Practical Aspects in Genetic Testing for Cardiomyopathies and Channelopathies

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Abstract

Genetic testing has an increasingly important role in the diagnosis and management of cardiac disorders, where it confirms the diagnosis, aids prognostication and risk stratification and guides treatment. A genetic diagnosis in the proband also enables clarification of the risk for family members by cascade testing. Genetics in cardiac disorders is complex where epigenetic and environmental factors might come into interplay. Incomplete penetrance and variable expressivity is also common. Genetic results in cardiac conditions are mostly probabilistic and should be interpreted with all available clinical information. With this complexity in cardiac genetics, testing is only indicated in patients with a strong suspicion of an inheritable cardiac disorder after a full clinical evaluation. In this review we discuss the genetics underlying the major cardiomyopathies and channelopathies, and the practical aspects of diagnosing these conditions in the laboratory.

Introduction

It is now known that a significant proportion of cardiomyopathies and channelopathies, which are associated with an increased risk of sudden cardiac death, might have an underlying genetic component.¹ Genetic testing has an increasingly important role in diagnosis and management of cardiac disorders and genetic findings have been incorporated into certain diagnostic criteria.²⁻⁴ A phenotype-genotype-based classification was proposed for cardiomyopathies and endorsed by the World Heart Federation in 2013.⁵ A genetic diagnosis confirms the diagnosis, aids prognostication and risk stratification and guides treatment strategies.^{6,7} Moreover, a genetic diagnosis in the proband enables clarification of the risk for family members, especially the asymptomatic ones, by cascade testing, which would only become possible when the causative genetic variant could be detected in the proband.⁸

Genetic results in cardiac conditions are mostly probabilistic in nature and should be interpreted in context of all the clinical information as well as family history after a full clinical evaluation; extra-cardiac manifestations might indicate certain syndromal diagnosis in the patient.^{9,10} Genetics in cardiac disorders is complex where epigenetic and environmental factors might come into interplay,¹¹ and oligogenic inheritance has been described in up to 5–10% of patients in the apparently

Mendelian conditions with multiple variants in genes coding the same function unit.^{7,12,13} Incomplete penetrance and variable expressivity are also common.¹ The evidence for the pathogenicity of various genes to cause cardiomyopathies and channelopathies is summarised by Garcia *et al.*¹⁴

With this complexity in cardiac genetics, genetic testing is indicated only in patients with a strong suspicion of an inheritable cardiac disorder after a full clinical evaluation, while cascade testing should be undertaken when there is an affected family member in whom a pathogenic or likely pathogenic variant has been detected.^{1,7} For post-mortem examination or molecular autopsy, pathologists have a special role in identifying family at risk and referring first-degree family members for relevant genetic testing.^{15,16}

Cardiomyopathies

Inheritable cardiomyopathies are a group of phenotypically and genetically heterogeneous conditions mainly caused by pathogenic variants in genes encoding the structural components of cardiomyocytes. The conditions are classified by their functional and morphological features into subtypes including arrhythmogenic cardiomyopathy (ACM), dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). These could present as arrhythmias, heart failure or

sudden cardiac death.¹⁷ The majority of these conditions are inherited in an autosomal dominant manner. The diagnostic yield is highest for HCM (30–60%) and ACM (10–50%), and less so for DCM (10–40%).^{8,18} The lack of targeted therapeutic modalities in cardiomyopathies may, however, limit the clinical utility of genetic testing to diagnosis and prognostication/risk stratification.⁷ Genetic testing is now recommended in all types of cardiomyopathies, while larger gene panels may include genes that cause syndromal disorders, neuromuscular conditions or metabolic conditions associated with cardiomyopathies.¹⁹ More recently, deep intronic variants have also been shown to contribute to cardiomyopathy phenotypes in selected previously unexplained cases.²⁰ RNA analysis might aid identification of these deep intronic variants, as well as reclassification of other splicing variants to likely pathogenic.²¹ Cascade testing in family members is a class I recommendation (i.e. is recommended) in the Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Statement for all inheritable cardiomyopathies where a familial pathogenic variant has been identified.⁸

Improved approaches were suggested with a large-scale evaluation of sequence data from patients with various cardiomyopathies compared to those deposited in a control database, highlighting the importance of interpreting the variants in light of benign background variant data among controls as well as the known disease mechanism for the cardiomyopathy gene in question.²² The framework of the Joint Consensus Recommendation developed by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG criteria) was designed for universal applicability.²³ In an attempt to improve consistency for variant interpretation, the ClinGen Inherited Cardiomyopathy Expert Panel has adjusted ACMG criteria to be used for *MYH7*-associated cardiomyopathies,²⁴ and will continue to evaluate the applicability of these adjusted criteria for other cardiomyopathy genes.

A large proportion of cardiomyopathy genes have also been implicated in skeletal myopathies or muscular dystrophies, especially in the group of limb-girdle muscular dystrophies, while many of these genes encode structural components of muscle in humans. It is increasingly recognised that cardiac manifestations could be present in predominantly skeletal myopathies and vice versa, with a certain degree of genotype-phenotype correlation.^{25–30} Provision of testing of the same genes utilising the expertise of the same team of genetic pathologists and liaison with both cardiologists and neurologists might be beneficial.

Arrhythmogenic Cardiomyopathy

ACM, or previously arrhythmogenic right ventricular

cardiomyopathy/dysplasia, is characterised by progressive fibrofatty replacement of the myocardium in association with risk of ventricular tachycardia and sudden cardiac death. The condition is predominantly inherited in an autosomal dominant manner apart from recessive forms associated with cutaneous manifestations including Naxos disease and Carvajal syndrome.³¹ Pathogenic variants in desmosomal genes (*JUP*, *DSP*, *PKP2*, *DSG2* and *DSC2*) account for >50% of ACM cases with evidence of genotype-phenotype associations.³² Biallelic inheritance has also been reported in up to 10% of cases.³³ Identification of a pathogenic ACM-associated variant is considered a major diagnostic criterion.³⁴

Dilated Cardiomyopathy

DCM is often defined as left ventricular dilatation together with systolic dysfunction; up to 40–50% of DCM cases could have a genetic variant identified in one of the 60 genes currently associated with the condition.³⁵ It was previously suggested that each of the multiple genes known to be associated with the condition contributed <5% of the cases, until the discovery of *TTN*-related DCM in the genomic era, which could account for up to 20% of cases.³⁶ Truncating variants in *TTN*, the largest gene in humans with alternate splicing, have been associated with DCM, yet are also identified in a normal control population.³⁷ While I-band in titin is a highly interactive structure with great potential for alternative splicing, the inextensible A-band in titin binds myosin and myosin-binding protein and is critical for biomechanical sensing and signalling.³⁸ It has been shown that the pathogenic DCM truncating variants are located predominantly in the A-band region of *TTN*.³⁹ Patients with pathogenic variants detected in *LMNA* or *DES* are reported to have a higher risk of concomitant conduction disease and sudden cardiac death.^{40,41} Genetic testing for DCM with significant conduction defect is thus recommended as a class I indication.⁸

Hypertrophic Cardiomyopathy

HCM is characterised by the presence of unexplained left ventricular hypertrophy.⁴² Eight genes (*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *ACTC1*, *MYL2* and *MYL3*) have currently been definitely associated with isolated HCM, while the evidence for other genes was determined to be only moderate or weaker.⁴³ Pathogenic variants in *MYBPC3* and *MYH7* are most frequently detected in HCM patients, accounting for up to 65–70% of cases in total.⁸ More severe phenotypes tend to be observed in patients with a pathogenic variant identified, and especially so when the variants are in genes encoding the thick filaments.⁴⁴ Compound or digenic heterozygosity may be present for up to 10% of HCM cases, which might also be of a more severe phenotype.¹³ It was recently shown that restrictive cardiomyopathy might also be associated with pathogenic variants in the same HCM genes.⁴⁵

Genetic testing for HCM is a class I recommendation in view of the potential benefit and detection rate.⁴² Other conditions such as Fabry disease and mitochondrial disorders, where treatments might be available, might also manifest as HCM and other cardiomyopathies, and the associated genes are often included in panel testing.^{46,47}

Channelopathies

Cardiac channelopathies are a group of clinically and genetically heterogeneous inheritable arrhythmic disorders in which there is no structural heart abnormality. They include Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and long QT syndrome (LQTS), with overlap between these phenotypes. These channelopathies are generally caused by defects in genes encoding cardiac ion channel macromolecular complexes and associated regulatory proteins,⁸ with heritable variabilities caused by modifier genes.⁴⁸ Most are inherited in an autosomal dominant manner with incomplete penetrance and variable expressivity, yet male patients appear to have a more severe phenotype and higher risk of sudden cardiac death, most probably related to hormonal effects.^{49,50} More than 40 genes have been associated with susceptibility to various channelopathies, while variants in the same gene could cause multiple phenotypes.^{7,51} Overlap syndromes have been described, in particular related to certain well-characterised *SCN5A* variants.^{52,53} Likewise, overlaps between cardiac and skeletal muscle channelopathies have been described.⁵⁴ Cascade testing in at-risk family members is also a class I recommendation for BrS, CPVT and LQTS whenever a familial pathogenic variant could be identified.⁸

Brugada Syndrome

Belonging to the group of J wave syndromes, BrS is characterised by a typical pattern of coved-type ST-segment elevation with successive negative T wave in the right precordial leads on electrocardiography, and susceptibility to ventricular tachyarrhythmias and sudden cardiac death.⁵⁵ Only up to 35% of cases with BrS have a variant identified in one of the genes encoding sodium channels, potassium channels and calcium channels or their functionally-related proteins,⁵⁶ with around 30% of patients having a pathogenic variant in *SCN5A*.⁵⁷ Patients with variants in the calcium channel genes might have a relatively short QTc interval.⁵⁸ Genetic testing is recommended in patients suspected to have BrS with Type 1 Brugada pattern on electrocardiography.⁸ A significant proportion of individuals carrying a pathogenic variant in BrS-susceptibility genes might, however, remain asymptomatic.⁵⁹

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT typically manifests as exercise-induced palpitations

and dizziness with polymorphic ventricular arrhythmias, which could be associated with syncope/seizures and sudden cardiac death.^{4,10} Up to 60% of cases with CPVT could be attributable to dominant pathogenic variants in *RYR2*⁶⁰ and, rarely, recessive variants in *CASQ2*,⁶¹ while the clinical significance of variants in other genes such as *CALM1* and *TRDN* might be unconfirmed.⁶² A minority of CPVT cases could be related to multiple genetic variants.⁶³ Genetic screening is recommended in *RYR2* and *CASQ2*; a pathogenic variant in these two genes contributes to diagnosis.⁶² The clinical significance of certain reported variants in these genes has, however, been questioned when considering the allele frequencies among control populations, and should be interpreted with caution.⁶⁴

Long QT Syndrome

LQTS is characterised by QTc interval prolongation and T wave abnormalities on electrocardiography, which could be associated with tachyarrhythmias or ventricular tachycardia torsade de pointes.⁶⁵ Pathogenic variants in one of the three canonical LQTS-susceptibility genes, namely *KCNQ1*, *KCNH2* and *SCN5A*, could account for up to 85% of cases.⁸ The remaining cases might have variants in one of the remaining minor LQTS-susceptibility genes, which might contribute less to risk stratification.^{66,67} Multisystemic manifestations have also been associated with LQTS, including: Jervell and Lange-Nielsen syndrome (with congenital profound bilateral sensorineural hearing loss);⁶⁸ Timothy syndrome (with limb, facial and neurodevelopmental features);⁶⁹ and Andersen cardiodysrhythmic periodic paralysis (Andersen-Tawil syndrome, with skeletal and facial features).⁷⁰

Up to 25% of patients with a pathogenic variant identified in a susceptibility gene could have a normal QTc interval and therefore a lower (yet still elevated) risk for life-threatening events.⁷¹ Genetic testing in LQTS is a class I recommendation for patients and at-risk family members, as lifestyle modification and beta-blockers might be recommended for patients with LQTS and implantable cardioverter-defibrillator therapy might be useful.⁴

While identification of a pathogenic variant in one of the canonical susceptibility genes would guide genotype-specific management including genotype-directed lifestyle modifications,⁷² a significant proportion of normal control population also harbour a protein-altering variant in the major susceptibility genes (the so-called background genetic noise), which highly complicates the variant interpretation process for LQTS.^{67,73}

Testing

Conventionally, genetic testing has been performed at the

level of individual genes by Sanger sequencing. This is still how cascade testing is performed, when a familial variant has already been identified in the proband and only targeted analysis is required. With the genetic heterogeneity in cardiomyopathies and channelopathies, testing in gene panels instead of individual genes is definitely desirable for making the diagnosis in the proband, especially for those patients with ambiguous or overlapping phenotypes clinically.¹ With the advent and availability of massively parallel sequencing technology in clinical settings, genomic testing for cardiac disorders in clinical patients is now more accessible. This also allows for testing for the most enormous genes, such as *RYR2* and *TTN*, that are implicated in these disorders. Testing for multiple genes using a multi-gene panel is the current standard of practice for cardiovascular genetic medicine.¹⁹ The number of approximate diagnostic yields for each gene in each condition is summarised in the **Table**. The sequencing cost per nucleotide has been dramatically decreasing, with shorter turnaround times for genomic tests as well. Acceptable specimens include whole blood, dried blood spots, buccal swabs or tissue specimens obtained at post-mortem

examination.^{6,15} External quality assurance organisations, e.g. European Molecular Genetics Quality Network,⁷⁴ now provide programs for cardiomyopathies and channelopathies for promoting quality testing in clinical laboratories.

Increasing the number of genes in the testing panel also possibly increases the number of variants of uncertain significance (VUS) to be reported.^{67,76} VUS could be difficult to interpret, especially in cases where the clinical phenotype is ambiguous.^{76,77} It has been argued that inclusion of additional genes might not confer a higher detection rate and significant marginal benefit, especially in cardiomyopathies.^{17,78,79} Further studies on an even larger scale might, however, be required to confirm this argument. Currently, testing a small specific panel of genes is usually recommended for each well-defined phenotype, to minimise costs as well as confusion related to detection of VUS.^{14,80}

Various approaches exist for massively parallel sequencing gene panel analysis, including amplicon-based, targeted capture, semiconductor and long-read sequencing,⁸¹⁻⁸³ as well

Table. Major genes involved in cardiomyopathies and channelopathies.

Disorder	Genes	% of Disease	Variants detected by sequencing	Variants detected by deletion/duplication analysis
Arrhythmogenic cardiomyopathy	<i>PKP2</i>	25-40% ⁸	96-97%	3-4% ^{142,143}
	<i>DSG2</i>	5-10% ⁸	~99%	<1% ¹⁴⁴
	<i>DSP</i>	2-12% ⁸	~99%	Isolated reports ^{145,146}
	<i>DSC2</i>	2-7% ⁸	~99%	<1% ¹⁴⁴
Dilated cardiomyopathy	<i>TTN</i>	20% ³⁶	~99%	Isolated reports ¹⁴⁴
Hypertrophic cardiomyopathy	<i>MYBPC3</i>	20-45% ⁸	98%	<2% ^{78,147-149}
	<i>MYH7</i>	15-20% ⁸	~99%	<1% ¹⁴⁴
	<i>TNNT2</i>	2-12% ⁸	~99%	Unknown ¹⁴⁴
	<i>TNNI3</i>	2-7% ⁸	~99%	<1% ¹⁴⁴
Brugada syndrome	<i>SCN5A</i>	11-30% ^{8,57}	83-99%	<17% ^{150,151}
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i>	60% ⁶⁰	~99%	Isolated reports ^{152,153}
	<i>CASQ2</i>	5% ⁶⁰	~99%	<1% ¹⁴⁴
Long QT syndrome	<i>KCNQ1</i>	30-35% ⁸	97-98%	2-3% ¹⁵⁴
	<i>KCNH2</i>	25-40% ⁸	97-98%	2-3% ¹⁵⁴
	<i>SCN5A</i>	5-10% ⁸	~99%	Unknown

as the use of virtual subpanels based on *a priori* selection of genes after clinical exome or whole exome sequencing.⁸⁴ It has been argued that, despite the reduction in costs and turnaround time, panel testing might not generate a significantly improved diagnostic yield, whereas findings with uncertain significance might increase.⁸⁵ The use of virtual panels allows more flexible strategies in data analysis and reporting according to available clinical information, in an attempt to maximise the diagnostic yield and minimise reporting of VUS.⁸⁶

The above massively parallel sequencing approaches are appealing for the number of genes they could cover in each analysis, yet many of these do not include gene dosage analysis and may not reveal gross deletion and insertion or other large-scale or complex rearrangements. In cases where the above analyses turn out negative, a small subset of cases might benefit from copy number assays utilising microarray or multiplex ligation-dependent probe amplification (MLPA),^{87,88} or copy number data derived in the above sequencing techniques.

Variant Interpretation

Variations from the reference sequences do not necessarily imply clinical diseases, and therefore identification of a variant in a gene is not equivalent to a diagnosis.⁸⁹ The ACMG criteria have been widely used to interpret sequence variants for diagnosing monogenic disorders in clinical settings in the past few years.²³ The ACMG criteria proposed classification of variants into pathogenic, likely pathogenic, of uncertain significance, likely benign and benign. Likely benign and benign variants are generally not reported, while whether to report VUS remains controversial.⁹⁰ Despite great efforts, variant interpretations have been discordant among different clinical laboratories.⁹¹ Further refinements and modifications of the ACMG criteria have been suggested to eliminate the discrepancies.^{92,93} Automated adaptation of the ACMG criteria has been developed for general purposes,⁹⁴⁻⁹⁶ as well as targeted for diagnosis of cardiac disorders.^{97,98}

The availability of public population databases, including the Exome Aggregation Consortium/Genome Aggregation Database project,⁹⁹ the 1000 Genome Project,¹⁰⁰ as well as the National Heart, Lung, and Blood Institute Exome Sequencing Project Exome Variant Server,¹⁰¹ has largely enabled exclusion of pathogenicity based on allele frequencies that are incompatible with disease prevalences. Some have suggested the use of ethnic-matched controls when considering data from these population databases to avoid false-positive interpretations due to underestimation of allele frequencies.¹ However, it might be worthwhile to consider the allele frequencies in all individual populations wherever there are available data, as the enrichment of a variant in one particular

population already speaks against its pathogenicity, unless it is in parallel with a consistently increased prevalence of the associated condition(s) in that particular population.

Databases containing variants with associated patient information and curation information by other laboratories are now available, including ClinVar,¹⁰² ClinGen¹⁰³ and VarSome.⁹³ Disease databases are also available, such as Human Gene Mutation Database,¹⁰⁴ Leiden Open Variation Database,¹⁰⁵ as well as other locus-specific databases. Caution must be used in interpreting the deposited variants as the information could be submitted by different parties or classified in accordance with guidelines other than the most current ones.

For autosomal dominant conditions, demonstration of variant segregation with disease in affected family members might provide further evidence for pathogenicity, which grows stronger with a larger number of family members tested. It illustrates the utmost importance of construction of a (at least) three-generation pedigree at the beginning of genetic consultation. To achieve this, testing should be performed in both clinically affected and unaffected groups in the family. The presence of the variant in an apparently unaffected individual could still be due to incomplete penetrance of the condition; while the observation of variant non-segregation in a single affected family member might indicate that the variant might not be causative of the phenotype.^{23,6} On the other hand, variants occurring *de novo*, i.e. only detected in the proband but not in the asymptomatic parents, are usually believed to be disease-causing, especially together with confirmed relationship testing results usually by microsatellite analysis.²³

Null variants, including initiation-loss, nonsense or frameshift variants, canonical splice site variants or exon deletion, are usually considered evidence for pathogenicity, with the exception in genes where haploinsufficiency is not a known disease mechanism, such as *MYH7*.²³ Functional study remains an important tool to confirm the biological effect of the variant. Transgenic animal models and cell lines could be used, yet these experiments might require dedicated expertise and time, which might be less feasible in diagnostic laboratories.¹⁰⁶ Patch clamp is the gold standard in characterising the electrophysiologic properties of variant cardiac channels,^{107,108} whereas immunohistochemistry and messenger RNA studies remain valuable tools to assess defects in cardiomyopathies.¹⁰⁹⁻¹¹¹ That said, the data should be interpreted with caution, and deleterious effects of variants *in vitro* might not necessarily translate into clinical manifestations *in vivo*.¹¹² *In silico* analyses, which predict the potential impact on the protein function by the variant,

could be attempted when functional data are not available (as in most cases). Prediction of the effect of a missense variant on the protein function is, in general, more heterogeneous than that of a variant on splicing. Various algorithms have been developed for prediction of effect on the resulting protein products by missense variants, including PolyPhen-2 (Polymorphism Phenotyping v2),¹¹³ PROVEAN (Protein Variation Effect Analyzer)¹¹⁴ and SIFT (Sorting Intolerant From Tolerant),¹¹⁵ whereas a list of scores by various prediction algorithms could be retrieved in a single attempt via dbNSFP.¹¹⁶ These prediction scores are, however, more likely to contradict each other when more algorithms are used and should be interpreted with caution. VarSome is a set of convenient bioinformatics tools to aid variant interpretation where different variant-related information could be retrieved from various databases and aggregated on a single platform.⁹⁴

Genetic Counselling

Genetic counselling has been recommended as a crucial part of the genetic services provided for patients with suspected inheritable cardiac conditions.^{4,8,117} The process aims to promote informed choices and adaptation to the risk related to the cardiac condition in question, and includes assessment of the chance of disease, education about inheritance, genetic testing, prevention, resources and research.¹¹⁸ Genetic counselling should be provided by genetic counsellors or medical professionals with up-to-date training in molecular genetics and genomics, preferably with a focus on cardiac genetics,¹¹⁹ and ideally in close collaboration with clinical cardiologists.

Pre-test Counselling

A three-generation pedigree should always be constructed at the beginning of the genetic consultation to delineate inheritance, characteristics of any cardiac disorders in family members, and presence of sudden unexplained death or extra-cardiac manifestations in the family which would subsequently also aid provision of specific clinical and genetic screening recommendations.¹¹⁹ Most of the genetic cardiomyopathies and channelopathies are inherited in an autosomal dominant manner, where 50% of the offspring (as well as 50% of the siblings if the familial variant was inherited from one of the parents) could carry the familial variant and are thus at risk of developing the condition. Incomplete penetrance in cardiac disorders might imply a larger proportion of asymptomatic carriers to be detected on cascade testing and a more significant issue of genetic discrimination and stigmatisation, especially when genetic non-discrimination regulations have not been implemented in many countries.¹²⁰ The Australian Genetic Discrimination Project revealed a concerning number of cases of alleged genetic discrimination in terms of negative treatment in insurance and health as well as employment domains.¹²¹

In no circumstance should family members be coerced into testing, and the issues of potential genetic discrimination in health insurance and employment might well prohibit patients from participating in cascade testing.¹²² The possibilities of incidental findings in genomic tests and the option to know or not to know should be discussed prior to testing, whereas the possibilities of having findings of uncertain significance, as well as the availability of regular review of these uncertainties in the future, should also be addressed.¹¹⁹

It has been suggested that patients with higher-risk variants, for instance, patients with cardiomyopathies harbouring variants in sarcomere or desmosome genes, might be more anxious about their results; yet evidence is lacking.¹²³ Parental guilt over transmission of the pathogenic variant to the offspring is not uncommon. While those tested positive could have related psychological issues, those who do not harbour the familial variants might also experience survivor guilt or feel neglected.¹²³ All these possible psychological impacts should be addressed thoroughly during the pre-test genetic counselling.

Genetic testing for cardiac conditions in asymptomatic children might raise controversies which are mostly about patient autonomy and confidentiality. Guidelines have emphasised that the primary reason for genetic testing in minors should be direct medical benefit and, when testing is considered beneficial, the tested minor should be involved in the counselling and decision-making process as much as possible.¹²⁴

There has been an emerging role of post-mortem genetic testing or molecular autopsy in cases of suspected sudden cardiac death.^{16,125,126} Post-mortem genetic analysis should be considered in all sudden cardiac deaths in which an inheritable channelopathy or cardiomyopathy is suspected.⁶² For the potentially huge impact on the family, genetic counselling of family members is recommended for molecular autopsy in the deceased.¹⁵

Post-test Counselling

Genetic testing results are probabilistic in nature and should be interpreted in context of all the clinical information as well as family history.^{9,10} The complex inheritance with incomplete penetrance and variable expressivity might increase the difficulty in conveying the risk for the proband as well as tested family members.⁹

Detection of certain variants might have prognostic or risk stratification information or might guide treatment,¹²⁷⁻¹³⁰ and these should be communicated to the tested individuals during post-test counselling. For example, beta-blocker prophylactic

pharmacotherapy may be considered for carriers of LQTS and CPVT pathogenic variants; whereas identification of a *SCN5A* pathogenic variant in BrS or LQTS patients would warrant consideration of the use of sodium channel blockers.¹³¹ On the other hand, the lack of significant genetic findings, which might occur in a large number of cases, provides no further information and excludes the family from cascade testing, yet this does not change any positive family history and does not exclude a genetic basis for the familial condition.¹¹² At times, genetic testing might reveal results of uncertain clinical significance with current medical knowledge, but which might or might not be better characterised in the near future.^{67,112,123} In any case, the psychological responses should be assessed and implications of genetic information for the patient and the family should be reiterated; another follow-up counselling session within 3-6 months is recommended.¹²³

Cascade testing enables closer clinical surveillance of those harbouring a pathogenic familial variant, although for many cardiac conditions, penetrance is incomplete. On the other hand, those who have been tested negative for a familial variant could be reassured that they are not at an increased risk.¹³² In practice, cascade testing is usually done in an ongoing stepwise fashion, where the offspring of one family member are tested only when that particular member has been tested positive. Cascade testing might have implications for the family dynamics. When a large number of family members could be at risk and receive pre-test counselling together, the post-test counselling and subsequent care should be provided individually and tactfully so as to protect patient confidentiality of the tested family member. While there is a perceived duty to warn at-risk relatives of those tested positive of the potentially significant nature of inherited cardiac disorders and availability of potentially therapeutic or prophylactic modalities, medical professionals disclosing the information to other family members has been controversial;¹²³ although there is a recent trend to support disclosure to genetic relatives by medical professionals.¹³³ On the other hand, family letters have been suggested as an effective means for accurate communication without full disclosure of personal medical information of the proband.¹³⁴

Future

With the advent of medical technology and bioinformatics, the cost of sequencing continues to decrease. Early studies of the use of whole-exome and whole-genome sequencing have been published and these previously sophisticated techniques might soon be adopted for routine clinical use in diagnostic laboratories.¹³⁵⁻¹³⁷ These technologies, used in conjunction with clinical data of cardiac patients, might enable discoveries of novel genes associated with cardiac conditions and provide new insights into the disease mechanisms. The American Heart

Association has recently issued a scientific statement on the establishment of specialised clinical cardiovascular genetics programs with a multidisciplinary care model, integrating clinical and genetic findings into the emerging subspecialty of genetic cardiology.¹³⁸ *In vitro* characterisation of new variants and/or new genes should catch up with the sequencing technology and provide further functional evidence for interpretation of genetic findings in these inheritable cardiac disorders. Collective international efforts are required to incorporate genetic information into diagnostic criteria in clinical guidelines and ensure standardisation of practices in genetic testing and variant interpretations. This would guide further development of targeted therapeutic modalities for cardiomyopathies and channelopathies, including the recently promising antisense oligonucleotides.¹³⁹⁻¹⁴¹

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