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Review Article

Update in the genetic causes of sudden cardiac death

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A B S T R A C T

Sudden cardiac death (SCD) is a devastating complication of several different cardiovascular disorders. Over the age of 40 years the most common cause of SCD is due to coronary artery disease and myocardial infarction. In the young under the age of 40 years, inherited/genetic cardiovascular disorders are more common, including the inherited arrhythmia syndromes and the primary cardiomyopathies. Detailed evaluation of the premorbid clinical history, including a detailed family history, and comprehensive expert postmortem examination is essential. In SCD cases where no cause of death is identified at postmortem, a "molecular autopsy", i.e. genetic testing of a blood or tissue sample collected at postmortem, should be performed, with the aim of identifying a pathological genetic variant that would account for the death of the decedent, i.e. the cause of death. Establishing a cause of SCD can provide a degree of psychological relief for loved ones by providing answers and relieving uncertainty. Furthermore, clinical and genetic screening of family members is essential in the prevention of adverse clinical outcomes and SCD events in surviving relatives. Care should ideally be provided in a specialized multidisciplinary clinic setting, and this model of care should be supported and developed in countries where such services do not currently exist, reducing racial disparities and overcoming socioeconomic factors. Newer genetic and molecular developments may further improve and refine our diagnostic and management strategies with the ultimate goal to prevent SCD in our communities.

1. Introduction

Sudden cardiac death (SCD), a tragic complication of many cardiovascular diseases, is often unexpected and occurs in apparently fit and healthy individuals across the age spectrum, with no history of symptoms or disease.[1,2] SCD is defined as a death occurring usually within an hour of the onset of symptoms, due to an underlying cardiac disease. The prevalence of SCD is significant, with up to 350,000 cases each year in the USA, translating to 950 deaths per day or one death every 1.5 min.[3] While the causes of SCD over the age of 40 years are dominated by ischaemic heart disease secondary to coronary artery disease, inherited (genetic) cardiac disorders, such as structural heart diseases (including the cardiomyopathies) and primary electrical diseases, are the predominant causes of SCD in the young aged under 40 years.

This review provides a summary of the role of inherited cardiac diseases as a cause of SCD, primarily in the young. The review highlights the importance of identifying a cause of SCD in the victim, the key role of post-mortem genetic testing, the so-called "molecular autopsy", and the importance of clinical and genetic screening in the family. Establishing a cause of SCD can provide a degree of psychological relief for loved ones by providing answers and relieving uncertainty, and it also targets the evaluation of surviving relatives aimed at preventing further SCD events in families. This multidisciplinary approach to care is discussed in the setting of racial disparities and socioeconomic challenges in trying to deliver this life-saving service on a global scale.

2. Causes of sudden cardiac death in the young

The cause of SCD strongly depends on the individual's age. In the young (range varies from < 35 years of age to < 50 years of age) monogenetic or near monogenic diseases dominate and these causes are generally subdivided into 'primary electrical diseases', such as congenital Long QT syndrome (LQTS) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and 'structural heart disease', including the inherited cardiomyopathies.[1,4–8] Coronary artery disease is almost absent in the very young but plays an increasing role in the age group between 35 and 50 years.[5,7,9] (Fig. 1) The yield of establishing a diagnosis is highest in the youngest age group, i.e. 1-10 years, where it may reach 60%, which is similar to the investigation of an out-of-hospital cardiac arrest victim of that age.[10] In this 1-10 years age group, electrical syndromes are identified.[5,10]

Despite extensive investigation after SCD, including toxicologic testing and expert pathological examination, 30-40% of sudden death cases remain unexplained, often referred to as "autopsy negative".[1,2,5] Recent studies suggest that in a sizable subset of this population, pathogenic variants in the cardiomyopathy genes are identified leading to

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the concept of a 'concealed cardiomyopathy' as the cause of death.[11,12] More importantly, within this sub-cohort, primary arrhythmia syndromes are prevalent and these cases (and those with a concealed cardiomyopathy) may be unmasked by performing a molecular autopsy, or by family screening, or both. The combined yield is up to 40%.[13] In the earlier studies the yield may have been over-estimated but with the more stringent ACMG criteria[14] the yield is in the range mentioned. Importantly, this includes active screening of 1st degree and 2nd degree family members of the decedent. In those cases where all other causes are excluded, Idiopathic Ventricular Fibrillation (IVF) is the category that remains. IVF is thus defined as 'a resuscitated cardiac arrest victim with a normal ECG, preferably with documentation of VF, in whom known cardiac, respiratory, metabolic, and toxicological causes have been excluded' through clinical evaluation. By definition this means that this cause can only be established in a cardiac arrest survivor.

3. Genetic testing in sudden death: the molecular autopsy

As mentioned, the term "molecular autopsy" is used to describe the genetic analysis of postmortem blood or tissue in cases of SCD that remain unexplained following conventional autopsy.[15] Early applications of genetic analysis following unexplained SCD focused on small panels of genes. Genetic analysis typically included the three most common genes implicated in congenital long QT syndrome (*KCNQ1*, *KNCH2*, *SCN5A)* and the ryanodine receptor gene (*RYR2*) known to cause CPVT.[16]

The rapid emergence of high throughput DNA sequencing techniques has led to an explosion in availability of genetic data. Large scale sequencing, from cardiac panels (usually 50-100 cardiac genes), through to whole exome and genome sequencing, has now been applied to unexplained SCD cohorts, shedding new light on the molecular drivers of these tragic events.[17–19] This includes the high rate of pathogenic variants found in genes implicated in inherited cardiomyopathies, which account for up to 70% of clinically-actionable disease-causing variants in unexplained SCD.[12,13,20,21] While genes implicated in arrhythmogenic cardiomyopathy (ACM), an entity which encompasses classical arrhythmogenic right ventricular cardiomyopathy (ARVC), as well as the more recently described left ventricular dominant arrhythmogenic cardiomyopathy, appear to predominate in unexplained SCD, disease-causing variants in hypertrophic and dilated cardiomyopathy genes are also seen in cases of SCD without overt structural phenotypes at autopsy. This phenomenon of malignant arrhythmia occurring in the absence of detectable structural changes in the inherited cardiomyopathies has been termed "*concealed cardiomyopathy*", as mentioned in the previous section.[12,22] Broadening of the molecular autopsy to include cardiomyopathy-associated genes has been shown to increase rates of diagnosis by revealing concealed cardiomyopathy where conventional arrhythmia syndrome-focused genetic testing has failed to reveal a cause.[19,22–24].

Importantly, comprehensive molecular autopsy (including primary arrhythmia and inherited cardiomyopathy associated genes) directly impacts the care of surviving relatives. It allows personalised care and targeted risk mitigation in genotype-positive relatives and reassurance and release of genotype-negative relatives from long-term follow-up. Updated guidelines and consensus documents recognise the emerging entity of concealed cardiomyopathy and now recommend a molecular autopsy that includes genes implicated in both inherited cardiomyopathy and the primary arrhythmia syndromes.[23] Fig. 2 presents a schema locating the comprehensive molecular autopsy within the holistic approach to caring for families who have experienced a SCD.

4. Management of sudden cardiac death families

4.1. Investigation of the decedent

Unraveling the cause of sudden death in a young individual relies on the three currently available post-mortem investigation tools namely autopsy, toxicology and genetics. The role of an autopsy is to identify unnatural causes of death, to differentiate between cardiac and non-cardiac causes of natural death and identification of potentially inherited causes of SCD and is best performed by an expert in cardiac pathology. Both macroscopic and microscopic cardiac examination,

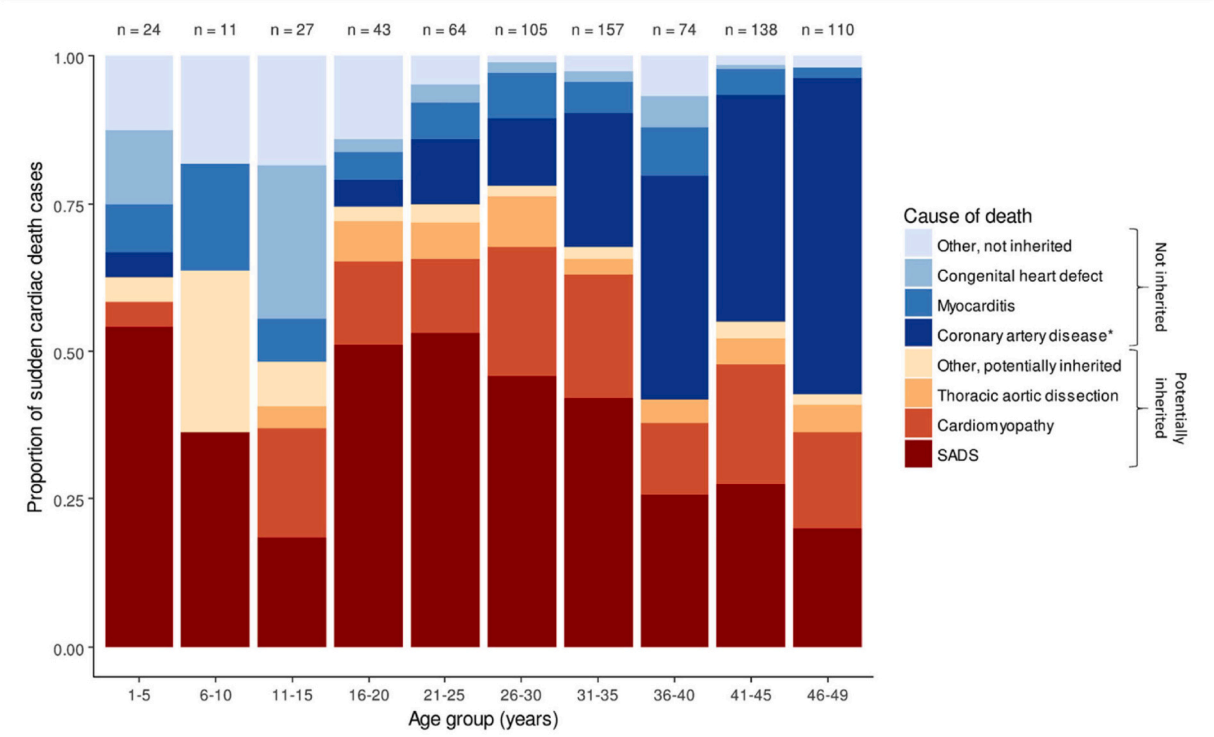

Fig. 1. Causes of sudden cardiac death and Age.

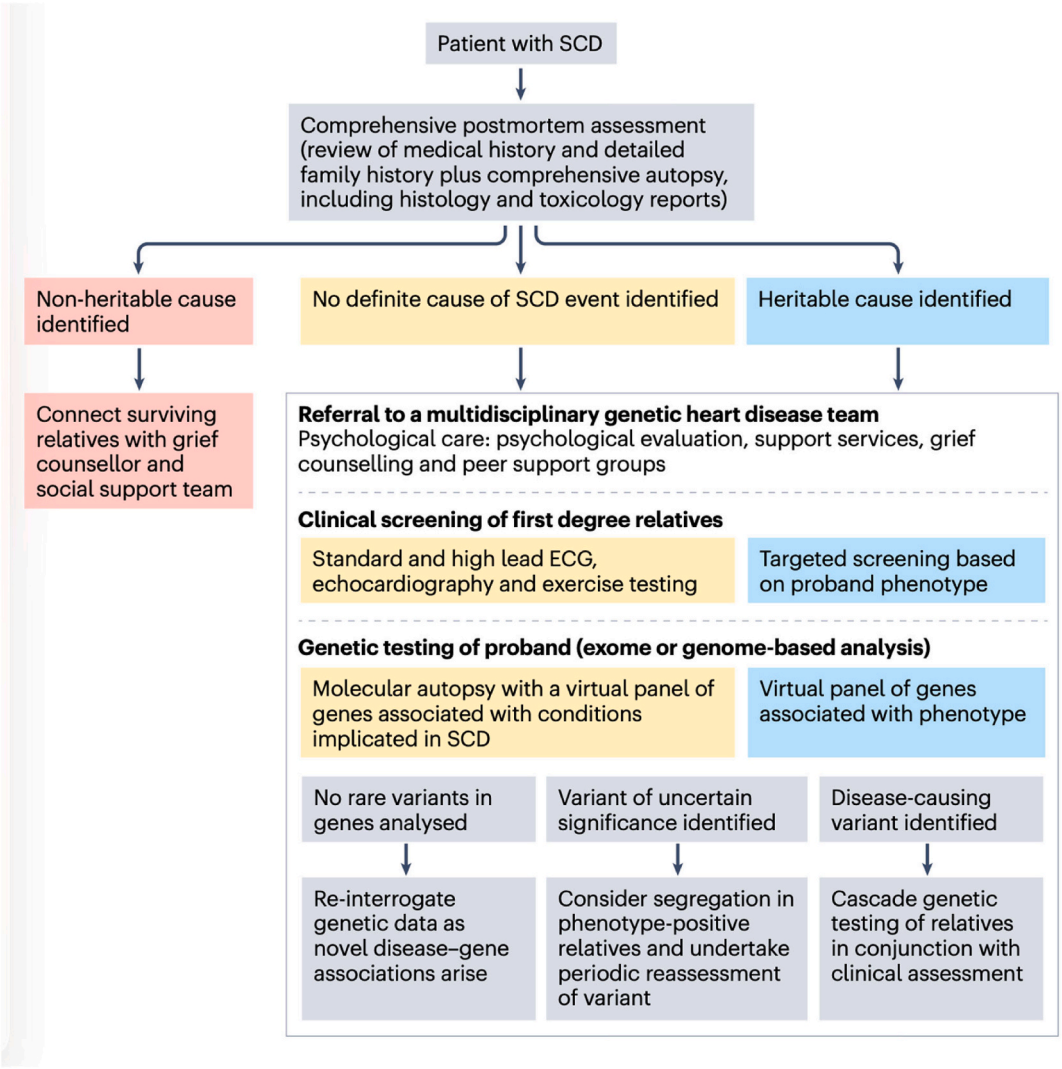

Fig. 2. Pathways for SCD investigation in decedent and family.

including conduction system and coronary artery sampling, should be carried out during the autopsy.[25,26]

Conventional autopsy will identify structural heart diseases like cardiomyopathies, aortopathies and premature coronary artery disease, all of which could have a genetic etiology, and therefore blood and tissue should be secured for targeted disease-specific genetic testing.[27] Toxicology investigation, in general, determines the ethanol level in peripheral blood and screens for common drugs and illegal substances.[28] When the cause of death remains unexplained after autopsy and toxicological examination, primary arrhythmogenic disorders should be suspected and followed up with molecular autopsy with arrhythmia-syndrome focused genetic testing, as shown in Figs. 2 and 3.

A comprehensive history, including a detailed medical history of the decedent, particularly circumstances of death if witnessed, past medical history and associated medical records, and at least a three-generational family history to identify other potentially affected members, is the essential and fundamental basis of diagnosing the cause of death in a SCD victim.[29] Table 1 summarizes some of the diagnostic clues that the circumstances of death may reveal.

Post-mortem genetic testing of SCD victims requires saved samples of one of the following three: a small piece of fresh frozen heart, a small piece of fresh frozen spleen/liver/thymus, and EDTA blood.[29] Pathogenic (P) and likely pathogenic (LP) variants, when identified, help confirm the diagnosis and should be utilized for targeted genetic testing of surviving family members.[30] On the other hand, variants of uncertain significance (VUS) may not be directly applied in family screening but should be corroborated with the phenotypic profiles of first degree and extended relatives and may subsequently assist with reclassification of the VUS to either pathogenic or benign, especially in populations like in India and other developing countries where reference genetic information is sparse.[31] Periodic re-assessment of all variants classified as LP and VUS is recommended.[32] **It should be noted that false positive and negative results can occur, and is influenced by many factors, including the type of DNA source being used (i.e. blood vs frozen tissue vs paraffin-embedded samples), as well as the methodology of genetic testing (i.e. panels vs exome vs genome testing).**

4.2. *Management of the surviving family*

The sudden death of a young and apparently healthy individual, irrespective of the cause of death, leaves the surviving family members devastated. While physicians, forensic experts and coroners should proceed investigating based on established protocols to get closure on the case at the earliest time, it is important to show empathy to the bereaved, share the developments at every stage of the diagnostic process, and provide counseling support and refer to a psychologist when needed.[29]

The other main task is identifying first-degree relatives (parents,

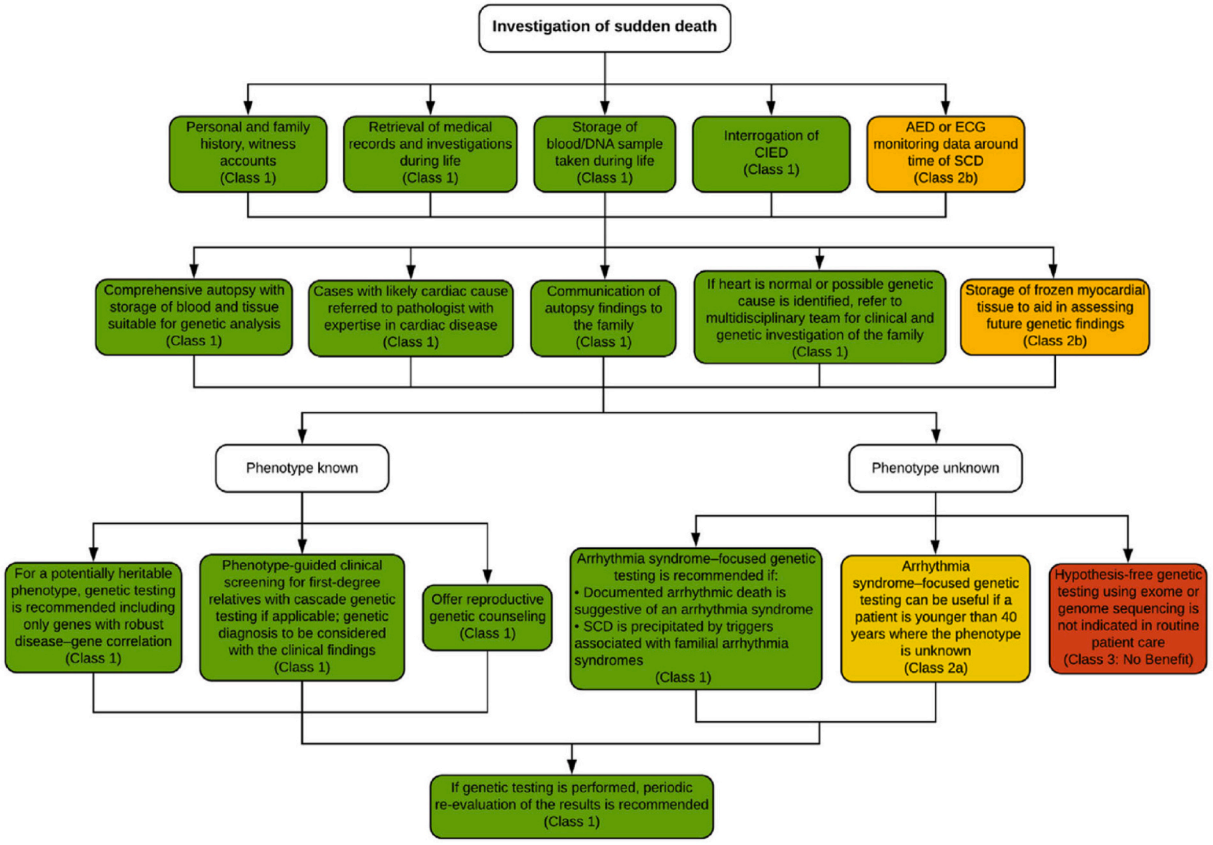

Fig. 3. Investigation flowchart of SCD.

Table 1
Potential diagnostic clues from medical history.

Circumstance of death	Likely cause of death	Next steps
• Exercise • Physical activity	LQTS, CPVT, HCM	Molecular autopsy
• Emotional stress • Acoustic trigger	LQTS	Molecular autopsy
• Febrile episode • Medication related	BrS, LQTS	Molecular autopsy
• Unexplained epilepsy • Drowning in good swimmers • Unexplained motor vehicle accidents	Arrhythmogenic disease ACM	Molecular autopsy

NB: LQTS, Long QT syndrome; CPVT, Catecholaminergic polymorphic ventricular tachycardia; BrS, Brugada syndrome; ACM, Arrhythmogenic cardiomyopathy; HCM, Hypertrophic cardiomyopathy.

siblings, children) of the deceased who may be at imminent risk of SCD. When the diagnosis has been established in the deceased, a disease-focused cascade screening should be undertaken in the relatives with imaging, provocative testing and targeted genetic testing. In situations where there is no clear diagnosis in the deceased after a thorough investigation or in case of lost opportunity to perform a complete investigation, including unavailability of stored sample of the deceased for genetic testing, the next of kin with phenotype positive findings on clinical screening may be considered as the proband and taken up for DNA testing to shed light on the diagnosis in that family. Clinical screening tests should include a medical history, standard and high precordial lead ECG, 2D-echocardiography, and exercise test, with select use of pharmacological provocation and advanced imaging (Fig. 4).[33]

Pre- and post-test genetic counseling by an experienced genetic counselor, or in some cases, experienced cardiologists or nurses, is an essential aspect of the genetic testing process, with an aim of pre-test counseling to discuss the nature of the test, its potential outcomes and their implications for the further management of the patient, and of post-test counseling to explain in lay terms the results and what it means for the concerned individual and their family, using the opportunity to address their emotional needs.[30]

In families with genetically affected individuals, family planning counseling should be offered, keeping in mind the implications of decreased penetrance and variable expression.[34] Invasive prenatal testing including amniocentesis or chorionic villus sampling may be employed to test the fetus for single-gene diseases that the family is known to have. Both test modalities are performed in different stages of pregnancy and carry a small risk of procedure-related pregnancy loss.[35] Preimplantation genetic testing, carried out on embryos to identify embryos with a monogenic disorder, helps families reduce the risk of conceiving a child with the familial condition. Centers specialized in reproductive risk counseling and testing should be entrusted with the care of individuals, and couples seeking prenatal diagnosis and preimplantation genetic testing as they are equipped to impart the most accurate information and provide expert services.[29,30,36]

4.3. Role of a specialized multidisciplinary team

Given the complexity involved in investigating SCD victims and screening their family, spanning several medical and paramedical specialties such as clinical cardiology, electrophysiology, pediatrics, pathology, forensic department, radiology, toxicology, psychology, genetics, genetic counseling, nursing and potentially obstetrics when preimplantation genetic testing is warranted, it is imperative to develop a multidisciplinary team that can act as a referral unit for managing affected families in a comprehensive manner. International guidelines and consensus documents recommend that genetic and clinical testing should be undertaken by a multidisciplinary team with professionals

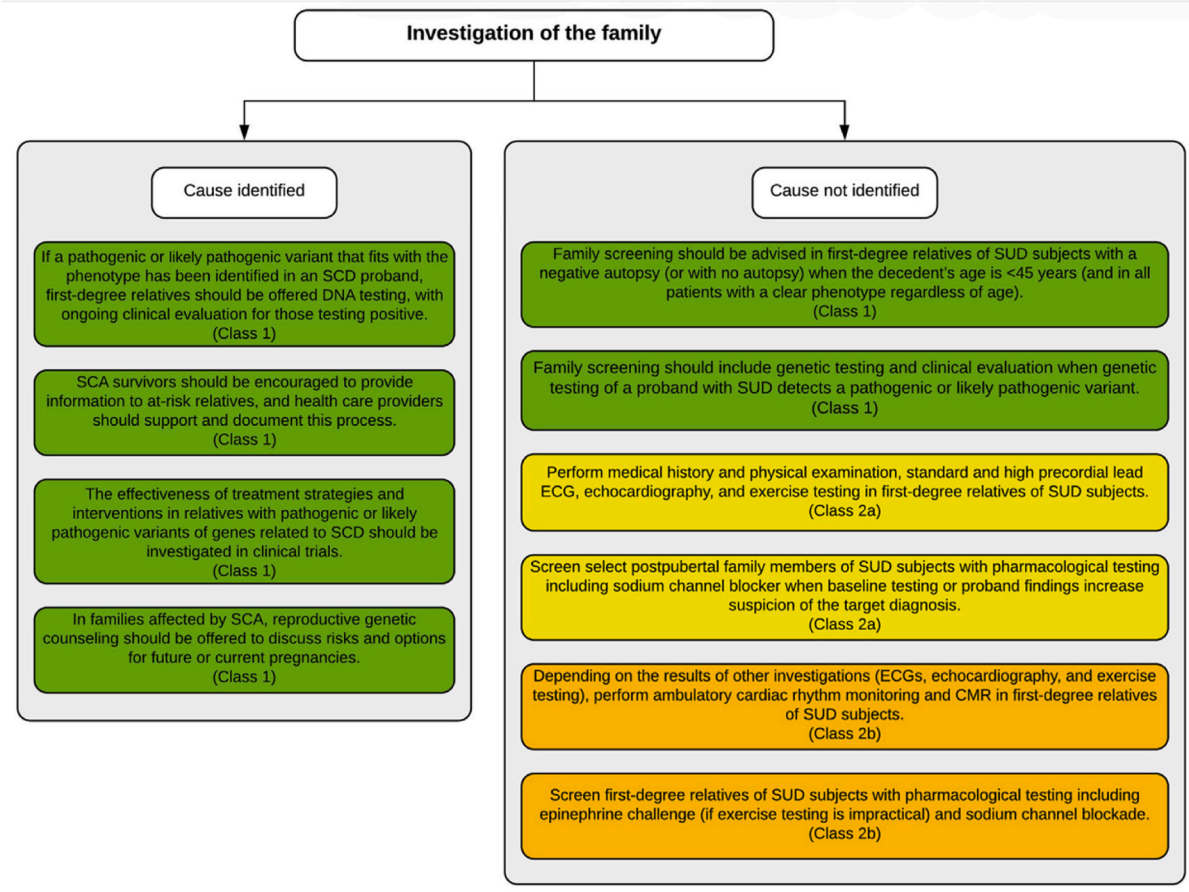

Fig. 4. Investigation flowchart for the family of SCD victims.

capable of counseling on the implications of the test, experienced cardiologists able to direct testing to the identified phenotype, and capacity to liaise with noncardiac specialists (Fig. 5).[29,33,37] Multidisciplinary team meetings should be held frequently, either physically or virtually, to communicate and coordinate the work carried out by the involved specialists who may be working in different geographic locations and institutions.[23,29]

5. Racial disparities and socioeconomic challenges

"Cardiogenetics", as the name implies, is the field of medicine dealing with genetic disorders of the heart, and has at its core, cardiologists, clinical geneticists and genetic counselors collaboratively caring for affected individuals and their families. The wealth of information and the depth of literature available in the domain today is primarily due to the immense developments in both cardiology and genetics over the past three to four decades.[38] Research-driven clinical care and registry-based knowledge sharing have propelled the field forward in developed countries, resulting in most of the available genetic information coming from data in White Europeans. While developing countries are currently catching up on the advances in the field and realizing the role of genetic testing in the diagnostic, prognostic and therapeutic aspects of inherited cardiac conditions, the focus needs to shift towards prevention of young SCD through a multidisciplinary team approach. A recent position statement by the Cardiological Society of India covers key aspects of genetic counseling and testing for cardiomyopathies and the need for a multidisciplinary team to handle SCD cases and family screening effectively.[39,40]

News coverage of the death of an apparently healthy athlete while running a marathon, SCD of a high school child during school hours, youngsters collapsing while at work and actors and models dying suddenly are unfortunately only getting brief attention in the media and fail to see the light of systematic investigation, ending up as missed opportunities to nail the diagnosis and identify at-risk family members.[40] While premature coronary artery disease is a huge threat in India, sudden unexplained SCD constitute a considerable proportion of young sudden deaths.

A recent study carried out at a tertiary referral center in North India in 59 young (18-45 years) autopsied SCD cases over a period of 4 years, showed 29% were due to coronary artery disease, 25% due to cardiomyopathies, 36% were unexplained SCD, and the remaining 10% due to congenital and other causes.[41] Whole exome sequencing identified genetic variants in 43% of unexplained SCD cases, with concealed cardiomyopathy related genes accounting for the majority (78%) and channelopathy-associated genes in 22%. Of the 18 cases with positive findings on genetic testing, P/LP variants were identified in 5 (28%) and the remaining were VUS. Another recent study on 41 Chinese SCD cases aged 1-40 years that underwent molecular autopsy at a single center in Hong Kong identified P/LP variants in ~10% and VUS in 17%, with a higher yield of LP variants in cases with a postmortem diagnosis of established cardiomyopathy compared with cases without structural causes identified.[40] The authors report that in Hong Kong, all young SCD cases are referred to coroners and hence the majority undergo an autopsy examination. Both the above studies have indicated the inability to perform systematic family screening as a major limitation, and a key aspect of family management and prevention of future SCD events.

The yield of genetic testing in SCD victims and their relatives, that includes deriving a certain or a probable diagnosis, is in the range of 15-40% in developed countries like The Netherlands, USA, Denmark, UK and Australia, where it is mandatory to perform guideline-based postmortem investigations in SCD.[1,5,42–44] In a recent systematic review and meta-analysis of 33 observational studies including approximately 1700

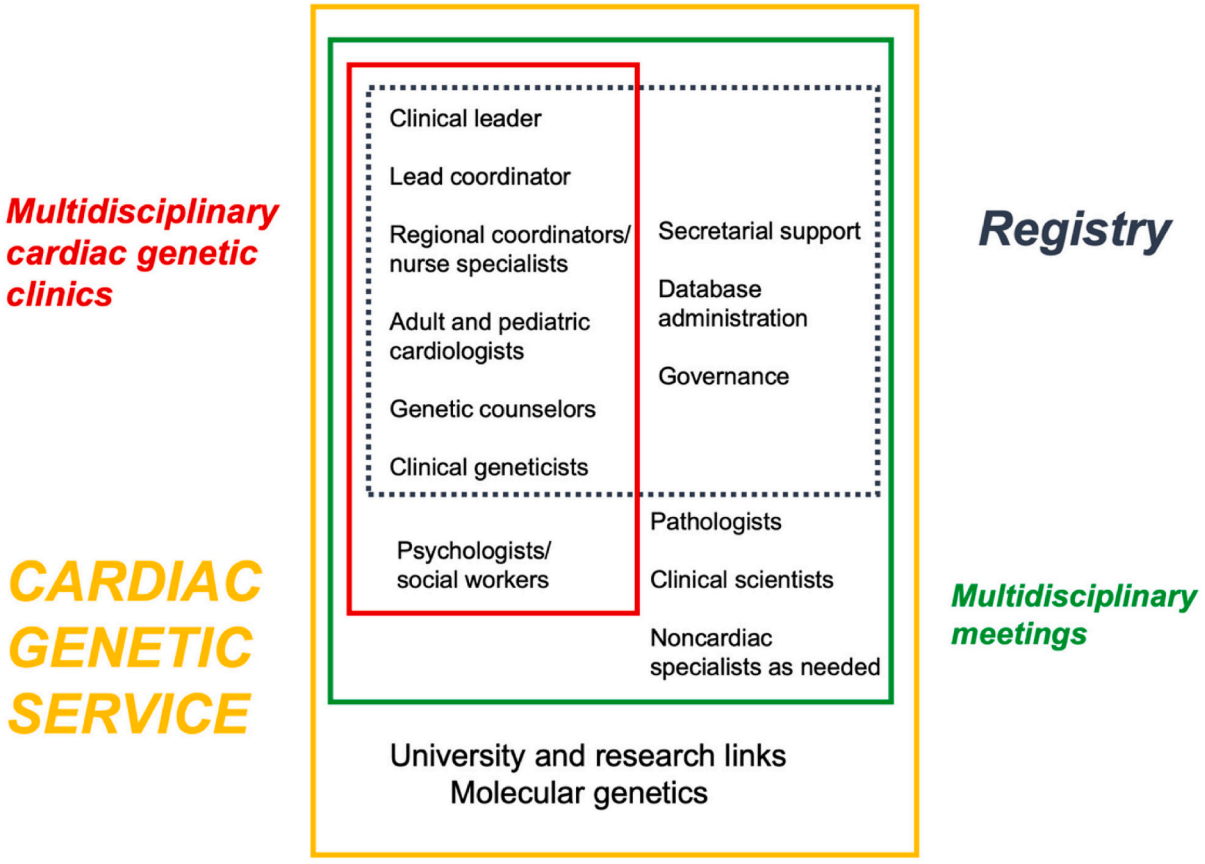

Fig. 5. Components of a multidisciplinary team.

sudden arrhythmic death syndrome (SADS) cases aged 1-50 years, P/LP variants in cardiomyopathy and channelopathy genes were identified in 11%.[45] In another study, in addition to reporting a diagnostic yield of 22% after molecular autopsy in 100 unrelated SCD cases in Czech Republic, the authors stated that in the course of the project cooperation, an expert group consisting of forensic pathologists, cardiologists, and cardiogeneticists was established with an aim to create Czech national autopsy guidelines based on European recommendations.[46]

An interesting insight into the multifactorial issues facing provision of multidisciplinary care in SCD families was reported in an elegant physician-based online questionnaire study in which 357 respondents from 69 European Society of Cardiology countries participated. Significant heterogeneity of genetic testing access and provision, issues attributable to the availability of dedicated cardiogenetics units, access to genetic laboratories, and complexities and availability of reimbursement.[47]

The key takeaway for clinicians is that the time is ripe for India and other developing countries, with an alarmingly high burden of SCD, to incorporate guideline-based genetic testing in suspicious cases, mandate clinical and molecular autopsy in unexplained young deaths, and invest in expert multidisciplinary teams that can function as referral centers across the country (Fig. 6), learning from and adopting the best practices from our Western counterparts. In parallel, establishing population-specific, genotype-phenotype databases is urgently needed to realize the full potential of genetic testing in different ethnic populations, and thereby reduce racial disparities in delivery of care.[48] Given that the cost of genetic testing has dropped dramatically from a decade ago, and with next generation sequencing (NGS) enabling much faster turnaround times of the test, India is well poised to realize its Cardiogenetic potential in the coming decade.[49]

6. Future directions

Based on the above it will have become clear that through molecular autopsy and active family screening, after an index SCD event, we are able, provided appropriate actions are taken, to prevent and protect a significant number of individuals from SCD in affected families. However, no apparent (genetic) cause is present in a large proportion of cases. Fortunately, in the vast majority of these families no further events occur.[50–52] This most likely indicates a non-inherited cause of the lethal arrhythmia in the index case of these families.

An alternative explanation is an additional genetic risk in the deceased or resuscitated individual. The identification of these extra genetic risk components, positively or negatively contributing to risk, has been less studied, and is now the topic of extensive research efforts. Most likely these extra genetic risk factors each harbor a low effect size but in aggregate they may tip the balance to either increased or decreased risk. Genetic studies in LQTS cohorts have served as a nice example of some of these recent developments. First, it was shown that the polygenic risk score (PRS, i.e. an aggregate of all genome-wide significant genetic loci associated with the QTc interval) was greater in genotype-negative compared with those who were genotype-positive and it was also greater in LQTS patients compared to controls.[53] This clearly indicates evidence for a polygenetic architecture in LQTS. Some of these additional risk factors may individually actually have a larger effect size,[54] and some of these may work in different directions in different LQTS genotypes.[55] And as such these variants may also contribute to risk,[55] although the study on the aggregate of variants with smaller effect size (i.e. the PRS) was not able to demonstrate this in either LQTS or Brugada syndrome cohorts.[53,56] In contrast, early data in hypertrophic cardiomyopathy seem to show that a PRS, including all genome wide significant SNP's, contributes to risk for development of

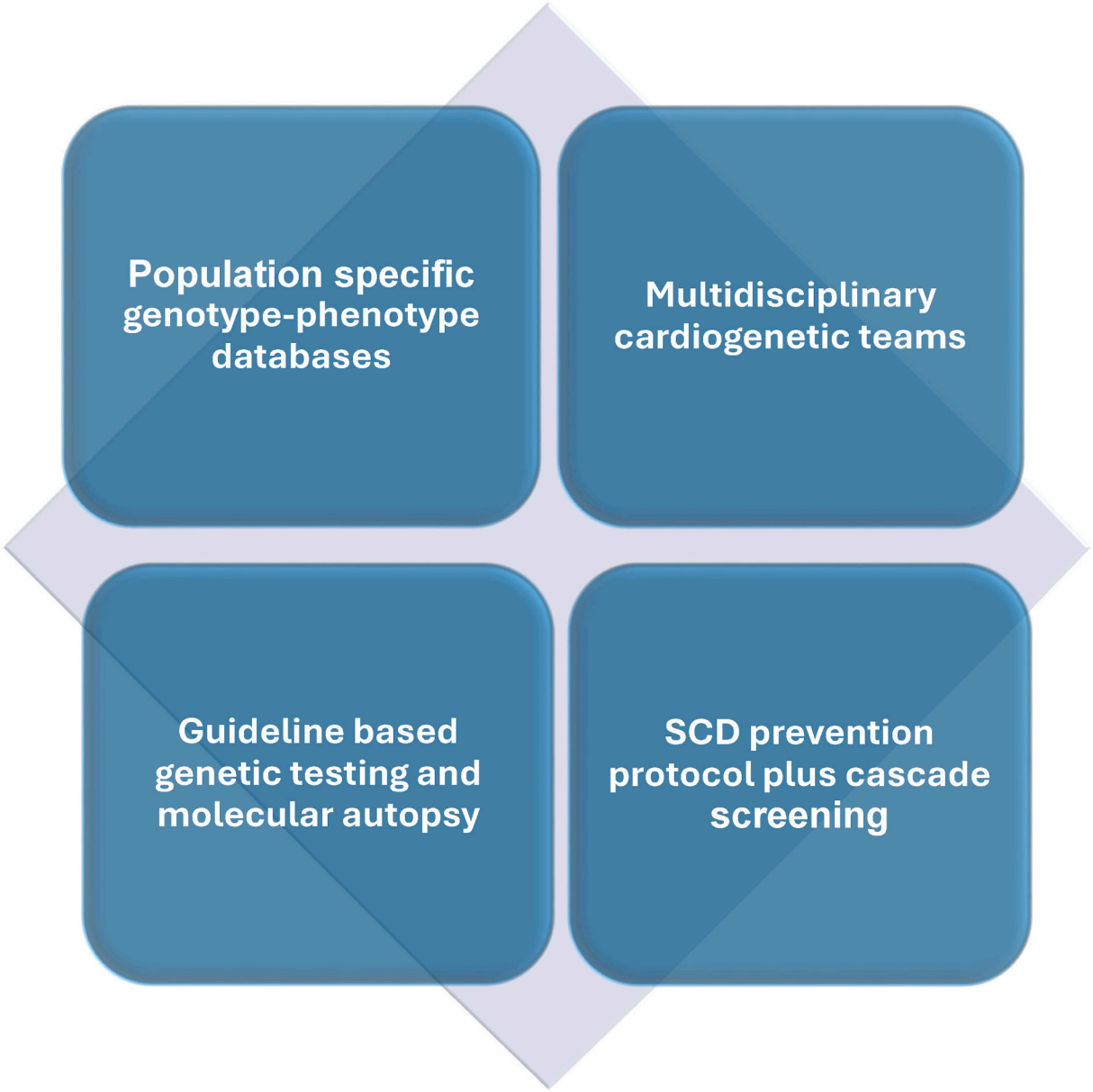

Fig. 6. Future focus areas for India and other developing countries.

hypertrophy and future events.[57,58] Whether these extra genetic factors either with a relatively large effect or many variants in aggregate play a role in SCD prediction in those without a clear cause remains to be established.

Finally, another critical factor in understanding the genetic underpinning of SCD-associated syndromes would be a significant reduction of the number of variants of unknown significance (VUS) that are currently identified. Because of a number of scientific developments there is a glimmer of hope at the horizon that the "VUS issue" might indeed become obsolete in the years to come.[59] One of these developments is the high throughput functional testing of ion channels, as has already been done for KCNE1 and KCNH2 with a promising result that for every amino acid change the potential functional effect can be predicted.[60,61]

7. Conclusions

SCD can occur at all ages is caused by a variety of cardiovascular diseases. In the young, inherited cardiac diseases are an important cause of SCD, and have major implications for surviving at-risk family members. Detailed evaluation of the premorbid history, a third-generation family history, and comprehensive expert postmortem examination is essential. In SCD cases where no cause of death is identified at postmortem, a molecular autopsy should be performed, with the aim of identifying a pathological genetic variant that would account for the death of the decedent. Clinical and genetic screening of family members is essential, with the ultimate goal to prevent future adverse clinical outcomes and SCD events in surviving relatives. Care should be provided in a specialized multidisciplinary clinic setting, and this model of care should be supported and developed in countries where such services do not currently exist, reducing racial disparities and overcoming socio-economic factors. Newer genetic and molecular developments may further improve and refine our diagnostic and management strategies for SCD families.

Data availability statement

Not applicable.

Ethics approval and consent to participate

Not applicable.

Author contributions

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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