Advances in the diagnosis and management of inherited cardiomyopathies

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Advances in the diagnosis and management of inherited cardiomyopathies

Clinical Update

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What you need to know

- Inherited cardiomyopathies are common and a major cause of heart disease across all age groups.
- Asymptomatic individuals may still be at risk from sudden cardiac death.
- The ECG and echocardiogram will detect the majority of cardiomyopathies, but further evaluation may include additional ECG testing, specialist imaging, and genetic testing.
- Assessment of family members should be considered at an early stage with involvement of specialist centres.

Cardiomyopathies are structural and functional disorders of the heart muscle. They are common, often inherited, and an important cause of sudden cardiac death. Herein, we provide an overview of diagnosis, genetic evaluation, and management of inherited cardiomyopathies for non-specialists. We focus on the key role of the general practitioner in recognising symptoms and clues from the family history. Further specialist evaluation is discussed alongside updated guidance from national and international bodies.

WHAT ARE THE CAUSES?

Cardiomyopathies are broadly divided into genetic and non-genetic causes, the former being inherited cardiomyopathies. Non-genetic causes are classified as idiopathic or may be acquired, resulting from metabolic, endocrinological, or inflammatory disorders, pregnancy, amyloidosis, infections, and toxic agents including drugs and alcohol. Most inherited cardiomyopathies are single gene (monogenic) disorders with an autosomal dominant pattern and a 50% risk of transmission to a child. The main inherited cardiomyopathies are: Hypertrophic Cardiomyopathy (HCM), Dilated Cardiomyopathy (DCM), and Arrhythmogenic Cardiomyopathy (ACM)(*Figure 1*). DCM may be considered genetic or acquired.

HOW COMMON ARE THEY?

Inherited cardiomyopathies are found among all ethnicities and populations. HCM is the most common

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with a global prevalence of approximately 1:500 adults across racial groups (1-3). A US population-based study estimated the prevalence of DCM at 1:2,500 adults (4), but this is considered an underestimate and closer to 1:250 (5). ACM is rarer and has a lower global prevalence of 1:2000-1:5000 adults (6,7).

HOW DO PATIENTS PRESENT?

Many patients affected by inherited cardiomyopathies are asymptomatic. Although clinical expression is uncommon before puberty, cardiomyopathy should be considered in young patients presenting with chronic symptoms of exertional breathlessness, chest pain, or reduced exercise capacity in the absence of respiratory causes. Symptoms and signs may, however, overlap with other common conditions such as asthma and anxiety.

Observational studies indicate that over two thirds of those with HCM are asymptomatic (8,9). Classical exertional symptoms are chest pain, breathlessness, and/or exercise-related limitations (*Table 1*). In children, symptoms may indicate more severe disease (10). Most inherited DCM presents between the ages of 20-40 (11), but can also be detected in children and older adults. Nearly one third of asymptomatic relatives exhibit mild abnormalities on echocardiography and over a quarter progress to overt DCM (12). ACM usually becomes apparent during early adulthood (13).

Acute presentations include heart failure, arrhythmia, syncope, or even sudden death (14), and may occur in the absence of prior warning signs. Diagnosis may also be incidental. Indeed, 16% of patients in a prospective multinational registry of 3,208 cardiomyopathy patients were diagnosed incidentally (15).

Symptoms*	Physical Examination**
*usually asymptomatic	**often normal

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• Exertional breathlessness or chest pain • Syncope • Palpitations • Orthopnoea • Paroxsymal nocturnal dyspnoea	• Ejection systolic murmur (left sternal border) – increased intensity on Valsalva, diminished by squatting (*Left ventricular outflow tract obstruction in HCM*) • Peripheral and/or pulmonary oedema • Elevated JVP • Irregular pulse
Red Flags • Exertional syncope and/or seizures • Palpitations associated with altered level of consciousness • Exertional chest pain in the young • Family history of cardiomyopathy • Family history of premature sudden cardiac death	

Table 1: Symptoms, examination findings, and red flags in the history prompting specialist referral according to consensus guidelines (16)

HOW ARE THE INHERITED CARDIOMYOPATHIES DETECTED?

Whilst most patients are asymptomatic, those presenting to their GP with new cardiac symptoms (*Table 1*) should undergo careful assessment. Consensus guidelines from the Association for Inherited Cardiac Conditions (AICC) recommend that red flag symptoms should result in urgent evaluation in secondary care (16). Onward referral to a specialist clinic should follow after exclusion of other causes such as ischaemic or valvular heart disease.

A three-generation family history may identify a red flag diagnosis of cardiomyopathy or premature sudden death in a relative. Other suggestive family history includes premature stroke, heart failure, or use of implantable cardiac devices. All patients diagnosed with an inherited cardiomyopathy or a red flag family history should be offered assessment in a specialist service.

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Cardiac Screening

The role of cardiac screening in the young is controversial. The UK National Screening Committee does not support a systematic population screening programme (17). However, young athletes are at increased risk of sudden death and pre-participation screening incorporating the 12-lead ECG is endorsed by the European Society of Cardiology (ESC) for all athletes aged 12-35 (18). A population-based observational study from Italy showed an 89% reduction in the incidence of sudden cardiac death following introduction of mandatory pre-participation screening (from 3.6/100 000 to 0.4/100 000 person-years over a 26-year period) (19). A UK study of 4,925 young athletes identified an ECG abnormality in 4.3%, although only 0.3% had a potentially serious cardiac condition (20). ECG abnormalities can be subtle, however, and suitably trained physicians should assess athletes. Advice should be sought by GPs if asked to declare such patients 'fit to participate' in endurance activities such as marathons.

Post-mortem diagnosis

A comprehensive post-mortem is crucial to inform accurate diagnosis following sudden death and direct appropriate investigations in the family (21). All sudden deaths should be considered cardiac after exclusion of non-cardiac causes and guidelines recommend a full autopsy, including histological examination (22). A prospective study of 490 consecutive sudden cardiac death victims aged 1-35 implicated inherited cardiomyopathies in 16% (23). When identified at autopsy, GPs should refer immediate relatives to a specialist clinic and consider bereavement support.

WHAT ARE THE INITIAL INVESTIGATIONS?

The 12-lead ECG is the first-line investigation. It may be undertaken in primary care, but often requires interpretation by a cardiologist and if abnormal should result in referral to secondary care. *Table 2* describes key investigations and possible findings according to aetiology. Those with an abnormal ECG, suggestive family history, or unexplained symptoms or physical signs should be referred to a cardiologist. Explain to patients that several tests requiring specialist referral and interpretation are often necessary (*Figure 2*). This may include signal-averaged, ambulatory, and exercise ECGs, in addition

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to advanced imaging. Determining whether a cardiomyopathy is genetic will frequently involve familial assessment.

	HCM	DCM	ACM
ECG	Pathological Q waves; ST segment depression (*Figure 3*); Abnormal T wave inversion (*Figure 3*); Left bundle branch block; Profound non-specific intraventricular conduction delay		Abnormal T-wave inversion (*Figure 4*) (anterior leads, or inferolateral leads in left ventricular variant); Epsilon waves; Abnormal signal-averaged ECG
Echocardiogram	Global or segmental hypertrophy (*Figure 5*); Left ventricular outflow tract obstruction; Systolic anterior motion of the mitral valve; Diastolic dysfunction	Dilatation of the left ventricular cavity; Impaired left ventricular systolic function; Normal or reduced wall thickness	Right ventricular dilatation and/or systolic impairment; Regional wall motion abnormalities (right ventricle); Left ventricular dilatation and systolic impairment in some
24-hour tape and exercise ECG	Sustained or non-sustained ventricular tachycardia; ST-segment depression / T-wave inversion during exercise Atrial fibrillation		Frequent ventricular ectopy; Exercise-induced arrhythmias; Sustained or non-sustained ventricular tachycardia

Table 2: Summary of key electrical and structural abnormalities in the inherited cardiomyopathies. These will not be present in all affected individuals.

Cardiovascular Magnetic Resonance Imaging (CMR)

CMR may be employed in a specialist clinic to better characterise hypertrophy, especially apical HCM missed on echocardiography. It may also differentiate specific causes such as amyloidosis and Fabry disease (24). The presence and distribution of late gadolinium enhancement, representing myocardial

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fibrosis, can distinguish different forms of disease and may confer a worse prognosis (25) as in HCM (26). CMR is also useful in the diagnosis of ACM, owing to its excellent visualisation of often subtle changes in the right ventricle (27).

WHAT IS THE ROLE OF GENETIC TESTING IN SUSPECTED CASES?

Genetic testing of suspected cases is undertaken through specialist clinics to confirm or aid diagnosis, and occasionally guide therapy and evaluate risk. Consensus guidelines recommend that patients with a clinical diagnosis of HCM are offered genetic testing (28). Testing is advised for DCM patients with significant cardiac conduction disease and/or a family history of premature unexpected sudden cardiac death, where carrying a mutation (e.g. in the *LMNA* gene) may indicate higher risk. Genetic testing can be useful in ACM patients fulfilling diagnostic criteria and occasionally beneficial in borderline cases to aid diagnosis (28).

Tips for the non-specialist: What to say to patients

Genetic testing can give us some insight into the underlying cause of your cardiomyopathy.

If we do not identify a gene change, this does not mean your condition is not inherited.

Positive genetic results can be useful to identify family members who may be at risk and sometimes allow discharge of those not at risk from follow-up.

Genetic testing might in some cases influence the treatment you receive.

Genetic testing might offer an opportunity to avoid passing on the disease in future pregnancies.

Genetic results can be revisited over time with more information.

Patients should be informed fully about the uncertainties of genetic testing. Genetic counsellors routinely discuss the potential for uncovering genetic variants of unknown significance (VUS), the need for future disclosure of genetic information for the benefit other family members, the psychological and social ramifications, and the rationale for pursuing testing in a family. Data from qualitative studies suggest testing does not inflict psychological harm and may alleviate uncertainty (29,30). However, the identification of a positive result in otherwise unaffected family members may cause increased anxiety

about transmission to children and fear of discrimination. The UK government has set out a voluntary code of practice with British insurers stipulating that the results of predictive genetic testing should not be disclosed, with few exceptions (31).

Family planning should also be discussed with patients. In selected gene-positive mothers, genetic conditions can be identified in embryos produced using *in vitro* fertilisation (pre-implantation genetic diagnosis). Gene-positive embryos will then not be implanted.

HOW ARE FAMILY MEMBERS EVALUATED?

The aim of family evaluation is to identify affected relatives through clinical and/or genetic evaluation, commence appropriate treatment if indicated, and reduce the risk of sudden death (32-34). Indeed, the main role for genetic testing is early diagnosis of relatives of a clinically affected individual with a disease-causing mutation. This is known as predictive or cascade testing and when there is clear evidence of disease-causation, this may permit early discharge of gene-negative relatives from follow-up. Thus, all immediate relatives of an affected individual should be referred to a specialist clinic to undergo clinical and predictive testing if appropriate (28). Predictive genetic testing in children should, however, always be carefully considered bearing in mind the child's best interests. The probability that a gene-positive individual will go on to develop disease is often unknown and genetic testing may impact upon the child's autonomy.

If there is no gene mutation identified, clinical testing of relatives should proceed dependent on the underlying cardiomyopathy. Frequency of clinic follow-up is determined by several factors such as identification of disease-causing mutations, age at presentation, family history, and the presence of symptoms (35). Those with a disease-causing mutation will usually be followed up on an annual basis, dependent on the results from clinical evaluation. In the absence of genetic information or signs of disease, investigations are repeated every 2-5 years. In children aged 10-20, tests are recommended on an annual basis, but may be performed at an earlier age in select cases or as a baseline to minimise parental anxiety.

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HOW ARE THE INHERITED CARDIOMYOPATHIES MANAGED?

The main goals of treatment are to ameliorate symptoms and prolong life. Management and risk stratification are best determined by a specialist and follow-up may involve a local cardiologist in partnership with primary care. General practitioners are well positioned to monitor and up titrate drug therapy, liaise with local heart failure community services (where appropriate), identify other family members, and refer patients in need of reassessment back to specialist care.

Risk stratification for sudden cardiac death

The aim of risk stratification is to identify patients at the highest risk of sudden death and facilitate preventative strategies including an implantable cardioverter defibrillator (ICD). In HCM, the ESC Risk-SCD calculator (36) combines clinical and family history with investigation findings to estimate an individual's 5-year risk of sudden cardiac death. This model has been externally validated in a large retrospective cohort study and is employed alongside other tools such as late gadolinium enhancement on CMR (26,37). In ACM, several observational studies have identified risk markers including sustained ventricular tachycardia, heart failure, and cardiogenic syncope (38-40). The severity of systolic impairment remains the main driver of risk in DCM, particularly patients with a left ventricular ejection fraction <35% (41), or those with *LMNA* gene mutations (28).

Prognosis

The natural history of the inherited cardiomyopathies varies according to underlying aetiology. In HCM, a large meta-analysis of 12,146 patients identified a pooled 10-year survival rate of 75% (95% CI 71.1-78.9%) (42). This analysis, however, has several limitations and larger prospective studies with longer follow-up are required. In ACM, cohort studies have estimated an annual mortality of <1% for treated patients (43). In DCM, prognosis is difficult to define due to its insidious onset and heterogeneous nature. An early retrospective observational study of 101 DCM patients reported a five-year survival of 55% for non-familial forms and 51% for patients with familial disease (44); however, more recent studies suggest a more favourable outcome, especially amongst idiopathic disease (45,46). Discussion of prognosis with patients must be individualised due to diverse clinical presentation, genetic causes, and evolving evidence-based therapies.

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Implantable cardioverter defibrillators

The ICD is the only effective way of preventing premature sudden cardiac death in high-risk groups. In patients with ventricular arrhythmias, a meta-analysis of ICD therapy versus medical treatment alone showed a marked reduction in sudden cardiac death (RR 0.49, 95% CI 0.34 to 0.69) and all-cause mortality (RR 0.75, 95% CI 0.61 to 0.93)(47). International guidelines recommend an ICD for secondary prevention in all inherited cardiomyopathy patients who have suffered a cardiac arrest, provided there have been no serious neurological sequalae or other life-limiting illnesses (48,49). Use of ICDs for primary prevention in selected patients is supported by several observational studies (40,50-52). However, in DCM, one high-quality randomised trial did not find survival benefit except in younger patients (53). Specialists must carefully discuss risks and benefits of ICD implantation, refer patients for counselling, and consider alternatives such as the subcutaneous ICD. The potential for harm should not be understated (54). A recent systematic review and meta-analysis of 4,916 young patients identified inappropriate shock therapy in 20% over a mean follow-up of 51 ± 38 months, with ICD-related complications (such as lead malfunction and infection) occurring in 22% (55).

Lifestyle modifications

General lifestyle measures such as smoking cessation and maintaining a healthy body mass index should be encouraged. Disease-specific advice is often derived from consensus opinion. For symptomatic left ventricular outflow tract obstruction, ESC guidelines recommend avoidance of dehydration and very hot temperatures, in addition to eating smaller more frequent meals (35). For patients with heart failure, NICE recommend that patients should not routinely restrict their salt or fluid intake, but avoid salt substitutes that contain potassium (56). Participation in regular exercise is generally advisable, but involvement in competitive sport will depend on underlying risk (57). ACM patients should not participate in most competitive and/or endurance sport (58). ESC guidelines favour an individualised approach directed by specialists for competitive sport participation in HCM and DCM patients (59). The AHA/ACC and ESC restrict competitive sport in unaffected ACM gene carriers (58,59); whereas unaffected HCM gene carriers may participate.

Treatment

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Treatment strategies are broadly similar for inherited and non-inherited cardiomyopathy. Gene-specific treatment has yet to enter clinical practice but is likely to play a future role. In HCM with symptomatic left ventricular outflow tract obstruction, several small retrospective studies support beta-blockers as first line therapy and ESC guidelines recommend titration to maximum dose (35,60-62). The ESC also recommend disopyramide or invasive and surgical options if symptom-control remains problematic (35). Arrhythmias, such as atrial fibrillation and heart failure, are managed as per standard guidelines (35,40,48,49,56). Antiarrhythmic medication is prescribed under cardiological advice in DCM patients (41). An international Task Force consensus statement supported by limited observational cohort studies recommend beta-blockers for most ACM patients (40). Those with complex or refractory arrhythmia may benefit from class III antiarrhythmic drugs such as sotalol or amiodarone, or even ablation (40).

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Information resources for patients

www.cardiomyopathy.org Support and information for patients diagnosed with cardiomyopathy.

www.myheart.org.uk Support for young people diagnosed with heart conditions.

www.c-r-y.org.uk Information, resources, and support for young people and family members affected by inherited heart conditions.

https://www.nhs.uk/conditions/cardiomyopathy NHS overview of the cardiomyopathies.

ttps://www.bhf.org.uk/heart-health/conditions/cardiomyopathy Digital patient resource from the British Heart Foundation.

Education into practice

Do you know what local support services are available for patients living with an inherited cardiomyopathy or for those that have experienced a young sudden death in the family?
Do you ask about family members when reviewing a patient with inherited cardiomyopathy?
How many of your inherited cardiomyopathy patients have been assessed in a specialist clinic?

A patient's perspective

I was diagnosed with ACM in April 2006, after my brother died playing football in January of that year. His ACM was diagnosed on post-mortem and the rest of the family were referred for screening. When I was diagnosed I don't think the enormity of the situation or the possible impact it was going to have on my life really occurred to me – nothing could equal his loss, so in some ways I saw myself as being lucky.

Within two months I had my first ICD implanted. As this happened so quickly there wasn't much time to think about it, but although I have since spoken to several people who have spent a long time thinking about whether to have an ICD, for me there wasn't any doubt that it was the right thing to do.

We were offered genetic testing in 2006, and the results came back with me having two genes, one from mum and one from dad – neither knowing before then that they carried them or had any symptoms. They then tested my brother's tissue and he had also had both, whereas my other brother only has one.

When it came to the decision to have children, the genetics didn't play a large factor but our understanding that any children should only inherit one gene was reassuring, as in our family it appears that both are needed for the condition to develop.

I am lucky in that ACM has not had any major impact on my life – I can still continue my level of sport, including horse riding and swimming at recreational level, and my heart has been pretty stable since diagnosis. Most days I even manage to forget I have a potentially life-threatening condition!

How this article was created

We searched PubMed, Clinical Evidence, and GeneReviews, in addition to personal archives and published guidelines from the National Institute for Health and Care Excellence (NICE), European Society of Cardiology (ESC), American Heart Association (AHA), American College of Cardiology (ACC), and UK Association for Inherited Cardiac Conditions (AICC). Articles were selected based on relevant and evidence-based recommendations pertaining to current investigation and management. The following search terms were used in isolation and in combination: “hypertrophic cardiomyopathy”, “inherited cardiomyopathies”, “arrhythmogenic cardiomyopathy”, “dilated cardiomyopathy”, “genetic testing”, “next generation sequencing”, “familial evaluation”, “sudden cardiac death”, and “risk stratification”.

How patients were involved in the creation of this article

A member of the Cardiac Risk in the Young (CRY) *myheart* network providing their patient perspective.

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Contributors

CM contributed to the planning, drafting, revision, and approval of the article; ZF contributed to drafting, revision, and approval; MT contributed to drafting, revision, and approval; ERB is guarantor and contributed to conception, drafting, revision, and approval. The authors would like to thank Professor Mary Sheppard at St George’s University of London for supplying histological images (Figure 1).

Competing interests

We have read and understood BMJ policy on declaration of interests and have nothing to declare.

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Figure legends

Figure 1: Overview of the main structural, genetic, and functional features of the inherited cardiomyopathies. *Prevalence of each cardiomyopathy in the general population. Modified from (63).

Figure 2: Specialised approach to diagnostic evaluation in the inherited cardiomyopathies.

Figure 3: 12-lead ECG of a patient with apical HCM. There is voltage criteria for left ventricular hypertrophy with deep T wave inversion in the anterior, inferior, and lateral leads (associated with ST segment depression).

Figure 4: Precordial ECG leads of a patient with ACM demonstrating pathological T wave inversion (arrowed) in V1-V4.

Figure 5: Echocardiographic findings of asymmetrical left ventricular septal hypertrophy (arrowed) in HCM.

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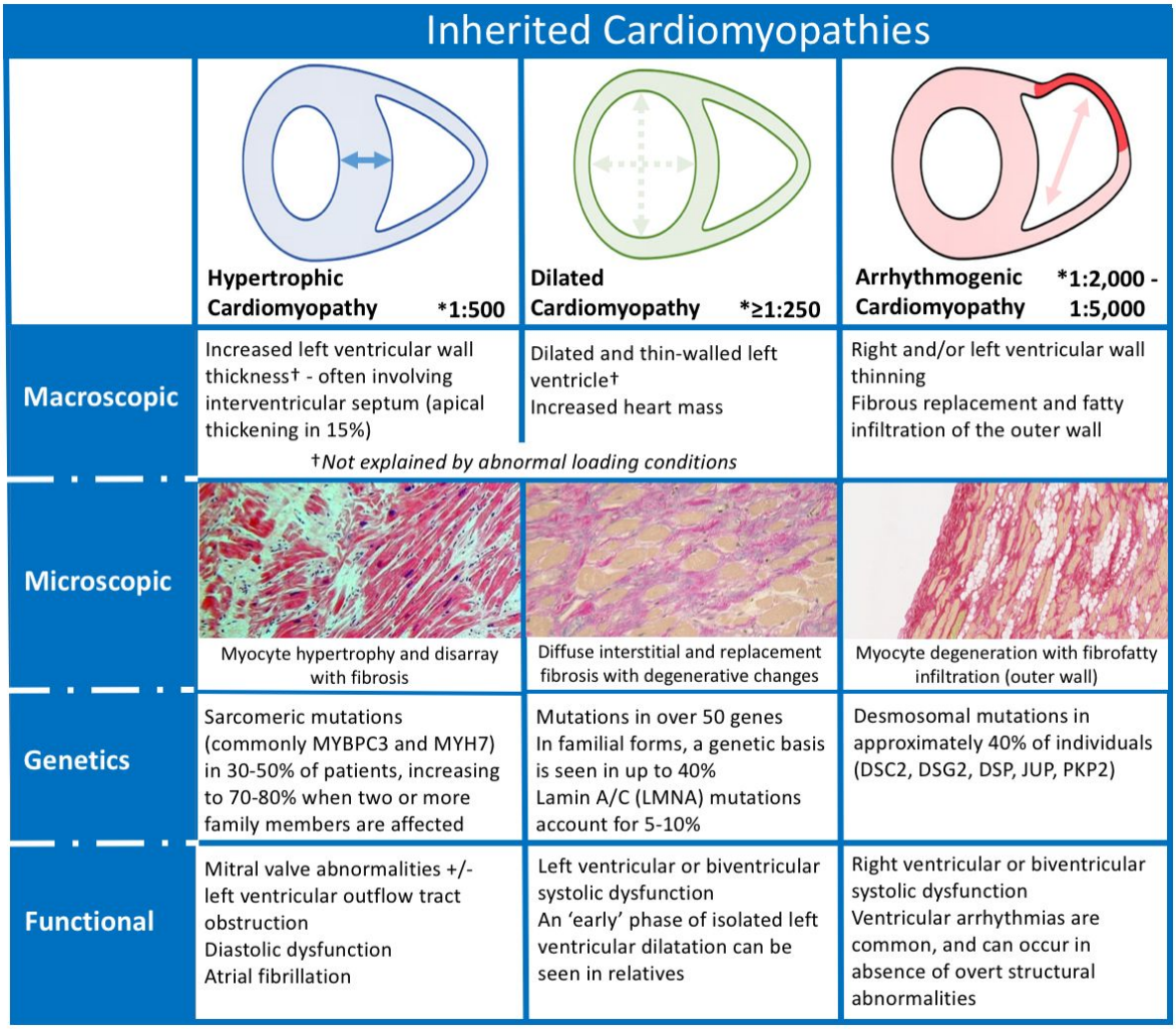

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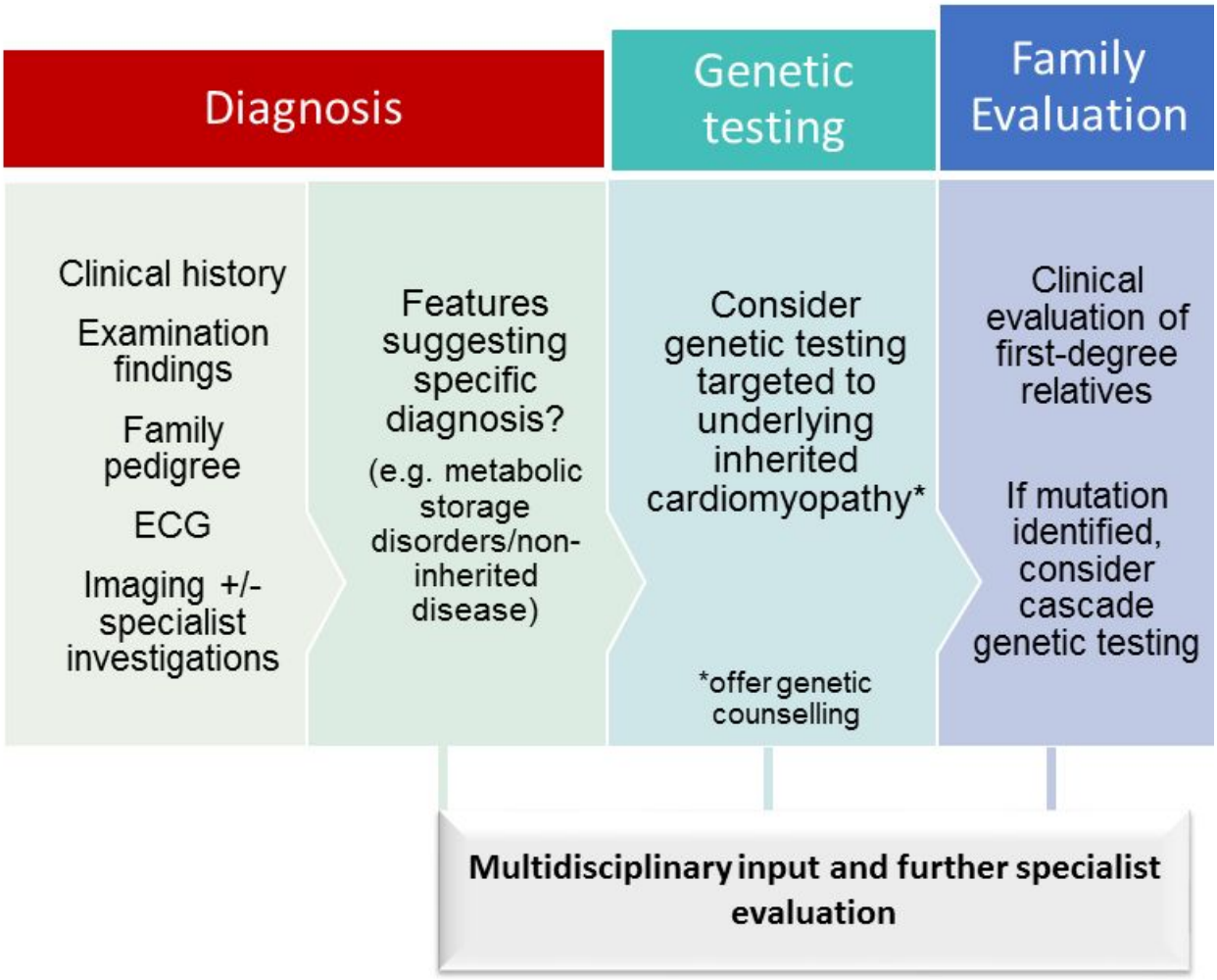

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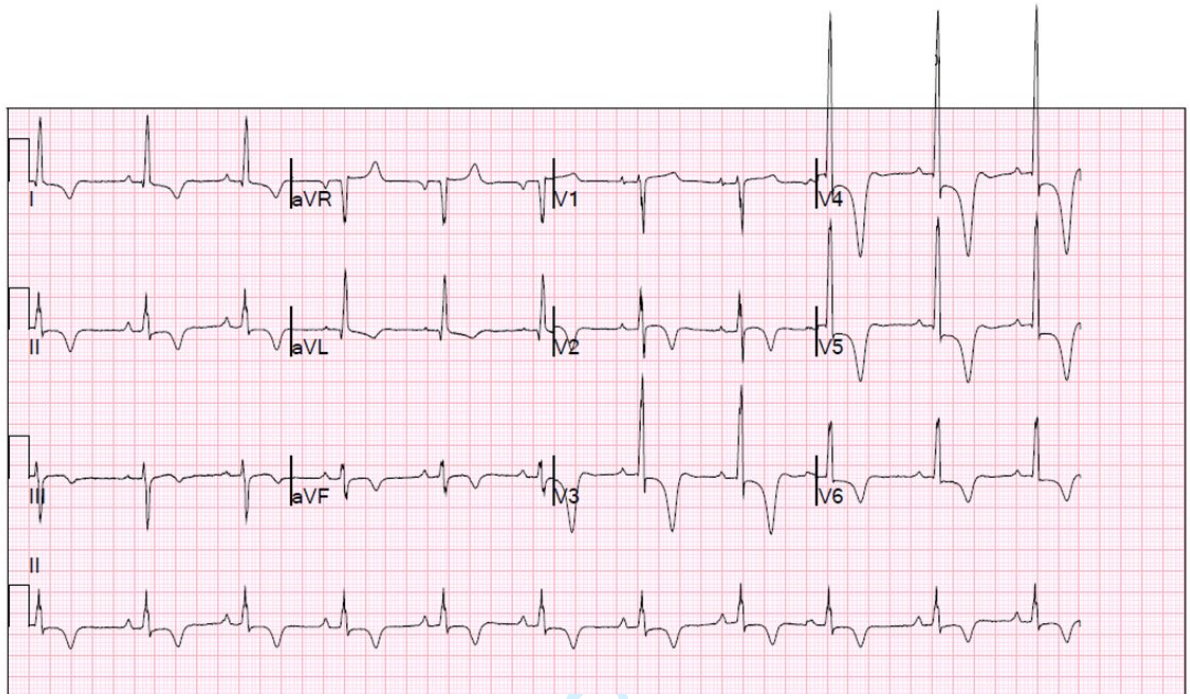

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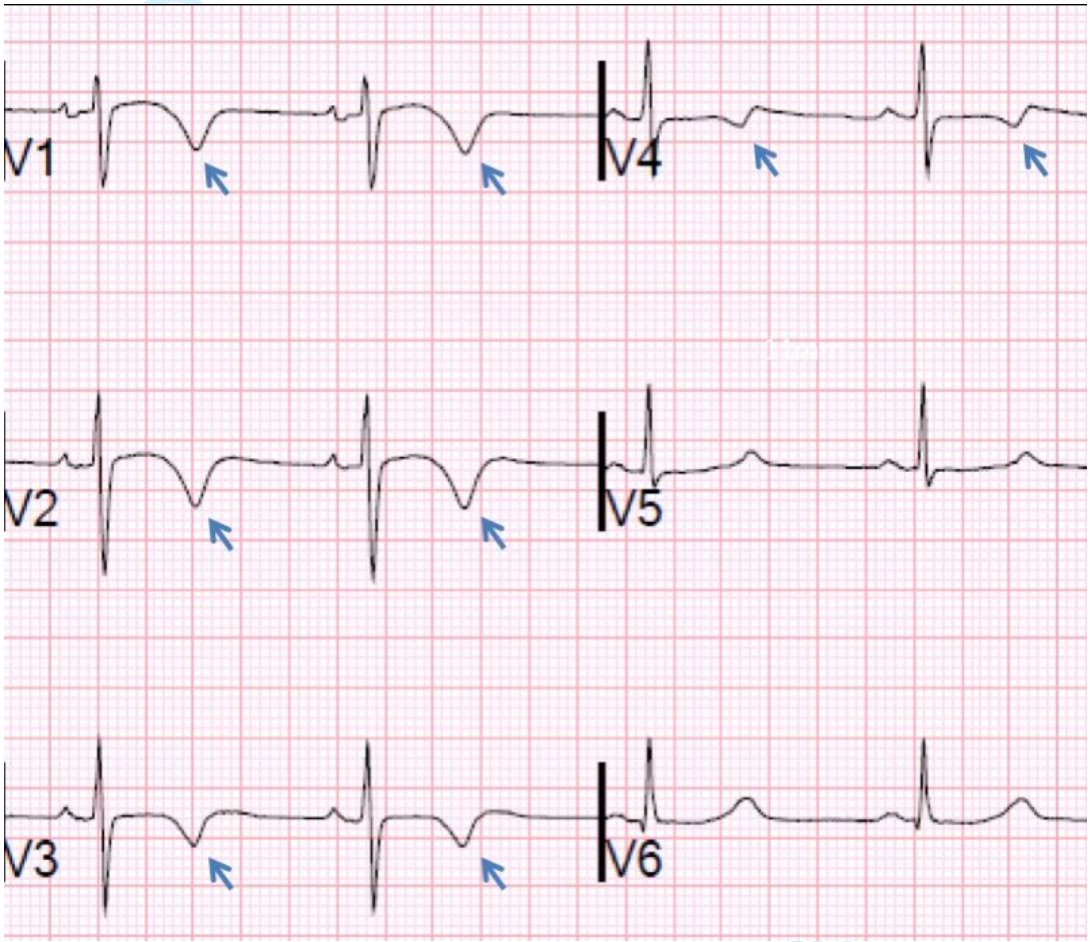

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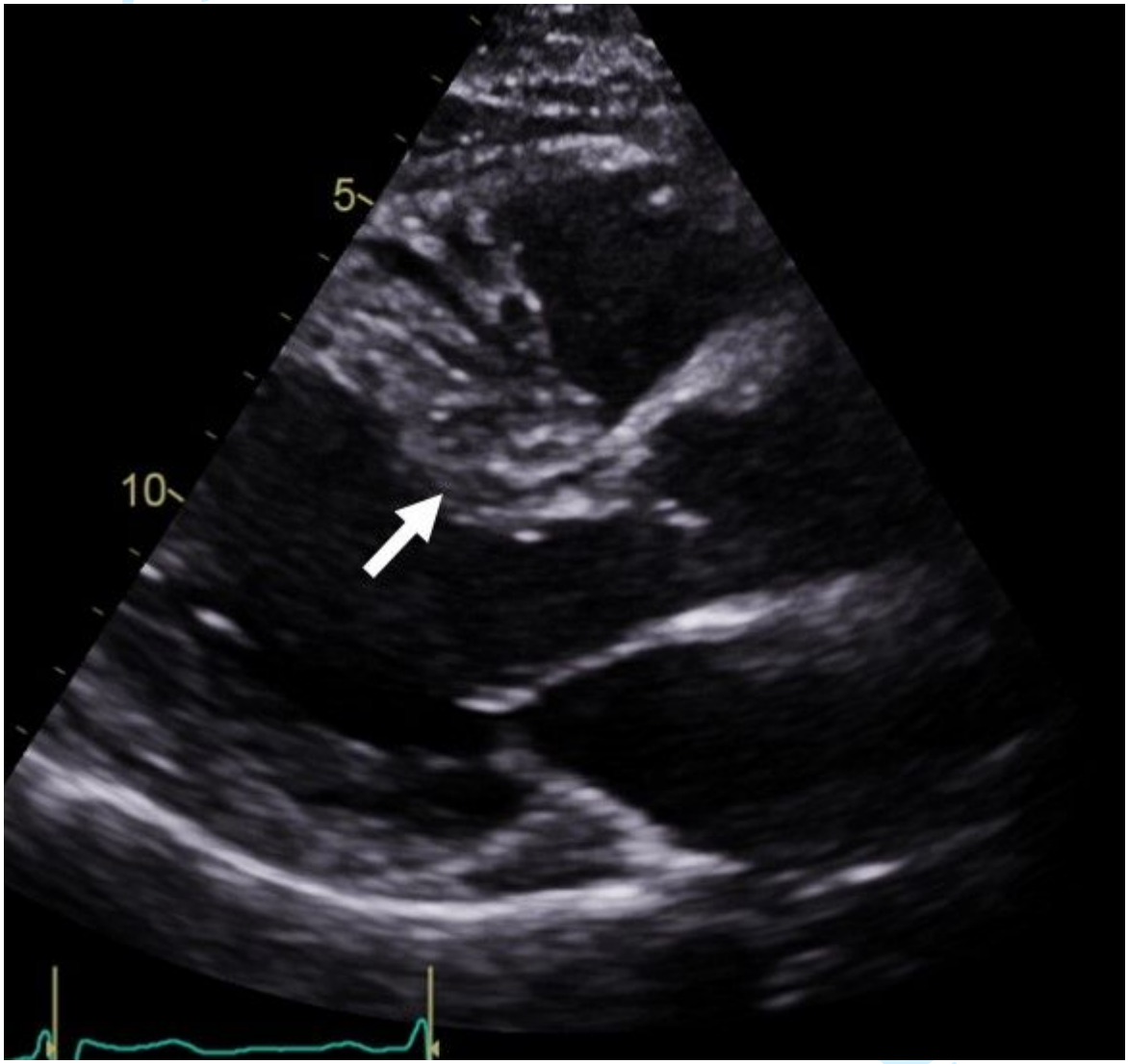

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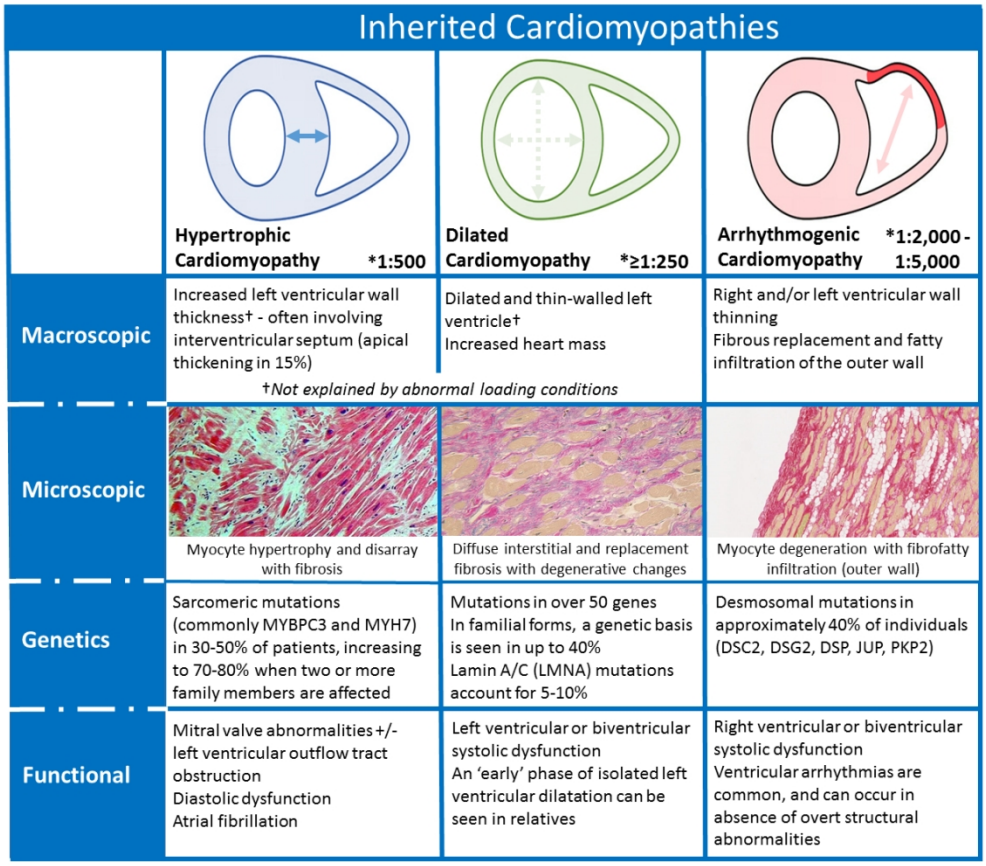

Overview of the main structural, genetic, and functional features of the inherited cardiomyopathies. *Prevalence of each cardiomyopathy in the general population. Modified from (63).

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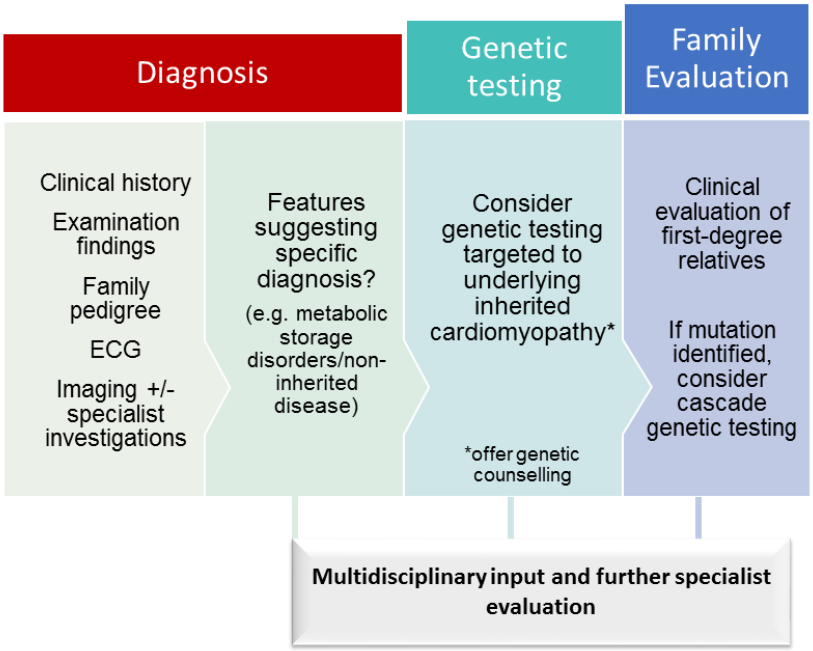

Specialised approach to diagnostic evaluation in the inherited cardiomyopathies.

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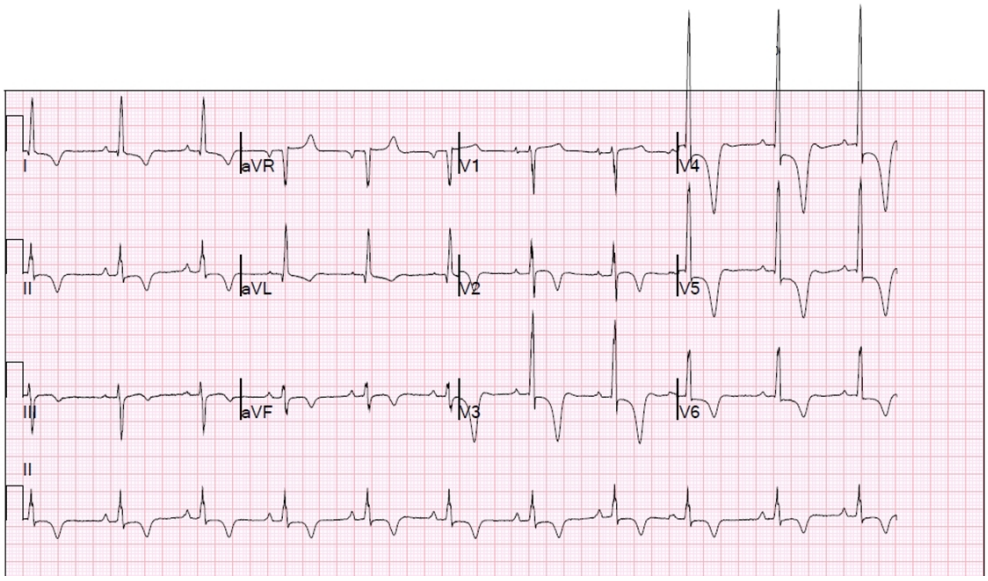

12-lead ECG of a patient with apical HCM. There is voltage criteria for left ventricular hypertrophy with deep T wave inversion in the anterior, inferior, and lateral leads (associated with ST segment depression).

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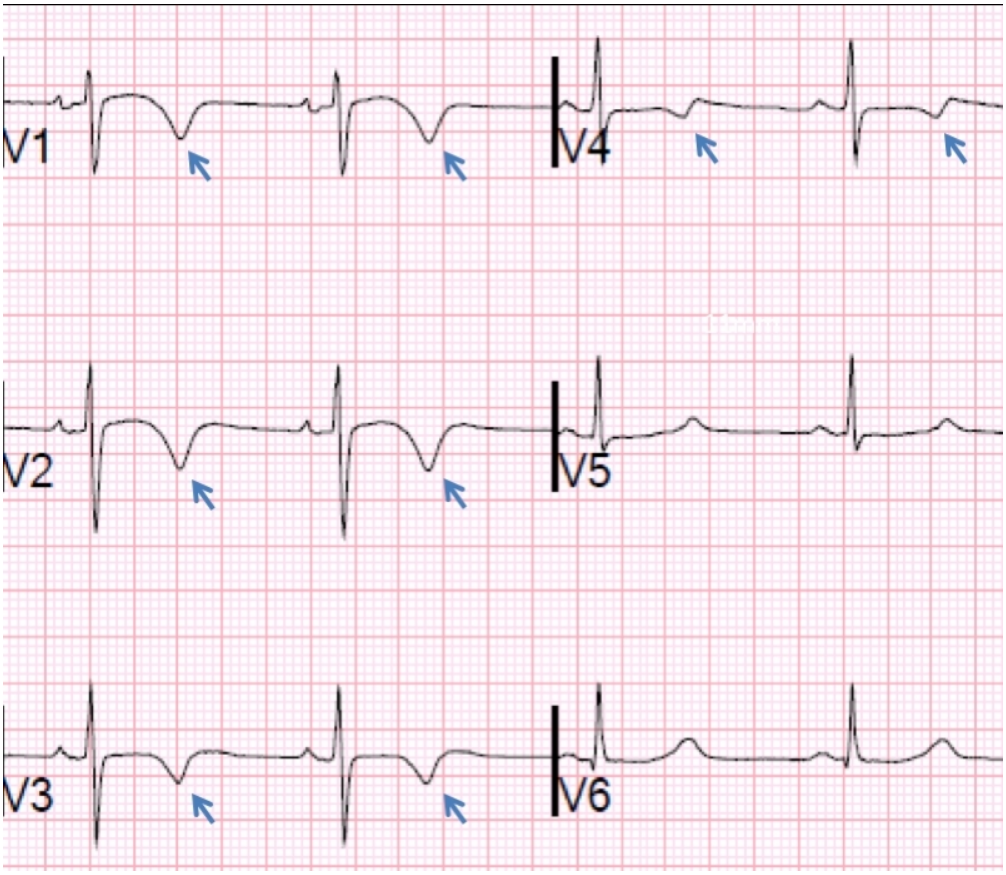

Precordial ECG leads of a patient with ACM demonstrating pathological T wave inversion (arrowed) in V1-V4.

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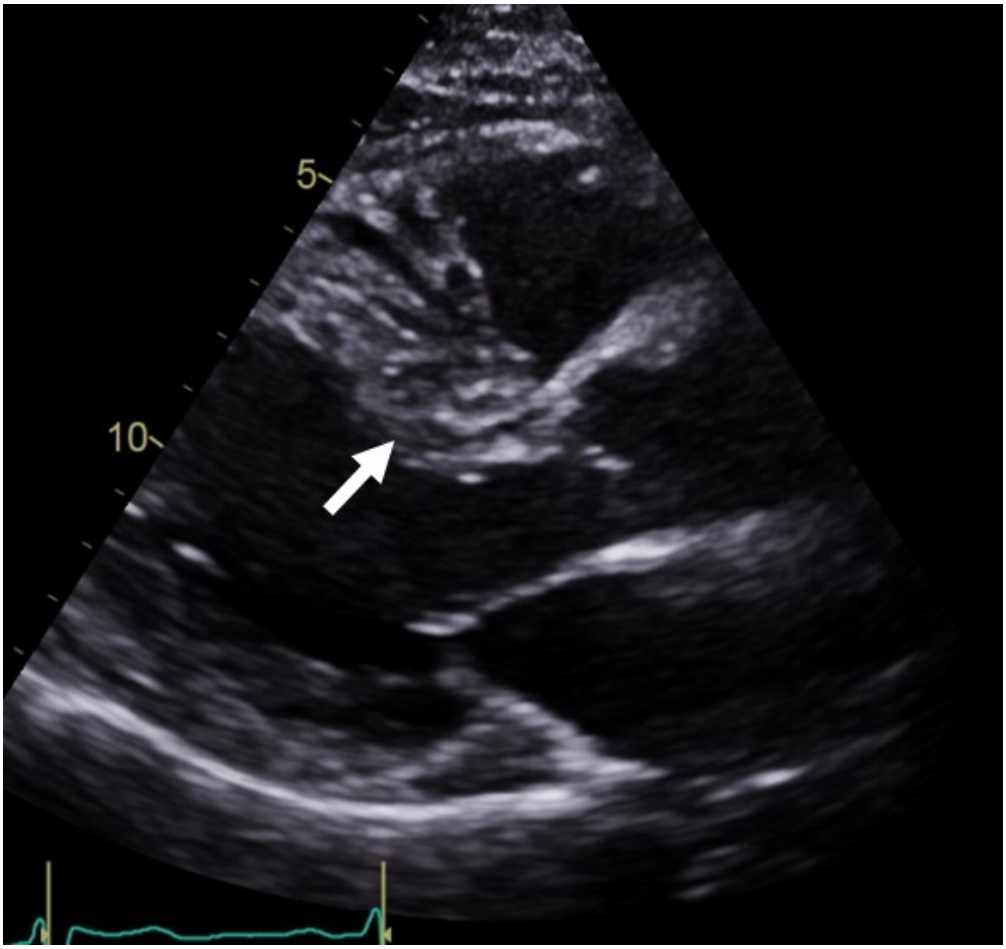

Echocardiographic findings of asymmetrical left ventricular septal hypertrophy (arrowed) in HCM.

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