Psychological Issues in Genetic Testing for Inherited Cardiovascular Diseases

Rajani D. Aatre, MSc, MS; Sharlene M. Day, MD

Clinical genetic testing is now available for many cardiovascular diseases, including hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, channelopathies such as long-QT syndrome (LQTS), aortic diseases such as Marfan syndrome, and disorders of cholesterol metabolism such as familial hypercholesterolemia (FH). Utility and interpretation of these tests can be complicated by incomplete penetrance (not everyone with a gene mutation will have the disease), variable expressivity (varying symptoms and presentation in those who have the mutation), reduced detection rates (gene mutations cannot be identified in all individuals with the condition), extensive allelic and locus heterogeneity (multiple genes with multiple mutations), and limited genotype-phenotype correlations. These factors can introduce confusion and uncertainty when test results are conveyed to the individual being tested. With the rapid expansion in knowledge of the genetic basis for inherited cardiovascular diseases, and the evolution and increasing availability of clinical genetic testing, there is a compelling need to understand and address the psychological implications of genetic testing in cardiovascular diseases. This article has been organized to reflect the issues of clinically affected individuals and unaffected at-risk family members.6 Gene testing for LQTS for risk stratification and therapeutic management supports genetic counseling for all families with cardiomyopathies and inherited arrhythmia syndromes. In general, pathogenicity is established or suspected based on previous publications, segregation data, control data, evolutionary conservation and functional predictions. Although a large number of mutations can confidently be classified as pathogenic, probably pathogenic, or benign, some variants may be of “uncertain significance.” In these cases, there are insufficient data to determine primary causality, presenting a significant challenge for clinicians and genetic counselors. Fortunately, the number of variants of unknown significance is relatively low and decreasing over time with increasing testing frequency, allowing for their reclassification into more definitive categories.2 Another consideration is the incidence of de novo mutations, which is highest for Marfan syndrome (~25%).3 In these instances, the risk to siblings of affected individuals is higher than the general population because of the possibility of genetic mosaicism.4

The Heart Failure Society of America recently published a practice guideline for evaluation of patients and families with cardiomyopathies (HFSAPG).5 A detailed 3-generation family history is recommended for all patients with cardiomyopathy to identify at-risk family members and to provide information on penetrance, disease manifestations, and risk of sudden cardiac death (SCD). The HFSAPG also strongly supports genetic counseling for all families with cardiomyopathies, and, in that context, recommends consideration of genetic testing for the most severely (and preferably youngest) affected person in the family because of the possibility of multiple, independently segregating mutations. The level of evidence supporting this latter recommendation varies, depending on the yield of testing for each cardiomyopathy. International guidelines for management of arrhythmia syndromes also strongly recommend the use of genetic testing for LQTS for risk stratification and therapeutic management of clinically affected and unaffected mutation carriers.6 Gene testing for all conditions can clarify on which side of the family the disease is present, so that subsequent screening can be focused on the at-risk relatives.

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Considerations and Recommendations for Genetic Testing and Counseling in Inherited Cardiovascular Diseases

Genetic counseling is the process of integrating family and medical histories, providing education, and promoting informed choices and adaptation to having, or being at risk of developing, a genetic condition.1 Counselors also play a fundamental role in interpretation of the results and conveying the implications of positive, negative, and uncertain molecular test results to the index patient and his/her family members considering predictive testing. A critical issue to consider with genetic testing for inherited cardiac diseases is the extent of allelic and locus heterogeneity with a large number of novel and private mutations, particularly for the cardiomyopathies and inherited arrhythmia syndromes. In general, pathogenicity is established or suspected based on previous publications, segregation data, control data, evolutionary conservation and functional predictions. Although a large number of mutations can confidently be classified as pathogenic, probably pathogenic, or benign, some variants may be of “uncertain significance.” In these cases, there are insufficient data to determine primary causality, presenting a significant challenge for clinicians and genetic counselors. Fortunately, the number of variants of unknown significance is relatively low and decreasing over time with increasing testing frequency, allowing for their reclassification into more definitive categories.2 Another consideration is the incidence of de novo mutations, which is highest for Marfan syndrome (~25%).3 In these instances, the risk to siblings of affected individuals is higher than the general population because of the possibility of genetic mosaicism.4

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which rare variants produce a large effect. However, rapid progress is being made in identifying risk alleles for complex multigenic cardiovascular disorders such as coronary artery disease and hypertension wherein common variants are associated with modest increases in disease risk. Genetic testing is becoming available to estimate risk for such conditions, in some cases with direct-to-consumer marketing. Although this topic will not be explicitly addressed in this review, psychological issues associated with genetic susceptibility testing for common complex diseases are in many ways similar to those for rare variants in mendelian diseases. However, because of the lower predictive values and uncertainty about absolute disease risk, the role of counseling may be even greater.

### Health-Related Psychological Issues in Affected Individuals

Before considering the psychological implications of genetic testing, it is important to first recognize the psychological issues that arise from the clinical diagnoses themselves and how they might influence one’s perception of genetic information. For HCM, health-related quality of life is negatively affected by the presence and severity of symptoms, activity restrictions, and adverse medication side effects. In patients who have had life-threatening arrhythmias, a high level of anxiety about the condition and uncertainty about the clinical course and prognosis have been shown to be the strongest predictors of poor psychological well-being and quality of life. An implantable cardiac defibrillator (ICD) may be indicated for the primary or secondary prevention of SCD associated with inherited cardiomyopathies and arrhythmia syndromes. The psychological implications of having an ICD have been well studied, yet its effects on quality of life, anxiety, and depression are conflicting. One small study suggested that quality of life and depression were worse in ICD patients with inherited diseases compared with those with ischemic or valvular heart disease. The influence of appropriate or inappropriate shocks on quality-of-life measures, as assessed as a secondary end point in randomized trials, as well as smaller observational studies, is mixed and does not consistently support a negative association or relationship between number of shocks and psychological effects. However, certain individual patients and their partners are clearly at risk of having adverse effects of shocks on psychological well-being. Patient education, psychosocial intervention, activity prescriptions, recall, and shock planning have been suggested as ways to help patients and families cope. Clinical and psychological interventions can positively affect self-worth, depression, anxiety, and physical functioning. Examples include gaining control (ie, self-education, maintaining privacy, and active participation in treatment decisions), talking or writing about experiences, and developing personal resources. In HCM patients, psychological well-being, good adjustment, low worry, and compliance with treatment are directly related to the information provided to and time spent with the patient, understanding of the condition, and relationship with the clinical providers, emphasizing the importance of a multidisciplinary approach. Perhaps for that reason, HCM patients who are followed at a specialty clinic have lower levels of depression and anxiety.

Although illness alone places substantial burden on patients and caregivers, inherited diseases carry unique anxieties over risk to family members and genetic transmission to children. Concern for relatives can elicit a range of emotions including guilt, fear, anger, denial, grief, and despair. Recognition of these emotions and referring for counseling is essential, irrespective of whether genetic testing is initiated.

### Psychological Issues of Genetic Testing in Affected Individuals

The concern for psychological distress in the affected index patient is tempered by the fact that gene test results for inherited cardiovascular diseases usually do not significantly alter diagnosis, prognosis, or treatment. Individual exceptions highlighted in Table 1 include the presence of more than 1 mutation, identification of certain highly penetrant mutations, or mutations in certain genes. Patients with these higher-risk genotypes may become more anxious after receiving their results, but this has not been studied. Conversely, patients with HCM or arrhythmogenic right ventricular cardiomyopathy without sarcomere or desmosome mutations could feel reassured in knowing that their disease may follow a more benign trajectory.

In our experience, clinically affected individuals often feel reassured by a definitively positive gene test result in knowing that interpretable information is available for predictive testing for their children or family members (Table 2). A positive genetic test can eliminate a patient’s doubt in his or her diagnosis and may motivate behavioral change and risk factor modification. A randomized and well-powered study of 342 FH patients and 128 relatives found that participants with a positive gene mutation perceived their diagnosis as more accurate. However, genetic diagnosis, regardless of whether a mutation was identified, did not alter perceptions of control or risk-reducing behaviors such as smoking, diet, exercise, or medication adherence. It is difficult to extrapolate results of this study and other studies of diseases with modifiable risk to most inherited cardiovascular diseases, where the effects of lifestyle modifications on disease course are largely unknown.

A negative genetic test can be frustrating for patients hoping to use predictive genetic testing for their offspring. A negative gene test may also cause skepticism about a given clinical diagnosis. These are important factors to recognize during pretest and posttest counseling. The uncertainty associated with identification of a variant of unknown significance is particularly problematic. In one study of 209 women with breast cancer, those who carried a variant of unknown significance in BRCA 1/2 had higher sustained levels of anxiety, depression, and distress compared with those receiving a negative result. Another small study in 24 women with breast or ovarian cancer suggested that some patients had a distorted perception of uncertain genetic test results, in that most felt that the result represented an increased genetic susceptibility to cancer. This may be a coping mechanism for establishing certainty and control and must be acknowledged during posttest counseling sessions.
In a study of 95 patients with familial risk of HCM or LQTS but unknown genotype, reduced health status in the domain of general health was observed. How might predictive genetic testing influence health perception? Individuals who test negative for a pathogenic familial mutation can be reassured that they and their offspring are no more at risk of developing that particular disease than the general population and can forego further clinical screening. Therefore a negative gene test would be expected to improve health status. Psychological issues are mainly a concern for those individuals who test positive for a familial mutation, but are clinically unaffected (Table 2). This section will focus on the psychological implications of predictive genetic testing in this subgroup.

### Uptake of Genetic Testing and Reactions to Test Results

A few studies have examined the interest and motivation in predictive genetic testing in HCM families. A retrospective analysis of 97 HCM families assessed uptake of genetic counseling, defined as the percentage of eligible relatives who attended a genetic counseling session after provision of a family letter to an HCM patient in whom a pathogenic sarcomere mutation was identified. Uptake of genetic counseling was 39% and did not differ by age, sex, or family history of sudden cardiac death. Factors that may have influenced frequency of uptake but could not be distinguished in this study include incomplete distribution of the family letter by the proband, and the relatives’ resources, insurance, and health beliefs. The uptake of genetic testing was ex-

| Table 1. Considerations for Genetic Testing in Inherited Cardiovascular Diseases |
|------------------|------------------|----------------|------------------|------------------|------------------|
| Disease          | Population Frequency | Mutation Detection Frequency | Genes Clinically Tested | Diagnostic Utility of Genetic Testing in Clinically Affected Individuals | Prognostic Utility of Genetic Testing |
| HCM              | 1/500           | 40% to 60%        | Sarcomere, metabolic, mitochondrial (n=11–18) | May help to distinguish HCM from other causes of hypertrophy (ie, hypertension, athlete’s heart) | Risk of more severe phenotype for affected carriers of certain highly penetrant sarcomere mutations or more than 1 mutation |
| DCM              | 1/2700         | 20% to 30%        | sarcomere, nuclear envelope, cytoskeleton, Z-disc, mitochondrial (n=17–27) | Support for familial DCM versus idiopathic DCM | Lamin A/C mutations are highly penetrant and associated with high rate of conduction disease and arrhythmias |
| ARVC             | 1/1000 to 1/5000 | −50%             | Desmosome, Ca handling (n=5–7) | Presence of pathogenic mutation constitutes a major diagnostic criteria | Earlier age of onset and higher risk of ventricular tachycardia in patients with any desmosome mutation |
| LQTS             | 1/2500         | 75%              | Na and K channels, ankyrin (n=10–12) | Delineation of subtype is based on genotype | Unique triggers for arrhythmias and responsiveness to β-blockers based on subtypes |
| Marfan and related aortic diseases | 1/5000 to 1/10 000 | 95%             | Fibrillin 1, Transforming growth factor β-1 and 2 receptors | May confirm a diagnosis and differentiate between aortic syndromes | Fibrillin gene mutations are fully penetrant (although w/ variable disease severity) |
| FH               | 1/500          | 50% to 85%        | LDLR, ApoB, PCSK9 | Earlier pharmacological intervention indicated when genotype positive | Homozygotes have higher lipid levels and may require more aggressive intervention (LDL pheresis, liver transplant) |

### Unaffected At-Risk Individuals and Predictive Testing

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Extremely high—99% of relatives who came in for genetic counseling proceeded with predictive genetic testing. Whether this can be extrapolated to other countries with different health care economics remains to be determined.

The same group evaluated the perceptions of genotype-positive asymptomatic first-degree relatives of HCM probands. Genetic counseling was viewed positively by the majority (≥90%) who opted for DNA testing. Desire to refine the risk to children was a strong motivator (64% tested for this reason). Only 4 of 123 wished they had not known their mutation status. The majority said they did not feel family pressure to be tested. About 75% of the genotype-positive individuals saw a cardiologist regularly for follow-up; older individuals and women were less likely to do so. In general, mutation carriers reported a sense of reassurance from their visits, particularly those with a family history of sudden cardiac death. Some studies on predictive testing in hereditary cancer suggest that individuals with self-reported optimism, a strong sense of control over their health, and less tolerance for uncertainty are more interested in genetic testing. These factors are likely to apply to inherited cardiovascular disease.

### Quality of Life and Psychological Well-Being

Understanding the potential psychological impact of acquiring gene mutation status in clinically unaffected individuals is critical to tailoring pretest counseling. This has been best evaluated for HCM and LQTS in the cardiovascular literature. A recent study assessed quality of life, anxiety, and depression in 3 groups: manifest HCM before genetic testing, manifest HCM diagnosed after predictive gene testing, and mutation carriers, regardless of whether or not they were subsequently diagnosed with HCM. Responses from these 3 groups were compared with national Dutch population data. Overall, respondents with manifest HCM before gene testing scored worse in terms of general health perceptions and anxiety than the other 2 groups or the general population. However, mutation carriers, regardless of whether or not they were subsequently diagnosed with HCM, reported similar or even better quality of life and less psychological distress than the general population. These differences were more pronounced in those carriers without manifest HCM.

### Table 2. Summary of the Potential Psychological Impact of Cardiovascular Genetic Testing

<table>
<thead>
<tr>
<th>Potential Positive Impact</th>
<th>Potential Negative Impact</th>
<th>Modifiers for Positive Adaptation</th>
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<tbody>
<tr>
<td>Affected individuals</td>
<td></td>
<td></td>
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<tr>
<td>Increased confidence in diagnosis with positive genetic test</td>
<td>Negative genetic test may lead to skepticism of diagnosis</td>
<td>Higher education and socioeconomic status</td>
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<tr>
<td>Relief at having interpretable information for unaffected relatives</td>
<td>Uncertainty associated with identification of variant of unknown significance can cause anxiety</td>
<td>Better understanding of the condition</td>
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<td>Increased compliance with screening and therapeutic management</td>
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<td>Being followed at a specialty center</td>
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<tr>
<td>Unaffected at-risk adults</td>
<td></td>
<td></td>
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<tr>
<td>Alleviates some uncertainty</td>
<td>Anxiety and distress from at-risk status</td>
<td>Being followed at a specialty center</td>
</tr>
<tr>
<td>Provides time to adjust to potential diagnosis</td>
<td>Increased worry over transmission to children</td>
<td>Lesser disease severity, better prognosis and lower incidence of sudden death in family</td>
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<tr>
<td>Promotes sense of control</td>
<td>Fear of discrimination</td>
<td>Higher education and socioeconomic status</td>
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<tr>
<td>Provides relief for those who are genotype negative</td>
<td>Survivor guilt for genotype negative</td>
<td></td>
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<tr>
<td>Unaffected at-risk children</td>
<td></td>
<td></td>
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<tr>
<td>Alleviates uncertainty for children and parents</td>
<td>For genotype positive, frustration over stigmatism</td>
<td>Better parental attitudes</td>
</tr>
<tr>
<td>For genotype negative, provides relief and alleviates concern about sports participation</td>
<td>Distress over uncertainty of risk with sports participation for genotype positive</td>
<td>Lesser disease severity, better prognosis and lower incidence of sudden death in family</td>
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<tr>
<td>For genotype positive, allows for adjustment to disease susceptibility as child matures</td>
<td>Alteration of self-esteem</td>
<td>Higher education and socioeconomic status</td>
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<tr>
<td>Promotes sense of control and empowerment</td>
<td>Feelings of the vulnerable child (genotype positive) and survivor guilt (genotype negative)</td>
<td>Accuracy and ease of clinical surveillance</td>
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<td>Difficulty forming personal relationships</td>
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<td></td>
<td>Modification of professional choices</td>
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<td></td>
<td>Elimination of the child’s autonomy</td>
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developing symptoms or experiencing sudden cardiac arrest. This underscores the importance of pretest counseling by a multidisciplinary team that includes genetic counselors and cardiologists. Although the heterogeneous and unpredictable nature of HCM does not allow caregivers to confidently provide reassurance or predict the future, improved patient education can often alleviate concerns over the perceived consequences of carriership. This concept is further supported by data suggesting that HCM patients and relatives who attended specialized cardiac genetics clinics had a better understanding of their disease-associated risks and were more likely to be well adjusted and less worried.17 However, this study did not assess the impact of predictive genetic testing.

Psychological implications of genetic testing have also been examined for LQTS.55 One study assessed the psychological effects of a definitive gene test result in adult relatives of LQTS patients, differentiating them into groups based on prior knowledge of an abnormal, uncertain, or normal ECG. Individuals with an abnormal ECG (ie, clinical diagnosis of LQTS) expressed a moderate level of anxiety that was not affected by mutation carrier status. Individuals with a normal or uncertain ECG likewise displayed a moderate level of anxiety at baseline, but, as expected, noncarrier status was associated with an immediate and sharp decline. Individuals with an initial uncertain ECG who were later identified as genotype-positive maintained moderate disease-related anxiety over time, although depression scores declined to a level comparable to the general population. Overall, noncarriers experienced relief and substantial reductions in distress levels, whereas positive carrier status did not compound existing distress levels predicated on clinical assessment.

The favorable responses to predictive genetic testing for HCM and LQTS are comparable to those of predictive testing for inherited neurological diseases and cancer.60 Although selection bias is always a consideration with these studies, no significant increase in emotional distress has been reported after predictive testing for a range of neurological diseases and cancers, including Huntington disease, myotonic dystrophy, spinocerebellar ataxia, hereditary breast and ovarian cancer, or familial adenomatous polyposis. In fact, studies examining genetic testing for susceptibility to inherited cancers reveal that genetic counseling and testing produce psychological benefits and improve accuracy of risk perception with no increase in depression or anxiety for mutation carriers.57–60 Similarly, predictive testing for myotonic dystrophy did not have adverse psychological impact, even in carriers, and all participants in the study recommended predictive testing for other family members.61 Even for Huntington disease, the psychological well-being of predictively tested subjects, regardless of carrier status, is not different than the general population.62 For carriers, distress levels are highest early after disclosure of test results and decline with time. However, anxiety and frustration can be reactivated at transition points in life such as starting a family.

Existing data, although relatively sparse, suggest that predictive genetic testing for inherited cardiovascular conditions does not inflict psychological harm and in fact can invoke significant benefits by providing reassurance or alleviating uncertainty as has been reported in the neurological and cancer literature. Nevertheless, a decision whether or not to proceed with predictive genetic testing must be carefully considered on an individual basis, taking into account many factors that can predict higher posttest distress levels, including female sex, preconceived consequences of carriership,54 and the pretest emotional state56 (see Table 3 for proposed practice guidelines).

Special Considerations for Predictive Testing in Unaffected At-Risk Children
Genetic testing in asymptomatic children for disease susceptibility for conditions that may not manifest until later in life or not at all raises a host of controversial ethical, legal, and psychosocial implications. The debate has largely centered around autonomy, confidentiality, and potential psychological harm.63,64 The American Society of Human Genetics65 and, more recently, the European Society of Human Genetics66 have put forth recommendations for predictive genetic testing in children. Both emphasize that the primary reason for genetic testing should be direct medical benefit, that the minor should be involved in the decision-making process to the greatest extent possible, and that genetic counseling is an absolute requirement. In the case in which predictive gene testing is being conducted for a condition that can manifest in childhood but cannot be effectively treated or prevented, both benefits and risks are acknowledged, neither of which may outweigh the other.66 This latter category, which has a lack of empirical data to inform professional guidelines, applies to most of the inherited cardiovascular diseases. Unique considerations relevant to determining a risk-benefit ratio for genetically susceptible children of families with inherited cardiovascular diseases are discussed in this section.

Potential Medical Benefits of Predictive Cardiovascular Genetic Testing in Children
Currently, the most well-established medical benefit to genetic testing for children of a genotype positive parent is to

Table 3. Proposed Practice Guidelines for Genetic Testing and Counseling for Families With Inherited Cardiovascular Diseases

| 1. Construct 3-generation family pedigree to identify affected and at-risk family members and range of disease severity. |
| 2. Conduct pretest genetic counseling and education session by multidisciplinary team, including cardiologists with expertise in clinical management and genetics of inherited cardiovascular diseases, and genetic counselors. Convey disease- and patient-specific indications for genetic testing, incorporating information about yield, diagnostic or prognostic utility, implications of test results for individual and family members, and address issues pertaining to insurance including coverage and out-of-pocket expenses. |
| 3. Assess baseline levels of anxiety, risk perception, health beliefs, and other social or demographic factors that could influence reactions to test results. |
| 4. Provide posttest counseling and assess psychological responses. Reinforce impact and implications of genetic information for patient and his or her family. |
| 5. Discuss preferred method of communication of results, if applicable, to at-risk family members (ie, family letter). |
| 6. Follow-up counseling within 3 to 6 months to assess for persistent or amplified levels of distress over results. |

Aatre and Day Psychological Issues in Genetic Testing

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[Table 3 continued or expanded here if necessary.]
exclude those who are genotype negative from further testing. In the absence of known genotype status, annual surveillance is generally recommended for at-risk children for all inherited cardiovascular conditions, beginning in puberty or earlier. Predictive genetic testing precludes unnecessary clinical testing in those 50% of children who are not at risk.

Another potential medical benefit of predictive genetic testing is prognostication. Unfortunately, the large number of private mutations for inherited cardiovascular diseases and broad phenotypic heterogeneity limits the ability to make prognostic predictions based on genotype alone. However, there are some exceptions. For example, in the case of multiple and independently segregating mutations within a family, inheritance of only one mutation would likely portend a better prognosis for that child.

A very important consideration is the lingering concern that some genotype positive individuals may be at risk for sudden cardiac death, even in the absence of a demonstrable phenotype by commonly used noninvasive testing. Anecdotal evidence for this phenomenon has been recently reported for HCM.67 In addition, certain HCM genotypes have been associated with a high risk of sudden death despite mild hypertrophy, at least in the context of familial studies.68,69 This is also the case for other inherited cardiomyopathies, particular arrhythmogenic right ventricular cardiomyopathy, in which the occurrence of potentially lethal arrhythmias is often out of proportion to the degree of structural disease.70 This concern has implications for athletic participation, to the extent that the European Society of Cardiology recommends exclusion of individuals who are genotype positive-phenotype negative for cardiomyopathies or arrhythmia syndromes from competitive sports.71 However, given that the risk of sudden death in children is clearly not exclusive to athletes, the implications of a positive gene test need to be considered in the context of the severity of disease and sudden death frequency in a particular family.

The ultimate opportunity of predictive gene testing is disease amelioration or prevention. Although preventive strategies have not yet been developed for any inherited cardiovascular condition to date, ongoing and anticipated trials hold promise for preventing onset and/or delaying progression of clinical disease in genetically affected individuals72 (http://clinicaltrials.gov/ct2/show/NCT00319982). It will be equally important to identify modifying effects of genetic and lifestyle factors.

Impact on Quality of Life and Psychological Well-Being
Real and potential medical benefits of predictive gene testing in children must be balanced by the possibility of psychological harm, such as loss of self-esteem, anxiety, depression, and stigmatism.63 However, there are currently no data to corroborate these concerns for cardiovascular or other inherited diseases. The few studies that have examined the psychological implications of predictive gene testing in children for inherited cardiovascular diseases have generally shown neutral or positive psychological responses. In one such study, 35 children aged 8 to 18 who carried gene mutations for HCM, LQTS, or FH were administered a quality-of-life questionnaire and responses were compared with those from a reference Dutch age-matched pediatric population. Questions were grouped into categories of physical and psychological well-being, moods and emotions, self perception, autonomy, home and school environments, social support, and social acceptance. In all categories, scores from children carrying disease-causing mutations were highly comparable to those of the Dutch reference group.73 Findings from a follow-up study by the same group using a more detailed interview largely corroborated the findings that gene carrier children coped quite effectively with their condition.74 Most were articulate about their disease and aware of its heritability and possible consequences. Children who can explain their disease to peers may be able to reduce social isolation and bullying.

Factors that must be considered in counseling and age-appropriate education include vulnerability and worry. These emotions were most pronounced in the referenced studies in cases in which a close relative with the same disease had died or had a serious event. Explaining how the child’s situation differs from that of a relative who is severely ill or has died can be helpful in alleviating anxiety. Controllability is also an important factor that reduces worry and increases adherence to medication or lifestyle modifications. Feelings of control were generally higher for FH carrier children, in whom more tangible feedback about their disease and effects of dietary, medication, and lifestyle changes could be continually provided.74 This is a more challenging issue for other inherited cardiovascular conditions, such as the cardiomyopathies and channelopathies, in which the future is less certain and there are few definitive interventions that can prevent or slow disease onset or reduce the risk of serious arrhythmias. Finally, it is important to recognize that the level of understanding and meaning of genetic susceptibility will change as children grow and their priorities shift. Counseling must be constantly tailored to the child’s maturity level and changing life circumstances.

Parental Influences and Perceptions
Children’s perceptions of disease and coping behavior are strongly influenced by parental adaptation and communication.65 Parents are faced with difficult choices in attempting to find a balance between protectiveness from risk of serious events (ie, SCD) and maintenance of normal peer interactions.74,75 Imposed physical activity restrictions can invoke frustration over social isolation from peers. It is important that parents and health care providers be cognizant of the psychological and social implications of such restrictions and make informed choices about the extent to which they must be applied. If future physical activity restrictions are possible (ie, development of manifest disease), children may adjust better if they have been encouraged to participate in a range of sports and nonsports activities.

There are few studies examining parental reactions to predictive cardiovascular genetic testing in their children, and these are limited to LQTS. As in the adult population, high levels of distress and anxiety were observed in ~50% of parents after disclosure of abnormal or uncertain ECG results in their children.76 The level of anxiety was essentially unchanged after receiving a positive gene test result, and persisted at 18 months of follow-up. In contrast, negative
gene test results lowered distress scores. In parents of gene mutation–positive children, the greatest fear was related to the ongoing threat of sudden symptomatic development and was essentially unrelated to the gene test results. Predictors of higher parental anxiety included lower level of education, preexisting high anxiety scores, longer familiarity with the disease, family history of SCD, and dissatisfaction with provided information. Interestingly, none of the parents expressed regret that they had proceeded with genetic testing for their children. These data are supported by another study that found that parents favored early genetic testing for LQTS and did not feel that it caused them unnecessary worry or anxiety.77 It is unclear whether these results can be extrapolated to other inherited cardiovascular diseases in which clinical diagnosis may be more challenging to establish and/or the age of onset of manifest disease and long-term prognosis are less predictable.

Impact on Family Relationships and Future Goals
Family relationships can be profoundly affected by genetic testing.65 Parental guilt over transmission of the mutation must be addressed through counseling. Parents may have difficulty treating mutation carrier and noncarrier children equally. Some parents may have the tendency to overprotect carrier children, whereas others may distance themselves emotionally as a reaction to the threatened loss. Siblings who test negative may feel guilty (“survivor guilt”) or sometimes neglected if the affected siblings receive extra attention. Additionally, genetic testing in a child has the potential to reveal the genetic status of parents or other family members who did not wish to know, misidentified paternity, or a previously undisclosed adoption.

The potential need for medication, an ICD, and the possibility of serious disease or early death can seriously affect educational, personal, and professional goals and development of personal and intimate relationships. Disclosure of genetic risk may also be devastating for a child who aspires to a physically demanding career such as in the military or law enforcement/emergency services.

Confidentiality, Duty to Warn, and Discrimination
Genetic information raises unique issues over other medical information. Concerns over personal and professional discrimination can place substantial burden on individuals and families. Identification of a person with a pathogenic mutation inadvertently implicates risk for first-degree relatives, challenging individual autonomy. Unaffected relatives who desire informative testing rely on the most severely affected family member being tested first. However, this relative may not desire testing, may not have the insurance/finances to pay, or may have geographic limitations.78 In addition, segregation studies to interpret the implications of a variant of unknown significance require the participation of other relatives who may not want to share their health information. This can create rifts or provoke anxiety among family members with strained relationships.

The duty to warn at-risk relatives is a consistent theme in genetic testing. The American Society of Human Genetics supports protection of genetic information with exceptions to disclosure being permissible when “attempts to encourage disclosure by the patient have failed; serious and foreseeable harm is likely to occur, the at-risk relative is identifiable, and the disease is preventable, treatable or modifiable by early monitoring.”79 This exception is protected under law. In a survey of Jewish women with an increased frequency of BRCA1/2 mutations, nearly all the respondents felt that at-risk family members should be informed when the disease was treatable compared with 85% for a nontreatable condition.80 However, only 20% of the participants believed that physicians should inform at-risk family members against a patient’s wishes for a preventable disease (16% for nontreatable). This obviously raises ethical issues for health care providers in cardiovascular disease given the potentially life-threatening nature of these diseases and treatability with drugs and/or ICD. Although interpersonal discussion within a family should be encouraged, family letters are a very effective means of accurately communicating relevant information without full disclosure of the affected individual’s personal health information.81

Concern over discrimination is cited repeatedly in the literature. On May 21, 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law (P.L. 110 to 233, 122 Stat. 881), prohibiting discrimination in health coverage and employment based on genetic information. Title II (section pertaining to employment) took effect on November 21, 2009, and Title I (section pertaining to health coverage) took effect on May 21, 2010 (http://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf).

GINA, along with provisions of the Health Insurance Portability and Accountability Act, generally prohibits health insurers or health plan administrators from using genetic information for decisions regarding coverage, rates, or preexisting conditions. The law also prohibits most employers from using genetic information for hiring, firing, or promotion decisions and for any decisions regarding terms of employment. GINA’s protection does not extend to life insurance, disability insurance, and long-term care insurance. Also not covered are the United States Tricare Military Health System, the Veterans’ Health Care Administration, the Federal Employees Health Benefits Plan, or the Indian Health Service.

Discrimination can still exist regardless of legal measures designed to protect against it and may restrict the uptake of genetic testing or have serious psychological consequences for those found to carry a disease susceptibility gene mutation. A recent survey of individuals affected or at-risk for Huntington disease, breast cancer, or α-1 antitrypsin deficiency demonstrated subjective feelings of discrimination even when it was not overt.82

Conclusion
With rapid advances in gene discovery and availability of clinical genetic testing for inherited cardiovascular diseases, the need for psychosocial assessment and counseling is becoming all the more critical. Although there is concern that predictive genetic testing in clinically unaffected adults and children could provoke undue anxiety and distress, current data suggest instead that it can provide reassurance, lessen uncertainty, and promote a sense of control (Table 2). However, data on the psychological...
implications of cardiovascular genetic testing are still very limited and more research is needed in many areas (Table 4). Most studies involve small numbers of patients from fairly uniform geographic and racial/ethnic populations with different health care economics than the US, and are restricted to gene testing for the most common inherited cardiovascular diseases (FH, HCM, and LQTS), which have the highest diagnostic yield. Therefore, results from these studies may not reflect experiences in more diverse populations and should be interpreted cautiously. Nevertheless, a consistent message is that psychological distress over the disease itself, and implications of carriership for recommended treatments.

5. Influence of economic, insurance, discrimination, and other factors on decisions to seek counseling or undergo gene testing.

6. Optimal method of family communication and accurate exchange of information to increase uptake of genetic counseling and predictive testing.

Disclosures

None.

References


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Key Words: arrhythmogenic right ventricular cardiomyopathy ■ cardiomyopathy ■ genetics ■ hypertrophic cardiomyopathy ■ long-QT syndrome ■ cardiomyopathy ■ arrhythmia