

# Postmortem genetic testing in young individuals: What clinical medical practitioners need to know

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The death of a young person is most often a tragic occurrence, more so when this death was unexpected. Forensic pathologists are mandated to investigate such deaths, and there has been a strong move internationally towards genetic testing as an additional investigative tool. The aim of our article is to bring the advantage of implementing the so-called molecular autopsy in a local setting to the attention of medical practitioners. When a multidisciplinary approach is taken in cases of sudden unexpected death, the benefits to family members, and society as a whole, are irrefutable.

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A general misconception regarding the field of forensic medicine seems to be that the purpose thereof is only to conduct medicolegal autopsies on cases that are criminal in nature, and to deal with the subsequent judicial matters resulting from such cases. However, forensic medical practitioners are in fact in a most fortunate and unique position, as they observe the exact pathology of various diseases (whether or not these are attributed as the cause of death) in thousands of autopsies performed each year. In most cases these medicolegal autopsies reveal an underlying, natural disease as the cause of death. All information pertaining to the cause and mechanism of these deaths are relayed to several entities, including the Department of Home Affairs and Statistics South Africa. This, perhaps, can be considered to be one of the most valuable contributions from the field of forensic medicine to society. Such data, relayed to the various stakeholders in the public health sector (including clinical medical practitioners), contribute to determining population health status as well as identifying and dealing with priority areas. Currently, one of the most important public health concerns in Africa and considered to be among the priority areas that should receive greater attention is that of the continuous increase in cardiovascular diseases (CVD). A particular subset of CVD in South Africa (SA) that is of great concern is sudden unexpected deaths (SUDs) in the young population.

It is a common occurrence to read poignant media headlines in SA of young, seemingly healthy, individuals who suddenly and unexpectedly die, often with family members in the dark as to the cause of the death. Fortunately, research on these SUDs has shown that postmortem genetic testing can detect if an inherited cardiac arrhythmogenic disease is the cause of death in many (up to 40%) of these cases.<sup>[1]</sup> Such cardiac diseases often present with no clinical symptoms or warning signs prior to a sudden death (SD), showing the added benefit of conveying autopsy findings to clinicians. The societal benefits from clinicians receiving such evidence-based findings associated with the cause of a patient's SD are currently underutilised in SA. Such practical recommendations are an added benefit for clinicians when evaluating patients presenting with a sudden cardiac arrest. It could even be said that of greater importance

is the benefit to patients with a family history of SUD. This matter urgently requires the attention it deserves.

## The role of genetic testing in SUDs

Rapid and continuing development in molecular techniques allows the field of forensic molecular biology, also known as forensic molecular pathology, to use a molecular approach in not only studying but also diagnosing the underlying genetic basis of human disease and death processes.<sup>[2-4]</sup> International reports show that no other scientific discipline has embraced the application of molecular biology techniques for diagnostic purposes more than the field of forensic science and pathology, particularly in the medicolegal investigation of SDs in the young.<sup>[2,5]</sup>

Approximately 70 - 85% of SDs in young populations are cardiac related (termed sudden cardiac death (SCD)), and up to 90% of these SCD cases are potentially caused by inherited cardiac diseases, making this an important global topic in molecular research.<sup>[6-8]</sup> Molecular screening in cases of SCD has provided an explanation to the aetiology underlying the inherited cardiac disease, ultimately leading to an increased understanding of critical conditions and the clinical management thereof.<sup>[2,9,10]</sup> Most international medical associations deem SCD a global public health issue, and are currently advocating for prioritising and aligning their research plans and healthcare delivery objectives to utilise the diagnostic benefits that molecular analysis can provide.<sup>[8,11,12]</sup>

The growing global burden of non-communicable diseases, of which CVD is the predominant cause, is one of the United Nations' health priorities.<sup>[13]</sup> A published editorial in *SA Heart* addresses the topic of global health and, more specifically, the CVD burden in Africa.<sup>[14]</sup> Not only is CVD one of the leading causes of death worldwide, but it has also been reported that ~85% of these deaths occur in low- and middle-income countries.<sup>[6,13,14]</sup> Apart from CVD being the second biggest killer in Africa, the mean age of these deaths has also been recorded as the youngest in the world.<sup>[13,15]</sup>

One of the greater health priorities in sub-Saharan Africa should be a focus on preventing and treating cardiac diseases. There are key

gaps in knowledge, and especially on research priorities on genetic causes of cardiac diseases specific to the African population.<sup>[13,16,17]</sup>

## The SD conundrum

SD is a leading cause of mortality in the young, and considered a public health problem worldwide owing to its prevalence and significant impact on society.<sup>[18-20]</sup> The global incidence of SD in the young ranges between 1.3 and 8.5 per 100 000 person years.<sup>[6]</sup>

In SA, a SUD of a person is classified as an unnatural death, and therefore mandated in terms of the Inquests Act No. 58 of 1959 to be investigated in the medicolegal environment, where the forensic medical practitioner will conduct a thorough autopsy of the case in order to determine a cause and mechanism of death. However, in many instances, a clinician has previously known a patient who presented with features of a heart disease, and consequently classifies these cases as natural, attributing the sudden death to ischaemic heart disease (acute myocardial infarction). In decedents who have documented clinically investigated coronary artery disease, this would be the reasonable cause of death. However, in a subset of individuals, ischaemic heart disease might not have been the most accurate cause of death to explain the SCD.<sup>[12,21]</sup>

It has long been assumed that ischaemic heart disease is responsible for most SDs. However, data from the young population obtained in the last decade have refuted this assumption.<sup>[22,23]</sup> Fortunately, with the rapid development of technology and our increase in genetic knowledge, postmortem genetic testing (the so-called molecular autopsy) has been an invaluable tool in identifying inherited cardiomyopathies and arrhythmogenic disorders as the cause of death in many SDs, including infant cases.<sup>[23-26]</sup> The American Heart Association, European Heart Rhythm Association and the Royal College of Pathologists of Australasia have published recommended guidelines that they consider the minimum standard required in the routine autopsy practice for adequate investigation of a SCD.<sup>[7,8,11,12]</sup>

## SCD

Approximately 5 000 000 lives per year are lost to SCD globally, with an annual incidence rate that ranges between 50 and 100 per 100 000 in the general population.<sup>[27,28]</sup> It has been reported that SCD accounts for 15 - 20% of all international deaths. Although the true incidence remains unknown, the Heart and Stroke Foundation estimated that approximately 2 000 young and healthy South Africans die suddenly each year as a result of SCD.<sup>[29]</sup> An increase in the incidence of SCD has been observed worldwide, regardless of socioeconomic status and ethnicity, and this creates a public health burden. In fact, the impact of SCD in the young has created a premature death burden exceeding any other cause of death, except those attributed to all types of cancers combined.<sup>[8,13]</sup>

The causes of SCD are greatly dependent on the age of the deceased. Although the incidence of cardiac-related death increases with age, the proportion of SDs is much higher in the young population.<sup>[6,23,30]</sup> Ischaemic heart disease is the most common cause of SCD in individuals >40 years old, but inherited cardiomyopathies and arrhythmogenic disorders rank higher than ischaemic heart and valvular disease in individuals <40 years of age, with up to 75% of SCD in the young a result of the former.<sup>[6,24,25,28,31]</sup>

## Using the molecular autopsy to identify causes of SUD

Although the molecular autopsy is not a novel concept to most First-World countries, it still eludes the radar of many clinicians practising in an economically and resource-strained country. The term 'molecular autopsy' can be described as the use of postmortem

genetic testing to identify genetic variants associated with, or causative of, a lethal disease, in order to help determine or better understand the cause of death (usually that of a SD).<sup>[28,32]</sup> Although its causes may vary, it has been determined that ~85% of all SDs are of cardiac origin.<sup>[6-8]</sup>

## Inherited cardiomyopathies

The most prevalent cardiomyopathies implicated in SCD can, in most cases, be macroscopically identified at autopsy.<sup>[33]</sup> Every so often, these cardiomyopathies will be described as idiopathic, postpartum or a consequence of chronic alcohol abuse, only to be recognised, after examining the relatives, to be familial.<sup>[34,35]</sup> A further challenge often experienced by forensic pathologists is the fact that these cardiomyopathies may at times present with very subtle or even absent cardiac alterations at autopsy, especially in infant cases.<sup>[33,36]</sup> This, in combination with sometimes minor, potentially misleading findings, substantiates the need for postmortem genetic testing.<sup>[33,36,37]</sup>

## Channelopathies

Alarming, not all SCDs in children, adolescents and young adults have an obvious cause of death that can be determined at autopsy. Research has estimated that between 3% and 53% of SCD cases have no identifiable abnormal morphological findings at autopsy and remain unexplained, whereas the number of unexplained sudden deaths in infants (SUDI) may rise to 80%.<sup>[24,38,39]</sup> Only through postmortem genetic testing has it been shown that inherited cardiac arrhythmogenic disorders, commonly referred to as channelopathies, are the cause of a large number of these unexplained cases.<sup>[28,36,38]</sup>

## The benefit of molecular autopsy

It could be argued that the greatest benefit of such testing is not to define the cause of death, but rather the highly disease-specific diagnostic, therapeutic and prognostic benefit derived from subsequent genetic screening of family members of the deceased.<sup>[40-42]</sup> Considering the high heritability of cardiac disorders and the fact that they are often treatable, genetic analysis of SUD/SUDI victims provides significant clinical benefit with regard to the diagnosis and treatment of family members at risk for the same disease. Over 95% of these genetic cardiac disorders are inherited in an autosomal dominant manner, leading to a 50% chance for first-degree relatives to inherit the same genetic variant.<sup>[41]</sup> Several authors have reported on studies that evaluated family members of SUD cases, and found that up to 53% of family members tested positive for an inherited cardiac disease.<sup>[30,42,43]</sup> In the majority of those affected family members, considerable lifesaving interventions such as  $\beta$ -blockers and implantable cardioverter-defibrillators proved to be highly beneficial.<sup>[40,41]</sup> Family members of SUD/SUDI cases are usually unaware of carrying a disease-causing variant associated with an arrhythmogenic disorder. With few, if any, clinical symptoms or warning signs (family history of syncope, SD, epilepsy, deafness or early pacemaker implantation) before a SUD, the critical importance of postmortem genetic testing cannot be overstated.<sup>[22,38,41]</sup> The confirmed marked reduction in mortality associated with the administration of proper treatment in such cases leaves no ethically arguable justification for allowing family members at potential risk to remain undiagnosed and untreated.<sup>[41,44]</sup>

Postmortem genetic testing is recommended (in published guidelines) in all SUDs in the young (0 - 40 years of age) and in all cases suggestive of cardiomyopathy.<sup>[7,8,11,12]</sup> The minimum requirements involve only targeted genetic testing of the major genes. However, the use of commercial panels consisting of a combination of up to 100 cardiomyopathy and channelopathy genes is becoming more common. These minimum guidelines aim to prevent criticism

of case analysis in the medicolegal setting and protect surviving family members with possible genetic disorders.<sup>[7,8,23]</sup>

With advancements in technology and the associated decrease in cost, the forensic medical profession is increasingly becoming aware of the dangerous implications that an unidentified aetiology of a possible inherited disorder can have on family members at risk.<sup>[45,46]</sup> The ethical duty and legal liability pertaining to the 'failure to diagnose' and 'duty to warn' in forensic pathology is currently debated on an international level. According to the Code of Medical Ethics of the American Medical Association, the implications of genetic information for the biological relatives of a patient must be included in the pre- and post-genetic counselling process.<sup>[47]</sup> Consequently, it is argued that the legal precedent laid down by two primary American court cases (Pate v Threlkel and Safer v Estate of Park) should be, and most probably will be, applied to the forensic pathology profession. The court held that the physician has a duty to warn biological relatives of an inheritable genetic condition, if the standard of care available will be to their benefit, and if the physician is aware of the existence of these biological relatives.<sup>[47]</sup> Forensic pathologists in the USA already recognise their duty to warn, and are currently in the process of drafting a standard national set of guidelines for the notification of family members of all cases where a possible genetically heritable aetiology is found.

## The way forward

Internationally, the application of postmortem genetic testing as routine investigation in all unexplained SUD/SUDI cases has been adopted.<sup>[7,8]</sup> The results produced by these molecular autopsies have successfully contributed to the public health sector in improving the population's health status by diagnosing and treating at-risk family members. Inevitably, it raises the question as to the current stance on the implementation of the molecular autopsy in African forensic medical institutions.

In SA, there is no medicolegal mortuary that offers targeted genetic testing in SUDs in the young, even though the departments of forensic medicine at the University of Pretoria and University of Cape Town both conduct valuable research on this topic.<sup>[48,49]</sup> Our pilot study, conducted on one gene linked to unexplained SUDI, yielded interesting results, with 22.5% of cases having possibly pathogenic SCN5A variants considered to be associated with the cause of death.<sup>[49]</sup>

SA needs to realise that SCDs, especially in the young, should be deemed a clinical health priority, and urgently treated as such. It can be inferred that a high proportion of these SD victims were actively occupying the workforce, and thus contributing to the national economy, emphasising the impact on society. Tackling this health concern can only be successful through a multidisciplinary approach, where all relevant stakeholders, including forensic medical practitioners, clinicians, governmental agencies and funding bodies, to name a few, accept their responsibilities and play their part. With adequate funding and resources, and stricter referral, according to legislation, of SUDs for medicolegal death investigation, a significant increase in molecular research can be conducted into these deaths. A direct result of this will be to enable researchers to detect with greater certainty the most prevalent genes associated with inherited cardiac diseases specifically targeted towards the SA population. The ultimate aim, through adequate research, is to reach that point of targeted genetic testing that can be used as affordable point-of-care testing, which will be of immense value to clinicians, forensic medical practitioners and society as a whole.

African medical professionals have often been at the forefront when it comes to innovative and ground-breaking medical procedures.

Therefore there is no excuse not to excel at the implementation of the molecular autopsy and reap the clinical benefits it has to offer.

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