Dilated cardiomyopathy: causes, mechanisms, and current and future treatment approaches

Stephane Heymans, Neal K Lakdawala, Carsten Tschöpe, Karin Klingel

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Department of Cardiology, Cardiovascular Research Institute Maastricht, University of Maastricht & Maastricht University Medical Centre, Maastricht, Netherlands (Prof S Heymans MD); **Department of Cardiovascular Sciences, Centre for Vascular and Molecular Biology, KU Leuven, Leuven, Belgium** (S Heymans); **Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (N K Lakdawala MD); **Department of Cardiology, Angiology, and Intensive Medicine (CVK), German Heart Center of the Charité (DHZC), Charité Universitätsmedizin, Berlin, Germany** (Prof C Tschöpe MD); **Berlin Institute of Health (BIH) Center for Regenerative Therapies (BCRT), Berlin, Germany** (Prof C Tschöpe); **German Centre for Cardiovascular Research (DZHK), Berlin, Germany** (Prof C Tschöpe); **Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tübingen, Tübingen, Germany** (Prof K Klingel MD)

Correspondence to: Prof Karin Klingel, Cardiopathology, Institute for Pathology and Neuropathology, University Hospital Tübingen, Tübingen 72076, Germany **karin.klingel@med.uni-tuebingen.de**

Dilated cardiomyopathy is conventionally defined as the presence of left ventricular or biventricular dilatation or systolic dysfunction in the absence of abnormal loading conditions (eg, primary valve disease) or significant coronary artery disease sufficient to cause ventricular remodelling. This definition has been recognised as overly restrictive, as left ventricular hypokinesis without dilation could be the initial presentation of dilated cardiomyopathy. The causes of dilated cardiomyopathy comprise genetic (primary dilated cardiomyopathy) or acquired factors (secondary dilated cardiomyopathy). Acquired factors include infections, toxins, cancer treatment, endocrinopathies, pregnancy, tachyarrhythmias, and immune-mediated diseases. 5–15% of patients with acquired dilated cardiomyopathy harbour a likely pathogenic or pathogenic gene variant (ie, gene mutation). Therefore, the diagnostic tests and therapeutic approach should always consider both genetic and acquired factors. This Seminar will focus on the current multidimensional diagnostic and therapeutic approach and discuss the underlying pathophysiology that could drive future treatments aiming to repair or replace the existing gene mutation, or target the specific inflammatory, metabolic, or pro-fibrotic drivers of genetic or acquired dilated cardiomyopathy.

Epidemiology

The main morphologic presentations of cardiomyopathies are dilated, hypertrophic, restrictive, and arrhythmogenic cardiomyopathies, the latter including both right ventricular and left ventricular forms. About one in every 250 people will develop dilated cardiomyopathy, one in 500 will develop hypertrophic cardiomyopathy, and one in 2500 people will develop arrhythmogenic right ventricular cardiomyopathy,[1] although robust epidemiological data are lacking, especially in diverse ancestries. Moreover, the end-stage presentations of hypertrophic, restrictive, and arrhythmogenic cardiomyopathies share elements with dilated cardiomyopathy, further complicating population data. The annual incidence of dilated cardiomyopathy, representing a common and final phenotype of several disease entities (table 1),[13] has been estimated at 5–8 cases per 100 000 people, but this is thought to be an underestimate due to incomplete ascertainment.[14] Notwithstanding epidemiological limitations, dilated cardiomyopathy accounts for up to 40% of patients participating in clinical trials in heart failure with reduced ejection fraction, requiring hospitalisation for heart failure, or undergoing cardiac transplantation. Sex might modulate the prevalence, morpho-functional manifestations, and clinical course of dilated cardiomyopathy.[15] Gene mutations in *LMNA* have a higher penetrance in men and younger individuals, and provide a higher risk of ventricular arrhythmias.[16] By contrast, desmoplakin mutations might be more penetrant in women.[17] Dilated cardiomyopathy accounts for approximately 60% of childhood cardiomyopathies, with diagnosis in infancy most common in tertiary centres.[18]

Causes

Direct causes of dilated cardiomyopathy include likely pathogenic or pathogenic gene variants, infections, autoimmunity, toxins (eg, ethanol, recreational drugs, and cancer therapy), endocrinopathies, and tachyarrhythmias (table 1). Some conditions can also act as modifiers, aggravating cardiomyopathy without being directly causal, such as the haemodynamic and hormonal changes of pregnancy leading to the clinical manifestation of previously asymptomatic dilated cardiomyopathy. In some patients, it is the combination of genetic susceptibility and exposure to myocardial stressors, infections, or toxins that leads to the development of dilated cardiomyopathy, with a more severe phenotype and a worse related outcome.[13] For example, truncating variants in *TTN* (*TTNtv*), affecting the giant sarcomere protein titin, are the most common genetic cause of dilated cardiomyopathy. Moreover, *TTNtv* are present in approximately 0·5% of the general population, many of whom will not develop dilated cardiomyopathy without a second environmental or genetic trigger (figure 1). A concerted interaction between a monogenic risk and an acquired cause is an important consideration directing the diagnostic tests. For example, the identification of an acquired cause of dilated cardiomyopathy such as myocarditis, anthracyclines, or alcohol abuse does not exclude underlying *TTNtv*[19] or another likely pathogenic or pathogenic gene variant. The morphological description of dilated cardiomyopathy should be amended by an aetiology-based schema based upon clinical presentation, genetics and acquired factors, disease modifiers, and co-morbidities. The MOGES classification, endorsed by the World Heart Federation, covers this complexity: MOGES, including Morpho-function, extra-cardiac Organ involvement, Genetic inheritance, Etiologies, and New York Heart Association Stage of disease.[13,20]

Genetic causes and underlying pathophysiology

Genetic causes of dilated cardiomyopathy have been pursued due to the highly heritable nature of this disease, which is recognised as familial in 30–40% of cases. The inheritance pattern of familial dilated cardiomyopathy is typically autosomal dominant, suggesting monogenic or

	Evidence	Comments
Genetic		
Titin (*TTN*)	Definitive	20–25% in familial DCM, 8–15% in acquired DCM; higher rate of left ventricular reverse remodelling (in up to 70%) in the first 2 years before declining,[2] and a higher risk of atrial tachyarrhythmias[3,4]
Lamin A/C (LMNA)	Definitive	Higher risk of sudden cardiac death: with early indication for primary prevention, ICD implantation should be considered (guided by risk factors as detailed);[5] near 100% risk of atrial fibrillation with associated high risk of stroke; frequent progression to end-stage heart failure
Myosin heavy chain (*MYH7*)	Definitive	Early age of onset; high phenotypic expression; low left ventricular reverse remodelling; frequent progression to end-stage heart failure[6]
Filamin C (*FLNC*)	Definitive	Mainly truncating variants with subsequent haploinsufficiency are associated with DCM and cardiac arrhythmias[7,8]
RNA-binding motif-20 (*RBM20*)	Definitive	Highly penetrant; high rates of heart failure, arrhythmias, and sudden cardiac death[9]
Troponin-T (*TNNT2*)	Definitive	Presentation as HCM or DCM; mild dysfunction
Troponin-C1 (*TNNC1*)	Definitive	Presentation as HCM or DCM; mild dysfunction but disproportionally prone to arrhythmias
Phospholamban (*PLN*)	Definitive	Specific PLN-R14del-associated DCM is prone to treatment-resistant heart failure and arrhythmias
Desmoplakin (*DSP*)	Definitive	Gene with overlapping DCM and AC presentation; prone to develop and present as acute myocarditis of unknown pathomechanism, even without typical imaging criteria
BLC2-associated athanogene 3 (*BAG3*)	Definitive	High disease penetrance in patients older than 40 years
Cardiac alpha-actin (*ACTC1*)	Moderate definitive	Can present as HCM or DCM; specific variants also lead to atrial-septal defect[10]
Sodium channel alpha unit 5 (*SCN5A*)	Moderate definitive	Initially described as a gene of long QT syndrome; can present as AC or DCM
Tropomyosin-1 (*TPM1*)	Moderate definitive	Can present as HCM, DCM, or restrictive CMP
Vinculin (*VCL*)	Moderate	Lower penetrance; often paediatric onset of disease[11]
Nexilin (*NEXN*)	Moderate	Can present as HCM or DCM[12]
Myosin-binding protein C (*MYBPC3*)	Low	Mainly presents as HCM but can progress into HCM with reduced LVEF, which can be misdiagnosed as DCM
Acquired		
Infection (viruses, bacteria, or parasites)	..	Virus presence in the heart only relevant if higher viral load or systemic infection and detection of cardiac inflammation
Immune-mediated diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, or dermatomyositis)	..	Immunosuppressive therapy in giant cell or eosinophilic myocarditis, sarcoidosis, or vasculitis, and in selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling (cardiology and immunology)
Toxic (eg, alcohol, amphetamines, or cocaine)	..	Except for alcohol, will cause irreversible injury or fibrosis to the heart, with frequent myocarditis and vascular involvement
Cancer treatment (anthracyclines, trastuzumab, and immune checkpoint inhibitors)	..	Anthracyclines can cause DCM long term, whereas immune checkpoint inhibitors can cause fatal acute myocarditis in 1–2% of patients
Peripartum (pregnancy)	..	Pregnancy or delivery can cause haemodynamic and hormonal alterations, and can trigger DCM in (genetically) susceptible women

AC=arrhythmogenic cardiomyopathy. DCM=dilated cardiomyopathy. HCM=hypertrophic cardiomyopathy. ICD=implantable cardioverter defibrillator. LVEF=left ventricular ejection fraction.

Table 1: **Possible causes of DCM**

mendelian cause, although X-linked, autosomal recessive, and mitochondrial inheritance are observed, particularly in paediatric populations.[18] There is an increasing recognition for the diversity of the genetic architecture of dilated cardiomyopathy: monogenic, polygenic, or multifactorial including environmental exposures (table 1). Monogenic dilated cardiomyopathy is characterised by locus and allelic heterogeneity with one of several disease genes and one of more than 1000 individual variants potentially the culprit in an individual patient. Penetrance varies on the disease gene but is typically incomplete and age-dependent. Likewise, clinical expression differs substantially, even within nuclear families.

Although more than 50 genes have been associated with dilated cardiomyopathy, evidence of causation is often incomplete. Previous studies utilising contemporary variant classification have highlighted the importance of 12 genes in which likely pathogenic or pathogenic variants have been found to be causative of dilated cardiomyopathy, and another seven genes where evidence for causation was moderate (table 1).[21–23] Approximately 25–40% of familial dilated cardiomyopathy and 10–20% of sporadic or acquired dilated cardiomyopathy have an identifiable monogenic cause.[21–23]

TTNtv variants account for up to 25% of all cases of autosomal-dominant dilated cardiomyopathy, with *LMNA*

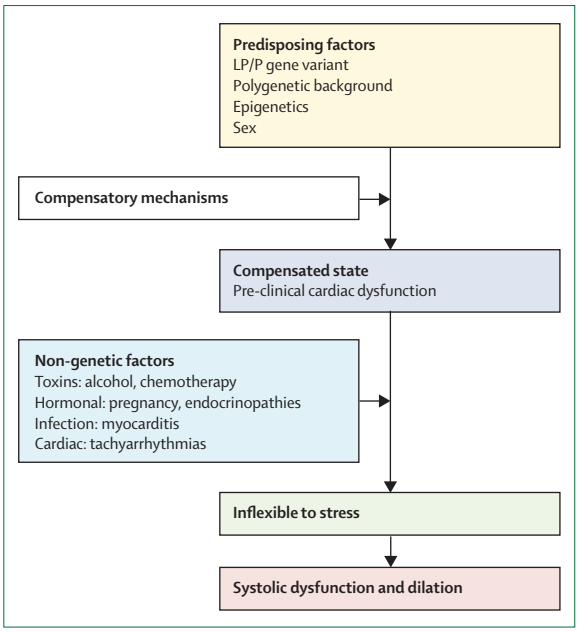

Figure 1: **Second hit paradigm in genetic DCM**
Predisposing genetic factors such as LP or P gene variants, polygenetic background, epigenetics, and sex make individuals more susceptible to develop DCM. However, the heart can maintain cardiac function but might be inflexible to stress. Non-genetic factors can act as disease modifiers or stressors in genetically predisposed hearts, leading to systolic dysfunction and a DCM phenotype. DCM=dilated cardiomyopathy. LP=likely pathogenic. P=pathogenic.

variants accounting for another 5%. Both have a unique cardiac molecular profile compared with other genetic and non-genetic dilated cardiomyopathy in the early diagnostic stage,[24] but also at the end stage.[25] Titin is the largest protein in the body and is part of the sarcomere structure. *TTNtv* can lead to a dilated cardiomyopathy phenotype with increased propensity for atrial and ventricular tachyarrhythmias. *TTNtv* are the most common identifiable cause of dilated cardiomyopathy, and are found in up to 25% of patients with familial dilated cardiomyopathy, 10–20% with sporadic dilated cardiomyopathy,[26] and approximately 10% with presumed alcoholic,[27] toxic,[28] or peripartum cardiomyopathy,[29] as well as in acute myocarditis.[30] Patients with *TTNtv*-dilated cardiomyopathy develop less cardiac hypertrophy than patients with other genetic forms of this condition when corrected for cardiac function or dilatation.[3,31] Truncating variants reduce full-length *TTN* levels and result in abundant *TTN* truncation peptides, both impairing myofibrillogenesis and sarcomere function through a poison-peptide mechanism.[32] Sarcomere insufficiency could explain in part the strong metabolic alteration with a shift towards glucose utilisation and increased oxidative stress in *TTNtv*-dilated cardiomyopathy.[24,32] These metabolic alterations are also seen when other sarcomeric genes—primarily encoding thick and thin filament sarcomere proteins, including *MYH7, TPM1,* and *TNNT2*—are mutated.[33] Sarcomere haploinsufficiency could thus result in an increased metabolic demand, a shift towards glucose utilisation, and oxidative and mitochondrial stress, stimulating hypertrophic growth of cardiomyocytes and eccentric remodelling of the heart.

Pathogenic *LMNA* variants are highly penetrant and cause dilated cardiomyopathy with conduction disease and arrhythmias, including atrioventricular block, atrial fibrillation, and ventricular arrhythmias that often precede the development of ventricular remodelling. *LMNA* variants also cause Emery-Dreyfuss muscular dystrophy and Dunnigan partial lipodystrophy.[16] Cardiac transcripts related to cardiomyocyte survival and reactive fibrosis are enriched in patients with laminopathies.[24,25] Nevertheless, as *LMNA* controls nuclear function in non-cardiomyocytes such as fibroblasts, endothelial, and inflammatory cells,[25] the pathophysiology is highly complex. This might explain in part the failure of the p38α mitogen-activated protein kinase (p38-MAPK) survival and fibrosis pathway treatment in the phase 3, placebo-controlled study (REALM-DCM) evaluating the efficacy and safety of PF-07265803 in patients with symptomatic *LMNA*-related dilated cardiomyopathy.[34]

Truncating likely pathogenic and pathogenic variants in the desmosomal gene *desmoplakin (DSP)* are a cause of arrhythmogenic left ventricular cardiomyopathy and can disrupt intercellular junctions and sodium and calcium channel handling, facilitating cardiac dilatation and arrhythmias.[1] Variants in *DSP* might lead to the release of plakoglobin from the desmosome complex and dislocation to the cytosol and nucleus. The latter causes downregulation of the canonical Wnt/β-catenin pathway involved in adipogenesis, fibrogenesis, and myocyte apoptosis.[35]

Truncating *FLNC* likely pathogenic or pathogenic variants are also a cause of arrhythmogenic left ventricular cardiomyopathy and result in saturation of the uniquitin-proteasome and autophagy pathways and impair Z-disc proteostasis.[36] The subsequent separation of FLNC from the Z-discs leads to the disintegration of myofibrils in *FLNC*-mutated mice.[37]

Phospholamban (*PLN*) likely pathogenic or pathogenic variants also have a distinct dilated cardiomyopathy molecular profile. Functional impairment and fibrofatty replacement is preceded by diverse alterations in calcium handling in cells of adult hearts of zebrafish.[38] In mice, alterations in proteostasis and PLN protein aggregation are among the first manifestations, preceding cardiac dysfunction and fibrosis.[39] The induction of the unfolded protein response pathway in PLN R14del human-induced pluripotent stem cells (hiPSC-CMs)[40] is in line with these findings.

Truncating likely pathogenic and pathogenic variants in the Bcl-2–associated athanogene 3 (*BAG3*) gene are a highly penetrant cause of dilated cardiomyopathy. The BAG3 protein maintains sarcomere integrity, autophagy, apoptosis, and mitochondrial function (as discussed in the review by Qu and colleagues[41]). Haploinsufficiency in *BAG3* might thereby induce disrupted Z-discs, enhanced

sensitivity to apoptosis in cardiac and skeletal myocytes,[42] disrupted binding with Heat Shock Protein 70 involved in autophagy,[43] and impaired sarcomeric protein turnover leading to reduced myofilament maximal force-generating capacity.[44]

Acquired causes and disease modifiers

Myocarditis

The most relevant acquired cause of dilated cardiomyopathy is myocarditis, a cardiac inflammatory disorder that can be differentiated in endomyocardial biopsies as lymphocytic, eosinophilic, granulomatous, and giant cell myocarditis. Lymphocytic myocarditis is induced predominantly by viruses but also by other infectious agents including bacteria (such as *Borrelia* spp), protozoa (such as *Trypanosoma cruzi*) and fungi (as discussed in the review by Tschöpe and colleagues[45]). Main cardiotropic viruses include enteroviruses, parvovirus B19 (B19V), and the Herpesviridae family (such as human herpesvirus 6 [HHV-6] and Epstein-Barr virus [EBV or HHV-4], as well as human cytomegalovirus [CMV] in immunocompromised patients). Comparable to influenza viruses, SARS-CoV-2 might also indirectly trigger myocarditis through cytokine-mediated cardiotoxicity in severely diseased patients, or by triggering an autoimmune response against components of the heart.[46,47] In some young men, myocarditis was found to occur in association with the development of anti-IL-1RA antibodies following SARS-CoV-2 mRNA vaccination.[48] A wide variety of systemic immune-mediated diseases and toxic substances and drugs (such as immune checkpoint inhibitors) can also cause different forms of acute and chronic myocarditis.[45] It is estimated that 20% of patients with myocarditis could develop dilated cardiomyopathy after 1 year. However, the rate of progression remains highly uncertain, mostly due to the difficult diagnosis of myocarditis and its underlying causes.[45,49] Systemic immune diseases, including systemic sclerosis,[45,50] and drug abuse[51] seem to be the main risk factors for the development of dilated cardiomyopathy related to lymphocytic myocarditis.

Toxins

Toxins, mainly anthracyclines, immune checkpoint inhibitors, ethanol, and recreational drugs (eg, amphetamines and cocaine) might cause dilated cardiomyopathy through direct cardiomyocyte toxicity, or indirectly by causing myocarditis or microvascular injury. Doxorubic-induced cardiomyocyte cell death might be caused by the generation of reactive oxygen and nitrogen species with resulting DNA damage and lipid peroxidation, impaired mitochondrial function, and the induction of DNA strand breaks.[52,53] It triggers inflammatory mediators, damage-associated molecular patterns, Toll-like receptors, and cytokines, activating macrophages and natural killer cells.[53]

Immune checkpoint inhibitors are effective and rapidly expanding contemporary cancer therapies. Direct cardiomyocyte injury by disinhibited T cells constitutes an important immune checkpoint inhibitor complication. Immune checkpoint inhibitors are monoclonal antibodies that bind to immune checkpoints and their ligands (cytotoxic T-lymphocyte antigen 4 [CTLA-4], programmed death protein 1 [PD-1] and its ligand PD-L1, and lymphocyte-activation gene 3 [*LAG-3*]) to prevent inhibition of T-cell activation by tumour cells. Trans-reactive inhibition of vascular and cardiac immune checkpoints could, however, induce T-cell mediated accelerated atherosclerosis, life-threatening myocarditis, and cardiomyopathy. T-lymphocyte infiltration occurs against cardiac antigens, caused by decreased self-tolerance and increased cardiac IgG expression, characteristic of an autoimmune response.[54]

In alcohol-induced cardiomyopathy, the direct toxic effect of long-standing high alcohol intake on the myocardium is mediated by high oxidative stress, apoptosis, and upregulation of the innate immune system and the neurohumoral axis.[55] Chronic alcohol intake can cause increased cardiac fibrosis, iron deposition, and epicardial fat along with cardiac dysfunction.[56] Indulgent drinking induces cardiac oedema, suggestive of inflammation.[57] However, abstinence or significant reduction of alcohol intake might result in a reversal of systolic dysfunction.

Recreational drugs, methamphetamines in particular, have been increasing in popularity, availability, and purity in recent decades.[58] Cardiovascular disease is the second most common cause of death in people who use these drugs. Methamphetamines and cocaine can induce direct cardiomyocyte toxicity by chronic, malignant overactivation of the sympathetic nervous system,[58] generalised endothelial dysfunction, and activation of reactive oxygen species and the innate immune system.[59,60] The damage to the heart and vessels is less likely to be reversible.[58,60]

Peripartum cardiomyopathy

Peripartum cardiomyopathy is another entity of dilated cardiomyopathy with a varying prevalence across different countries and ancestries. It is defined as cardiomyopathy diagnosed in the last month of pregnancy or within 5 months of delivery in the absence of another cause. African ancestry, multiparity, hypertensive disorders of pregnancy (eg, pre-eclampsia), and increased maternal age are associated with increased risk of peripartum cardiomyopathy. Diagnosis of peripartum cardiomyopathy might be delayed as presenting symptoms of oedema and dyspnoea are common in late-stage pregnancy. Outcomes are highly variable, ranging from complete recovery to persistent systolic dysfunction to rapid deterioration, requiring mechanical circulatory support or transplantation.[61]

The pathophysiology of peripartum cardiomyopathy—however incompletely understood—is in line with the concept of gene–environmental interactions or the

multiple hits concept, with pregnancy being a disease modifier.[62] Insufficient vascular and metabolic adaptation of the heart and the peripheral vascular system, and the profound and rapid hormonal fluctuations (mainly prolactin, oestrogen, progesterone, and fibroblast growth factor-21) might be central in the pathophysiology of peripartum cardiomyopathy.[63] Both monogenic or polygenic risk,[29] as well as acquired factors such as pre-eclampsia and hormonal fluctuations, nutritional deficiencies, autoimmune processes, and myocarditis, might contribute to the development of peripartum cardiomyopathy (as discussed in the review by Hoes and colleagues[63]).

As for most of the acquired causes, a genetic susceptibility—mainly *TTNtv*—might facilitate the development of a peripartum dilated cardiomyopathy[29] and indicate worse prognosis. Therefore, genetic counselling and testing is recommended, and treatment should be adapted accordingly.[64]

Diagnosis

Clinical and ECG

The diagnostic tests for all patients with known or suspected dilated cardiomyopathy include clinical history, laboratory tests, electrocardiogram (ECG), and cardiac imaging. Classically, a diagnosis of dilated cardiomyopathy requires the identification of both ventricular dilation and systolic dysfunction; however, as noted earlier, there is a consensus to expand the diagnosis to patients with systolic dysfunction without left ventricular dilation. Moreover, with some aetiologies, the initial phenotypic manifestations can be restricted to conduction disease or arrhythmias. Although these would not constitute a diagnosis of dilated cardiomyopathy without systolic dysfunction, they might represent an early stage of disease.[65] Detailed questions should be asked on systemic diseases, toxic agents (chemotherapy, alcohol, and drugs), and a familial history of cardiac or neuromuscular disease or sudden cardiac death at a young age (<50 years). Dilated cardiomyopathy can be considered familial if two or more first-degree or second-degree relatives have a history of the disorder, or a first-degree relative has autopsy-proven dilated cardiomyopathy and sudden death aged younger than 50 years. A 12-lead ECG should be performed to look for electrical abnormalities. In view of the high arrhythmogenic risk, inclusive of both atrial and ventricular arrhythmias, in patients with variants in certain genes (eg, *LMNA, TTN, RBM20, FLNC,* and *DSP*) ambulatory electrocardiographic monitoring might be prudent. Despite the traditional opinion that ECG abnormalities in dilated cardiomyopathy are non-specific, in contrast to arrhythmogenic or hypertrophic cardiomyopathy, there are specific ECG patterns suggestive of specific genetic or acquired forms of dilated cardiomyopathy.[66] For example, sinus bradycardia, atrioventricular block, and atrial fibrillation could precede or supersede dilated cardiomyopathy in patients with likely pathogenic or pathogenic variants in *LMNA*. Lateral T-wave inversions, low QRS voltage, and frequent ventricular premature beat might suggest *DSP*, *FLNC*, and *PLN* likely pathogenic or pathogenic variants. Although these findings might be more common with certain forms of dilated cardiomyopathy, ECG does not have sufficient diagnostic accuracy to supplant the central role of cardiac imaging for diagnosis.

Echocardiography is central for the diagnosis and monitoring of cardiac systolic function, whereas cardiac magnetic resonance (CMR) imaging provides more detailed morphological and prognostic information and should be performed early in the diagnostic investigation. Genetic testing and counselling should be considered in all patients with a diagnosis of dilated cardiomyopathy independent of their family history, in view of its high prevalence and clinical relevance for the patients and their family members.

Imaging

Transthoracic echocardiography allows for both anatomical and functional assessment and is central at baseline and follow-up. Three-dimensional transthoracic echocardiography is increasingly used with more accurate and reproducible automated left ventricular measurements, but requires more advanced technical skill and lacks established normal values.[67] Left ventricular ejection fraction (LVEF) remains the strongest predictor of events in dilated cardiomyopathy. Patients with an LVEF of 35% or less, in spite of several months of optimal medical therapy, can be considered for a primary prevention implantable cardioverter defibrillator (with or without cardiac resynchronisation therapy) on top of optimal medical treatment.[64] However, the DANISH trial challenged the use of a primary prevention implantable cardioverter defibrillator,[68,69] and it is now no longer considered a strong indication for patients with non-ischaemic dilated cardiomyopathy (especially older patients). This approach leaves younger patients vulnerable, especially those with a genetic cause of dilated cardiomyopathy associated with a higher risk of sudden cardiac death (eg, *LMNA, RMB20, FLNC, DSP*). Since an LVEF of 35% or less could have a low sensibility and specificity for sudden cardiac death prediction, additional imaging predictors on top of other clinical—mostly age and genetics—predictors are required. Cardiac fibrosis and strain parameters, in particular left ventricular global longitudinal strain, have been associated with cardiovascular events, with an incremental prognostic value over LVEF.[70] Individuals with sarcomere variants associated with dilated cardiomyopathy demonstrate reduced global longitudinal strain even in the absence of an abnormal LVEF.[71]

We recommend that CMR be performed as part of the initial evaluation of dilated cardiomyopathy (table 2). It is the gold standard technique for the assessment of biventricular volumes, systolic function, and tissue

characterisation. Late gadolinium enhancement is common in dilated cardiomyopathy and indicates myocardial oedema or fibrosis. Patterns of late gadolinium enhancement are not distinguishable in *TTNtv*-related dilated cardiomyopathy,[31] whereas mid-myocardial late gadolinium enhancement of the basal septum appears to be predominant in *LMNA*-related dilated cardiomyopathy,[72] and inferior sub-epicardial late gadolinium enhancement was relatively common in *DSP*-related dilated cardiomyopathy.[17] The presence and extent of late gadolinium enhancement is a strong and independent predictor of outcomes, sudden cardiac death, and lack of reverse remodelling, incremental over LVEF.[73] If myocarditis is considered, T1 (also extracellular volume) or T2 mapping in addition to late gadolinium enhancement is required to detect and quantify oedema and fibrosis. Global longitudinal strain by CMR, as with transthoracic echocardiography, predicts outcomes in dilated cardiomyopathy beyond LVEF and late gadolinium enhancement.[74] Left atrial conduit strain has emerged as an independent prognostic predictor in dilated cardiomyopathy, superior to LVEF and left atrial volume and incremental to late gadolinium enhancement.[75] Considering the independent prognostic role of LVEF, global longitudinal strain, late gadolinium enhancement and left atrial strain, algorithms combining multiple clinical, genetic, biomarker, histopathology, and imaging parameters to enhance the identification of patients with dilated cardiomyopathy at high risk for sudden cardiac death requiring prophylactic cardioverter defibrillator implantation are urgently required[76] to improve upon LVEF-based clinical guidelines.[64]

PET is used to evaluate myocardial metabolism and blood flow. The radiotracer [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), a glucose analogue, is the most frequently used tracer for the assessment of tumour, cardiac viability, brain function, and active inflammation. Combined PET and CT scanning is an alternative to CMR to detect cardiac inflammation (table 2). A full body PET-CT scan might also be required in patients with suspected sarcoidosis to identify extra-cardiac organ involvement.

	Indications and current implications	Future implications
Genetic counselling and testing	Genetic counselling and testing should be considered in all patients with DCM. If a disease-causing variant is present, genetic counselling and testing in family members can efficiently identify individuals at risk for future disease and enable the prevention of disease transmission via preimplantation genetic testing. Genetic testing can inform risk stratification for cardiac arrest and ICD utilisation based on the presence of variants in certain disease genes (eg, *LMNA*, *FLNC*, *RBM20*, *DSP*).	Gene-specific molecular treatment; gene therapy, including replacement, correction, or silencing; identification of novel disease genes; polygenic risk scores for risk stratification
CMR	CMR imaging (LGE, T1/ECV, and T2 parameters) to visualise structural changes, storage diseases, oedema or inflammation, and scarring (fibrosis) should be considered in all patients with DCM. Increased LGE and strain abnormalities (left ventricular and left atrium) can inform risk stratification for cardiac arrest and heart failure.	Development of risk scores of cardiac arrhythmias based upon multimodality imaging (eg, strain and tissue characterisation)
EMB	EMB should be performed in patients with DCM with suspected myocarditis, especially with rapidly progressive course or life-threatening ventricular arrhythmias or Mobitz type 2 second-degree or higher AVB or with persistent severe cardiac dysfunction. EMB are helpful to differentiate storage disorders and genetic heart diseases. Anti-inflammatory therapy is advised for certain pathologically defined causes of myocarditis or DCM (eg, giant cell, eosinophilic myocarditis, sarcoidosis, SLE).	Omics in diagnostic EMB might help to discover disease-specific therapeutic targets; EMB will be required to study the efficacy of gene therapy
PET-CT scanning	In patients with idiopathic DCM, a total body PET-CT scan can be considered to see increased metabolic activity (inflammation or tumour) in the heart and other organs to refine a diagnosis of suspected autoimmune, inflammatory, or systemic disease.	None

AVB=atrioventricular block. CMR=cardiac magnetic resonance. DCM=dilated cardiomyopathy. ECV=extracellular volume. EMB=endomyocardial biopsies. ICD=implantable cardioverter defibrillator. LGE=late gadolinium enhancement. SLE=systemic lupus erythematosus.

Table 2: **Specific diagnostic modalities, their indication, and (future) implications**

Genetic

When considering genetic testing for dilated cardiomyopathy, the key questions are whom to test, which test to use, and how to ensure appropriate patient and family education and engagement. Clinical genetic testing should be considered for any patient with hitherto idiopathic dilated cardiomyopathy, not exclusively those with apparent familial disease, and has been endorsed by multiple professional societies with varying degrees of veracity (table 2).[64,77,78] If limited resources mandate restrictions in the provision of genetic testing, a published clinical score which utilises elements from a patient's medical history and their 12-lead ECG could help to identify patients most likely to have an informative result.[79] In that study, the patient characteristics independently associated with a positive result for genetic testing were a family history of dilated cardiomyopathy, low QRS amplitude on ECG, skeletal myopathy, and the absence of hypertension or left bundle branch block. With the costs of genetic testing going down, and with the clinical impact for both the proband and their family, genetic counselling and testing should be advised for all patients with dilated cardiomyopathy.

Variable expression, and locus and allelic heterogeneity, drive the application of genetic testing in clinical practice. If diagnostic genetic testing is being offered to an individual with familial dilated cardiomyopathy, it is recommended that the family member with the most overt phenotype be tested first. Genetic testing for an index case or proband should utilise next-generation sequencing,[80] and cover all exons and flanking introns of disease genes clearly associated with dilated cardiomyopathy.[22] A chromosomal microarray and/or whole exome or genome sequencing can be performed with complex multisystem disorders, a clear familial history in the absence of culprit gene variants on initial testing, or in those motivated to engage in research testing. With whole exome or genome sequencing becoming more affordable, it might become routine in tertiary centres to drive research and determine the polygenetic and epigenetic risk.

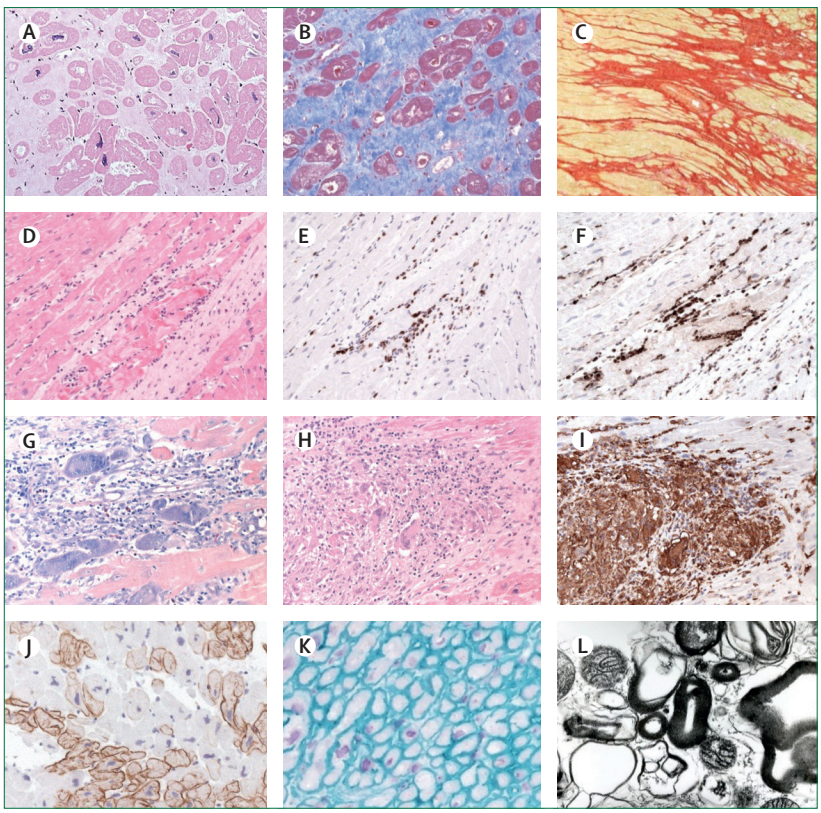

Figure 2: **Histological, immunohistological, and ultrastructural findings in heart tissue of patients with DCM (A–C), chronic lymphocytic myocarditis (D–F), giant cell myocarditis (G), sarcoidosis (H–I), and genetic and storage diseases (J–L)**

Haematoxylin and eosin (A), Masson trichrome (B), and picrosirius red stain (C) revealing fibrosis and changes in cardiomyocyte structure, haematoxylin and eosin illustrating interstitial fibrosis (D), $CD3^+$ T cells (E), $CD68^+$ macrophages (F), giant cell myocarditis with Giemsa staining with myocyte necrosis, eosinophilic granulocytes, and giant cells (G), haematoxylin and eosin staining with granuloma (H), immunohistochemistry revealing MHCII (I), dystrophinopathy with immunohistochemistry with mosaic pattern of dystrophin in cardiomyocytes (J), AL amyloidosis with immunohistochemical staining for lambda light chains (K), Fabry disease with electron microscopy showing lamellar myelin-like inclusion bodies in cardiomyocytes (L). DCM=dilated cardiomyopathy.

Once a disease-causing variant has been identified in a proband, confirmation testing (also cascade testing) should be used to determine which family members are at risk for future dilated cardiomyopathy development or might have an asymptomatic cardiomyopathy phenotype. Due to age-dependent penetrance, individuals who harbour a disease-causing variant without overt dilated cardiomyopathy should undergo longitudinal clinical assessments including cardiac imaging, at an interval of 2–3 years and adjusted to the genetic cause. The age at which clinical screening should commence can be informed by which disease gene is the culprit in a family. Genetic counselling is a strongly recommended component of genetic testing[64,80] and provides value in the context of family-based management.

Biomarkers

Routine laboratory examinations include cardiac and muscular enzymes, liver and renal function, haemoglobin, white blood cell count (including differential white blood cell count to detect eosinophilia), natriuretic peptides, thyroid function tests, iron status, and markers of systemic autoimmune diseases. Natriuretic peptides (B-type natriuretic peptide and N-terminal-proBNP) are the most widely adopted biomarkers for diagnosis and prognostication of heart failure. Increased creatine kinase could indicate overt or subclinical skeletal muscle involvement in muscular dystrophinopathies (Duchenne, Becker, and limb girdle muscular dystrophy), mitochondrial cardiomyopathies, glycogen storage diseases, and sarcomeric cardiomyopathies.[81]

High-sensitivity troponin is a representative biomarker for myocardial injury due to acute myocarditis or myocardial stress in dilated cardiomyopathy, associated with adverse clinical outcomes and cardiac remodelling.[82] Patients with recurrent increased high-sensitivity troponin levels and excluded coronary artery disease should be investigated for myocarditis and cardiac inflammatory diseases. Levels of high-sensitivity troponin might also increase during the hot (inflammatory) phase of arrhythmogenic cardiomyopathy. Approximately 30% of patients with DSP-related arrhythmogenic cardiomyopathy will present with a constellation of chest pain, troponin release, and ECG abnormalities with normal coronary arteries.[17,30] This incompletely understood hot phase of arrhythmogenic cardiomyopathy, with possible involvement of auto-antibodies,[83] could therefore present as acute myocarditis.

The value of other biomarkers, such as soluble suppression of tumorigenicity 2 (sST-2, marker of stress), galectin-3 (inflammation and fibrosis), carboxy-terminal propeptide of procollagen type I (PICP, fibrosis), or growth differentiation factor-15 (GDF15, inflammation and fibrosis) beyond the well-established pro-BNP, in the clinical management of dilated cardiomyopathy remains unclear. The combination of late gadolinium enhancement reflecting myocardial fibrosis at CMR and circulating PICP levels could provide additive prognostic value and is accompanied by a pro-fibrotic and pro-inflammatory cardiac transcriptomic profile in patients with dilated cardiomyopathy.[84] These findings indicate that a multidimensional approach might be required to predict risk and guide therapeutic management in dilated cardiomyopathy.[84]

Endomyocardial biopsies

Dilated cardiomyopathy is morphologically the late stage of diverse acquired and genetic disorders. To evaluate the etiopathogenesis of dilated cardiomyopathy, endomyocardial biopsies are decisive in the differentiation of inflammatory and non-inflammatory cardiac diseases, distinguishing different types of myocarditis,[85] storage disorders (including amyloidosis, glycogenosis, Fabry disease, or haemochromatosis),[86] and genetic heart diseases (figure 2, tables 1, 2).[86] According to the intersociety position statement,[87] endomyocardial biopsies should be considered

in patients with suspected fulminant myocarditis or acute myocarditis with acute heart failure, left ventricular dysfunction or rhythm disorders, suspected myocarditis (in haemodynamically stable patients), autoimmune disorders with progressive heart failure, dilated cardiomyopathy with recent onset heart failure and moderate-to-severe left ventricular dysfunction, suspected immune checkpoint inhibitor-mediated cardiotoxicity, high-degree atrioventricular block, syncope or unexplained ventricular arrhythmias, myocardial infarction with non-obstructive coronary arteries or takotsubo syndrome with progressive left ventricular dysfunction, and unexplained restrictive or hypertrophic cardiomyopathy. An endomyocardial biopsy is also required to identify the cause of cardiac inflammation, thus guiding immunosuppressive treatment in non-infectious cases especially with giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis.[87]

Historically, the histopathologic diagnosis of myocarditis was based upon the Dallas criteria, defined by the presence of myocytolysis and inflammatory cells in haematoxylin and eosin staining.[88] Currently, immunohistological quantification of mainly CD3$^+$ T cells and CD68$^+$ macrophages, but also of other immune cells and inflammatory markers such as HLA-DR on paraffin tissue sections, has considerably improved the diagnostic sensitivity and reliability (figure 2).

Endomyocardial biopsies also allow for detection of the well known cardiotropic viruses by using quantitative RT-PCR and in situ hybridisation.[89] In cases with acute cardiac infections and systemic viral infections, immunosuppressive regimens must be avoided. In selected patients with chronic myocarditis and latent B19V and HHV-6 infection, immunosuppressive or immunomodulatory treatment might still be considered.[45]

Beyond viral infection, genetic host susceptibilities have been linked to cardiac dysfunction following acute myocarditis. Biopsy-proven myocarditis could also be present in genetic dilated cardiomyopathy, both in adults[30] and children.[90] Next-generation sequencing from patients with histologically manifested acute myocarditis provided evidence that pathogenic variants in cardiac genes, traditionally associated with cardiomyopathies (especially DSP and TTN), might increase the risk for cardiac inflammation. Patients with myocarditis with a dilated cardiomyopathy phenotype and an likely pathogenic or pathogenic gene variant revealed early-onset heart failure and a poor outcome.[30,90–92]

Management

Medical

Patients with dilated cardiomyopathy should be treated with guideline-directed medical therapy for heart failure with reduced ejection fraction, as it has been proven to decrease morbidity and mortality and impact cardiac remodelling.[64] Such treatments include angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers,[93] mineralocorticoid receptor antagonists[94] and SGLT2 inhibitors.[95,96] An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker can be replaced by sacubitril–valsartan in patients with dilated cardiomyopathy who remain symptomatic despite optimal treatment.[64,97]

Studies examining the relative efficacy of these therapies in genotyped populations are scarce. Patients with *TTNtv*-related dilated cardiomyopathy might experience greater early reverse remodelling that might wane over time than patients with idiopathic dilated cardiomyopathy, as shown in retrospective studies.[2,98] By contrast, patients with *LMNA*-related dilated cardiomyopathy appear to derive less benefit from conventional medical therapy.[98]

Medical therapy should not be withdrawn from patients with dilated cardiomyopathy who experience reverse remodelling, including normalisation of cardiac function. A randomised pilot study, TRED-HF, in 51 patients investigated the possibility of withdrawing medical treatment in those patients with non-ischaemic dilated cardiomyopathy who had partial-to-complete recovery of LVEF (>40% with normal natriuretic peptide concentration). However, relapse of dilated cardiomyopathy within 6 months was observed in 44% of patients. Rapid left ventricular remodelling with early tissue and functional changes was found, even among patients who did not relapse.[99,100] Whether patients with recovered ejection fraction following acute myocarditis without underlying immune disease will require lifelong heart failure treatment remains unclear. Current guidelines advise a 6-month treatment period after recovery from systolic dysfunction.[64]

Oral anticoagulation therapy is generally recommended for patients with dilated cardiomyopathy with associated atrial fibrillation. The benefit of anticoagulation therapy might be highest in *LMNA*-related dilated cardiomyopathy where the risks of thromboembolism could be up to five times higher than in patients with other dilated cardiomyopathy with atrial arrhythmias.[101]

Sport and training

Exercise training improves functional capacity and quality of life in patients with dilated cardiomyopathy. Low-to-moderate intensity recreational exercise or guided exercise training should be considered as an integral part of the management of affected individuals.[102] However, high intensity exercise and competitive sports could trigger sudden cardiac death in dilated cardiomyopathy,[103,104] and shared decision making regarding risks and values should precede such participation. In particular, an LVEF lower than 45%, unexplained syncope, extensive cardiac fibrosis at CMR or endomyocardial biopsy, high-risk genotype (eg, *LMNA* or *FLNC* among others), or frequent ventricular tachyarrhythmias on ambulatory Holter monitoring or exercise testing are negative prognostic markers in patients considering high intensity activities. However, risk scores for sudden cardiac death developed for

specific activities are scarce and will require large, collaborative, international dilated cardiomyopathy cohorts to be developed.

Devices

The indication for placement of a primary prevention implantable cardioverter defibrillator in dilated cardiomyopathy has been a major topic of discussion since the publication of the DANISH trial. This study revealed that prophylactic cardioverter defibrillator implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly improved all-cause survival.[68] However, younger patients in this study did benefit from prophylactic cardioverter defibrillator implantation. Long-term follow-up of patients younger than 70 years in the DANISH trial revealed that cardioverter defibrillator implantation was associated with a lower incidence of all-cause mortality, cardiovascular death, and sudden cardiovascular death.[69] Although the DANISH trial did not show a significant benefit from implantable cardioverter defibrillator therapy in patients with dilated cardiomyopathy, certain genetic or inflammatory subgroups (eg, *LMNA* or sarcoidosis) are at higher risk of sudden death and therefore merit careful consideration of cardioverter defibrillator implantation. A meta-analysis of all randomised controlled trials comparing implantable cardioverter defibrillator therapy and optimal medical treatment to optimal medical treatment alone for primary prevention of dilated cardiomyopathy showed a survival benefit from implantable cardioverter defibrillator therapy.[105] In view of the established increased risk of ventricular arrhythmias, sudden cardiac death, and overall mortality in certain patients with dilated cardiomyopathy, we advise careful consideration for primary prevention implantable cardioverter defibrillator placement in this population, in line with current guidelines.[64,77,106,107] Factors that should influence this decision include age, a family history of sudden cardiac death, the presence of a variant in a gene associated with arrhythmic risk (*LMNA*, *FLNC*, *DSP*, or *RBM20*), the degree of systolic dysfunction, the presence of myocardial fibrosis, and a history of lower-grade ventricular ectopy. Here again, large multicentre international cohorts are required to develop a sudden cardiac death risk score in distinct dilated cardiomyopathy subgroups. *LMNA*[5] and *PLN*[108] risk scores of life-threatening ventricular tachyarrhythmias are illustrative first efforts.

Cardiac resynchronisation therapy is also indicated for patients with symptomatic dilated cardiomyopathy with sinus rhythm, an LVEF of 35% or more despite optimal medical therapy, and a QRS duration of greater than 130 ms with left bundle branch block.[64,77,106,107] In response to cardiac resynchronisation therapy, patients with dilated cardiomyopathy experienced greater improvements in LVEF and left ventricular cavity size coupled with a greater survival benefit than ischaemic cardiomyopathy[109] (as discussed in the review by Yokoshiki and colleagues[110]).

End stage: mechanical support and transplantation

Dilated cardiomyopathy is a common indication for cardiac transplantation or implantation of a durable left ventricular assist device. Outcomes in patients with a durable left ventricular assist device are strongly related to the severity of heart failure and magnitude of multiorgan dysfunction. Because patients with dilated cardiomyopathy are younger and often free of underlying disease associated with atherosclerotic heart disease and organ dysfunction (eg, diabetic nephropathy), their outcomes are generally favourable compared with those with ischaemic heart disease.[111]

Treatment of myocarditis

Acute and chronic myocarditis (also inflammatory cardiomyopathy) are to be considered as separate disease entities when thinking of their treatment. Acute myocarditis is characterised by troponin release and dynamic ECG alterations within hours or days, and mostly confirmed by the presence of oedema at CMR or increased metabolic activity at PET scanning. Admission to hospital for at least 48 h is indicated for patients with acute myocarditis and heart failure, especially when troponins are elevated or when cardiac dysfunction or arrhythmias are present at initial presentation. Spontaneous recovery of cardiac systolic dysfunction could occur within days in up to 90% of cases. Despite the lack of evidence in the specific setting of acute myocarditis, treatment of heart failure with reduced ejection fraction with standard of care heart failure treatment is advocated.[64] When cardiac systolic dysfunction persists, or in case of major ventricular arrhythmias, atrioventricular block, or other persistent arrhythmias, a diagnosis of systemic inflammatory and autoimmune disorders such as sarcoidosis or giant cell myocarditis must be excluded by imaging and endomyocardial biopsy, and treated accordingly. Other than cytolytic enteroviruses,[112] detection of B19V and herpesviruses in the heart only appears to be relevant and antiviral treatment indicated if viral DNA or RNA load is high and when viral nucleic acid is also present in the blood, reflecting a systemic infection.[45,113] Immune checkpoint inhibitor-induced acute myocarditis requires high-dose prednisolone, alemtuzumab or abatacept after holding immune checkpoint inhibitor treatment.[114]

In chronic myocarditis with systolic dysfunction, troponins are mostly negative or with a minor and stable increase, ECG alterations are unchanging, and oedema or inflammation at imaging are often absent. With the limited sensitivity of CMR for diffuse or low-grade inflammation, endomyocardial biopsies are required to confirm the presence of increased cardiac inflammation, and to uncover and accordingly treat underlying systemic

immune disease. Immunosuppression should be considered in non-infectious chronic myocarditis proven by endomyocardial biopsy, as suggested by retrospective and scarce prospective studies.[115–117]

Future diagnostic and therapeutic perspectives

For too long, dilated cardiomyopathy has been synonymous with non-ischaemic, non-valvular cardiomyopathy, a diagnosis where two diagnoses have been excluded. This approach precludes broad-based development of prognostic and therapeutic tools rooted in a precise gene-acquired cause. Although diagnostic tools (eg, genetic testing or CMR) are well established and widely available, due to overpricing or unavailability in some health-care systems, they remain woefully underutilised. Establishing these diagnostic tests as a priority[118] is crucial, as they are central in prognostic risk stratification and the development of new precision medicine treatment.

Need for combined phenoclustering, omics, and risk stratification

The *LMNA*[5] and *PLN*[108] risk score for life-threatening ventricular tachyarrhythmias are examples of the clinical impact of diagnostic precision on predicting and preventing sudden cardiac death. Retrospective studies have begun to assess the efficacy of established guideline-directed therapies for specific causes of dilated cardiomyopathy.[2] In the future, large, in-depth, clinically and genetically characterised multicentre cohorts—including lifestyle, comorbidities, quality of life, and reproductive and environmental factors—will provide similar insights across the spectrum of diagnoses. The identification of dilated cardiomyopathy subgroups by degree of cardiac dysfunction, inflammation at endomyocardial biopsies, gene–environmental interactions, and imaging characteristics, will help identify new, or repurpose existing, specific molecular (eg, anti-inflammatory, metabolism-modulating, or anti-fibrotic) or existing heart failure therapies in prospective clinical trials. A combination of deep clinical phenotyping, genotyping, imaging, proteomics and cardiac transcriptomics resulted in different cardiac molecular phenotypes being described: first, metabolic along with diabetes or severe systolic dysfunction; second, inflammatory with a history of systemic diseases or chronic myocarditis; and third, pro-fibrotic or metabolic in genetic dilated cardiomyopathy with moderate systolic dysfunction.[76,119]

Precision medicine treatment in genetic dilated cardiomyopathy

Perhaps the most compelling argument for a molecular and genetic diagnosis is the rise of gene-specific therapies[120] (figure 3). This includes the repurposing of established renin-angiotensin-aldosterone targeting therapies for genetic cardiomyopathies (as has been successful for valsartan in hypertrophic cardiomyopathy),[121] novel small molecule therapies which are being tested in specific genetic causes of dilated cardiomyopathy (NCT04572893),[122] and the broad category of gene therapy. Depending on the type of genetic variant and mechanism of disease, approaches to gene therapy will include gene replacement therapy, direct genome editing (CRISPR-cas9), and allele-specific silencing (with siRNA or antisense oligonucleotides). A viral vector (eg, adeno-

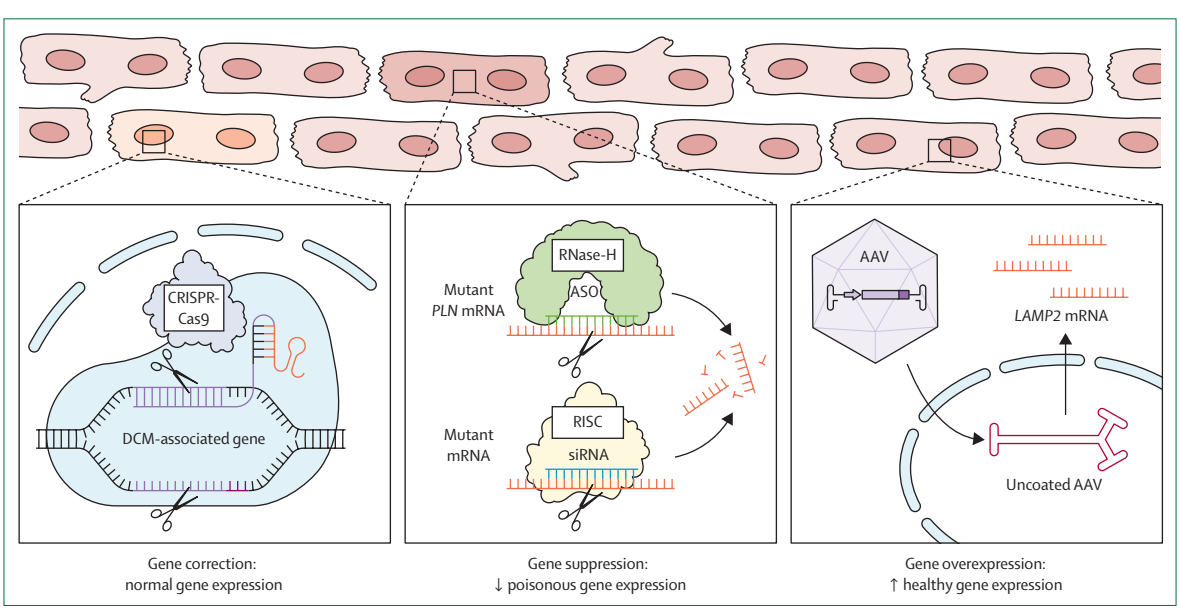

Figure 3: **Future individualised gene therapy in genetic DCM**
Examples of gene correction, gene suppression, and gene overexpression by CRISPR-Cas9, ASO and siRNA, and AAV. Poisonous gene silencing by ASO has been achieved in *PLN* mice. Overexpression of wild-type *LAMP2* RNA by AAV is being investigated in a phase 1 clinical trial (NCT03882437). AAV=adeno-associated virus. ASO=antisense oligonucleotides. DCM=dilated cardiomyopathy.

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE (PubMed), and Embase from Jan 1, 1991, to Jan 1, 2023, with the search terms "dilated cardiomyopathy" for articles published in English. We largely selected publications from the past 5 years but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we deemed relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for.

associated virus [AAV]) could overexpress a deficient gene product into the myocardium. AAV presents both safety and efficacy challenges secondary to the host immune response and lack of cardiac-specific delivery. At the forefront of AAV-gene therapy for genetic dilated cardiomyopathy is an ongoing phase 1 study of AAV9 gene replacement therapy for *LAMP2*-related Danon disease (hypertrophic cardiomyopathy), with the promise of being efficient without prohibitive toxicity.[123] Additionally, allele-specific silencing with siRNA or antisense oligonucleotides is used to silence a poisoned gene product from a mutated allele. In *PLN* R14del mice, administration of *PLN*-antisense oligonucleotides prevented PLN protein aggregation, reduced cardiac dysfunction, and increased survival rate.[124] Finally, the Nobel Prize-winning invention CRISPR-Cas9 is a genome editing technology able to overcome frameshift variants, and restore the gene product functionality. It is currently being investigated in a phase 3 clinical trial (NCT05329649) in severe sickle cell disease by editing stem cells ex vivo, and its application in genetic cardiomyopathies in vivo will depend on achieving cardiac-specific delivery with minimal off-target effects. It is anticipated that early phase studies in different genetic cardiomyopathies will be initiated in the coming months. Questions remain on when to start gene therapy, balancing the potential benefit against the risks of gene therapy and adjunctive therapies.

In conclusion, dilated cardiomyopathy is a challenging but rewarding field where multidimensional clinical, histopathologic, genetic, biomarker, and imaging diagnostics could result in the development of risk scores for sudden cardiac death and heart failure progression, and the prospect of personalised molecular or gene therapy in specific genetic and acquired dilated cardiomyopathy subgroups.

Contributors

All authors contributed to the literature search, conceptualisation, and writing, review, and revision of the manuscript.

Declaration of interests

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