

















# Indications and utility of cardiac genetic testing in athletes

Silvia Castelletti <sup>1†</sup>, Belinda Gray <sup>2,3,4†</sup>, Cristina Basso <sup>5,6</sup>, Elijah R. Behr <sup>2</sup>, Lia Crotti <sup>1,6,7</sup>, Perry M. Elliott <sup>8</sup>, Cecilia M. Gonzalez Corcia <sup>9</sup>, Flavio D'Ascenzi <sup>10</sup>, Jodie Ingles <sup>3,4,11,12</sup>, Bart Loeys <sup>13,14</sup>, Antonis Pantazis<sup>15</sup>, Guido E. Pieleš<sup>16,17</sup>, Johan Saenen<sup>18</sup>, Georgia Sarquella Brugada <sup>6,19</sup>, Maria Sanz de la Garza <sup>20</sup>, Sanjay Sharma <sup>2</sup>, Emeline M. Van Craenebroek <sup>18</sup>, Arthur Wilde <sup>6,21</sup>, and Michael Papadakis <sup>2\*</sup>

<sup>1</sup>IRCCS Istituto Auxologico Italiano, Cardiology Department, Milan, Italy; <sup>2</sup>Cardiovascular Clinical Academic Group and Cardiology Research Centre, Institute of Molecular and Clinical Sciences, St George's, University of London and St George's University Hospitals NHS Foundation Trust, London, UK; <sup>3</sup>Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; <sup>4</sup>Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; <sup>5</sup>Cardiovascular Pathology Unit, Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Padua, Italy; <sup>6</sup>European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart, Amsterdam, The Netherlands; <sup>7</sup>Department of Medicine and Surgery, University of Milano-Bicocca, Milano, Italy; <sup>8</sup>Centre for Heart Muscle Disease, Institute of Cardiovascular Science, University College London, London, UK; <sup>9</sup>Department of Sports Cardiology and Screening, Aspetar Sports Medicine Hospital, Doha, Qatar; <sup>10</sup>Division of Cardiology, Department of Medical Biotechnologies, University of Siena, Siena, Italy; <sup>11</sup>Centenary Institute, The University of Sydney, Sydney, Australia; <sup>12</sup>Centre for Population Genomics, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, Australia; <sup>13</sup>Department of Clinical Genetics, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>14</sup>Center for Medical Genetics, Antwerp University Hospital & University of Antwerp, Antwerp, Belgium; <sup>15</sup>Cardiomyopathy Service, Royal Brompton Hospital, London, UK; <sup>16</sup>National Institute for Health Research (NIHR) Cardiovascular Biomedical Research Centre, Congenital Heart Unit, Bristol Heart Institute, Bristol, UK; <sup>17</sup>Institute of Sport, Exercise and Health, University College London, London, UK; <sup>18</sup>Department of Cardiology, Faculty of Medicine and Health Sciences, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; <sup>19</sup>Arrhythmia, Inherited Cardiac Diseases and Sudden Death Unit, Hospital Sant Joan de Déu, Barcelona. Science Department, Medical School, Universitat de Girona, Girona, Spain; <sup>20</sup>Cardiovascular Institute, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Barcelona, Spain; and <sup>21</sup>Department of Clinical and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Heart Center, Amsterdam, The Netherlands

Received 14 January 2022; revised 14 April 2022; accepted 15 April 2022; online publish-ahead-of-print 16 June 2022

Sports Cardiology practice commonly involves the evaluation of athletes for genetically determined cardiac conditions that may predispose to malignant arrhythmias, heart failure, and sudden cardiac death. High-level exercise can lead to electrical and structural cardiac remodelling which mimics inherited cardiac conditions (ICCs). Differentiation between 'athlete's heart' and pathology can be challenging and often requires the whole armamentarium of available investigations. Genetic studies over the last 30 years have identified many of the genetic variants that underpin ICCs and technological advances have transformed genetic testing to a more readily available and affordable clinical tool which may aid diagnosis, management, and prognosis. The role of genetic testing in the evaluation and management of athletes with suspected cardiac conditions is often unclear beyond the context of specialist cardio-genetics centres. This document is aimed at physicians, nurses, and allied health professionals involved in the athlete's care. With the expanding role and availability of genetic testing in mind, this document was created to address the needs of the broader sports cardiology community, most of whom work outside specialized cardio-genetics centres, when faced with the evaluation and management of athletes with suspected ICC. The first part of the document provides an overview of basic terminology and principles and offers guidance on the appropriate use of genetic testing in the assessment of such athletes. It outlines key considerations when contemplating genetic testing, highlighting the potential benefits and pitfalls, and offers a roadmap to genetic testing. The second part of the document presents common clinical scenarios in Sports Cardiology practice, outlining the diagnostic, prognostic, and therapeutic implications of genetic testing, including impact on exercise recommendations. The scope of this document does not extend to a comprehensive description of the genetic basis, investigation, or management of ICCs.

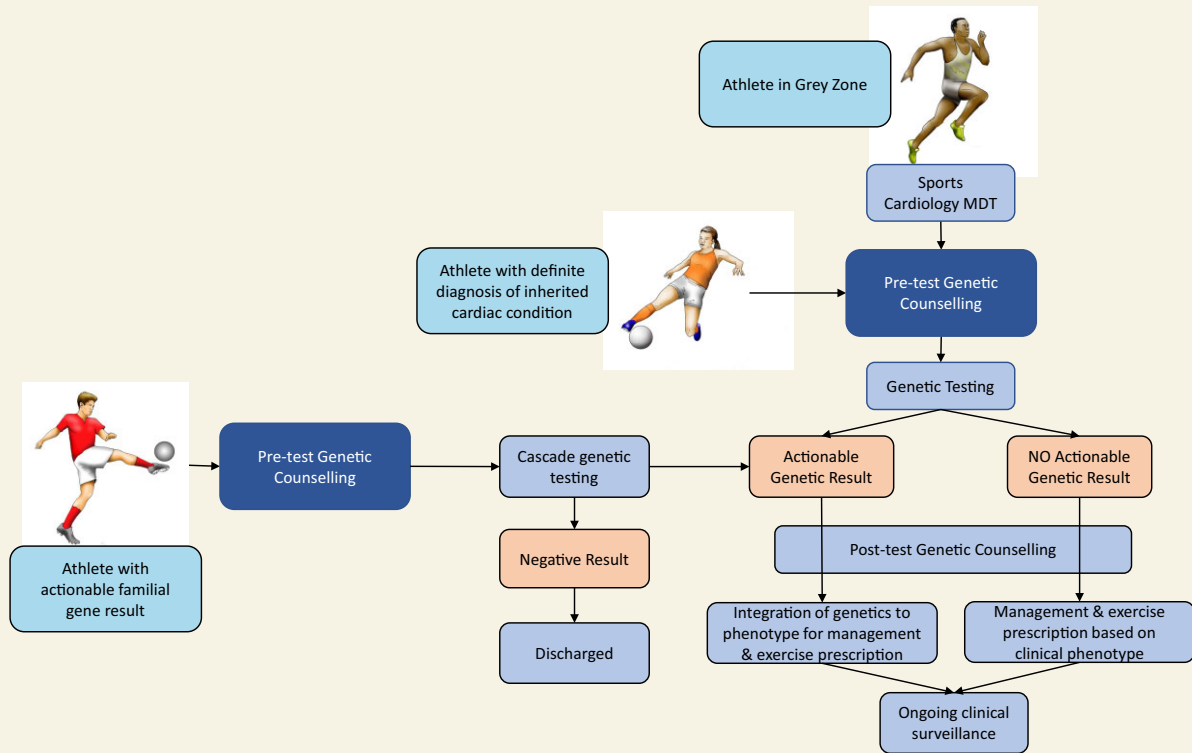
\* Corresponding author. Tel: +44 2087255909, Email: [mipapada@sgul.ac.uk](mailto:mipapada@sgul.ac.uk)

† Joint first authors.

A scientific statement from the Sports Cardiology and Exercise Section of the European Association of Preventive Cardiology, the European Heart Rhythm Association, the ESC Working group of myocardial and pericardial diseases, the ESC Council on Cardiovascular Genomics, the European Society of Human Genetics, and the Association for European Paediatric and Congenital Cardiology. © The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## Graphical Abstract



Flow chart demonstrating pathways for athletes to proceed with cardiac genetic testing depending whether they have a known diagnosis of inherited cardiac condition (ICC), they are an athlete in the grey zone, or they have a known actionable (pathogenic or likely pathogenic) genetic result in their family. Multidisciplinary should consist of individuals with expertise in sports cardiology, cardiac genetics and the diagnosis, and management of ICCs and genetic counsellors.

**Keywords** Genetic testing • Athletes • Sudden cardiac death • Inherited cardiac conditions • Channelopathies • Cardiomyopathies

## Introduction

### Background

Sports Cardiology practice commonly involves the evaluation of athletes for genetically determined cardiac conditions that may predispose to malignant arrhythmias, heart failure, and sudden cardiac death (SCD). High-level exercise can lead to electrical and structural cardiac remodelling which mimics inherited cardiac conditions (ICCs), often referred as the 'grey zone'. Differentiation between 'athlete's heart' and pathology can be challenging and often requires the whole armamentarium of available investigations.<sup>1–5</sup> Genetic studies over the last 30 years have identified many of the genetic variants that underpin ICCs and technological advances have transformed genetic testing to a more readily available and affordable clinical tool which may aid diagnosis, management, and prognosis. The role of genetic testing in the evaluation and management for athletes with suspected cardiac conditions is often unclear beyond the context of specialist cardio-genetics centres.

### Aim of the document and target audience

This document is aimed at physicians, nurses, and allied health professionals involved in the athlete's care. With the expanding role and availability of genetic testing in mind, this document was created to address the needs of the broader sports cardiology community, most of whom work outside specialized cardio-genetics centres, when faced with the evaluation and management of athletes with suspected ICC. The first part of the document provides an overview of basic terminology and principles and offers guidance on the appropriate use of genetic testing in the assessment of such athletes. It outlines key considerations when contemplating genetic testing, highlighting the potential benefits and pitfalls, and offers a roadmap to genetic testing summarized in the Graphical abstract. The second part of the document presents common clinical scenarios in Sports Cardiology practice, outlining the diagnostic, prognostic, and therapeutic implications of genetic testing, including subsequent impact on exercise recommendations. The scope of this document does not extend to a comprehensive description of the genetic basis, investigation, or management of ICCs.

## Cardiac genetic testing

### Genetic testing in the inherited cardiac conditions

Most ICCs are inherited in an autosomal dominant manner, meaning that there is a 50% risk of transmission to offspring. Depending on the disease in question, genetic testing may identify a disease-causing (pathogenic or likely pathogenic) genetic variants in up to 70% of patients.<sup>6</sup> The common ICCs, their prevalence and the approximate yield of genetic testing are shown in [Table 1](#). The likelihood of finding a causal genetic variant is highest in patients with known familial disease and lowest in older patients and individuals with atypical clinical features.

Genetic counselling is essential prior to any individual undergoing genetic testing and should be performed by trained health care professionals, ideally working within a multidisciplinary team,<sup>6,10</sup> in specialized centres. This is particularly important in complex cases. The aim is to help patients understand and manage the psychological, social, professional, ethical, and legal implications of a genetic test, as well as gather information for other family members, including cardiac and non-cardiac symptoms and autopsy reports. When a causative genetic variant is identified in the index case, often referred as 'proband', relatives can be genetically tested for the same variant, a process known as 'predictive or cascade testing'. If the variant is present, a baseline clinical evaluation is necessary to look for the clinical phenotype and manage according to established protocols. Asymptomatic carriers with no clinical phenotype, referred as 'genotype positive-phenotype negative', can be offered clinical surveillance and reproductive advice.<sup>11</sup> If the variant is absent, relatives can be discharged but should be advised to seek reassessment if new symptoms develop or if new clinically relevant data emerge in the family.<sup>11</sup> A more cautious approach may be considered in situations where the genetic basis of the disease is more complex. A cautious approach is also necessary when considering genetic testing in children when issues of consent, the long-term implications of a positive genetic test, and age-related disease penetrance need to be considered.

In families where there has been a sudden cardiac death, comprehensive macroscopic and histopathological evaluation of the heart, ideally by a cardiac pathologist, is required for an accurate assessment as to the potential cause of death.<sup>12,13</sup> Genetic analysis using DNA from post-mortem tissue or blood samples, also referred as 'molecular autopsy', can be invaluable and assist in the risk assessment of surviving relatives.<sup>12–15</sup> A diagnosis of an ICC or the absence of an identifiable cause, also referred as sudden arrhythmic death syndrome (SADS) will guide genetic and familial evaluation. Similar to clinical testing, molecular autopsy results must always be interpreted in tandem with the results of the post-mortem examination and in accordance with consensus criteria for assigning pathogenicity to genetic variants.<sup>12,13,16,17</sup>

### Nomenclature, techniques, and result interpretation

Cardiac genetic testing has been transformed with the advent of next-generation sequencing (NGS) techniques. These sequencing technologies provide high-throughput of millions of DNA fragments

thereby allowing rapid analysis of large sections of DNA as well as providing more complete coverage of larger genes, such as the ryanodine receptor (*RYR2*) and titin (*TTN*) which have been historically challenging to comprehensively sequence.<sup>18</sup>

In many diagnostic laboratories, genetic testing is performed with NGS-panels which include sequencing genes known to be associated with the disease diagnosed or suspected. More comprehensive approaches include: whole-exome sequencing (WES), which encompasses all coding regions of the genome and whole-genome sequencing (WGS), which involves sequencing of all coding and non-coding regions of the DNA. Whole-genome sequencing provides a comprehensive dataset at the expense of significant challenges in terms of volume and interpretation of data and financial cost.<sup>19,20</sup> It is important to acknowledge that when performing WGS or WES, only variants in genes relevant to the phenotype should be reported.

Genetic testing results are not binary but represent a spectrum of pathogenicity. Variants are grouped in five classes according to guidelines of the American College of Medical Genetics and the Association of Molecular Pathologists (ACMG/AMP).<sup>21</sup> When there is sufficient evidence to consider a variant as the cause of disease, it is classified as pathogenic (Class 5) or likely pathogenic (Class 4). When the evidence indicates that the variant is unlikely to cause disease, it is classified as benign (Class 1) or likely benign (Class 2). When there is insufficient or conflicting evidence, the variant is classified as a variant of uncertain significance (VUS) (Class 3).<sup>21</sup> The classification of a variant is based on a combination of variables: (i) frequency of the variant in large population databases such as the genome aggregation database (gnomAD),<sup>22</sup> (ii) presence of the variant in individuals with the respective disease in genetic testing result databases (e.g. Clinvar), (iii) predicted effect of the variant using computational (in-silico) models (e.g. SIFT, Polyphen-2, mutation taster), (iv) functional data assessing the effect of the variant, and (v) segregation analysis of the variant in families.

Careful variant interpretation and classification is essential to avoid diagnostic errors and should be performed in experienced centres. Only pathogenic and likely pathogenic variants should be viewed as causal variants and used for cascade genetic testing of relatives. If a variant is classified as a VUS, then the variant cannot be used to support a suspected diagnosis or for cascade genetic testing of relatives. For the purpose of sports cardiology practice, a VUS should be ignored, similar to benign or likely benign variants. Some variants may be of future clinical relevance but this needs to be explored in the context of specialist cardio-genetics clinics.<sup>23</sup> It is worth noting that a negative genetic test does not exclude a diagnosis in the presence of a clear or highly suspicious phenotype.

### Genetic testing in Sports Cardiology

Identification, evaluation, and management of ICCs are an integral part of Sports Cardiology practice, as ICCs are implicated as a leading cause of SCD in young (<35 years) athletes.<sup>24</sup> Hypertrophic cardiomyopathy (HCM) accounts for the majority of deaths in a long-standing national registry in the USA,<sup>25</sup> while arrhythmogenic cardiomyopathy (ACM) has been reported as the main cause of death in the North East of Italy.<sup>26</sup> Studies in the UK and Australia indicate that SADS, characterized by a negative or normal post-mortem, is more common than previously thought, suggesting that inherited

arrhythmia syndromes such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) account for a significant proportion of SCDs in young and athletic individuals.<sup>27,28</sup> In an attempt to minimize such tragedies, preventive efforts include targeted evaluation of high-risk individuals, as well as wider screening of low-risk individuals.<sup>24</sup> Athletes with cardiac symptoms, a family history of an ICC or SCD at a young age and those with electrocardiogram (ECG) or structural traits suggestive of cardiac disease should be referred to specialist centres for comprehensive assessment.

Similar to the general population, genetic testing in sports cardiology has primarily been used in athletes with a clear phenotype of an ICC in order to facilitate familial cascade testing, or for predictive testing in athletes with a family history of an ICC and a known causative variant.<sup>24</sup> Recently, a broader scope was proposed, where, genetic testing is used for diagnostic and prognostic purposes, including guiding medical therapy and exercise prescription.<sup>7</sup> The utility of genetic testing for diagnostic purposes is particularly relevant in sports cardiology, as the effects of exercise on electrical and structural cardiac remodelling often pose significant challenges and differentiation between 'athlete's heart' and ICC requires the use of several diagnostic tools (Figure 1). Athletes may exhibit increased left ventricular (LV) wall thickness, dilatation of the left ventricle and right ventricle (LV/RV) with associated impairment in function or prominent LV trabeculations<sup>24</sup> (Figure 1). Compared with the general population, athletes are also more likely to demonstrate longer QT intervals and a higher prevalence of T-wave inversion, partial, or complete right bundle branch block and early repolarization patterns.<sup>24,29,30</sup>

Similar to the core principles of genetic testing in any setting, genetic testing for diagnostic purposes should only be used in athletes after careful consideration of a number of factors in the context of a multidisciplinary team (MDT) and after appropriate pre-test counselling.<sup>6,10</sup> The physician should assess the pre-test probability of a positive test based on the suspected condition and strength of the phenotype and consider the potential prognostic and therapeutic implications. For some conditions, such as LQTS, the utility of genetic testing in the athlete can be broad as the identification of different genetic subtypes (LQT 1–3) can inform the risk of arrhythmic events, identify potential triggers to be avoided and help to target medical therapies and plan exercise advice.<sup>6,31</sup> The utility of genetic testing for ICCs commonly encountered in clinical practice is outlined in Table 1.

Genetic testing is incorporated into contemporary exercise guidelines which aim to promote safe participation in exercise through tailored exercise prescription for elite and recreational athletes with ICC.<sup>24</sup> For most conditions, risk stratification and exercise prescription are dictated by the clinical phenotype, allowing for a liberal approach in athletes with a positive genotype but no or very mild phenotype.<sup>24</sup> A notable exception is ACM, where individuals carrying a casual variant, even in the absence of phenotypic evidence of disease, are restricted from the competitive sport as they have a greater chance of progression to overt disease, heart failure, and life-threatening arrhythmias with high-level athletic activity.<sup>24,31</sup>

## Pathway for genetic testing in athletes

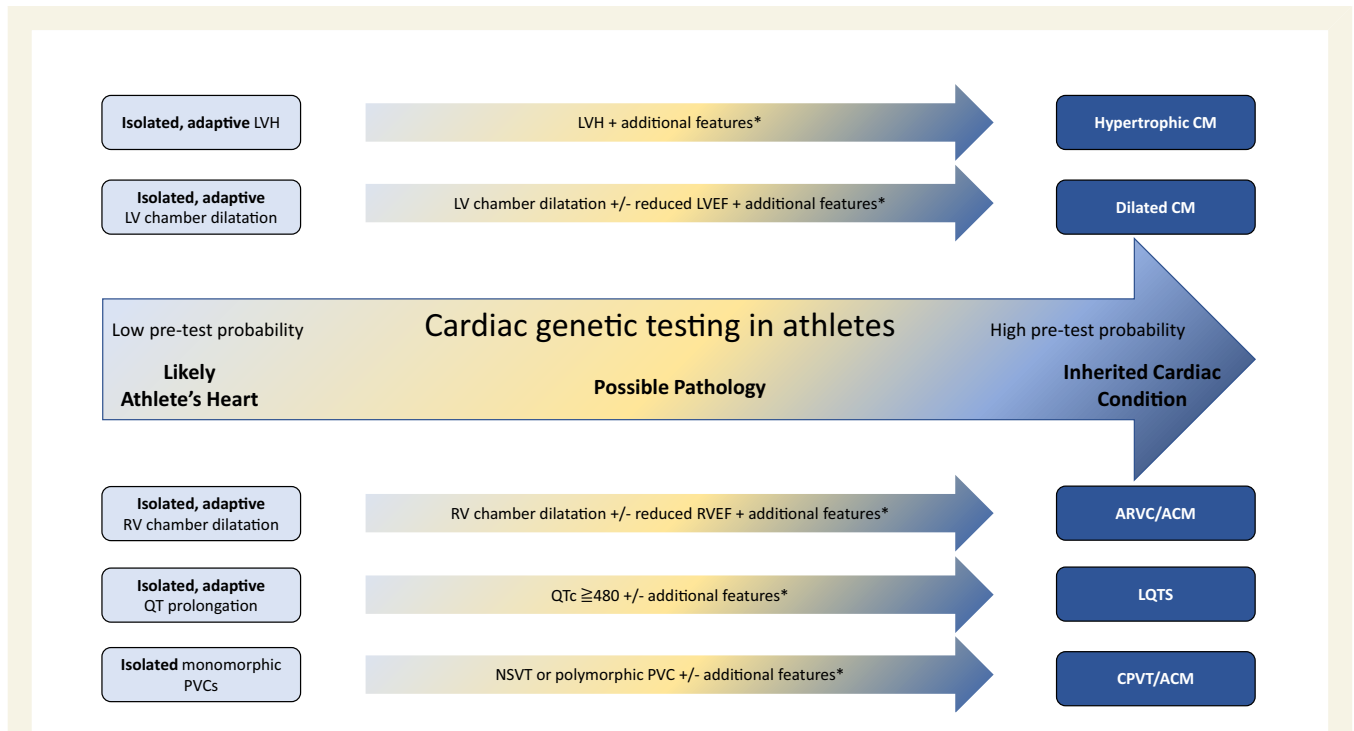
Genetic testing of athletes requires an MDT approach in specialized centres. Individuals with expertise in sports cardiology, cardiac

genetic testing and the diagnosis and management of ICCs should be involved. Key components are outlined in the graphical abstract and include the following:

- (1) *Comprehensive clinical evaluation* to ascertain whether findings indicate physiological or pathological changes in the athlete. Sports physicians, cardiologists, cardiac physiologists, genetic nurses, and clinical geneticists all require expertise pertinent to their roles in the diagnosis of ICCs.<sup>8</sup> In the absence of a clear or highly suggestive phenotype or family history of an ICC there will be a low pre-test probability for identifying a monogenic cause.
- (2) *Pre-test genetic counselling* provides information and psychological support to the athlete and should be performed by appropriately trained health professionals.<sup>24,25</sup> Athletes are supported to make an informed decision, having explored all possible outcomes and respective implications of genetic testing for them and their family. Issues relating to competitive sport participation, insurance, and broader financial and ethical issues should be explored.
- (3) *Expertise in cardiac genetic testing* is important in determining that the correct genes are tested for the right phenotype, as well as accurate interpretation of findings. This requires testing by approved clinical laboratories in collaboration with the MDT. Confining sequencing to high confidence genes<sup>32–35</sup> and careful interpretation of variants minimizes the risk of misclassification of genetic variants and inappropriate feedback to the individual.<sup>36–38</sup> With ever-changing knowledge of genetic variants, reclassification is always a possibility. This can include upgrading a VUS to a likely pathogenic or pathogenic variant or downgrading a variant from likely pathogenic or pathogenic to VUS or even likely benign/benign. The laboratories and MDT should, therefore, have mechanisms in place to ensure variants are periodically reviewed.
- (4) *Post-test genetic counselling* provides the results and reviews potential implications with the athlete. Psychological support may be necessary when an athlete has dealt with significant uncertainty or stress or in cases where there has been exclusion from competitive sports.<sup>39–42</sup> Furthermore, there can be symptoms of anxiety and posttraumatic stress in athletes with a family history of premature SCD, a diagnosis of an ICC or where an implantable cardioverter defibrillator is recommended.<sup>43–46</sup>
- (5) *Clinical follow-up and family evaluation* will be necessary for athletes with a definite or possible diagnosis of an ICC.<sup>16</sup>

## Ethical and legal aspects of genetic testing in athletes

There are specific ethical and legal aspects of genetic testing that need to be considered in competitive and especially professional athletes prior to undertaking the test. The decision about whether to pursue genetic testing should be made following pre-test genetic counselling. Genetic counselling should include all the key stakeholders with whom the athlete wishes to share the decision-making process (family, club doctor, club representative, sporting association) but at the same time, it is important to ensure that decisions are made by the athlete without undue duress. Relevant parties should be fully informed of the possible results and the potential implications prior to undertaking the test. Post-test counselling is critical given the potential psychosocial, financial, and



**Figure 1** Diagrammatic representation of the utility of genetic testing in Sports Cardiology for some of the common clinical scenarios including the 'grey zone'. The system is based on the pre-test probability of a positive yield across the spectrum with on the left adaptive changes due to exercise where genetic testing should not be used and on the right an established diagnosis of an inherited cardiac condition when genetic testing should be performed. A multidisciplinary team discussion is paramount when genetic testing is considered in the 'grey zone' depicted by the arrows. \*Additional features for individual phenotypes as reported in the main text.

**Table 1** Prevalence, estimated genetic yield, and utility of genetic testing in athletic individuals for the most commonly encountered cardiomyopathies and channelopathies (modified from Wilde et al.<sup>6</sup> and Gray et al.<sup>7</sup>)

Disease under investigation in the athlete	Estimated prevalence <sup>6,8,9</sup>	Estimated genetic testing yield (%)	Diagnostic utility in the athlete	Prognostic utility in the athlete	Therapeutic implications (medical/device)	Impact of exercise on disease expression <sup>a</sup>	Impact on exercise recommendations <sup>b</sup>
LQTS	1 in 2000	70	+++	+++	+++	+	++ <sup>c</sup>
CPVT	1 in 10 000	60	+++	+	+	++	++
BrS	1 in 2000	10	+	+	+	+/-	-
HCM	1 in 500	50	+++	++	++	+/-	-
ACM	1 in 10 000	50	+++	++	++	++	+++
DCM	1 in 500	20	++	+++	++	+	+

Table scale (-, +, ++, +++) indicates likely utility of genetic testing with '-' indicating unlikely to be helpful and '++++' indicating highly likely to be helpful. LQTS, long QT syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; BrS, Brugada syndrome; HCM, hypertrophic cardiomyopathy; ACM, arrhythmogenic cardiomyopathy; DCM, dilated cardiomyopathy.

<sup>a</sup>Degree to which exercise influences how the disease phenotype manifests in the athlete.

<sup>b</sup>How a genetic testing result can influence exercise prescription. The scoring represents a consensus view from the authors based on evidence and existing recommendations.

<sup>c</sup>Specific genotype of LQTS can influence exercise recommendations (e.g. swimming with LQT1).

mental health implications, particularly if the athlete is excluded from play.<sup>23</sup>

The implications relating to insurance for the athlete and their club are largely defined by the country in which the athlete resides. As a general rule, insurance companies require the athlete to disclose any family history but do not require them to disclose the results of genetic testing. In

athletes with a family history of ICC proceeding with predictive testing can be beneficial as the absence of the familial variant effectively excludes the condition and thereby may improve their insurance assessment. It is also worthwhile noting that for some conditions (such as LQTS) genetic testing can also be beneficial by facilitating genotype-directed management and prognosis and ultimately even return-to-play.<sup>23,47-49</sup>



## Special considerations in children and adolescent athletes

### General considerations

In the paediatric athlete genetic testing for ICC should adhere to the same principles as the adult athlete,<sup>50</sup> but requires some specific considerations. Children may not fully understand the future implications of genetic testing. Depending on the child's age, genetic counselling in expert paediatric centres may be necessary. Specialist centres will be able to facilitate a more comprehensive approach to genetic counselling, including the assistance of a child mental health specialist if required. Indeed, the psychological impact of a positive genetic test result may be significant for the child, especially if this leads to sports exclusion even in the absence of a phenotype.

In children with a highly suggestive or established ICC phenotype, diagnostic genetic testing may confirm the diagnosis, facilitate familial cascade screening and in some cases aid with risk stratification.<sup>51</sup> In phenotype negative children with a familial diagnosis of inherited channelopathies, such as LQTS and CPVT, cascade genetic testing may aid with risk stratification and the introduction of effective prophylactic therapies, given the risk of sudden death in the early stages of life. Genetic testing may influence sports participation even in the absence of established phenotype in both LQTS and CPVT where a positive genetic result is sufficient for diagnosis.<sup>24,31,52</sup> On the contrary, the timing of cascade genetic testing in phenotype negative children with a familial diagnosis of inherited cardiomyopathy requires a more individualized approach, depending on the impact of genetic testing on patient management and risk stratification. This cautious approach takes into consideration the significant psychological and social implications of a genetic diagnosis and needs to be balanced with the benefits of a positive genotype, which may lead to more comprehensive clinical evaluation, more frequent monitoring for evidence of disease expression, and offer a better understanding of the individual risk related to sport participation and therefore steer decisions regarding the pursue of a sporting career. There is no strong evidence to date demonstrating that, similar to adults, high-level exercise expedites disease expression in paediatric ACM. However, the possible impact of strenuous exercise, as well as the possibility of sports disqualification if an ACM disease-causing variant were identified, should be taken into consideration when discussing ACM genetic testing in a young athlete.<sup>24,31,53</sup> In addition, certain genotypes such as filamin-C (*FLNC*), desmoplakin (*DSP*), Transmembrane Protein 43 (*TMEM-43*), or lamin A/C (*LMNA*) are highly arrhythmogenic and the arrhythmia can pre-date the cardiomyopathy phenotype so early genetic diagnosis may be important.<sup>10</sup>

### Athletes with congenital heart disease

Congenital heart disease (CHD) can occur as a chromosomal syndrome (12%), a heritable syndrome with Mendelian pattern (8%), or a sporadic mutation (80%) with variable penetrance and heritability. A genetic origin has been established for a small proportion (< 5%) of CHDs.<sup>54</sup> Consequently, genetic testing in athletes with CHD should be contemplated in cases with: (i) a strong family history of CHD, (ii) where the syndromic disease is suspected, or (iii) in specific phenotypes with increased risk for cardiac events and known genetic association [e.g. atrial septal defects with arrhythmias (*NKX 2.5*)].<sup>55</sup>

## Common clinical scenarios

### Left ventricular hypertrophy and T-wave inversion

Left ventricular hypertrophy (LVH) is a well-documented trait of athletic adaptation. In most cases, the hypertrophy does not exceed 15 mm and is associated with LV cavity dilatation (eccentric remodelling).<sup>24,56</sup> It is more prevalent in black compared with white athletes, males compared with females and individuals who participate in high endurance sports.<sup>56,57</sup> Further evaluation for HCM is necessary, in the absence of hypertension or use of performance-enhancing substances, when the degree of LVH exceeds 15 mm, it is out of proportion to the athlete's demographics and athletic activity or is associated with additional features suggestive of cardiomyopathy.<sup>24,53</sup> Such features include cardiac symptoms, family history of SCD in a first-degree relative under the age of 40 years, ECG abnormalities, asymmetric hypertrophy, and eventually late-gadolinium enhancement suggesting cardiomyopathy on cardiac magnetic resonance (CMR).

In HCM, genetic testing is indicated for athletes with an unequivocal diagnosis and can be used for predictive testing in athletes with a known familial genetic result.<sup>10,53</sup> Occasionally, after an informed discussion with the athlete, genetic testing may be useful in athletes with a highly suggestive but not diagnostic HCM phenotype. The role of genetic testing in risk stratification for HCM is limited and does not usually influence decisions relating to sport participation in individuals with no or mild LVH and no conventional risk factors for SCD.<sup>53</sup>

T-wave inversion on the ECG of an athlete may be a normal variant or may be indicative of underlying heart disease.<sup>29,58–60</sup> For individuals judged to have pathological T-wave inversion, comprehensive clinical evaluation, including CMR imaging, may identify a cardiomyopathy in up to 41% of athletes.<sup>10</sup> In contrast, the diagnostic yield of genetic testing in this setting, is limited to 10% and in most cases is associated with a clinical phenotype.<sup>60</sup> Therefore, the use of routine genetic testing in asymptomatic athletes with T-wave inversion is not advisable in the absence of a family history or other features suggestive of an ICC.

### Ventricular cavity dilatation

Dilation of the left ventricle is a common feature of the athlete's heart, but when it is associated with mildly reduced systolic function and/or non-ischemic scar on CMR, it falls into the grey zone between physiological remodelling and dilated cardiomyopathy (DCM).<sup>53</sup> Comprehensive clinical evaluation in most cases suffices for the differential diagnosis of these two entities, however, genetic testing can aid in prognostic information and management decisions for certain genotypes.<sup>10</sup>

Genetic testing should be contemplated in any athlete who has been diagnosed with a familial DCM, especially when clinical features point to specific genotypes: conduction abnormalities (*LMNA*<sup>61</sup> and *SCN5A*<sup>62</sup>), disproportionate arrhythmic burden and/or multiple cases of sudden cardiac arrest, or SCD within the family (*LMNA*,<sup>59</sup> *SCN5A*,<sup>62</sup> *FLNC*,<sup>63</sup> *DSP*,<sup>64</sup> *BAG3*, *PLN*, *TTN*,<sup>65</sup> and *RBM20*<sup>66</sup>). Although the impact of exercise on arrhythmic DCM forms is not established, recent data from small cohorts suggest that

high-intensity exercise may be contributing to worse outcomes in *LMNA* patients<sup>67</sup> and may exacerbate skeletal muscle dysfunction in *FLNC* carriers.<sup>68</sup> An athlete with mild left ventricular dilatation, no or mild left ventricular dysfunction, prominent non-ischemic myocardial fibrosis, and significant burden of ventricular arrhythmia is most likely affected by a left-dominant ACM and a molecular genotyping for ACM-causing gene mutation, either desmosomal or non-desmosomal is needed to achieve a definite diagnosis, guide management, and prognosis.<sup>24,31,53,69</sup> Finally, cascade genetic testing should be offered in apparently healthy athletes with a familial diagnosis of DCM when an actionable variant has been identified in the family.<sup>70</sup>

## Prolonged QT interval

Athletic individuals tend to exhibit longer QT intervals compared with sedentary counterparts. Consequently, corrected QT (QTc) intervals of up to 470 ms for male and 480 ms for female athletes are accepted as normal. Although a QTc of  $\geq 500$  ms is commonly associated with congenital LQTS, the diagnosis may be challenging in those with lower QTc values in the absence of symptoms or documented family history. Moreover, recently a study suggested the existence of an acquired, exercise-induced QT prolongation phenotype, which is typical of LQTS, but reverts back to normal after a period of de-training.<sup>30</sup> In the cases so far described no arrhythmic events were recorded, however, more data are needed to fully understand the arrhythmic risk in such individuals.<sup>30</sup> A correct diagnosis in athletes is crucial as arrhythmia-related triggers often include increased adrenergic activity, such as exercise or emotional stress,<sup>71</sup> and effective treatments are available.<sup>72</sup>

Genetic testing is an invaluable tool both for diagnosing LQTS as well as informing risk and guiding medical therapy and exercise prescription. The genetic yield is  $>70\%$  in individuals with congenital LQTS<sup>73</sup> and can identify individuals with incomplete penetrance, who display a normal QTc,<sup>71,73–74</sup> but still have a 10% risk of experiencing a cardiac event by the age 40 years.<sup>75</sup> Genetic testing should be offered to all athletes with a familial diagnosis of LQTS and those athletes with a QTc of  $\geq 500$  ms. Genetic testing should also be considered in athletes with a QTc  $\geq 480$  ms regardless of personal and family history. If negative, in the absence of symptoms and/or family history, re-evaluation of the athlete after a period of de-training of at least 3 months and clinical screening of first-degree family members in a specialized cardio-genetic centre, may help distinguish between physiological adaptation and LQTS.<sup>30</sup> Genetic testing in athletes with a QTc  $>440$  ms but  $<480$  ms is justified only in the context of additional features suggestive of a LQTS diagnosis, including symptoms, congenital deafness, family history of unexplained SCD, T-wave notching, documented polymorphic arrhythmias, paradoxical prolongation of the QT interval during exercise, or T-wave alternans.

## Ventricular arrhythmias

Premature ventricular beats in an athlete are fairly common and usually benign. Ventricular arrhythmias (VAs) in young athletes can be classified as common or uncommon, according to their morphology (i.e. site of origin), complexity, response to exercise, and associated clinical findings.<sup>76–78</sup> Genetic testing should only be considered following comprehensive clinical phenotyping,<sup>23</sup> when an underlying

ICC is suspected. In particular, exercise-induced polymorphic or bi-directional VAs should raise suspicion of CPVT.<sup>8</sup> Other ICCs that can present with exercise-induced VAs include ACM,<sup>64,78,79</sup> DCM,<sup>80</sup> and more rarely HCM.<sup>81</sup> The presence of isolated VAs with benign features (i.e. most often left bundle branch block, inferior axis) should not prompt genetic testing.<sup>31</sup>

## Aortic dilatation

Aortic aneurysm is present in up to 1% of the Western population. Thoracic aortic aneurysm and dissection (TAAD) occurs more frequently in young adults compared with the abdominal aneurysms of the elderly. Approximately 20% of TAAD patients have a positive family history of presumed genetic aetiology, with  $>30$  genes currently identified. Cases are typically divided into syndromic and non-syndromic forms.<sup>82–84</sup> The diagnostic yield of genetic testing is estimated to be 20–30% with higher yield in patients with family history.<sup>85,86</sup> In the case of bicuspid aortic valve (BAV) related aortopathy, the diagnostic yield of genetic testing is  $\sim 5\%$ .<sup>86</sup>

Athletes tend to exhibit slightly larger aortic dimensions compared with sedentary individuals. A dilated aortic root, however, beyond conventional normal limits is not a characteristic of the athlete's heart and athletes do not typically demonstrate progressive aortic dilatation.<sup>87,88</sup> Therefore, an athlete presenting with aortic dilatation should undergo counselling and genetic testing according to the general population criteria<sup>83,84,86</sup>: (i) Aortic root diameter  $> 40$  mm in the absence of clear aetiology; (ii) associated features of connective tissue diseases, (iii) TAA with positive family history of aortic dissection ( $<60$  year) or SCD  $<45$  years, (iv) BAV with TAA. When a genetic mutation causing TAA is identified in the family predictive testing is advised in 1st degree relatives, from the age of 10 years in non-syndromic forms and earlier in syndromic presentations. In athletes with a rapid progression of aortic dilatation ( $>3$  mm/year), genetic testing can be considered. In athletes with BAV with normal diameters of the ascending aorta, genetic testing is of little additive value, as diagnostic yield is low.

## Conclusions

Genetic testing in athletes may aid diagnosis, inform arrhythmic risk and prognosis, guide management, including informing athlete's exercise prescription and ultimately facilitate safe 'return to play' to recreational or competitive sport. As genetic testing becomes more widely available there is an increasing expectation that it is considered as part of a comprehensive cardiac assessment in athletes when appropriate. It is, therefore, imperative that health care professionals involved in the athlete's care have an understanding of the indications, as well as the strengths and limitations of genetic testing. An MDT through liaison with an experienced cardio-genetics centre will ensure that both the physician and the athlete are supported. Appropriate pre- and post-test counselling will ensure that the athlete and all the stakeholders understand the potential implications of genetic testing in terms of ethical, legal, and financial repercussions.

## Authors' contributions

S.C., B.G., and M.P. contributed to the conception and design of the work. All authors contributed to drafting and critically revising the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

**Conflicts of interest:** none declared.

## References

- Pelliccia A, Caselli S, Sharma S, Basso C, Bax JJ, Corrado D, D'Andrea A, D'Ascenzi F, Di Paolo FM, Edvardsen T, Gati S, Galderisi M, Heidbuchel H, Nchimi A, Nieman K, Papadakis M, Pisicchio C, Schmied C, Popescu BA, Habib G, Grobbee D, Lancellotti P, Halle M, Gimelli A, Gerber B, Donal E, Flachskampf F, Haugaa K, Cardim N. European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete's heart. *Eur Heart J* 2018;**39**:1949–1969.
- Claessen G, Schnell F, Bogaert J, Claeys M, Pattyn N, De Buck F, Dymarkowski S, Claus P, Carré F, Van Cleemput J, La Gerche A, Heidbuchel H. Exercise cardiac magnetic resonance to differentiate athlete's heart from structural heart disease. *Eur Heart J Cardiovasc Imaging* 2018;**19**:1062–1070.
- Millar LM, Fanton Z, Finocchiaro G, Sanchez-Fernandez G, Dhutia H, Malhotra A, Merghani A, Papadakis M, Behr ER, Bunce N, Oxborough D, Reed M, O'Driscoll J, Tome Esteban MT, D'Silva A, Carr-White G, Webb J, Sharma R, Sharma S. Differentiation between athlete's heart and dilated cardiomyopathy in athletic individuals. *Heart* 2020;**106**:1059–1065.
- Brosnan MJ, te Riele ASJM, Bosman LP, Hoorntje ET, van den Berg MP, Hauer RNW, Flannery MD, Kalman JM, Prior DL, Tichnell C, Tandri H, Murray B, Calkins H, La Gerche A, James CA. Electrocardiographic features differentiating arrhythmogenic right ventricular cardiomyopathy from an athlete's heart. *JACC Clin Electrophysiol* 2018;**4**:1613–1625.
- Malhotra A, Sharma S. Hypertrophic cardiomyopathy in athletes. *Eur Cardiol* 2017; **12**:80–82.
- Wilde AAM, Semsarian C, Márquez MF, Sepeshri Shamloo A, Ackerman MJ, Ashley EA, Sternick EB, Barajas-Martinez H, Behr ER, Bezzina CR, Breckpot J, Charron P, Chockalingam P, Crotti L, Gollub MH, Lubitz S, Makita N, Ohno S, Ortiz-Genga M, Sacilotto L, Schulze-Bahr E, Shimizu W, Sotoodehnia N, Tadros R, Ware JS, Winlaw DS, Kaufman ES; Document Reviewers, Aiba T, Bollmann A, Choi JJ, Dalal A, Darrieux F, Giudicessi J, Guerschicoff M, Hong K, Krahn AD, MacIntyre C, Mackall JA, Mont L, Napolitano C, Ochoa JP, Peichl P, Pereira AC, Schwartz PJ, Skinner J, Stellbrink C, Tfelt-Hansen J, Deneke T. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Europace* 2022;**00**:1–61. doi:<https://doi.org/10.1093/europace/euac030>
- Gray B, Papadakis M. *Textbook of Sports Cardiology*. Switzerland: Springer Nature; 2019.
- Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang C-E, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm* 2013;**10**:1932–1963.
- Gollob MH, Blier L, Brugada R, Champagne J, Chauhan V, Connors S, Gardner M, Green MS, Gow R, Hamilton R, Harris L, Healey JS, Hodgkinson K, Honeywell C, Kantooh M, Kirsh J, Krahn A, Mullen M, Parkash R, Redfearn D, Rutberg J, Sanatani S, Woo A. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. *Can J Cardiol* 2011;**27**:232–245.
- Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, Pankuweit S, Perrot A, Rapezzi C, Ristic A, Seggewiss H, van Langen I, Tavazzi L. 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.
- Mogensen J, van Tintelen JP, Fokstuen S, Elliott P, van Langen IM, Meder B, Richard P, Syrris P, Caforio ALP, Adler Y, Anastasakis A, Gimeno JR, Klingel K, Linhart A, Imazio M, Pinto Y, Newbery R, Schmidtke J, Charron P. The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics. *Eur Heart J* 2015;**36**:1367–1370.
- Fellmann F, van El CG, Charron P, Michaud K, Howard HC, Boers SN, Clarke AJ, Duguet A-M, Forzano F, Kaufersstein S, Kayserili H, Lucassen A, Mendes Á, Patch C, Radojkovic D, Rial-Sebbag E, Sheppard MN, Tassé A-M, Temel SG, Sajantila A, Basso C, Wilde AAM, Cornel MC; on behalf of European Society of Human Genetics, European Council of Legal Medicine, European Society of Cardiology working group on myocardial and pericardial diseases, European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-Heart), Association for European Cardiovascular Pathology. European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. *Eur J Hum Genet* 2019;**27**:1763–1773.
- Basso C, Aguilera B, Banner J, Kohle S, d'Amati G, de Gouveia RH, di Gioia C, Fabre A, Gallagher PJ, Leone O, Lucena J, Mitrofanova L, Molina P, Parsons S, Rizzo S, Sheppard MN, Mier MPS, Kim Suvarna S, Thiene G, van der Wal A, Vink A, Michaud K; on behalf of the Association for European Cardiovascular Pathology. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch* 2017;**471**: 691–705.
- Ackerman MJ, Tester DJ, Porter CJ, Edwards WD. Molecular diagnosis of the inherited long-QT syndrome in a woman who died after near-drowning. *N Engl J Med* 1999;**341**:1121–1125.
- Ackerman MJ, Tester DJ, Driscoll DJ. Molecular autopsy of sudden unexplained death in the young. *Am J Forensic Med Pathol* 2001;**22**:105–111.
- Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, Chugh SS, Cornel MC, Gardner K, Ingles J, James CA, Jimmy Juang J-M, Käab S, Kaufman ES, Krahn AD, Lubitz SA, MacLeod H, Morillo CA, Nademanee K, Probst V, Saarel EV, Sacilotto L, Semsarian C, Sheppard MN, Shimizu W, Skinner JR, Tfelt-Hansen J, Wang DW. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm* 2021;**18**:e1–e50.
- Lahrouchi N, Raju H, Lodder EM, Papatheodorou E, Ware JS, Papadakis M, Tadros R, Cole D, Skinner JR, Crawford J, Love DR, Pua CJ, Soh BY, Bhalshankar JD, Govind R, Tfelt-Hansen J, Winkel BG, van der Werf C, Wijeyeratne YD, Mellor G, Till J, Cohen MC, Tome-Esteban M, Sharma S, Wilde AAM, Cook SA, Bezzina CR, Sheppard MN, Behr ER. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. *J Am Coll Cardiol* 2017;**69**:2134–2145.
- Koboldt DC, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. *Cell* 2013;**155**:27–38.
- Crotti L, Johnson CN, Graf E, De Ferrari GM, Cuneo BF, Ovadia M, Papagiannis J, Feldkamp MD, Rathi SG, Kunic JD, Pedrazzini M, Wieland T, Lichtner P, Beckmann BM, Clark T, Shaffer C, Benson DW, Käab S, Meitinger T, Strom TM, Chazin VJ, Schwartz PJ, George AL. Calmodulin mutations associated with recurrent cardiac arrest in infants. *Circulation* 2013;**127**:1009–1017.
- Mayosi BM, Fish M, Shaboodien G, Mastantuono E, Kraus S, Wieland T, Kotta MC, Chin A, Laing N, Ntusi NBA, Chong M, Horsfall C, Pimstone SN, Gentilini D, Parati G, Strom TM, Meitinger T, Pare G, Schwartz PJ, Crotti L. Identification of *Cadherin 2 (CDH2)* mutations in arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Genet* 2017;**10**:e001605.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–424.
- Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, Collins RL, Laricchia KM, Ganna A, Birnbaum DP, Gauthier LD, Brand H, Solomonson M, Watts NA, Rhodes D, Singer-Berk M, England EM, Seaby EG, Kosmicki JA, Walters RK, Tashman K, Farjoun Y, Banks E, Poterba T, Wang A, Seed C, Whiffin N, Chong JX, Samocha KE, Pierce-Hoffman E, Zappala Z, O'Donnell-Luria AH, Minikel EV, Weisburd B, Lek M, Ware JS, Vittal C, Armean IM, Bergelson L, Cibulskis K, Connolly KM, Covarrubias M, Donnelly S, Ferriera S, Gabriel S, Gentry J, Gupta N, Jeandet T, Kaplan D, Llanwarne C, Munshi R, Novod S, Petrillo N, Roazen D, Ruano-Rubio V, Saltzman A, Schleicher M, Soto J, Tibbetts K, Tolonen C, Wade G, Talkowski ME, Aguilar Salinas CA, Ahmad T, Albert CM, Ardissino D, Atzmon G, Barnard J, Beaugerie L, Benjamin EJ, Boehnke M, Bonnycastle LL, Bottinger EP, Bowden DW, Bown MJ, Chambers JC, Chan JC, Chasman D, Cho J, Chung MK, Cohen B, Correa A, Dabelea D, Daly MJ, Darbar D, Duggirala R, Dupuis J, Ellinor PT, Elosua R, Erdmann J, Esko T, Färkkilä M, Florez J, Franke A, Getz G, Glaser B, Glatt SJ, Goldstein D, Gonzalez C, Groop L,



- Haiman C, Hanis C, Harms M, Hiltunen M, Holi MM, Hultman CM, Kallela M, Kaprio J, Kathiresan S, Kim BJ, Kim YJ, Kirov G, Kooner J, Koskinen S, Krumholz HM, Kugathasan S, Kwak SH, Laakso M, Lehtimäki T, Loos RJF, Lubitz SA, Ma RCW, MacArthur DG, Marrugat J, Mattila KM, McCarroll S, McCarthy MI, McGovern D, McPherson R, Meigs JB, Melander O, Metspalu A, Neale BM, Nilsson PM, O'Donovan MC, Ongur D, Orozco L, Owen MJ, Palmer CNA, Palotie A, Park KS, Pato C, Pulver AE, Rahman N, Remes AM, Rioux JD, Ripatti S, Roden DM, Saleheen D, Salomaa V, Samani NJ, Scharf J, Schunkert H, Shoemaker MB, Sklar P, Soininen H, Sokol H, Spector T, Sullivan PF, Suvisaari J, Tai ES, Teo YY, Tiinamäija T, Tsuang M, Turner D, Tusie-Luna T, Vartiainen E, Vawter MP, Ware JS, Watkins H, Weersma RK, Wessman M, Wilson JG, Xavier RJ, Neale BM, Daly MJ, MacArthur DG. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 2020;**581**:434–443.
23. Gray B, Semsarian C. Utility of genetic testing in athletes. *Clin Cardiol* 2020;**43**: 915–920.
  24. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesseling JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2020;**42**:17–96.
  25. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation* 2009;**119**:1085–1092.
  26. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA* 2006;**296**:1593–1601.
  27. Finocchiaro G, Papadakis M, Robertus JL, Dhutia H, Steriotis AK, Tome M, Mellor G, Merghani A, Malhotra A, Behr E, Sharma S, Sheppard MN. Etiology of sudden death in sports: insights from a United Kingdom Regional Registry. *J Am Coll Cardiol* 2016;**67**:2108–2115.
  28. Dennis M, Elder A, Semsarian C, Orchard J, Brouwer I, Puranik R. A 10-year review of sudden death during sporting activities. *Heart Rhythm* 2018;**15**:1477–1483.
  29. Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, La Gerche A, Ackerman MJ, Borjesson M, Salerno JC, Asif IM, Owens DS, Chung EH, Emery MS, Froelicher VF, Heidbuchel H, Adamuz C, Asplund CA, Cohen G, Harmon KG, Marek JC, Molossi S, Niebauer J, Pelto HF, Perez MV, Riding NR, Saarel T, Schmied CM, Shipon DM, Stein R, Vetter VL, Pelliccia A, Corrado D. International recommendations for electrocardiographic interpretation in athletes. *Eur Heart J* 2018;**39**: 1466–1480.
  30. Dagradi F, Spazzolini C, Castelletti S, Pedrazzini M, Kotta M-C, Crotti L, Schwartz PJ. Exercise training-induced repolarization abnormalities masquerading as congenital long QT syndrome. *Circulation* 2020;**142**:2405–2415.
  31. Heidbuchel H, Arbelo E, D'Ascenzi F, Borjesson M, Boveda S, Castelletti S, Miljoen H, Mont L, Niebauer J, Papadakis M, Pelliccia A, Saenen J, Sanz de la Garza M, Schwartz PJ, Sharma S, Zeppenfeld K, Corrado D. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part 2: ventricular arrhythmias, channelopathies, and implantable defibrillators. *Europace* 2020;**23**:147–148.
  32. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, Dougherty K, Harrison SM, McGlaughon J, Milko LV, Morales A, Seifert BA, Strande N, Thomson K, Peter van Tintelen J, Wallace K, Walsh R, Wells Q, Whiffin N, Witkowski L, Semsarian C, Ware JS, Hershberger RE, Funke B. Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med* 2019;**12**: e002460.
  33. Adler A, Novelli V, Amin AS, Abiusi E, Care M, Nannenber EA, Feilotter H, Amenta S, Mazza D, Bikker H, Sturm AC, Garcia J, Ackerman MJ, Hershberger RE, Perez MV, Zareba W, Ware JS, Wilde AAM, Gollob MH. An international, multicentered, an international, multicentered, evidence-based reappraisal of genes reported to cause congenital long QT syndrome. *Circulation* 2020;**141**:418–428.
  34. Hosseini SM, Kim R, Udupa S, Costain G, Jobling R, Liston E, Jamal SM, Szybowska M, Morel CF, Bowdin S, Garcia J, Care M, Sturm AC, Novelli V, Ackerman MJ, Ware JS, Hershberger RE, Wilde AAM, Gollob MH. Reappraisal of reported genes for sudden arrhythmic death. *Circulation* 2018;**138**:1195–1205.
  35. Rivera-Muñoz EA, Milko LV, Harrison SM, Azzariti DR, Kurtz CL, Lee K, Mester JL, Weaver MA, Currey E, Craigen W, Eng C, Funke B, Hegde M, Hershberger RE, Mao R, Steiner RD, Vincent LM, Martin CL, Plon SE, Ramos E, Rehm HL, Watson M, Berg JS. ClinGen variant curation expert panel experiences and standardized processes for disease and gene-level specification of the ACMG/AMP guidelines for sequence variant interpretation. *Hum Mutat* 2018;**39**:1614–1622.
  36. Kelly MA, Caleshu C, Morales A, Buchan J, Wolf Z, Harrison SM, Cook S, Dillon MW, Garcia J, Haverfield E, Jongbloed JDH, Macaya D, Manrai A, Orland K, Richard G, Spoonamore K, Thomas M, Thomson K, Vincent LM, Walsh R, Watkins H, Whiffin N, Ingles J, van Tintelen JP, Semsarian C, Ware JS, Hershberger R, Funke B. Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen's inherited cardiomyopathy expert panel. *Genet Med* 2018;**20**:351–359.
  37. Furqan A, Arscott P, Girolami F, Cirino AL, Michels M, Day SM, Olivetto I, Ho CY, Ashley E, Green EM, Caleshu C. Care in specialized centers and data sharing increase agreement in hypertrophic cardiomyopathy genetic test interpretation. *Circ Cardiovasc Genet* 2017;**10**:e001700.
  38. Das K J, Ingles J, Bagnall RD, Semsarian C. Determining pathogenicity of genetic variants in hypertrophic cardiomyopathy: importance of periodic reassessment. *Genet Med* 2014;**16**:286–293.
  39. Luiten RC, Ormond K, Post L, Asif IM, Wheeler MT, Caleshu C. Exercise restrictions trigger psychological difficulty in active and athletic adults with hypertrophic cardiomyopathy. *Open Heart* 2016;**3**:e000488.
  40. Subas T, Luiten R, Hanson-Kahn A, Wheeler M, Caleshu C. Evolving decisions: perspectives of active and athletic individuals with inherited heart disease who exercise against recommendations. *J Genet Couns* 2018;**28**:119–129.
  41. Asif IM, Price D, Fisher LA, Zakrajsek RA, Larsen LK, Raabe JJ, Bejar MP, Rao AL, Harmon KG, Drezner JA. Stages of psychological impact after diagnosis with serious or potentially lethal cardiac disease in young competitive athletes: a new model. *J Electrocardiol* 2015;**48**:298–310.
  42. Ingles J, Yeates L, Semsarian C. The emerging role of the cardiac genetic counselor. *Heart Rhythm* 2011;**8**:1958–1962.
  43. Ingles J. Psychological issues in managing families with inherited cardiovascular diseases. *Cold Spring Harb Perspect Med* 2020;**10**:a036558.
  44. Ingles J, Spinks C, Yeates L, McGeechan K, Kasparian N, Semsarian C. Posttraumatic stress and prolonged grief after the sudden cardiac death of a young relative. *JAMA Intern Med* 2016;**176**:402–405.
  45. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H. 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.
  46. Hamang A, Eide GE, Rokne B, Nordin K, Øyen N. General anxiety, depression, and physical health in relation to symptoms of heart-focused anxiety- a cross sectional study among patients living with the risk of serious arrhythmias and sudden cardiac death. *Health Qual Life Outcomes* 2011;**9**:100.
  47. Johnson JN, Ackerman MJ. Competitive sports participation in athletes with congenital long QT syndrome. *JAMA* 2012;**308**:764–765.
  48. Johnson JN, Ackerman MJ. Return to play? Athletes with congenital long QT syndrome. *Br J Sports Med* 2013;**47**:28–33.
  49. Tobert KE, Bos JM, Garmany R, Ackerman MJ. Return-to-play for athletes with long QT syndrome or genetic heart diseases predisposing to sudden death. *J Am Coll Cardiol* 2021;**78**:594–604.
  50. Sarquella-Brugada G, Campuzano O, Iglesias A, Sánchez-Malagón J, Guerra-Balic M, Brugada J, Brugada R. Genetics of sudden cardiac death in children and young athletes. *Cardiol Young* 2013;**23**:159–173.
  51. Authors/Task Force members, Elliott PM, Anastakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
  52. Levine BD, Baggish AL, Kovacs RJ, Link MS, Maron MS, Mitchell JH. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task force 1: Classification of Sports: Dynamic, static, and impact: a scientific statement from the American Heart Association and American College of Cardiology. *J Am Coll Cardiol* 2015;**66**:2350–2355.
  53. Pelliccia A, Solberg EE, Papadakis M, Adami PE, Biffi A, Caselli S, La Gerche A, Niebauer J, Pressler A, Schmied CM, Serratos L, Halle M, Van Buuren F, Borjesson M, Carrè F, Panhuyzen-Goedkoop NM, Heidbuchel H, Olivetto I, Corrado D, Sinagra G, Sharma S. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2019;**40**:19–33.
  54. Burn J, Brennan P, Little J, Holloway S, Coffey R, Somerville J, Dennis NR, Allan L, Arnold R, Deanfield JE, Godman M, Houston A, Keeton B, Oakley C, Scott O, Silove E, Wilkinson J, Pembrey M, Hunter AS. Recurrence risks in offspring of adults

- with major heart defects: results from first cohort of British collaborative study. *Lancet* 1998;**351**:311–316.
55. McElhinney DB, Geiger E, Blinder J, Woodrow Benson D, Goldmuntz E. NKX2.5 mutations in patients with congenital heart disease. *J Am Coll Cardiol* 2003;**42**:1650–1655.
  56. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M, Carré F, Sharma S. Clinical profile of athletes with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging* 2015;**8**:e003454.
  57. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med* 1991;**324**:295–301.
  58. Papadakis M, Basavarajiah S, Rawlins J, Edwards C, Makan J, Firoozi S, Carby L, Sharma S. Prevalence and significance of T-wave inversions in predominantly Caucasian adolescent athletes. *Eur Heart J* 2009;**30**:1728–1735.
  59. Papadakis M, Carre F, Kervio G, Rawlins J, Panoulas VF, Chandra N, Basavarajiah S, Carby L, Fonseca T, Sharma S. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. *Eur Heart J* 2011;**32**:2304–2313.
  60. Sheikh N, Papadakis M, Wilson M, Malhotra A, Adamuz C, Homfray T, Monserrat L, Behr ER, Sharma S. Diagnostic yield of genetic testing in young athletes with T-wave inversion. *Circulation* 2018;**138**:1184–1194.
  61. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal J-M, Androulakis AFA, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016;**68**:2299–2307.
  62. McNair WP, Sinagra G, Taylor MRG, Di Lenarda A, Ferguson DA, Salcedo EE, Slavov D, Zhu X, Caldwell JH, Mestroni L. SCN5A mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. *J Am Coll Cardiol* 2011;**57**:2160–2168.
  63. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, Padrón-Barthe L, Duro-Aguado I, Jiménez-Jáimez J, Hidalgo-Olivares VM, García-Campo E, Lanzillo C, Suárez-Mier MP, Yonath H, Marcos-Alonso S, Ochoa JP, Santomé JL, García-Giustiniani D, Rodríguez-Garrido JL, Domínguez F, Merlo M, Palomino J, Peña ML, Trujillo JP, Martín-Vila A, Stolfo D, Molina P, Lara-Pezzi E, Calvo-Iglesias FE, Nof E, Calò L, Barriales-Villa R, Gimeno-Blanes JR, Arad M, García-Pavía P, Monserrat L. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol* 2016;**68**:2440–2451.
  64. Castelletti S, Vischer AS, Syrris P, Crotti L, Spazzolini C, Ghidoni A, Parati G, Jenkins S, Kotta M-C, McKenna WJ, Schwartz PJ, Pantazis A. Desmoplakin missense and non-missense mutations in arrhythmogenic right ventricular cardiomyopathy: genotype-phenotype correlation. *Int J Cardiol* 2017;**249**:268–273.
  65. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, Celeghein R, Edwards M, Fan J, Ingles J, James CA, Jarinova O, Johnson R, Judge DP, Lahrouchi N, Lekanne Deprez RH, Lumbers RT, Mazzarotto F, Medeiros Domingo A, Miller RL, Morales A, Murray B, Peters S, Pilichou K, Protonotarios A, Semsarian C, Shah P, Syrris P, Thaxton C, van Tintelen JP, Walsh R, Wang J, Ware J, Hershberger RE. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation* 2021;**144**:7–19.
  66. van den Hoogenhof MMG, Beqqali A, Amin AS, van der Made I, Aufiero S, Khan MAF, Schumacher CA, Jansweijer JA, van Spaendonck-Zwarts KY, Remme CA, Backs J, Verkerk AO, Baartscheer A, Pinto YM, Creemers EE. RBM20 mutations induce an arrhythmogenic dilated cardiomyopathy related to disturbed calcium handling. *Circulation* 2018;**138**:1330–1342.
  67. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, Mannarino S, Gambarin F, Favalli V, Grasso M, Agozzino M, Campana C, Gavazzi A, Febo O, Marini M, Landolina M, Mortara A, Piccolo G, Viganò M, Tavazzi L, Arbustini E. Long-term outcome and risk stratification in dilated cardiomyopathies. *J Am Coll Cardiol* 2008;**52**:1250–1260.
  68. Chevessier F, Schuld J, Orfanos Z, Plank A-C, Wolf L, Maerkens A, Unger A, Schlötzer-Schrehardt U, Kley RA, Von Hörsten S, Marcus K, Linke WA, Vorgerd M, van der Ven PFM, Fürst DO, Schröder R. Myofibrillar instability exacerbated by acute exercise in filaminopathy. *Hum Mol Genet* 2015;**24**:7207–7220.
  69. Corrado D, Perazzolo Marra M, Zorzi A, Boffagna G, Cipriani A, Lazzari MD, Migliore F, Pilichou K, Rampazzo A, Rigato I, Rizzo S, Thiene G, Anastakis A, Asimaki A, Bucciarelli-Ducci C, Haugaa KH, Marchlinski FE, Mazzanti A, McKenna WJ, Pantazis A, Pelliccia A, Schmiech C, Sharma S, Wichter T, Baucé B, Basso C. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol* 2020;**319**:106–114.
  70. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm M, Duboc D, Gimeno J, de Groot P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio ALP, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016;**37**:1850–1858.
  71. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;**348**:1866–1874.
  72. Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, Hauer RNW, Beckmann BM, Spazzolini C, Rordorf R, Rydberg A, Clur S-AB, Fischer M, van den Heuvel F, Käbb S, Blom NA, Ackerman MJ, Schwartz PJ, Wilde AAM. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2. *J Am Coll Cardiol* 2012;**60**:2092–2099.
  73. Schwartz PJ, Ackerman MJ. The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy. *Eur Heart J* 2013;**34**:3109–3116.
  74. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999;**99**:529–533.
  75. Goldenberg I, Horr S, Moss AJ, Lopes CM, Barsheshet A, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Platonov PG, Priori SG, Qi M, Schwartz PJ, Shimizu W, Towbin JA, Vincent GM, Wilde AAM, Zhang L. Risk for life-threatening cardiac events in patients with genotype-confirmed long-QT syndrome and normal-range corrected QT intervals. *J Am Coll Cardiol* 2011;**57**:51–59.
  76. D'Ascenzi F, Zorzi A, Alvino F, Bonifazi M, Corrado D, Mondillo S. The prevalence and clinical significance of premature ventricular beats in the athlete. *Scand J Med Sci Sports* 2017;**27**:140–151.
  77. Corrado D, Drezner JA, D'Ascenzi F, Zorzi A. How to evaluate premature ventricular beats in the athlete: critical review and proposal of a diagnostic algorithm. *Br J Sports Med* 2020;**54**:1142–1148.
  78. Novak J, Zorzi A, Castelletti S, Pantazis A, Rigato I, Corrado D, McKenna W, Lambiase PD. Electrocardiographic differentiation of idiopathic right ventricular outflow tract ectopy from early arrhythmogenic right ventricular cardiomyopathy. *Europace* 2016;**19**:622–628.
  79. Dominguez F, Zorio E, Jimenez-Jaimez J, Salguero-Bodes R, Zwart R, Gonzalez-Lopez E, Molina P, Bermúdez-Jiménez F, Delgado JF, Braza-Boils A, Bornstein B, Toquero J, Segovia J, Van Tintelen JP, Lara-Pezzi E, Garcia-Pavia P. Clinical characteristics and determinants of the phenotype in TMEM43 arrhythmogenic right ventricular cardiomyopathy type 5. *Heart Rhythm* 2020;**17**:945–954.
  80. Thuillot M, Maupain C, Gandjbakhch E, Waintraub X, Hidden-Lucet F, Isnard R, Ader F, Rouanet S, Richard P, Charron P. External validation of risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers. *Eur J Heart Fail* 2019;**21**:253–254.
  81. Cavigli L, Olivetto I, Fattiroli F, Mochi N, Favilli S, Mondillo S, Bonifazi M, D'Ascenzi F. Prescribing, dosing and titrating exercise in patients with hypertrophic cardiomyopathy for prevention of comorbidities: ready for prime time. *Eur J Prev Cardiol* 2021;**28**:1093–1099.
  82. Hasham SN, Lewin MR, Tran VT, Pannu H, Muilenburg A, Willing M, Milewicz DM. Nonsyndromic genetic predisposition to aortic dissection: a newly recognized, diagnosable, and preventable occurrence in families. *Ann Emerg Med* 2004;**43**:79–82.
  83. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwöger M, Haverich A, Jung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2873–2926.
  84. Verstraeten A, Luyckx I, Loeys B. Aetiology and management of hereditary aortopathy. *Nat Rev Cardiol* 2017;**14**:197–208.
  85. Guo D-c, Hostetler EM, Fan Y, Kulmacz RJ, Zhang D, Nickerson DA, Leal SM, LeMaire SA, Regalado ES, Milewicz DM. Heritable thoracic aortic disease genes in sporadic aortic dissection. *J Am Coll Cardiol* 2017;**70**:2728–2730.
  86. Ostberg N, Zafar M, Ziganshin B, Elefteriades J. The genetics of thoracic aortic aneurysms and dissection: a clinical perspective. *Biomolecules* 2020;**10**:182.
  87. Iskandar A, Thompson PD. A meta-analysis of aortic root size in elite athletes. *Circulation* 2013;**127**:791–798.
  88. Pelliccia A, Di Paolo FM, De Blasiis E, Quattrini FM, Pisicchio C, Guerra E, Culasso F, Maron BJ. Prevalence and clinical significance of aortic root dilation in highly trained competitive athletes. *Circulation* 2010;**122**:698–706, 3 p following 706.