Information sheet: Genetic testing for inherited cardiac conditions

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Step 1:
Determining who needs to undergo genetic testing?

Genetic testing may be indicated in individuals who have been diagnosed with a cardiac arrhythmia or a cardiomyopathy, particularly when acquired or environmental causes for their condition have not been found. Genetic testing should only be undertaken in individuals where a diagnosis of a likely genetic cardiac condition has been made, or a relative of a patient who has been diagnosed with a genetic cardiac condition.

The clinical evaluation is very important and is the first step in the genetic testing journey, as it helps clinicians determine which genes should be tested, and how the genetic test result is interpreted. We call this 'phenotyping' - the process of measuring and quantifying the observable, physical characteristics, that allows us to make a more accurate diagnosis.

Genetic cardiac conditions are caused by genetic "spelling mistakes or errors", referred to as genetic variants, in one of the heart genes within our DNA (genetic code). Our DNA is made up of many genes. Each gene codes an instruction that tells the body how to make a specific protein that will have a specific function within our body. If there is a 'spelling error' or variation in the code of one of the heart genes, it may result in a faulty instruction and the development of heart disease. Genetic cardiac conditions include two main groups, namely, channelopathies and cardiomyopathies.

Cardiomyopathies

Cardiomyopathies occur when the heart muscle structure and/or function is impaired in some way, depending on which component within the heart muscle cell is abnormal. There are a number of different types of cardiomyopathies including hypertrophic cardiomyopathy (when the heart muscle becomes thickened), dilated cardiomyopathy (where the heart muscle becomes weakened), arrhythmogenic right ventricular cardiomyopathy (when the heart muscle cells become disconnected from one another and die, leaving behind scarred tissue which causes electrical instability), restrictive cardiomyopathy (where the heart muscle becomes very stiff and rigid) or non-dilated left ventricular cardiomyopathy (where the heart muscle is impaired or scarred). Cardiomyopathies are diagnosed by performing several specialised tests, including an electrocardiogram (ECG) and an echocardiogram (an ultrasound of the heart). Cardiac MRI (CMR) is very useful in diagnosing cardiomyopathies because it allows us to not only examine the heart structure and function but also allows us to visualise scar tissue or inflammation within the heart muscle itself, providing the same type of information we get when we do a cardiac muscle biopsy.

Channelopathies

Channelopathies are cardiac arrhythmia syndromes that are caused by a disruption in the ion channels and electrical signalling within the heart muscle cells. Examples include Long QT syndrome (LQTS), Brugada syndrome, Short QT syndrome (SQTS), and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Channelopathies are usually diagnosed by doing an electrocardiogram (ECG) and/or by capturing the arrhythmia on an ECG or Holter. The heart structure and function are usually normal.

Step 2:
Evaluating the family history and determining who in the family may be at risk of developing heart disease

Before we consider doing genetic testing, it is important to take a detailed family history and construct a family pedigree (or family tree). This is very important because it helps us determine whether there a high or low likelihood of a genetic condition within the family, and whether genetic testing would be helpful.

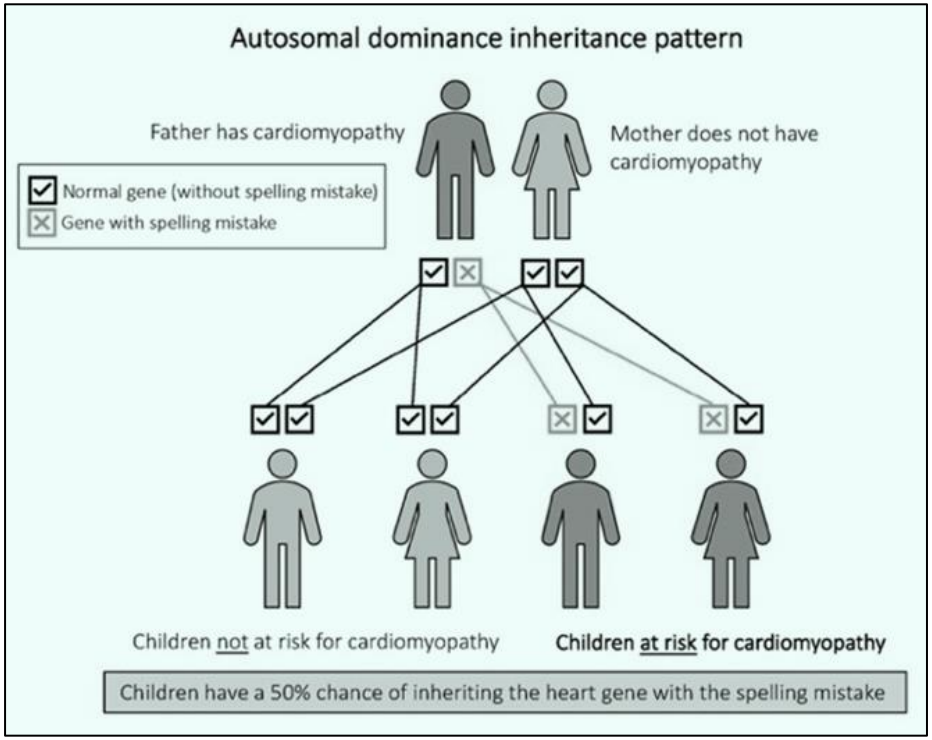
If more than one person in the family has been diagnosed with the same heart condition, it is very likely that the cause is genetic (i.e. familial) and genetic testing is strongly indicated. If there is no family history of heart disease or sudden death in the family, it makes it less likely to be a genetic condition, however, it does not exclude a genetic condition. In some cases, the diagnosis of a genetic heart condition may be made for the first time in an individual in a family, we called this *De Novo*. In this case, prior generations (grandparents, parents, siblings) remain unaffected and are not at risk, however, future generations (children, grandchildren) may be at risk.

The family pedigree (or family tree) helps us determine the **pattern of inheritance** which may be useful when interpreting the genetics results and evaluating who else in the family may be at risk of developing the same condition. This also helps the clinician determine the urgency by which other members in the family need to be evaluated.

Most cardiomyopathies and channelopathies are **autosomal dominantly inherited**. Importantly, everyone has two copies of every heart gene, one they inherit from their mother and one from their father.

If there is a 'spelling mistake' in one of the copies of a specific heart gene, a person may be at risk of developing a genetic heart condition. It is important to remember that not everyone who carries a genetic variant will develop the heart condition; it only increases the risk of developing the heart condition.

This type on inheritance ('passing on') is called **autosomal dominant inheritance** (see picture). This means that if you carry one genetic variant, there is a 50% chance that each of your children could also inherit the variant.



Step 3:
Pretest genetic counselling

Pretest genetic counselling is a crucial step before undergoing genetic testing. This should be done by a trained genetic counsellor or a doctor with specific expertise in inherited cardiac conditions. Genetic counselling is aimed at providing a patient and their family with information about genetics and how *variants* (or spelling errors) in the genetic code lead to the development of heart disease. This is an opportunity to discuss patient fears, expectations and concerns, and address any questions they have about their condition or how the genetic test may alter their medical care or the care of their family members that may also be at risk. The genetic counsellor will discuss the potential outcomes that may be expected.

Step 4:
Genetic testing

Genetic testing is done as a **blood test**. Blood is taken and sent to an international laboratory for testing. The DNA is extracted from the blood cells and sequenced using a special 'next generation sequencing' machine. The results are analysed and filtered through computer programming. In most cases, only cardiac genes are sequenced (i.e. cardiomyopathy and/or arrhythmia panels including ±50-100 genes). Within our DNA, we have many variations or 'spelling errors', most of which are benign (i.e. do not cause disease). We use a variety of criteria to determine whether a gene variant is significant (i.e. causing disease) or not. Variant interpretation is conducted by experts in the field. Each variant is evaluated and classified as benign, likely benign, variant of unknown significance (VUS), likely pathogenic or pathogenic. Only pathogenic/likely pathogenic variants (and sometimes VUS) are reported.

Step 4:
Results feedback and post-test counselling

Genetics results should always be discussed in person (or in a virtual consultation). There are 3 possible outcomes:

A positive result – this means that a pathogenic or likely pathogenic gene variant has been identified. In this case, we can offer to do genetic testing for the same gene variant on other family members to determine who in the family carries the gene variant and may be at risk for developing the same cardiac condition. We call this predictive genetic testing.

A negative result – this means that no pathogenic or likely pathogenic gene variants have been identified. A negative test does not necessarily mean that the cause of the heart condition is not genetic, however, it makes it less likely if no one else in the family is affected. Importantly, if multiple individuals in a family have the same heart condition, we would then assume that it is genetic and the gene causing the condition has not yet been discovered (gene elusive). In cases such as these, we would offer clinical family screening to those at risk, including regular cardiac follow-up with routine ECG and echocardiograms.

Variants of unknown significance ("VUS") – in some cases, we find a gene variant that may be rare and unique to an individual in a gene that is known to cause heart disease, however, it is unclear whether the change is significant enough to cause heart disease. In such cases, we cannot rely on this result to diagnose cardiomyopathies or channelopathies in other individuals within a family and we often approach it like a negative test and offer clinical screening to families.

Step 5:
How does a genetic test results impact care?

For the **individual patient**, knowing the genetic diagnosis can alter the way in which we manage their heart condition. Each gene behaves in a unique way, and therefore, if we know which gene is abnormal, we may be able to predict how the heart condition may change over time. We may be able to introduce specific medications or provide lifestyle advice that may slow progression of disease and prevent complications. Most importantly, some genes are associated with arrhythmias and sudden cardiac death. In some cases, we have specific risk scores to help us predict whether an individual has a high or a low risk of developing ventricular arrhythmias (such as ventricular tachycardia or ventricular fibrillation) that may lead to sudden death. In high-risk patients, we may recommend insertion a special device, called an implantable cardioverter defibrillator (ICD) that is able monitor the heart rhythm and shock the heart back into a normal rhythm if needed. In low-risk patients, an ICD may not be necessary. While there are currently no specific curative therapies for cardiomyopathies or channelopathies, science is rapidly evolving, and curative gene therapy may become available in the not-so-distant future.

For **families**, having a confirmed genetic diagnosis in an affected individual is extremely useful as it provides an opportunity to screen family members before they develop symptoms or get sick. We can do a genetic test on asymptomatic members of the same family to determine whether they carry the disease-causing gene variant or not, and in that way determine who may be at risk of developing the same heart condition.

Family members that carry the deleterious gene variant (i.e., have a POSITIVE test) should be referred to a cardiologist for cardiac assessment, which usually includes an electrocardiogram and echocardiogram (ultrasound of the heart) to determine whether they have any evidence of the heart condition or not.

Importantly, **not all gene carriers will develop the heart condition**. If the cardiac assessment in a gene carrier is normal, no treatment is required, however, we do recommend continuing annual follow-up assessments with a cardiologist. If we can detect heart muscle or electrical abnormalities early on before the development of symptoms, there are a number of treatment options available to prevent and manage symptoms, help preserve normal heart function, prevent cardiac arrhythmias and treat heart failure.

Family members that DO NOT carry the gene variant (i.e. a NEGATIVE test) are not at risk for developing cardiomyopathy, DO NOT need a cardiac assessment, and their children do not require genetic testing. These individuals can be reassured and discharged.