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PERSPECTIVE

When to Offer Predictive Genetic Testing to Children at Risk of an Inherited Arrhythmia or Cardiomyopathy

The Family Perspective

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Individuals found to carry a pathogenic variant for a dominantly inherited arrhythmia or cardiomyopathy have a 50% likelihood of passing the variant on to their children, placing them at increased risk to develop the potentially life-threatening condition. Cascade predictive genetic testing can assist with early diagnosis and initiation of preventative treatment, protecting individuals from arrhythmic events and potentially improving cardiac outcome. However, determining the optimal time to perform predictive genetic testing in children is complex and involves balancing the ethical principles of beneficence, nonmaleficence, autonomy, and informed consent.

A consensus statement by the Heart Rhythm Society and the European Heart Rhythm Association recommends offering predictive genetic testing as early as infancy for children at risk of long QT syndrome (LQTS) because of possible early onset of the condition and because the result may directly impact medical management with the initiation of β-blocker therapy.[1] In comparison, North American guidelines do not directly address the issue of predictive genetic testing for minors at risk of a cardiomyopathy, such as hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC). Whereas the European Society of Cardiology's position statement and the Australian and New Zealand guideline recommend deferring predictive genetic testing until after 10 years of age for these conditions when the likelihood of onset is higher, cardiac screening is recommended and assent may be possible.[2,3]

We wanted to better understand families' perspectives about when predictive genetic testing should be offered to children at risk of LQTS, HCM, or ARVC, as well as factors that influence their point of view. An invitation to an online survey was circulated to members of the Sudden Arrhythmia Death Syndrome Foundations in the United States and Canada, the Hypertrophic Cardiomyopathy Association in the United States, and the ARVDHeart for Hope Facebook group. A total of 231 individuals responded to the survey. Characteristics of respondents are shown in Table.

OPTIMAL AGE TO OFFER PREDICTIVE GENETIC TESTING

Families with a genetic diagnosis of LQTS, HCM, or ARVC were asked to indicate the youngest age at which predictive genetic testing should be offered to children. Ninety-two percent of respondents (n=76/83) reported that testing should be offered before 5 years of age for children at risk of LQTS (Figure 1). This is consistent with published guidelines which recommend testing as early as possible.[3] Early diagnosis has the potential to be lifesaving based on variable onset of the condition and initiation of prophylactic β-blocker therapy.[4]

The majority (77%, n=114/148) of respondents reported that predictive genetic testing should be offered before 10 years of age for children at risk of HCM or ARVC (Figure 1). This is contrary to the European and Australian/New Zealand

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Table. Characteristics of Respondents

Characteristics (Total No. of Responses)	n (%)
Female (n=210)	173 (82)
Age (n=213)	
<20 y	6 (3)
21–30 y	25 (12)
31–40 y	47 (22)
41–50 y	70 (33)
51–60 y	39 (18)
>60 y	26 (12)
Diagnosis (n=231)	
LQTS	83 (36)
HCM	133 (58)
ARVC	15 (6)
Self-report	201 (87)
Spouse-report	30 (13)
Diagnosed <30 y of age (n=226)	108 (48)
Presence of symptoms (n=231)	190 (82)
Biological children (n=230)	183 (80)
Tested children during childhood	111 (61)
Country (n=211)	
Canada	32 (15)
United States	160 (76)
Other	19 (9)
Education (n=213)	
No postsecondary	32 (15)
Postsecondary	181 (85)
Annual net income (n=210)	
<$100 000/y	100 (48)
≥100 000/y	80 (38)
Prefer not to answer	30 (14)
Family history of SCA (n=212)	133 (63)

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; and SCA, sudden cardiac arrest.

position statement and guideline which recommend deferring testing until after 10 years of age.[2,3] Whereas, these results support the more general American Society of Human Genetics guideline which recommends leaving the decision around predictive genetic testing in minors to the parents in situations where the risks and benefits are less clear.[5]

FACTORS INFLUENCING WHEN TO OFFER TESTING

A 5-point Likert scale (1=not important, 5=very important) was used to assess the importance of 8 factors in deciding when predictive genetic testing should be offered (Figure 2). Regardless of diagnosis, respondents ranked factors relating to beneficence (clarify cardiac screening and β-blocker therapy, guiding sport participation, decreasing worry, and adaptation) higher than factors relating to nonmaleficence (increasing worry and risk of discrimination) and autonomy/informed consent (child assent).

The impact of a positive genetic result on medical management may empower families to be proactive and potentially improve the outcome for their child(ren). The impact on sport participation is less clear. Although there is a growing body of evidence linking physical activity with onset and severity of ARVC, the published guidelines are inconsistent with regard to physical activity recommendations for phenotype-negative carriers of a pathogenic variant for LQTS and HCM.[6–10] The European Society of Cardiology recommends avoiding high-intensity competitive sport, whereas the Heart Rhythm Society indicates that there is insufficient evidence at this time for restriction. It is unclear if parents would consider discouraging participation in high-intensity competitive sport, in the absence of a recommendation of restriction, in an effort to avoid psychological distress relating to possible later disqualification from sport. A qualitative study interviewing adults who underwent predictive genetic testing for HCM postulated that the psychological impact of testing is linked to risk perception and the need for behavior change related to the result.[11]

Decreasing worry for children that test negative for a familial variant had an average rating of importance of 4.3 out of 5 compared with an average score of 2.8 out of 5 for the possibility of increasing worry for children that test positive. Two systematic reviews on predictive genetic testing in minors concluded that, although the research is limited, testing does not seem to negatively impact the emotional state, self-perception, or social well-being of a child.[12,13] In addition, the health-related quality of life scores were similar between children diagnosed with a cardiomyopathy and those at risk of developing a cardiomyopathy based on family history.[14] This suggests that children at risk of a cardiomyopathy may already be negatively impacted by their family history and further supports the families' perception that the ability of testing to decrease worry is more important than the possibility of increasing worry. Additional evidence is provided by Michie et al[15] who found that predictive genetic testing significantly reduced worry, anxiety, and distress for children who tested negative for a familial variant for familial adenomatous polyposis.

Many families acknowledged the risks associated with insurance discrimination; however, most seem to feel that the potential benefits of testing outweigh the risks related to discrimination. Similar concerns were expressed about employment and insurance discrimination by a group of adults with or at risk of HCM, however, the majority still chose to pursue genetic testing.[16]

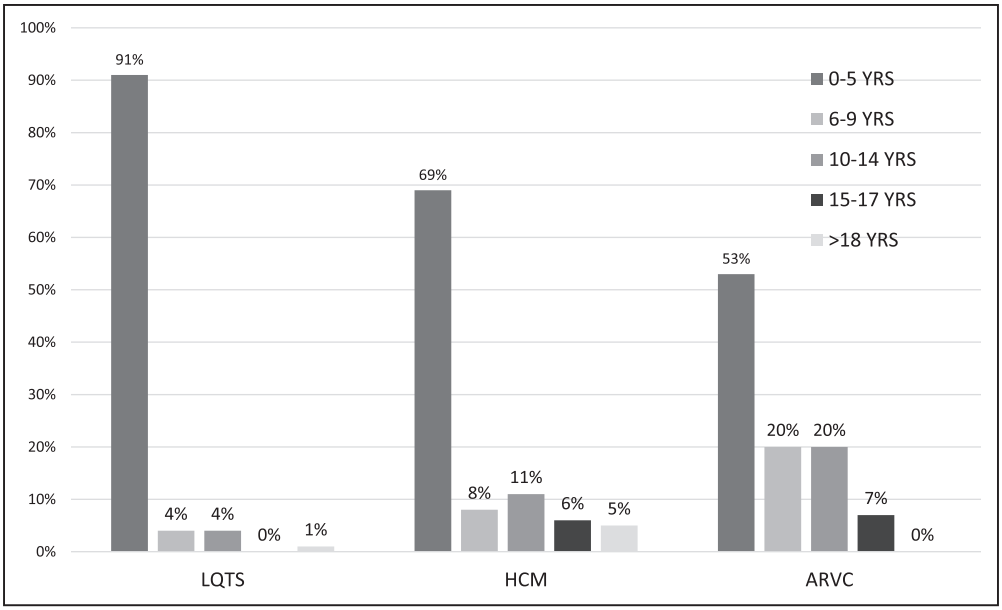

Figure 1. When to offer predictive genetic testing to children at risk of LQTS, HCM, or ARVC.
ARVC indicates arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, and long QT syndrome.

Finally, allowing a child to take part in the decision-making process was given an average rating of 2.5 out of 5. This is consistent with a study by Alderfer et al[17] which interviewed a group of adolescents and young adults who underwent predictive genetic testing during childhood for familial adenomatous polyposis. Only 1 of the 12 participants interviewed felt that testing should be deferred until an age at which a child can take part in the decision-making process.

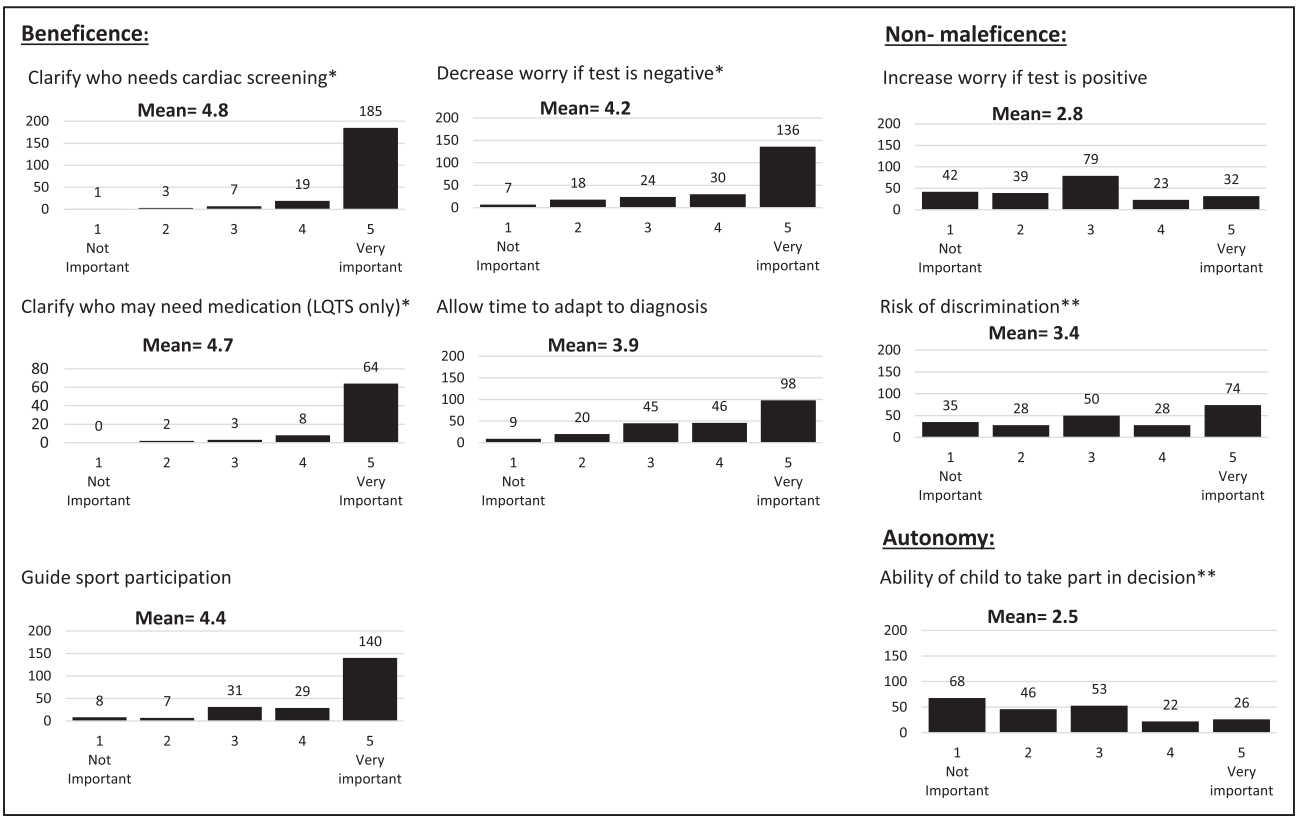

Figure 2. Rating of importance of 8 factors with regard to deciding when to offer predictive genetic testing for a child at risk for LQTS, HCM, or ARVC.
ARVC indicates arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy; and LQTS, long QT syndrome.

Overall, variation was reported for all 8 factors ranging from not important to very important (Figure 2). Similarly, a qualitative study by Geelen et al[18] reported that families differ with regard to the importance they place on the potential risks and benefits of predictive genetic testing, which may result in opposing decisions around uptake of testing or the timing of testing. Respondents in our study who placed higher importance on the benefits were significantly more likely to support offering testing at an earlier age whereas individuals who place higher importance on the potential risks were more likely to support testing at an older age ($P<0.05$). These findings support a personalized shared decision-making approach to testing in which the decision around testing is discussed in the context of a family's personal values and perspectives. We feel that published guidelines should be updated to reflect the value of offering testing to children at a young age to allow consideration of the potential benefits and harms of performing predictive genetic testing at different points in childhood.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Ackerman MJ, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8:1308–1339. doi: 10.1016/j.hrthm.2011.05.020
2. Charron P, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2010;31:2715–2726. doi: 10.1093/eurheartj/ehq271
3. Ingles J, et al; CSANZ Cardiac Genetic Diseases Council Writing Group. Guidelines for genetic testing of inherited cardiac disorders. *Heart Lung Circ*. 2011;20:681–687. doi: 10.1016/j.hlc.2011.07.013
4. Alders M, Bikker H, Christiaans I. Long QT Syndrome. In: Adam MP, et al, eds. GeneReviews. Seattle, WA: University of Washington, *Seattle*. https://www.ncbi.nlm.nih.gov/books/NBK1129/. Accessed August 14, 2018.
5. Botkin JR, et al. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet*. 2015;97:6–21. doi: 10.1016/j.ajhg.2015.05.022
6. James CA, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol*. 2013;62:1290–1297. doi: 10.1016/j.jacc.2013.06.033
7. Kirchhof P, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation*. 2006;114:1799–1806. doi: 10.1161/CIRCULATIONAHA.106.624502
8. Saberniak J, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail*. 2014;16:1337–1344. doi: 10.1002/ejhf.181
9. Maron BJ, et al. Introduction: eligibility recommendations for competitive athletes with cardiovascular abnormalities-general considerations. *J Am Coll Cardiol*. 2005;45:1318–1321. doi: 10.1016/j.jacc.2005.02.006
10. Pelliccia A, et al; Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology; Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2005;26:1422–1445. doi: 10.1093/eurheartj/ehi325
11. Bonner C, et al. Psychosocial impact of a positive gene result for asymptomatic relatives at risk of hypertrophic cardiomyopathy. *J Genet Couns*. 2018;27:927–934. doi: 10.1007/s10897-018-0218-8
12. Wade CH, et al. Effects of genetic risk information on children's psychosocial wellbeing: a systematic review of the literature. *Genet Med*. 2010;12:317–326. doi: 10.1097/GIM.0b013e3181de695c
13. Wakefield CE, et al. The psychological impact of genetic information on children: a systematic review. *Genet Med*. 2016;18:755–762. doi: 10.1038/gim.2015.181
14. Friess MR, et al. Health-related quality of life assessment in children followed in a cardiomyopathy clinic. *Pediatr Cardiol*. 2015;36:516–523. doi: 10.1007/s00246-014-1042-z
15. Michie S, et al. Predictive genetic testing in children and adults: a study of emotional impact. *J Med Genet*. 2001;38:519–526.
16. Khouzam A, et al. Factors associated with uptake of genetics services for hypertrophic cardiomyopathy. *J Genet Couns*. 2015;24:797–809. doi: 10.1007/s10897-014-9810-8
17. Alderfer MA, et al. Parent decision-making around the genetic testing of children for germline TP53 mutations. *Cancer*. 2015;121:286–293. doi: 10.1002/cncr.29027
18. Geelen E, et al. Constructing "best interests": genetic testing of children in families with hypertrophic cardiomyopathy. *Am J Med. Genet A*. 2011;155A:1930–1938. doi: 10.1002/ajmg.a.34107