CONTEMPORARY REVIEW

Conveying a probabilistic genetic test result to families with an inherited heart disease

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The evolution of genetic testing in the past few years has been astounding. In a matter of only a few years, we now have comprehensive gene tests comprising vast panels of "cardiac" genes, whole exome sequencing (the entire coding region) and even whole genome sequencing (the entire genome). Making the call as to whether a DNA variant is causative or benign is difficult and the focus of intense research efforts. In most cases, the final answer will not be a simple yes/no outcome but rather a graded continuum of pathogenicity. This allows classification of variants in a more probabilistic way. How we convey this to a patient is the challenge, and certainly shines a spotlight on the important skills of the cardiac genetic counselor. This is an exciting step forward, but the overwhelming complexity of the information generated from these tests means our current practices of conveying genetic information to the family must be carefully considered. Despite the challenges, a genetic diagnosis in a family has great benefit both in reassuring unaffected family members and removing the need for lifetime clinical surveillance. The multidisciplinary specialized clinic model, incorporating genetic counselors, cardiologists and geneticists, provides the ideal framework for ensuring the best possible care for genetic heart disease families.

KEYWORDS Genetic counseling; Genetic heart disease; Multidisciplinary team; Next generation sequencing

ABBREVIATIONS **ARVC** = arrhythmogenic right ventricular cardiomyopathy; **BrS** = Brugada syndrome; **HCM** = hypertrophic cardiomyopathy; **LQTS** = long QT syndrome; **SCD** = sudden cardiac death; **VUS** = variant of uncertain significance; **WES** = whole exome sequencing; **WGS** = whole genome sequencing

(Heart Rhythm 2014;11:1073–1078)

Introduction

Recent advances in gene sequencing technologies have been phenomenal. Only a decade ago, the option of genetic testing for families with inherited heart diseases was minimal, typically requiring the sample to be sent to a research laboratory with a result expected to take at least 6 months. The commercialization of genetic tests for hypertrophic cardiomyopathy (HCM), long QT syndrome (LQTS), arrhythmogenic right ventricular cardiomyopathy (ARVC), catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome (BrS) evolved rapidly, and the increasing availability and uptake allowed a better understanding of the genetic basis of these diseases. Commercial testing laboratories offered limited panels of known causative genes for each disease, with a quoted mutation identification rate between 20% and 75%, depending on the test and the specific disease in question. In this setting, testing was limited by the expense and time required to sequence 1 gene, and in many cases there were only 2 outcomes—either a causative (pathogenic) mutation could be found or it remained unidentified.

In 2014 this is no longer the case. Next generation sequencing technologies have paved the way for testing of a vast number of genes, with a typical "cardiac gene chip" (or "panel") now comprising 20–100 genes.[1] No longer does a genetic test for HCM include only those genes previously shown to definitively cause disease but now includes a number of additional genes, many of which have only minimal evidence of disease association or causation (ie, accounting for $<5\%$ of disease). Whole exome sequencing (WES; sequencing of the entire coding region of the genome) and whole genome sequencing (WGS; sequencing of the entire genome) are powerful tools for research and gene discovery, but in the commercial setting expand testing beyond the scope of just evaluating cardiac-related genes, to sequencing of the remaining 22,000 genes encoded in our DNA. Coupled with rapidly decreasing costs and wider access and uptake, the complexity of the results generated

Dr Ingles is the recipient of a National Health and Medical Research Council (NHMRC) and National Heart Foundation of Australia Early Career Fellowship (#1036756). Dr Semsarian is the recipient of an NHMRC Practitioner Fellowship (#1059156). **Address reprint requests and correspondence:** Dr Chris Semsarian, Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Locked Bag 6, Newtown, NSW 2042, Australia. E-mail address: c.semsarian@centenary.org.au.

Table 1 Probabilistic outcomes of cardiac genetic testing

Possible outcome	Consequences for the proband	Consequences for the family
No variants of potential clinical importance identified (benign)	An indeterminate gene result does not exclude a cardiac genetic disease, but reassessment of the phenotype should be considered	Predictive genetic testing cannot be offered to the family. At-risk relatives are advised to be clinically assessed according to current guidelines
Variant of uncertain significance identified	Efforts to delineate pathogenicity of the variant are required, including cosegregation studies involving phenotyped family members	While pathogenicity of a variant is under question, it cannot be used to inform clinical management of family members. Predictive genetic testing cannot be offered. At-risk relatives are advised to be clinically assessed according to guidelines
Pathogenic mutation identified (pathogenic or likely pathogenic)	Confirm clinical diagnosis and limited therapeutic and prognostic application except in familial long QT syndrome[3]	Predictive genetic testing of asymptomatic family members is available after genetic counseling
Multiple pathogenic mutations identified	Confirm clinical diagnosis and potentially explain a more severe clinical phenotype.[4–6]	Complex inheritance risk to first-degree relatives must be discussed.[5] Predictive genetic testing of asymptomatic family members is available after genetic counseling
Incidental or secondary pathogenic mutation identified	Action regarding incidental or secondary findings must be discussed with the proband pretest.	Genetic counseling to determine clinical and genetic effects to family members is available

when a LQTS or HCM gene test is now ordered goes beyond the basic expertise and scope of current practices.

The outcome of these genetic advances is that a proband genetic test should not be considered a binary (yes/no) outcome, but rather a complex and carefully considered result placed somewhere along a continuum from benign to variant of uncertain significance (VUS), probably/likely pathogenic, and pathogenic (Table 1). The genetic test result is therefore a *probabilistic* one, in which the weight of evidence for pathogenicity determines the likelihood (or probability) of the specific variant being disease causing. Adding a further layer of complexity, it is now evident that ongoing periodic reassessment is required to ensure new genetic information has not altered previous variant calls.[2] Despite this, the clinical applicability of genetic testing within a family at risk of a cardiac genetic condition has significant power, with the ability to exclude asymptomatic family members from years of unnecessary clinical screening and to target those who carry a causative gene mutation to regular clinical surveillance. Finding a way to negotiate this new era of genomics and provide the best possible care to families remains the ultimate goal. This brief review highlights the challenges associated with conveying complex genetic information to families in the setting of inherited heart diseases.

The probabilistic genetic test result and the VUS

The greatest clinical utility of genetic testing is when a pathogenic disease-causing mutation is identified. This enables cascade or predictive genetic testing to be undertaken in asymptomatic relatives, so that family members with and without the mutation can be identified. In up to 5% of cases, multiple (2 or more) pathogenic mutations may be identified and generally correlate with more severe disease.[5,7,8] In some diseases, such as LQTS, the identification of a pathogenic mutation in a particular gene may also guide therapy and prognosis.[9] Where there is uncertainty about the significance of a reported variant, the so-called VUS, the subsequent decision to offer predictive genetic testing to asymptomatic family members is not always clear to the clinician.

Where a variant remains under a cloud of uncertainty, it should not be used for predictive genetic testing. If cascade family screening is performed on the basis of an incorrectly classified variant, then there is the real possibility of

Table 2 Common characteristics of variant pathogenicity guidelines

Variant characteristic	High suspicion of causation
Variation type	Loss of function, de novo variant
Frequency	Absence or low frequency in race-matched control populations such as the 1000 Genomes Project. Allele frequency may take disease prevalence into account.[17] Variant previously reported to be causative (with strong evidence of causation, ie, family cosegregation)
Functional data	In vivo functional data relating to the same variant
Region	Mutation exists in the essential protein domain (eg, transmembrane and binding site)
Conservation	Protein alignment across many species shows highly conserved position
Family studies	Where available, cosegregation data to demonstrate coinheritance with disease. Large family analysis provides greatest evidence of disease association

In silico analysis using predictive software programs such as SIFT (J. Craig Venter Institute, La Jolla, CA) and Polyphen2 (Harvard Medical School, Boston, MA) may provide supportive evidence for pathogenicity, relating to functional effects, conservation, and biochemical properties.