated with dilated cardiomyopathy, * excluding Troponin rise after strenuous exercise

ERK1/2, JNK and p38 MAP kinases. Treatment with a p38 inhibitor in *LMNA*-mutated mice showed prevention of LV dilation and LV dysfunction [127]. Increasing evidence of beneficial effects of p38 inhibition led to an international phase 3 clinical trial (NCT03439514), investigating the benefit of ARRY-371797 in symptomatic DCM patients carrying the pathogenic *LMNA* variant. This randomized, double-blind study is the first genotype-specific treatment study which will hopefully pave the way for other gene-specific treatments.

- Truncating mutations in the *TTN* gene seem to cause an increase in the cardiac metabolism that eventually leads to sarcomere dysfunction [128, 129]. Targeting the metabolic alterations caused by *TTN* mutations could offer a

potential gene-directed treatment for preventing progression into the DCM phenotype.

- Several gene-editing methods that may directly alter variants are currently under investigation. One such method is the genome-editing tool known as CRISPR/Cas9 which can target specific single-gene mutations such as DMD [130]. An in vivo genome editing study showed restoration of dystrophin expression and cardiac function in dystrophic mice [131].

- Another attractive approach is the utilization of induced pluripotent stem cells (iPSCs) and their subsequent differentiation into cardiomyocytes (iPSCs-CMs). Studies using iPSC-CM modeling have been used in *LMNA* [132], *DES* [133], *TNNT2* [134, 135], *PLN* [136], *RBM20* [137], *TTN* [138], *and BAG3* [139] variants, with a great fraction of these describing disruption of sarcomeres, decreased contractile force and dysfunctional regulation of calcium. In vivo use of β-blockers and calcium antagonists showed phenotype attenuation. Two iPSC-CM studies on PLN R14Del used targeted gene correction and lead to full phenotype reversion in vitro [136, 140].

Therefore, functional genomics may help in guiding treatment after the identification of the specific function-altering effects of genetic defects. The main challenges in this field are to identify the specific functional change and study any modifier genes or environmental factors that possibly affect the phenotype expression.

Genetic screening and variant classification

The most important step in genetic testing is the correct identification and interpretation of a pathogenic variant. Not only there is a multitude of variants of unknown significance (VUS), but also already published genes are currently being re-analyzed and re-classified. The ClinGen Cardiovascular Clinical Domain Working Group for cardiovascular disorders is currently in the process of adapting some guidelines of variant interpretation in the genes known to be involved in DCM [141]. Table 2 shows a list of the most up-to-date genes that should be included in the screening of DCM according to the latest position papers and guidelines. In addition, specific ICD indications and genotype–phenotype correlations are included.

Decoding the impact of disease-modifying factors

The large heterogeneity in phenotype expression of a specific genetic variant is a common clinical conundrum. It highlights the complex genetic architecture of DCM including the presence of multiple variants in the same individual, modifier genes, and the effect of environmental and demographic variables such as age, ethnicity [142], sex, and lifestyle. For example, deleterious *TTN* variants are more likely to manifest with a DCM phenotype in Europeans than in African-Americans [141]. A multi-parametric score, predicting the likelihood of DCM expression or arrhythmic risk, while considering the genotype and disease-modifying factors of each individual would be an ideal clinical tool but an enormous amount of research is needed before this is achieved and applied in practice.

Prognostic markers and genotype correlation: the importance of long term follow-up

An important parameter used during follow-up of DCM patients, that reflects improvement and a better prognosis is LVRR.

With adequate pharmacological and device treatment, about 40% of DCM patients experience significant LVRR [143]. After treatment initiation, the process of LVRR usually needs from 6 months to 2 years to take place [144]. LVRR and the time required to achieve it seem to be strongly related to the long-term prognosis of DCM patients [145]. Some important parameters shown to be affecting the prognosis of the disease and the likelihood of LVRR in the first stages of DCM, should be systematically assessed both at diagnosis and during follow-up. These include right ventricular function [146, 147], functional mitral regurgitation (MR) [148, 149], the presence of LBBB at diagnosis or during follow-up [81, 143].

Recent studies researched the correlation between genotype and the likelihood of LVRR independent of other clinical parameters. Verdonshot et al. suggest an increased likelihood of LVRR with *TTN* pathogenic variants [150]. In contrast, *LMNA* mutations seem to be strongly associated with a lower rate of LVRR. Likewise, another study by dal Ferro et al. demonstrated a lack of LVRR with specific genotypes including *FLNC*, *DES*, *DMD*, and other cytoskeletal Z-disk genes, followed by *LMNA* while again *TTN* mutations seemed to be associated with higher rates of LVRR under optimal medical treatment [151].

About 15% of DCM patients show normalization of their LV size and function after sufficient medical treatment. It seems that they maintain an apparently normal cardiac function during a 10-year follow-up. However, in a longer follow-up duration (15 years) 5% of these patients seem to deteriorate again. Their cardiac function progressively worsens and may die of refractory heart failure, require heart transplantation or ICD implantation [29, 152]. This is known as the "apparent healing phenomenon". Therefore, even patients that have apparently healed should continue their lifelong follow-up and medical treatment.

Table 2 Genes to be screened in the workup of DCM — genotype–phenotype correlation and ICD indications [20, 68–70, 154]

Gene (protein)	Frequency in patients with DCM [155]	Inheritance pattern	Phenotype [77, 156]
TTN [157] (Titin)	Truncating variants 18–25% [30, 53, 54]	AD, AR	Low prevalence of LBBB, atrial fibrillation Higher frequency of LVRR [158, 159]
ACTC1 [160] (Actin — alpha cardiac 1)	<1%	AD	p. Gly247Asp variant is associated with atrial septal defect and late onset DCM [161] p.(H175R) and p.(Y220H) have been associated with severe forms of childhood DCM [160]
LDB3 [162] (LIM domain binding 3)	<1%	AD	Associated with LVNC phenotypes [163]
MYBPC3 [164] (Myosin-binding protein C)	2%	AD	Weak evidence — has been reported in end stage (burned out phase) HCM LVNC phenotype
MYH6 [165] (Myosin heavy chain 6, alpha)	4%	AD	AV conduction defects, sick sinus syndrome
MYH7 [166] (Myosin heavy chain 7)	4%	AD	AV conduction defects may coexist with myopathy early onset
TAZ [167] (Tafazzin)	Unknown	X-linked	DCM with syndromic features: Barth syndrome (DCM, myopathy, neutropenia, short stature)
TNNC1 [168] (Troponin C)	<1%	AD	
TNNI3 [169] (Troponin I)	<1%	AD, AR	
TNNT2 [166] (Troponin T)	<1%	AD	
TPM1 [170] (Tropomyosin 1)	<1%	AD	
LMNA [171] (Lamin A/C)	6% [25, 27]	*AD*	Accelerated disease Atrial fibrillation VAs often before overt LV dysfunction *AV conduction defects* (marked bradycardia/AV block)
BAG3 [67] (BCL2–associated anthanogene)	Unknown	AD	High penetrance > 40 years worse prognosis in nonsense variants Male sex, reduced LVEF and increased LVEDD associated with a worse prognosis [172] (p. 3) May coexist with myopathy
FLNC [173] (Filamin C)	0–3%	AD	VAs often before overt LV dysfunction Low QRS voltage Overlapping phenotype of dilated and left-dominant arrhythmogenic cardiomyopathies complicated by frequent premature SCD
RBM20 [66] (RNA binding motif protein 20)	Unknown	AD	Malignant VAs High risk of SCD
TMEM43 [174] (Transmembrane protein 43)	<1%	AD	Poor R wave progression in precordial leads Founder variant in Newfoundland SCD (M > F) [174]
PLN [175] (Phospholamban)	0–12%	AD	Low QRS amplitude, RBBB and loss of inferior R waves Founder mutation in Netherlands High risk of SCD Significant posterolateral and free wall fibrosis in *PLN R14del*
DSP [107] (Desmoplakin)	1–13%	AD, AR (Carvajal syndrome),	Low QRS Voltage, VAs Extensive fibrosis may precede LV systolic dysfunction and LV dilatation Episodic myocardial injury Cardiocutaneous syndrome
DSG2 [176] (Desmoglein 2)	4–15	AD	Frequent LV involvement
DSC2 [155] (Desmocollin 2)	Unknown	AD, AR	

Table 2 (continued)

Gene (protein)	Frequency in patients with DCM [155]	Inheritance pattern	Phenotype [77, 156]
SCN5A [177] (sodium channel voltage-gated type V, alpha)	0–2%	AD	Sinus bradycardia, atrial arrhythmias, sinus node arrest, AV conduction disease VAs often occur before overt LV dysfunction May coexist with Brugada Syndrome and/or Long QT Syndrome type 3
DES [178] (Desmin)	<1%	AD	VAs often before overt LV dysfunction Skeletal myopathy, conduction disease, RBBB [179]
DMD [62, 63] (Dystrophin)	Unknown	X-linked	Inferolateral pseudoinfarction pattern, short PR interval, RBBB Duchenne's muscular dystrophy–cardiomyopathy
EMD [180] (Emerin)	Unknown	X-linked	Low P-wave amplitude, atrial standstill, atrial arrhythmias Emery–Dreifuss muscular dystrophy

It is recommended that genes primarily associated with HCM and ARVC are also included in the screening [154]

HCM: MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, ACTN2, CSRP3, PLN, TTR, PRKAG2, LAMP2, GLA

ARVC: DES, DSC2, DSG2, DSP, JUP, LMNA, PKP2, PLN, RYR2, SCN5A, TMEM43, TTN

AD autosomal dominant, *AR* autosomal recessive, *AV* atrioventricular, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *DCM* dilated cardiomyopathy, *HCM* hypertrophic cardiomyopathy, *LBBB* left-bundle branch block, *LV* left ventricular, *LVRR* left ventricular reverse remodeling, *LVNC* left ventricular non-compaction, *NSVT* non-sustained ventricular tachycardia, *RBBB* right bundle branch block, *SCD* sudden cardiac death, *VAs* ventricular arrhythmias

Conclusions

Dilated cardiomyopathy, an "umbrella" term describing the final common phenotype of various etiologies and gene–environment interactions, is now entering a new epoch. We are witnessing the end of the "one-size-fits-all" approach aiming to alleviate symptoms or possibly delay disease progression and the beginning of the precision medicine era. We endorse the concept that we are no longer targeting symptomatic treatment, but instead, we are searching and targeting for the root of the disorder in each individual, with disease prevention or even disease reversal as a goal [153]. We believe that the creation of multi-disciplinary teams in healthcare units may form the core of the individualized management of DCM patients bringing the best patient care possible.

Declarations

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