1. Clinical Characteristics

1.1 Definition and prevalence
Dilated cardiomyopathy (DCM) is a myocardial disorder characterised by dilatation and contractile dysfunction of the left ± right ventricles. DCM may be caused by a diverse range of conditions that promote cardiomyocyte injury or loss, eg. coronary artery disease, viral myocarditis, alcohol excess. In approximately 50% cases, an underlying cause is unable to be identified. This group has traditionally been termed “idiopathic” DCM. It is now recognised that approximately 25% of cases of “idiopathic” DCM have a positive family history, suggesting that an inherited gene defect might be the cause of the disorder (“familial DCM”).

1.2 Clinical presentation
Familial DCM may be inherited as an autosomal dominant, autosomal recessive, maternal or X-linked trait; autosomal dominant inheritance is present most commonly. In autosomal dominant inheritance, each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation, with males and females equally at risk. Clinically-affected individuals generally present with symptoms and signs of heart failure or arrhythmias. Some families have a clinical presentation (phenotype) that is characterised by DCM alone, while in others, DCM may be associated with additional cardiac manifestations eg. conduction-system disorders, valve defects, atrial/ventricular septal defects, left ventricular non-compaction, or with non-cardiac manifestations eg. skeletal myopathy, partial lipodystrophy, sensorineural deafness.

1.3 Clinical diagnosis
The diagnosis of familial DCM is made when DCM (with or without associated features) is present in the setting of a positive family history (at least 2 family members affected). There are no specific clinical features that reliably distinguish familial from non-familial DCM.

*Family history:* A detailed family history and a high level of clinical suspicion are essential. While inherited gene defects alone may be sufficient to cause disease, some individuals in families may have concurrent risk factors for DCM that may confound the recognition of familial disease. In addition, familial clustering may not be immediately apparent if the clinical presentation differs between members of the same family. For example, in DCM with conduction-system disease, some individuals may present with heart failure, while others may have a history of arrhythmia symptoms, pacemaker implantation or sudden death. The severity of disease, and the age of onset, may differ between families and within members of
the same family. While familial DCM generally shows high penetrance, some individuals may remain non-penetrant (ie. genotype-positive but with no clinical manifestations of disease) throughout life.

**Family screening:** It is currently recommended that all first-degree family members of individuals with “idiopathic” DCM, and of individuals with suspected familial DCM on the basis of a positive family history, should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography to identify familial disease and to determine the number of affected individuals within families. Measurement of CK levels is useful to identify subclinical skeletal muscle abnormalities and provides supportive evidence for the presence of an inherited myopathic disorder. Exercise treadmill testing and/or coronary angiography may be indicated in family members aged over 50 years who are found to have a new diagnosis of DCM, to distinguish a familial from a non-familial cause.

### 2. Molecular Genetics

#### 2.1 Familial DCM disease genes

Familial DCM is a genetically-heterogeneous disorder. To date, at least 40 genes have been associated with various forms of adult-onset DCM. These disease genes encode a variety of proteins in the cardiomyocyte sarcomere, cytoskeleton, sarcolemma, and nucleus. These findings indicate that diverse molecular mechanisms may underlie familial DCM. In general, the clinical phenotype provides no real clues for identifying the underlying genotype, with a few notable exceptions. These include the *LMNA* gene, that encodes the nuclear lamina proteins lamin A and lamin C, and the *SCN5A* gene that encodes the cardiac sodium channel α-subunit, that are both associated with DCM and conduction-system abnormalities, and *DMD* mutations that are associated with X-linked DCM. Despite the relatively large number of genes identified, mutations in the majority of these genes are uncommon and have been found in only a minority of cases of familial DCM. In 2012, a landmark paper from the Seidman group at Harvard Medical School reported that truncating mutations in the *TTN* gene, that encodes the giant sarcomeric protein titin, were present in 25% familial DCM cases and 18% sporadic DCM cases. This was a remarkable finding that suggested that the prevalence of truncating *TTN* mutations was equivalent to the combined prevalence of all the known DCM disease genes. Although these results have yet to be replicated in additional patient populations, these initial observations strongly point to *TTN* being a major disease gene for familial DCM.

#### 2.2 Genetic testing

Due to the large numbers of disease genes and the fact that families with DCM generally have unique mutations, genetic testing in familial DCM has been prohibitively time-consuming and costly. With the advent of high-throughput sequencing technologies, it is now feasible to perform targeted re-sequencing of selected known DCM genes and there are several commercial laboratories, mainly based overseas, that offer this service. Whole-exome and whole-genome sequencing are also rapidly becoming affordable and accessible and provide an alternative method for genetic testing. The optimal sequencing method for genetic testing has yet to be established and will depend on the relative reliability, costs and differences in the extent of coverage of the known disease genes between the various techniques.

Until recently, the yield of genetic testing, even with the aid of high-throughput technologies, has been relatively low (25-30%), and hence this has not been routinely performed as part of family management. With inclusion of *TTN* on screening panels, the yield of genetic testing promises to be substantially higher (perhaps up to 50%) and it can be anticipated that expert consensus guidelines will be amended accordingly.
New sequencing tools are generating huge numbers of variants in every person and the major challenge is how to interpret the data and identify those variants that are likely to be disease-causing. The interpretation of DNA sequence variants identified in individual patient samples is not straightforward and it is becoming increasingly apparent that many of the criteria relied upon in the past to define pathogenicity lack specificity. For example, variants that are novel or high impact (i.e. those that significantly alter the encoded protein such as nonsense mutations, splice site mutations, and frameshift insertion/deletion mutations) have been thought to be potentially pathogenic. However, it is now appreciated that a majority of all rare variants are novel and that even healthy people carry numerous high-impact variants. Moreover, many variants reported in the literature as causing inherited heart disease are now being recorded in population databases. These issues highlight the need for careful interpretation of the significance of variants detected before giving “positive” results to patients with DCM and their families. It is highly recommended that the results of genetic testing are reviewed by experienced molecular cardiology personnel, and that testing is carried out in an appropriate setting that includes pre-test and post-test genetic counselling.

3. Management

3.1 Affected individuals
Clinically-affected family members with DCM should receive standard pharmacological management as indicated by the severity of symptoms and signs of heart failure. In families with DCM and conduction-system disease, young family members who present with conduction-system disturbances (sinus bradycardia, atrioventricular conduction block, ± atrial fibrillation) should be followed for arrhythmias that might necessitate pacemaker implantation and for the onset of DCM in later life. Electrophysiological studies ± AICD implantation should be considered in individuals with syncopal episodes, and/or a strong family history of sudden death. The natural history of familial DCM can vary within families and between members of the same family. It is likely that family genotype will be a very important determinant of prognosis. Genotype-phenotype correlations in large populations of family members will be a useful guide in the future for patient therapy and counselling.

3.2 Asymptomatic family members

Longitudinal follow-up: Periodic cardiac screening (ECG and transthoracic echocardiography) of family members of probands with familial DCM is recommended, to identify arrhythmias and asymptomatic abnormalities of left ventricular size and function. The frequency of follow-up assessments should be determined in each individual case by factors such as the typical age of onset of disease in symptomatic family members, and “suspicious” echocardiographic changes (eg. borderline normal, or suggestive of early disease [see below]), and may range from 6-12 months to 5 years. Familial DCM exhibits age-related penetrance, ie. family members who are born with a gene defect may not develop manifestations of disease until later in life. The age of onset of disease in families is variable, with clinical signs appearing from the second to ninth decades. Young family members with a normal ECG and echo, particularly offspring of an affected parent, should not be dismissed as “unaffected” and require ongoing medical surveillance.

Early disease: As part of clinical screening for molecular genetics studies, a previously unrecognised subgroup of family members with asymptomatic echocardiographic changes (left ventricular dilatation and/or mild impairment of contractile function) has been identified. Although left ventricular dilatation is not specific for early disease and may result from unrelated pathologies, or physiological variation, particularly in young, fit individuals engaged in competitive sporting activity, several studies have suggested that at least one third of these individuals have latent cardiomyopathy, indicated by the presence of myocardial
histological changes, reduced maximal exercise oxygen consumption, or cardiac autoantibodies. Detailed characterisation of left ventricular function using a range of echocardiographic techniques and/or magnetic resonance imaging may help to better differentiate individuals with early cardiomyopathy, but sensitive and specific markers of early disease have yet to be established. Longitudinal studies have shown that approximately 10% of individuals with left ventricular dilation and/or mild impairment of contractile function will develop DCM over a 5-year period. The development of risk stratification algorithms to reliably identify those individuals at greatest risk of disease progression is still required. The ability to recognise early disease has important management implications, since early intervention may prevent, or attenuate progression to symptomatic heart failure. Large-scale clinical trials with long-term follow-up are needed to evaluate the role of pharmacologic intervention in this subgroup of family members. Such trials would ideally be performed in genotyped familial DCM populations.

3.3 Counselling
All family members potentially at risk of disease should receive lifestyle modification advice, eg. avoidance of alcohol excess, regular moderate exercise, etc. Female family members who are considering pregnancy should have initial cardiological review and regular follow-up during pregnancy, since familial DCM may be unmasked or accelerated in the peri partum period, especially in the last trimester and first 6 months postpartum. The diagnosis of a genetic disorder in a family and the possibility of testing for the disorder raises a number of issues that are best addressed by experienced cardiovascular genetics counsellors.

Key references