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Editorial

AHA scientific statement highlights the utility of genetic testing for young cardiology patients

The combination of decreasing costs and our ever-increasing genomics knowledge has led to genetic tests being more commonly incorporated into medical evaluations. Indeed, in some cases it would be remiss not to offer a patient genetic testing. Recognition of the utility of genetic testing has been seen in disciplines beyond medical genetics, including oncology, neurology, ophthalmology, and cardiology. Genetic tests can aid in establishing a diagnosis, guiding medical management, and add to our understanding of inheritance patterns and for family counseling purposes. However, the utility of genetic testing depends on a multitude of factors including but not limited to the specific condition, the patient's age, and the testing methodology.

To help guide clinicians in the use of genetic testing in the pediatric cardiology population, the American Heart Association recently published a scientific statement reviewing the utilization of genetic testing within this subspecialty. The authors reviewed previously published guidelines, statements, and seminal papers within the field to formulate the statement [1].

1. Utility of genetic testing in cardiovascular patients

Genetic testing is available for a large number of cardiac conditions including cardiomyopathies, channelopathies, aortopathies, dyslipidemias, and congenital heart defects [2–5]. The yield depends on the specific condition [6]. In most cases, testing involves next-generation sequencing to identify nucleotide variations, although a chromosomal microarray to analyze for larger cytogenetic duplications or deletions may be ordered in some cases [7]. The statement reviews the utility of genetic testing in two broad categories: diagnostic testing and risk-predictive genetic testing (Table 1).

1.1. Diagnostic testing

Diagnostic testing not only confirms an individual's diagnosis but, in many cases, can inform medical management. For example, for individuals with arrhythmogenic cardiomyopathy secondary to a pathogenic variant in *FLNC*, *PLN*, or *LMNA*, an implantable cardioverter-defibrillator (ICD) is recommended if the ejection fraction is <45%, which is higher than used in other cardiomyopathy patients [8].

For patients with long QT syndrome, identifying the specific subtype aids in recognizing specific triggers. Loud noises are especially triggering for individuals with long QT type 2, while swimming and other forms of exercise are more triggering for patients with type 1 [9]. Furthermore, genetic testing also identifies syndromic forms of conditions such as Fabry disease which might go otherwise undiagnosed and consequently patients may miss out on potential therapies [10].

Across the different subspecialties within hereditary cardiac conditions, genetic testing has recently been shown to aid in risk stratification. For instance, individuals with familial hypercholesterolemia secondary to an identifiable pathogenic variant have a higher risk of developing coronary artery disease compared to peers with similar cholesterol levels but negative genetic test results [11]. Additionally, in patients with aortic aneurysms, the risk of dissection is higher in those with an identifiable genetic cause [12]. Finally, patients with hypertrophic cardiomyopathy due to a pathogenic variant in a sarcomere gene typically have more diastolic dysfunction and a higher amount of myocardial fibrosis compared to peers with negative test results [13].

The genetic test should be tailored to an individual's suspected condition rather than ordering a broad panel [7]. Typically the yield does not increase for many cardiac conditions when the number of genes on a testing panel expands outside that specific phenotype [14]. Additionally, broad panels increase the likelihood of a "variants of uncertain significance" (VUS) [15]. A VUS is a result where the significance of a genetic variation is unknown. It may later be reclassified as "pathogenic" or "benign" as further information becomes available. However, in the meantime it can increase a patient's anxiety and further confuse the clinical picture, especially if it is in an unrelated gene [7]. If a VUS is identified, any changes to clinical care or family screening should be only made after careful review of the evidence surrounding the variant by a team with expertise in cardiac genetics [6].

1.2. Risk-predictive genetic testing

Using a relative's previous positive genetic test results (pathogenic or likely pathogenic variant) to identify other family members who are at risk is known as both cascade screening and risk-predictive genetic testing. In this scenario, genetic testing identifies individuals who should have further cardiac screening such as an echo, ECG, and/or mobile cardiac telemetry monitor depending on the condition. These tests typically need to be repeated every few years due to the reduced penetrance of hereditary cardiac conditions which can lead to significant expense, stress, and time for patients and families [2–5].

A negative test result for a familial variant often allows that individual to forgo ongoing surveillance [2–5]. The majority of hereditary cardiac conditions are inherited in an autosomal dominant manner, indicating that all first-degree relatives have a 50% chance to also carry the pathogenic/likely pathogenic variant and associated risk to either have or develop the condition [2–5]. Therefore, genetic testing can be very informative for guiding who in the family needs to undergo repeat cardiac screening [7].

Another area of risk predictive genetic testing is polygenic risk

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Table 1
Genetic test yield and utility in cardiology. The genes listed are genes commonly associated with the conditions but are not an exhaustive list in most cases.

Condition (Commonly associated genes)	Diagnostic yield among pediatric cases	Utility of a positive genetic test result
Channelopathies (KCNQ1, KCNH2, SCN5A, RYR2)	~30%–75%	- Diagnostic confirmation - Arrhythmia risk stratification and prediction of triggers - Optimization of pharmaceutical treatment - Cascade screening
Cardiomyopathies (MYH7, MYBPC3, TNNT2, TNNI2, TNNI3, ACTC1, ACTN2, DMD, TTN, LMNA, DSP, PKP2, DSG2, FLNC, RBM20, SCN5A)	~10–70%	- Diagnostic confirmation, including identification of syndromic forms of cardiomyopathy - Arrhythmia risk stratification - Indication for exercise avoidance - Cascade screening
Familial hypercholesterolemia (LDLR, APOB, PCSK9, LDLRAP1)	~80–95%	- Diagnostic confirmation - Coronary artery disease risk stratification - Cascade screening
Aortopathies (FBN1, COL3A1, TGFBR1, TGFBR2)	~20–80%	- Diagnostic confirmation, including identification of syndromic forms of aortopathies - Aortic dissection risk stratification - Cascade screening

Created by Emily Brown, CGC based on Landstrom AP, et al. and Brown EE, et al.

scores. This subtype of genetic testing utilizes thousands of single nucleotide polymorphisms to assess the likelihood of an individual developing a specific phenotype. Polygenic risk scores at least partially explain some of the variable penetrance we see between individuals with the same hereditary condition [15]. In other cases, an individual with an otherwise negative genetic test may have a high polygenic risk score [16]. However, this type of testing is not yet widely clinically available in the cardiac setting which is likely why it was largely omitted from the statement.

2. Importance of pre and post-test counseling

The statement highlights the importance of patients having both pre- and post-test genetic counseling. Genetic testing often has far reaching consequences and can affect the whole family, not just the patient who underwent testing. It is essential to explore with patients both the medical management implications and the psychosocial implications of genetic testing [18].

Prior to sending the testing a clinician should review the possible outcomes, likelihood of an informative result, familial risk, and the psychosocial impact of a positive or negative result [6,7]. This includes the possibility of genetic discrimination, which is especially important to consider in the case of cascade screening in an otherwise healthy individual. The Genetic Information Nondiscrimination Act (GINA) is a federal law which protects against employers and health insurances from using genetic test results to determine coverage and employment status in many situations, but there are loopholes including life insurance [17].

Once the genetic tests are available, there should be a thorough discussion reviewing next steps for the patient and family members. This should include review of who else in the family is at risk and needs clinical or genetic screening and providing practical steps on how to disseminate this information within the family [4,6,7]. Often a family letter can be a helpful tool to provide the family with to help share this information [19].

There can be a wide array of reactions to genetic test results ranging from "survivor guilt" in family members who test negative for a familial variant to relief at finally finding an answer for their health condition to anxiety regarding an individual's risk to develop cardiovascular disease. Exploration of a patient's reactions to the results is an important piece of the results disclosure and should not be overlooked [7,19–21].

Given this vast array of topics to be discussed, patients generally benefit from seeing a genetic counselor [20–22]. Telemedicine genetic counseling is becoming increasingly available and may be an option for patients who don't have access to a local genetic counselor. Furthermore, the National Institutes of Health recently awarded grants researching innovative genetic counseling models to help address novel ways to increase access to genetic counselors. The National Society of Genetic Counselors has a directory to help patients and clinicians find genetic counselors in their area: https://findageneticcounselor.nsgc.org/.

3. Special considerations for genetic testing in the pediatric population

The statement also reviews special considerations for genetic testing in children as they are considered a vulnerable population due to their inability to provide consent. Ideally, genetic testing would be postponed until adulthood in the case of adult-onset conditions or at least until the child is old enough to provide assent in cases with an earlier presentation [18,22].

However, since some hereditary cardiac conditions present in early-childhood (such as mitochondrial disorders, muscular dystrophies, and cardiomyopathy secondary to inborn errors of metabolism), genetic testing early in life may be indicated and an important component of an individual's medical management [2–5]. In these cases, special care should be taken to ensure there is thorough pre-test counseling with the family outlining the potential benefits and limitations of genetic testing for the child as a positive genetic test result can have lifelong impacts including a child's ability to obtain life insurance in the future, medical management recommendations, and sports participation [18,22].

4. At home genetic testing

Given the popularity of at-home genetic testing, the statement discusses both direct-to-consumer tests such as 23andMe and consumer-initiated tests. In contrast to direct-to-consumer tests which can be bought at a drugstore and sent into the lab, consumer-initiated tests are genetic tests ordered by a clinician at the request of the consumer. Typically, these are generally "healthy screening tests." Direct-to-consumer tests typically utilize genotyping and focus on ancestry, genetic traits, and in some cases adult-onset conditions [23]. Childhood onset conditions are not usually included in this type of testing, and therefore given the lack of immediate medical actionability and that children are not able to provide consent, direct-to-consumer testing is not usually recommended in the pediatric population [18].

Some consumer-initiated tests do include childhood onset conditions; however, if a child is suspected to have a specific condition, more thorough genetic testing than a "healthy panel" may be appropriate as often this type of testing may not include all of the genes associated with a condition or only report known pathogenic variants [23]. Ideally, if a test is being ordered for medical management, a child should meet with a genetics professional for an evaluation including their family history and medical history in order to ensure an appropriate test is ordered [6,7].

5. Conclusion

Genetic test results can provide useful information regarding medical management, risk stratification, and cascade screening for pediatric cardiology patients and families. Whether genetic testing is appropriate

should be decided on a case-by-case basis taking into consideration age of onset, utility, and potential yield. Ideally, pediatric patients and families have pre-and post-test genetic counseling to understand the possible implications of these results.

Declaration of competing interest

SSM reports consulting for Amgen, AstraZeneca, Sanofi, Regeneron, Novo Nordisk, Novartis, Esperion, Dalcor, Kaneka, REGENXBIO, and 89bio. All other authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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