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PERSPECTIVE

Managing Secondary Genomic Findings Associated With Arrhythmogenic Right Ventricular Cardiomyopathy

Case Studies and Proposal for Clinical Surveillance

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DNA variants that are expected to confer risk for arrhythmogenic right ventricular cardiomyopathy (ARVC) are recommended as returnable secondary findings from clinical genomic sequencing. However, ARVC presents several distinct challenges for the care and management of patients ascertained through this genome-first approach. We discuss these challenges and present recent cases that exemplify their impact in a clinical setting. We also propose a standard approach to management of genome-first ARVC evaluations and surveillance and finally discuss potential diagnostic innovations that may provide substantial benefits to patients in this setting, particularly given the acceleration of precision health.

SECONDARY GENOMIC FINDINGS

The increasing use of wide-scale sequencing in both clinical medicine and research is creating scenarios in which genetic risk for cardiovascular diseases are identified unexpectedly, often before symptoms manifest. The cardiovascular genetic community has developed recommendations for detection and management of genotype-positive, phenotype-negative patients in the context of directed familial cascade screening. However, approaches to managing secondary findings identified through diagnostic sequencing for other conditions or as part of large-scale exome or genome sequencing research efforts remain uncertain.[1] These scenarios pose novel challenges to medical care by necessitating clinical decisions about what constitutes an actionable genetic finding and what particular action should be taken. As a starting point, the American College of Medical Genetics and Genomics has published recommendations for the reporting of secondary findings from clinical sequencing.[2,3] These recommendations currently include a minimum list of 59 genes representing 27 conditions, which were selected based on the availability of confirmatory diagnostic testing and the existence of potential preventive or treatment measures. Research studies often use this list as a starting place to design their return of results protocols.

One of these conditions is ARVC, also known as arrhythmogenic right ventricular dysplasia. Although the identification of a pathogenic DNA variant associated with ARVC is potentially life saving, complexities and uncertainties about (1) the population penetrance of ARVC-associated pathogenic or likely pathogenic variants, (2) their associated phenotypic spectrum, and (3) their pathogenicity present management challenges. Psychosocial implications are also a key consideration. Although these challenges are also present for variants associated with other cardiomyopathies and arrhythmia syndromes, ARVC is associated with a particularly high risk of sudden cardiac death (SCD) as a presenting symptom. In addition, in ARVC, there is the unique opportunity to reduce the likelihood of developing this genetic condition through lifestyle modification. Hence, the application of

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American College of Medical Genetics and Genomics recommendations to predicted pathogenic variants for ARVC warrants focused consideration and discussion, particularly for those individuals without a personal or family history.

To that end, this article presents the existing knowledge enabling a genome-first approach to ARVC and describes the major challenges. We also present findings for some of the first individuals ascertained with secondary genomic findings associated with ARVC at 2 institutions: Geisinger, a leader in genomic sequencing of unselected patients through its MyCode project, and Johns Hopkins that runs the largest national program for evaluation and management of ARVC patients and at-risk individuals. Finally, we review the current consensus best practices for ARVC diagnosis and surveillance, discuss the application of these practices to genome-first cases, and discuss potential diagnostic innovations that may complement this new paradigm to facilitate early detection and intervention.

ARVC GENETICS

ARVC is an inherited heart condition characterized by the replacement of cardiac myocytes by fibrofatty tissue, leading to contractile dysfunction and potentially deadly ventricular arrhythmias.[4] Despite its relatively rare prevalence (1:1000–1:5000),[5] ARVC is an important cause of SCD in young athletes[6,7] and responsible for up to 20% of SCD cases in individuals < 35 years.[6–8] Moreover, SCD has been reported as a presenting symptom of ARVC in 16% of index cases.[9]

The current diagnostic criteria for ARVC[10] are based on overt, generally later stage symptoms and lack sensitivity to detect early abnormalities.[11] A potential alternative for earlier detection to prevent SCD is a genome-first approach—using genetic risk factors for ARVC to identify at-risk, otherwise asymptomatic individuals. Genomics-based ascertainment is already being used successfully through cascade screening in at-risk relatives of diagnosed ARVC probands.[9] In the era of precision medicine and large-scale genomic sequencing, this usage is accelerating.

ARVC is predominately a disease of the cardiac desmosome. Variants in the genes for plakophilin-2 (*PKP2*),[12] desmoplakin (*DSP*),[13] desmoglein-2 (*DSG2*),[14] desmocollin-2 (*DSC2*),[15] and junction plakoglobin (*JUP*)[16] have all been causally implicated in ARVC pathogenesis. Several nondesmosomal genes have also been implicated, including founder mutations in transmembrane protein 43 (*TMEM43*)[17] and phospholamban (*PLN*).[18] Five of these genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, and *TMEM43*) are recommended by American College of Medical Genetics and Genomics for return of secondary findings. Inheritance is typically autosomal dominant with age-related, incomplete penetrance, but recessive inheritance has also been reported.[19] Collectively, rare variants in these genes have been identified in up to two thirds of diagnosed cases of ARVC,[20,21] with *PKP2* variants the most prevalent.[20]

Genetic testing for ARVC index cases is recommended.[22,23] The presence of a pathogenic variant constitutes a major criterion for ARVC diagnosis.[10] Knowledge of the underlying genotype in rare instances may also provide prognostic insights based on limited understanding of genotype-phenotype association. For instance, individuals carrying >1 desmosomal variant have a more severe disease course with an increased likelihood of SCD[24] and a higher incidence and earlier onset of sustained arrhythmias.[25] Also, male carriers of the founder *TMEM43* variant p.(Ser358Leu) have a high risk of sudden death that is disproportionate to the extent of structural involvement.[17]

The more impactful application of genetic sequencing for ARVC, to date, has been for cascade screening of at-risk relatives (a class I recommendation[22]). Relatives who did not inherit a definitively pathogenic variant are generally cleared of ongoing cardiac screening while those who carry the variant are recommended for close surveillance.[26–28] Among carriers of a familial pathogenic variant, disease risk is difficult to predict given incomplete penetrance.[29] For example, Quarta et al[29] reported that only 34% of first-degree relatives with an identified variant had a definite diagnosis of ARVC while another 27% satisfied a borderline diagnosis. More recently, Groeneweg et al[20] reported that 40% of at-risk family members with an identified variant met diagnostic criteria from a large cohort (385 subjects). Hence, a considerable percentage of individuals from ARVC families inheriting a causal genetic variant for ARVC do not develop the disease for reasons that remain unclear although participation in frequent endurance athletics is thought to be a significant risk factor.[30] Endurance athletics in this context can be defined as physical activity with a high dynamic demand (>70% max O_2) done at vigorous intensity regularly and frequently (at least 50 h/y).

MANAGING ARVC SECONDARY FINDINGS: CHALLENGES AND OPPORTUNITIES

The extent to which this research applies to patients from the general population who carry putatively causal genetic variants is uncertain. In light of the trends in precision medicine and reporting of secondary findings described above, there are several important challenges that must be addressed.

First, it is likely that the population rate of nonpenetrance is higher than reported in family studies.[31] In a recent analysis of the first 30 000 individuals with

exome sequencing from the Geisinger MyCode project, we showed a paucity of phenotypic expression among 18 individuals with a database-listed pathogenic/likely pathogenic ARVC variant, as well as another 184 individuals with a rare variant of uncertain significance (previously reported as pathogenic/likely pathogenic).[32] In fact, none of these individuals had an existing diagnosis of ARVC, and only 1 of the 18 satisfied any other diagnostic criterion for ARVC from review of available clinical data.

In addition to incomplete penetrance, the full phenotypic spectrum associated with desmosomal variants has yet to be fully understood. Variants in some desmosomal genes are already known to be associated with phenotypic heterogeneity. For instance, variants in *DSP* are commonly observed in patients with dilated cardiomyopathy, and pathogenic variants in *PKP2* have been reported in patients with Brugada syndrome.[33] This overlap complicates approaches to screening for genome-first patients.

Furthermore, the definition of what is an actionable genetic finding for ARVC is also nontrivial. Rare variants documented in public ARVC databases as pathogenic/likely pathogenic may fail to demonstrate phenotypic association in an unselected clinical population.[32] In general, variants are less likely to be classified as pathogenic in the absence of clinical symptoms or family history than when performing disease-targeted testing in a symptomatic individual.[34] Therefore, appropriate conservative rigor in variant adjudication is needed in the determination of actionable findings for ARVC.

Finally, there are potential psychosocial implications for some patients that are unpredictable. Emerging data suggest that typically research participants who receive actionable secondary findings experience little measurable distress, view their research participation as positive, and report sharing genetic results with their family and healthcare providers.[35–37] However, these publications have included only a limited number of individuals receiving variants associated with genetic cardiovascular disease and fewer for ARVC (n=2). In contrast, living with ARVC has been associated with elevated levels of clinically significant anxiety, reduced physical and mental quality of life, and perceived economic burden.[38–40] Genetic testing in the context of diagnosis of genetic cardiovascular disease is generally positively perceived, with a key driver being perceived benefit to the next generation. However, studies have shown familial cascade testing for a variety of types of inherited heart disease can lead to worry, particularly about children, distress at recommended behavior changes, and complicated family interactions surrounding cascade screening.[41,42]

It is important to balance these challenges with the potential opportunity not only for early disease detection but also for possible avoidance of ARVC based on identification of ARVC-associated pathogenic variants.

CASE STUDIES

The following case studies demonstrate these challenges in a clinical setting and highlight the diverse circumstances in which secondary findings associated with ARVC are being detected and returned.

1. Secondary finding from genome sequencing research: The 25-year-old brother of a young man with a regressive neuromuscular condition was referred by an undiagnosed disease research study for genetic counseling and clinical evaluation after identification of *DSP* c.478C>T; p.(Arg2160*) as a secondary finding of exome sequencing. This variant was classified as pathogenic. Their father, who also carried this pathogenic variant, had been adopted and knew no family history. The father's evaluation was unremarkable. In contrast, at evaluation, the 25 year old was asymptomatic with a normal ECG, normal exercise treadmill test, cardiac magnetic resonance showing a normal right ventricle (RV) but mildly dilated left ventricle (left ventricle end-diastolic volume/body surface area: 120 mL/m^2), and a 24-hour Holter monitor revealing 10 premature ventricular complexes and 8400 premature atrial complexes. Although ARVC disproportionately affects the RV, variants in *DSP* are frequently associated with left ventricular involvement,[25] and *DSP* variants are sometimes identified in patients with dilated cardiomyopathy.[43] Atrial arrhythmias are relatively frequent in established patients with ARVC although not a typical presentation. Whether this patient's premature atrial complexes were related to his *DSP* variant was uncertain. The predictive value of a negative history for typical ARVC findings in both the 59-year-old father and his 25-year-old son is unknown. Periodic screening evaluations are, therefore, planned. Finally, whether exercise restriction was warranted in this asymptomatic man was unclear, and he was counseled to limit himself to recreational exercise. The family was grateful for the identification of this potentially pathogenic variant with no apparent psychological distress.
2. ARVC-related secondary finding from diagnostic cardiovascular panel testing: An 8-year-old girl was evaluated for palpitations, found to have a 10-mm hypertrophic asymmetrical septum with obstruction on echocardiogram, and an ≈50 mm Hg mid cavitary obstruction with exercise on stress echocardiogram. She was, therefore, diagnosed with hypertrophic cardiomyopathy (HCM). Because of the patient's young age, and corresponding possibility of multiple disease-causing

variants, a 90-gene cardiomyopathy panel was ordered. No sarcomeric mutation or other HCM-associated variant was identified, however, a well-established desmosomal ARVC variant was found: *PKP2* c.2509delA; p.(Ser837Valfs*94). She underwent evaluation for ARVC, including ECG, 24-hour Holter monitoring, and cardiac magnetic resonance imaging (MRI), which did not reveal any evidence of ARVC but did confirm HCM. Because there is no mechanistic explanation for an association of *PKP2* variants with HCM and no published association of desmosomal variants in HCM cases, she was counseled that she did not have ARVC. Typical HCM management commenced. The remainder of her family was tested, and the variant was found to be paternally inherited. Her father underwent evaluation locally with ECG, Holter, and echocardiogram that were normal. On 3 generation pedigree, no family history of cardiomyopathy or sudden death was ascertained. Therefore, although *PKP2* p.(Ser837Valfs*94) is known to be a disease-causing ARVC variant, it does not seem to be causative in this family, and its role in the pathogenesis of HCM in this young girl is unknown. However, for the family, identification of this variant has prompted regular Holter monitoring in addition to the usual HCM familial screening in carriers.

3. Psychosocial implications: A 38-year-old woman was evaluated at a large academic medical center because of a history of hip and sacrum dislocations and diagnosed with hypermobility type Ehlers Danlos syndrome. Clinical whole-exome sequencing revealed no cause for her condition but identified a splice variant frequently identified in ARVC patients: *PKP2* c.2146-1G>C. Cardiac evaluation at 2 medical centers revealed no clear evidence of ARVC despite premature ventricular contractions and palpitations. Her family history was significant for SCD of unknown cause in her father, paternal uncle, and paternal grandfather in their 50s and 60s. The proband's mother was not tested for the *PKP2* variant, and thus the potential for this variant to be linked to SCD from the paternal lineage could not be ruled out. Ongoing evaluation every 2 to 3 years was recommended. The patient was upset. She expressed that she already had one diagnosis, and the stress and cost of the ARVC evaluation had considerably raised her anxiety. In addition, in her career as a public safety officer, the ambiguity of her phenotype and repeated medical evaluations was putting her job in jeopardy. The patient stated on several occasions that she wished she never knew this information and that it had caused her nothing but stress and anxiety.
4. Secondary finding from Geisinger MyCode project: A 67-year-old man with a history of hypertension, type 2 diabetes mellitus, morbid obesity status postgastric bypass surgery, obstructive sleep apnea, and bladder incontinence status postelectrical stimulator had a pathogenic *PKP2* c.1237C>T; p.(Arg413*) variant returned to his electronic health record after initial identification in a research project.[44] The patient had prior echocardiography and nuclear stress testing for preoperative assessments, which were technically limited but grossly within normal limits other than mildly increased (concentric) left ventricular wall thickness. He had several prior 12-lead ECG, which had been essentially unremarkable other than inferior q-waves. After receipt of his result, the patient had a genetics consult in which he reported a family history significant for SCD in a maternal cousin in his 40s, stroke in his mother, and an enlarged heart in his father. He reported that receiving this result was somewhat stressful because it could mean that something was wrong with him, and he was also concerned about the potential reaction of family members. He was referred to cardiology for a diagnostic evaluation, which included a technically limited echocardiogram that was within normal limits and no significant change in his 12-lead ECG. The patient could not undergo cardiac MRI because of his implanted electrical stimulator device. It remains unclear whether this patient's personal or family history is related to the genetic variant.

None of these patients, nor any others with secondary findings for ARVC at our institutions, has met full task force criteria for ARVC diagnosis. Systematic, longitudinal follow-up is ongoing to learn the diagnostic yield and natural history of patients ascertained in this manner.

CURRENT DIAGNOSTIC, SCREENING, AND TREATMENT GUIDELINES FOR ARVC

Our approach to managing such patients with an ARVC-associated secondary finding is derived from best practices in caring for ARVC patients and their at-risk relatives. Therefore, we briefly review current literature and recommendations for diagnosis, screening, and treatment.

ARVC Diagnosis

The diagnosis of ARVC is based on fulfillment of the multifactorial task force criteria.[10] Among the criteria are depolarization and repolarization abnormalities

from 12-lead and signal averaged ECG, incidence of arrhythmia via 24-hour Holter monitoring, relevant family history (including identification of a pathogenic mutation), and structural and functional abnormalities of the RV with both echocardiogram and cardiac MRI criteria provided. Two-dimensional echocardiography is often used as the first-line approach although MRI is ultimately better suited for imaging the RV.

Although these criteria have helped to standardize clinical diagnosis, they are known to be an imperfect solution because of factors such as low specificity of ECG and imaging findings (particularly in athletes) and the multiple potential causes of RV arrhythmias.[4] In addition, recent appreciation of a broadening phenotypic scope of the disease (biventricular involvement or left-sided predominant disease[45]) has not been reflected in the diagnostic criteria.

Screening of At-Risk Family Members

Diagnostic screening of first-degree relatives of diagnosed patients is recommended although the expected yield and the best practices for the frequency of this screening are not entirely known. Only a few studies have detailed findings from serial evaluations in such cases.[26,27] These studies found that 28% to 37% of relatives (39%–45% with a familial variant) were definitively diagnosed on their initial evaluation. In the remaining patients, the appreciable rate of disease progression in follow-up screening was slow because only 30% developed new symptoms[26] and 14% received a new diagnosis (mean follow-up of 6.7 years).[27] Reevaluation of these data including only family members with pathogenic or likely pathogenic variants shows an overall incidence of 2.8 new diagnoses per 100 person years with a peak rate (9.3) in patients between ages 30 and 40 years (Figure 1).

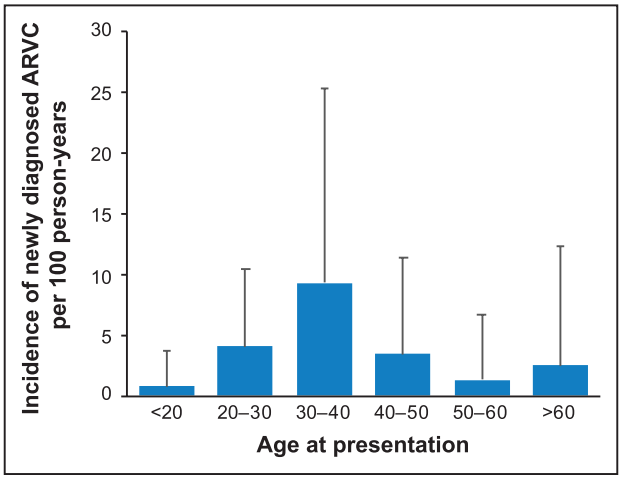

Figure 1. Incidence of new arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnoses among first-degree family members with a class 4 or 5 variant per American College of Medical Genetics and Genomics criteria by patient age. Data from te Riele et al.[27]

Arrhythmic Risk Stratification and Treatment

A comprehensive description of current guidelines and recommendations for treatment was recently detailed.[28] We present a limited overview.

After diagnosis, primary therapeutic options for ARVC consist of pharmacological treatment (eg, antiarrhythmics or β-blockers), lifestyle modification, implantable cardioverter defibrillator (ICD) placement, and catheter ablation. In more severe cases of refractory ventricular arrhythmias, treatment with sympathectomy may also be considered.[46] The risk of major adverse outcomes is highly variable, but the variables that portend poor outcomes are beginning to be understood.[28] In addition, recent studies have shown a link between endurance exercise or frequent physical activity and ventricular arrhythmias, heart failure, and transplant.[30,47] Hence, lifestyle modification through avoidance of high intensity endurance athletics is recommended.[28]

PROPOSED APPROACH TO EVALUATING AND MANAGING PATIENTS WITH SECONDARY FINDINGS

Multidisciplinary Team

We recommend a multidisciplinary team approach incorporating expertise in inherited heart disease and genetics/genetic counseling. Multidisciplinary models are emerging as standard of care for cardiovascular disease, including for families affected by inherited cardiovascular disease.[48,49] In our experience caring for patients with unanticipated ARVC-associated pathogenic variants, ARVC-specific expertise in diagnosis and management is of paramount importance as is integrated genetic counseling (Figure 2).

Genomic Evaluation

Identification and interpretation of actionable ARVC-associated variants should be performed by a certified laboratory with appropriate expertise in ARVC genetics and using current best practices.[34] Consistent with American College of Medical Genetics and Genomics recommendations, only variants of known or expected pathogenicity (class 4 or 5) should be considered for evaluation. The genetic pathogenesis of desmosome variants is predominantly through a loss-of-function mechanism, so a conservative focus on loss-of-function variants is appropriate, especially given the prevalence of rare, missense variants of uncertain significance that have been reported in these genes.[32,50,51] This conservative approach will help to minimize the number of false-positive individuals identified.

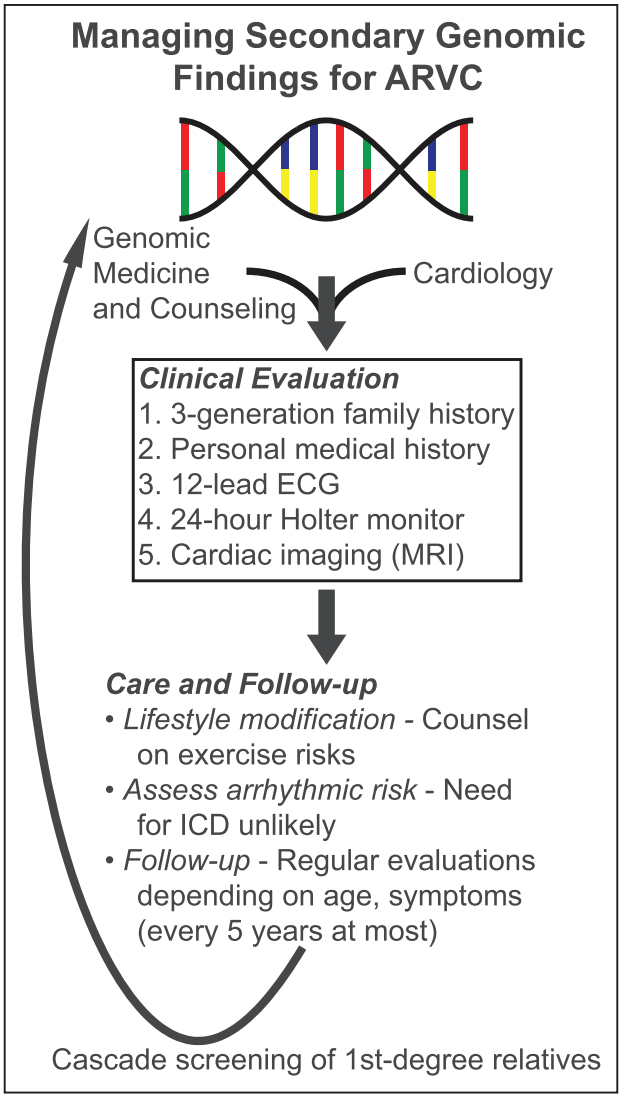

Figure 2. Overview of proposed clinical surveillance for individuals with secondary genomic findings for arrhythmogenic right ventricular cardiomyopathy (ARVC). ICD indicates implantable cardioverter defibrillator; and MRI, magnetic resonance imaging.

Diagnostic Evaluation

The diagnostic work-up should include a detailed (3-generation) pedigree, family, and personal medical histories, 12-lead ECG, 24-hour Holter monitor, and cardiac imaging. The comprehensive, cardiac-focused personal and family histories should come first in these evaluations so that they inform the subsequent cardiac screening and interpretation of the variant-specific phenotypes. It is also noted that although full application of the task force criteria in individuals <14 years poses a challenge (specific elements in the diagnostic criteria only apply to individuals >14 years[10]), screening beginning in later childhood is appropriate given the high risks of SCD presentation in adolescence.[9]

For imaging, although echocardiography often serves as the first-line imaging technique to evaluate ARVC,[52] cardiac MRI, if available at an experienced cardiovascular center, should be considered for the primary structural evaluation of patients with secondary genetic findings. MRI is well-suited to assessing ventricular volumes and function based on its excellent reproducibility and is particularly effective at assessing the RV compared with 2-dimensional echocardiography.[53]

Risk Stratification

In translating knowledge from existing clinical experience to the novel scenario of patient ascertainment through secondary genomic findings, it is unclear whether the natural history and prognosis for these patients are expected to resemble typical ARVC index patients, the slightly lower risk course seen in family members, or some other distinct pattern with intermediate or even lower associated risks. This question has particular relevance for decisions on the use of ICDs. Given the presumed asymptomatic nature of clinical presentation, it would be prudent to assume that these patients are more like family members (who themselves are primarily evaluated because of inherited risk factors rather than direct symptoms) than index patients. Using the recommendations of the international task force consensus for ICD implantation,[28] these patients will, therefore, generally fall into the low or intermediate risk categories. Patients in the low risk category were not recommended for ICD implantation (class III) while ICDs could be considered for intermediate/minor risk patients (class IIb).[28] The natural history of patients with secondarily identified ARVC variants should be followed to evaluate the applicability of existing evidence to these decisions.

Lifestyle Modification

Based on the evidence that endurance athletics and vigorous physical exercise play an important role in ARVC pathogenesis,[30] a detailed assessment of the patient's lifestyle is also indicated. The patient should be counseled on the association between competitive and high intensity aerobic exercise and ARVC, as well as the current recommendations on competitive sports,[28,54] thus enabling shared decision making for any potential lifestyle changes. Data are not yet available on the risk of high level sports in patients with secondary findings, so less restriction may be warranted than in members of ARVC families. A recent analysis suggested that the American Heart Association's recommended minimum levels of exercise for healthy adults was associated with lower risk of diagnosis among ARVC family members with *PKP2* mutations.[55] It is important to note these studies of genotype-positive, phenotype-negative family members are small, and more data are needed to definitively address the question of appropriate exercise dose in at-risk individuals.

Follow-Up

With negative phenotypic findings on the initial clinical evaluation, follow-up screening is still warranted. The optimal intervals of this follow-up are not well defined and again depend on clinical findings, age, and exercise history/plans. Pending further natural history evidence, we recommend that individuals identified with secondary genetic findings should be managed similarly to genotype-positive family members, as discussed below. Over time, and with the aggregation of data from a sufficient number of cases, we anticipate that more precise evidence-based management strategies will be developed for individuals who come to light as secondary findings from genomic sequencing.

Marcus et al[56] recommended that full screening of family members occur every 2 years through age 20 years, and every 5 years between 20 and 60 years. More recently, the international task force consensus statement indicated that full repeat clinical assessments for individuals at high risk for ARVC—inclusive of individuals carrying pathogenic variants—be performed every 2 to 3 years during adolescence and young adulthood.[28] More frequent follow-up is warranted for individuals with abnormalities detected on initial screening or for those participating in frequent vigorous endurance sports.

Cascade Family Testing

As with phenotypically ascertained families, cascade genetic testing of immediate relatives of the index patient is indicated to assess the segregation of the identified variant within the family. As they are identified, these family members should similarly undergo phenotypic evaluation for evidence of disease.

POTENTIAL DIAGNOSTIC INNOVATIONS

The natural history of ARVC is typically described as the progression through distinct phases, beginning with an early subclinical or concealed phase.[5] One of the fundamental diagnostic challenges with ARVC is the lack of appropriately sensitive techniques and end points to reflect this subclinical or concealed state. This limitation factors into both the incidence of SCD from ARVC, as well as definitive risk stratification for family members. As with family members, identification of a pathogenic or likely pathogenic genetic variant for ARVC may provide some assistance in identifying at-risk patients; however, identification of variant carriers who will never develop disease is inevitable. Therefore, for all of these cases, new diagnostic innovations are needed for early detection in genotype-positive/phenotype-negative cases. This need is especially imperative because the use of next-generation sequencing continues to accelerate toward applications in the general population.

New techniques in cardiac MRI provide several promising opportunities. MRI has an existing role in ARVC diagnosis, but its value is limited because electrical abnormalities are often detectable before the imaging criteria are met.[11] This limitation may, however, reflect the insensitivity of the current MRI criteria, rather than a shortcoming of the imaging itself. Indeed, there is strong evidence suggesting that advanced measurements of cardiac structure and function from MRI may provide novel diagnostic insights. For example, T1 mapping MRI is capable of quantifying diffuse myocardial fibrosis and has been shown to distinguish carriers of HCM genetic variants from healthy controls.[57] High-resolution T1 mapping techniques may soon extend these abilities to enable evaluation of the thin wall of the RV in ARVC.[58]

Quantitative MRI of myocardial deformation/mechanics (eg, strain) is another potential innovation. Ventricular mechanics are impaired in advanced ARVC[59]; however, abnormalities in mechanics may precede the global function changes in the task force criteria,[60,61] making mechanics a possible early diagnostic marker. For example, Réant et al[61] reported that asymptomatic, variant-carrying relatives of patients with ARVC had reduced subepicardial longitudinal strain (despite normal ejection fraction) compared with healthy controls. Strain abnormalities, particularly with exercise,[62] may thus help to discriminate affected versus nonpenetrant individuals carrying ARVC variants, but more research is needed to test this hypothesis.

CONCLUSIONS

Secondary genetic findings for ARVC pose unique challenges to patient care and management. Although genome-first ascertainment may provide the best opportunity to prevent patients from presenting with SCD, that must be balanced by the effects on individuals identified without penetrant disease. Hence, as with other conditions associated with secondary DNA variant findings, the significance and full disease spectrum associated with such secondary findings remain to be defined. The conservative approach we propose is intended to help find this balance, but standardized evaluations, aggregation of data from multiple sites, and long-term outcomes data will all be important to provide evidence-based refinement. Such refinements will also benefit from new diagnostic innovations that can better segregate affected individuals at early stages of disease versus nonpenetrant genetic variant carriers.

ARTICLE INFORMATION

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