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Towards European Recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death

Status of this manuscript:
This draft summarizes the results of the expert workshop on "Ethical, legal and practical aspects of post-mortem genetic analysis for sudden cardiac death in young adults" held at the Brocher Foundation in Geneva on November 23-25, 2016. The ESHG Public and Professional Policy Committee of the European Society of Human Genetics organized this workshop sponsored by the Brocher Foundation and ESHG. A first draft was distributed among speakers and participants of the workshop to solicit comments and was presented at several conferences in genetics and cardiology.
After integrating comments the updated draft manuscript is now online on the ESHG website for membership consultation from end of March until 30 April 2018, and is available for discussion and endorsement by professional societies.

Background

After sudden unexpected death (SUD), forensic or clinical pathological examination may suggest an underlying cardiac disorder, which can be hereditary. These deaths can then be classified as cases of Sudden Cardiac Death (SCD) (Priori et al, 2015, Basso et al 2017). Taking personal and family history is of crucial importance and access to the related genetic information can be relevant for medical reasons (for example, to identify the likely or possible cause(s) of death and then refine the prevention strategies for surviving relatives), as well as for public health or research purposes. Autopsy procedures are generally well described in various European regulations, however, they often poorly incorporate post-mortem genetic test information into the autopsy findings (Rial-Sebbag 2008), and procedures differ between countries. The proportion of SUD in which autopsy takes place also varies among countries. This lack of connection between autopsies and genetic testing is highlighted by the increased potential of new technologies in genetics, to shed light on genetic mechanisms in SCD. At the same time new techniques result in exponentially greater amounts of genetic data compared to former tests, much of which cannot yet be interpreted, or has uncertain significance. Distinguishing genetic results of clinical utility from the uncertain output needs expert interpretation and use of detailed phenotypic information. Moreover, conducting genetic or genomic testing in the context of post-mortem DNA analysis raises practical, legal and ethical challenges; including issues around consent, confidentiality and dissemination of familial information.

To address the lack of coordination between different professional domains and improve guidance on post-mortem genetic testing for cardiac disorders, the Public and Professional Policy Committee of the European Society of Human Genetics (PPPC ESHG) organized a multidisciplinary Workshop sponsored by the Brocher Foundation and ESHG, on 23-25 November 2016. The workshop consisted

of presentations by 12 experts in (forensic) pathology, cardiology, genetics, ethics and law, and group work to identify common challenges and draft recommendations. The workshop was attended by members of the PPPC and invited experts. After the workshop, participants drafted a document listing recommendations. A first draft was distributed among speakers and participants of the workshop to solicit comments and the recommendations were presented at several conferences in genetics and cardiology. An updated draft has now been prepared for professional societies to discuss according to their own procedures for membership or expert consultation. The ESHG will post this draft manuscript on its website for membership consultation from the end of May until April 30, 2018. After careful consideration of the suggestions relevant comments will be integrated, and the document will be submitted for endorsement to the board of ESHG and other professional organizations. The final manuscript will be submitted for publication, and potentially a combined publication in several relevant journals can be established.

Introduction

Sudden cardiac death (SCD) is a major public health problem. Based on studies in the USA, the Netherlands, Ireland and China, SCD incidence ranges from 50 to 100 per 100 000 inhabitants annually and increases with age (Deo and Albert 2012). It accounts for almost 20% of total mortality, i.e. 1 in 5 individuals will eventually die suddenly. Among these sudden deaths cases, the majority is SCD (de Vreede-Swagemakers 1997). For younger persons (under 40 years of age), the incidence of sudden death is lower, between 0.7 and 6.2/100 000 person-years (Hofer et al. 2014), and in ±70% of cases the cause is cardiac (van der Werf 2010). SCD can be caused by a number of underlying cardiovascular disorders. Coronary artery disease and acute myocardial infarction are the most common causes in individuals over 40 years of age, while in younger persons genetically determined cardiac diseases (e.g.: cardiomyopathies, ion channel diseases) account for an important proportion of cases (Basso et al, 2017, Semsarian, Ingles et al. 2015, 2015 ESC guidelines, 2015, Eur J Heart, 2010). Given the substantial genetic component of SCD in younger cases, postmortem genetic testing may be particularly useful to elucidate aetiological factors in the cause of death in this subset (Semsarian, Ingles et al. 2015).

It is well acknowledged that the results of such autopsies, including genetic testing, may be relevant for living blood relatives and public health prevention strategies.[1] The identification of genes responsible for cardiac diseases such as arrhythmic syndromes or cardiomyopathies, have led to the organization of cardiogenetic consultations in many countries worldwide. Expert recommendations are available, emphasizing the importance of genetic testing and appropriate information provision of affected individuals as well as their relatives (Ackerman, Priori et al. 2011, Priori et al. 2015 Charron et al, 2010). Furthermore, more research on this topic is recommended (Fishman 2010). However, the context of post-mortem genetic testing raises some particular ethical, legal, and practical (including economic or financial) challenges which are the subject of this paper.

The first challenge stems from the fact that general autopsy procedures are not always implemented and autopsy rates for SUD differ per region and country (Basso, 2017). A SUD most often will be investigated using forensic procedures, focusing on ascertaining whether the cause of death is to be attributed to an underlying disease or if there is any legal implication, thereby distinguishing 'natural'

[1] In this document we will concentrate on cardiovascular disorders. The resulting guidance may inspire efforts to integrate post mortem genetic testing for other purposes. For instance, genetic susceptibility to adverse drug reactions could be relevant both for forensic and public health purposes.

versus ‘unnatural’ causes of SCD. Establishing the precise definition of the disease and informing the family members are not necessarily part of the aim of this procedure. There are also practical barriers related to organizational aspects, such as the lack of connection between the judicial system and the medical system. So far, it has been difficult to establish an effective communication between “post-mortem professionals”, especially in the context of the forensic setting (pathologists), and specialized cardiogenetics experts. Insufficient communication between different medical specialties (i.e. pathology, cardiology and genetics), further hinders the adequate provision of information to relatives of the deceased person (Claustres, Kozich et al. 2014).
Furthermore, there is a concern that medicolegal experts (forensic pathologists and/or medical examiners) may not have sufficient training and/or resources (including time) to properly interpret genetic testing results (Claustres, Kozich et al. 2014; Sajantila 2015).
Clinical genetic services focused on a cautious approach, respectful of “the right-not-to-know”, when the clinical utility of genetic testing was low or absent (Takala1999; Andorno2004). As genetic testing is increasingly able to identify conditions for which there is surveillance, prevention or treatment, a hypothetical right not to know becomes more difficult to balance with a potential duty to warn (Boers et al 2015.; Tassé; Rothstein M, 2014). Family members of an index patient diagnosed with, or suspected of, a heritable sudden cardiac death might not be aware of the death of their relative and/or of the possibility of an inherited genetic condition within the family, so that they might not have the opportunity to proactively look for appropriate advice and genetic information. A sudden cardiac death clearly prevents seeking consent for genetic testing and subsequent familial dissemination of relevant information, adding to clinical paralysis about what can legitimately be done with genetic findings in the deceased. Limited communication among family members and concerns about privacy might further complicate this.
Furthermore, there is lack of international guidance about the reporting of forensic postmortem genetic test results with few local practice guidelines (Claustres, Kozich et al. 2014; Wilhelm et al. 2015).

In the following paragraphs, we will summarize specific procedural, ethical, legal and practical challenges on post mortem genetic testing after sudden cardiac death that have been examined during the workshop. The key elements that would ideally need to be adopted will be depicted in the flowchart (page 6), though the actual organization of these actions may vary between countries or jurisdictions. We will conclude by making recommendations on how best to include post-mortem genetic testing in the context of SCD in order to contribute to the identification of the cause of death and then contribute to a better management of relatives by optimizing screening strategies and treatment of preventable disorders.

Sudden Cardiac Death

In this document, we will focus on cardiovascular disorders. The WHO definition of Sudden Cardiac Death (SCD) is an ‘unexpected death due to a cardiac cause within one hour after the onset of symptoms in a person with known or unknown cardiovascular disease’. Knowing the cause of sudden death may be particularly relevant for family members, (i) if the condition is hereditary and therefore relatives might also be at risk, and (ii) if prevention or treatment is available. Apparently healthy people who die while performing sports, during sleep, while swimming or while driving may be victims of arrhythmias as a consequence of a cardiogenetic condition. Some cardiogenetic conditions might be identified in the course of the autopsy, e.g. in case of myocardial disease such as

cardiomyopathies. However, a number of cases remain unexplained after complete autopsy including laboratory analyses, referred to as Sudden Arrhythmic Death Syndrome (SADS), in which the underlying mechanism of death might be an arrhythmia due to an inherited ion channel disorder (Priori et al, 2013; Basso et al, 2017).Our focus will be on individuals over 1 year old, since implications related to Sudden Infant Death Syndrome (SIDS) are somewhat different and protocols for management- including information for the family - are more clearly defined. SIDS is defined as the unexpected death of a seemingly healthy infant less than a year old (Priori et al, 2013). We however acknowledge SIDS cases might be related to a genetic cause in up to 20% of cases, mainly related to inherited cardiac diseases (channelopathies 9%, cardiomyopathies 7%) (Neubauer 2017), even if this high rate has not been confirmed in more recent studies (Tester et al, 2018).

Post mortem investigations in different countries

How post mortem investigations are organized, differs between countries. For forensic purposes, the procedures in place reflect the aim of investigating the potential involvement of third parties (e.g. homicide or an accident), while for the medical context a different system exists that aims to discover the underlying pathological cause of unexpected death (Basso et al, 2017). The first is often called “medicolegal autopsy”, the second “medical autopsy”. For some of these contexts and in some countries autopsy may be mandated (e.g. in sudden infant death), while for other situations relatives may be asked for permission to perform autopsy but this is not consistent across various European countries. Health insurance may end with a person’s death, so funding for an autopsy and/or genetic testing may be a major obstacle even when it may be of benefit to surviving relatives.

Aim of a medicolegal autopsy

The traditional aim of a medicolegal autopsy is to ascertain the cause of death in cases of unexpected, sudden death. If homicide, suicide or an accident can be ruled out then a ‘natural death’ is assumed. Especially in younger cases, ‘natural causes’ may be related to underlying genetic conditions, such as a cardiogenetic disorder.

Given the potential significant medical relevance of autopsy information for family members, autopsies, including medicolegal autopsies, should have a dual aim of both ascertaining the cause of death and providing information to family members in case the findings indicatea substantial risk that family members may also have inherited the predisposing disease.

Percentage of autopsies performed

There is considerable variation among countries and regions in the numbers of autopsies conducted and for many countries data are missing. In a study from the Netherlands, an autopsy was found to be performed in about 43% of sudden deaths of persons aged 1-44 years (van der Werf 2016). In many countries, the rate is unknown and might even be lower. In the United Kingdom, in all cases of sudden unexpected death a coroner is involved and an autopsy is required. In some other countries medical professionals, such as general practitioners may be primarily responsible for establishing the cause of death and varied arrangements may exist in different juridictions for requesting an autopsy, whether medical or medicolegal. Even though the Committee of Ministers of the European Council adopted in 1999 a recommendation on the harmonization of medico-legal autopsy rules and established clear criteria in what circumstances an autopsy is required, including sudden, unexpected death, there is an urgent need for instructing the relevant professionals regarding these criteria (Basso et al, 2017)

(https://www.coe.int/t/dg3/healthbioethic/Texts_and_documents/INF_2014_5_vol_I_textes_%20CoE_%20bio%C3%A9thique_E%20(2).pdf).

Need for a full autopsy

A full autopsy (i.e. including exclusion of non-cardiac causes of natural death, search for cardiac causes of SD, macroscopic and histologic examination of the heart, post-mortem laboratory (toxicology, chemistry and microbiology) tests and storage of adequate samples for genetic testing) is necessary to identify cases where a cardiac disorder is the likely cause of death and to collect supporting evidence. Procedural and technical guidance is available in a published protocol (Basso 2017), which should be implemented in all European countries. This protocol provided by the Association for European Cardiovascular Pathology (AECVP) includes a complete analysis of the heart. Funding may be a major obstacle in increasing the number of autopsies in case post mortem investigation is not mandatory. In the United Kingdom, for instance, all full autopsies are funded by the coroner but specialist cardiac examination is funded by the charity CRY (http://www.c-r-y.org.uk/). To allow for sufficient expertise and standard procedures, regional centers and/or experts in examination of the heart would be ideal, as would appropriate funding for the necessary investigations.

Genetic testing in relation to full autopsy

In many European countries, legal provisions do not allow pathologists to request genetic testing after a full autopsy including a thorough examination of the heart and only geneticists can order a genetic test. In the practice of forensic autopsies, a genetic test can be requested for diagnostic purposes in some countries. However, the interpretation of genetic test results for inherited cardiac arrhythmia disorders requires highly specialized expertise (Van Driest 2016) and it may be difficult, if not impossible, to use the test as a diagnostic tool. If there is a clear indication for genetic testing, for instance, in case of inherited cardiac disease, such as cardiomyopathy, a panel of genes related to the condition could be used. However, the indication for genetic testing is more debated when the phenotype is unclear (the autopsy is normal, unexplained SCD, SADS). Interpretation of the result would often require not only phenotypic information of the deceased, but also extensive family investigation to see whether the genotype segregates with a cardiac phenotype. Often, at most an indication of the possible diagnosis may be obtained but without confirmation. In practice, it may take too much time for the test results to be available to be included in the final autopsy report. Moreover, genetic analysis currently remains expensive despite advances in technology and coroners may be reluctant to pay for investigations that have no impact on the judicial procedure.To allow for future genetic analysis, in the course of an autopsy, a blood or tissue sample (spleen, muscle, skin, kidney) should be taken and stored frozen together with detailed phenotypic information.

Storing samples for future genetic testing

If a DNA sample (or frozen fresh tissue from which DNA could be extracted) is stored, it becomes possible to use the sample for testing in the future on family request, and potentially for research. Consent for such DNA testing and storage in clinical or biobank repositories is not a trivial matter. Guidelines and legislation about who can or should give such consent varies in different countries. In the UK for example, the Human Tissue Act recognizes that the spouse of a deceased person – although often be the person with whom consent is discussed- does not have the same interests in

such storage as biologically related family members. Refusal of consent by a spouse for storage could deny family members relevant information and so should only be accepted in case of an informed refusal and if there is no one else who can provide relevant consent.
Sample storage requires good communication between the forensic pathologist and relevant clinicians (e.g. geneticists or cardiogenetic department). Sample handling and storage should be part of standard procedures. Currently, European Recommendations exist about the use of samples from a deceased person. In 2004, a multidisciplinary expert group invited by the European Commission published 25 Recommendations on the ethical, legal and social implications of genetic testing (McNally et al. 2004). The 24th recommendation addresses post-mortem genetic analysis. It was stated that member states are to take action to promote the right of access to samples and data from a deceased person, in the case of the overriding interest of blood relatives. However, in practice, forensic departments often do not have the facilities to store material for a long period of time. Long term storage in clinical or biobanking systems, and subsequent access by family members, raise questions about what type of consent is appropriate.

Informing the family

After a medico-legal autopsy a report is sent to the representative of the legal system (e.g. coroner, district attorney). However, whether and how the family is involved in receiving the results of the autopsy differs between countries. Even if information is provided to family members about an underlying hereditary cardiovascular disorder, it may not be clear to them whether this might be relevant for their own health, nor may it be clear how they can act on the information by seeking appropriate referral. More work to close the gap between medicolegal reporting about the deceased, and appropriate care of relatives is required. Examples include: establishing procedures for providing “family letters” that provide clear information on the possibility of a genetic disorder and where further information and care can be obtained from; making clear who is responsible for providing such information or letters; having accessible online information and/or dedicated medical professionals that can be contacted by families or by their general practitioners. These procedures, however, do not ensure that all relevant relatives will be reached. Intrafamilial communication of genetic risk information is a complex, multifaceted process and ongoing support for the communication with family members is often needed.
Family members also need to be informed when a medical autopsy is performed if the results indicate the possibility of an underlying hereditary cardiovascular problem. This requires good communication and collaboration between most notably the pathologist, the physician who ordered the post mortem investigation, the genetics department and the general practitioner (family doctor).

Consent

In the context of a forensic investigation, consent is not required for post mortem investigations. It is common practice to obtain consent from a patient to contact family members during life but this is obviously not possible after the patient’s death. Since relatives may have an interest in knowing about the deceased’s results, and serious harm might be prevented in their gaining of this knowledge, this is generally held to tip the balance in favour of familial disclosure than any professional obligation to maintain confidentiality after death. However, ethical debate remains (Tassé et al. 2011; Boers et al. 2015). The communication of relevant information is difficult to standardize, but needs careful balancing of relevant information in a clear manner that allows relatives to make informed decisions about whether or not they want to pursue investigations.

Furthermore deciding who is informed and when is not a trivial task. Clinical Genetic Services have several tools in their armory to facilitate such familial communication, so early contact or referral is recommended where possible.

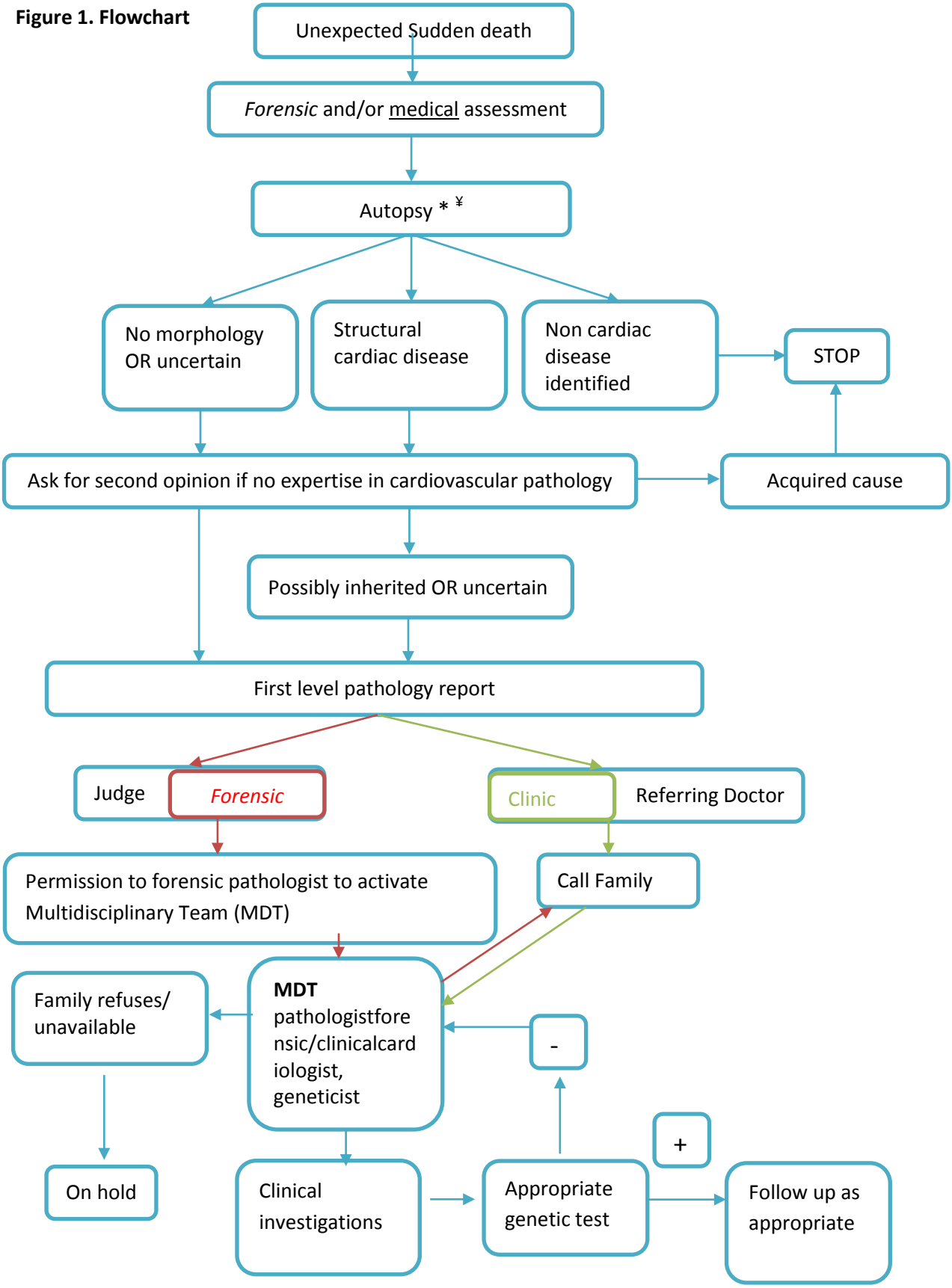
Family investigation

The first step in family investigation is a cardiology referral of first degree family members, either in case of a clear autopsy diagnosis of a cardiac disease that is usually inherited, or in case of no clear cardiac disease diagnosed at autopsy in a young person (especially if less than 40 years). The genetic investigations should be performed in first instance on the deceased person's sample as a general requirement before any potential predictive testing in relatives. The genetic analyses are based on a targeted gene panel when a clear cardiac disease has been identified at autopsy, or might be enlarged to large gene panels or even exome sequencing in case of no clear cardiac diagnosis at autopsy (Hofman et al. 2013; Nunn et al. 2016). However in the last situation (when no clear cardiac disease is identified) the interpretation of genetic results should be highly cautious and can be considered as hypothesis-generating rather than claiming the cause of death has been identified. Predictive genetic testing of relatives can then be offered in cases where a clear pathogenic mutation has been detected in the deceased. In case of no genetic results in the deceased person but a cardiac disease identified in a relative after systematic screening, then genetic testing can be performed in this particular relative. A careful consideration of clinical information and investigations on the deceased and on the relatives will be essential for a meaningful interpretation of the genetic test results; it will often be wise for this to be conducted as a multidisciplinary review process.

Multidisciplinary collaboration

To connect the hitherto distinct fields of forensics, pathology, genetics and cardiology, the establishment of (regional) multidisciplinary teams is vital. Their role is: (i) to examine individual cases to improve their management; (ii) to share information on management of samples, tests results and family investigations so as to enhance the overall management of each case as well as to improve individual professionals practices and expertise; (iii) to support professionals seeking advice; (iv)to contribute to establishing local and national protocols and improve their implementation; (v) to collaborate with the relevant institutions to collect and provide information about critical or strategic matters for public health purposes; (vi) to designate a case manager that can be contacted by health care and forensic professionals as point of reference.

Figure 1. Flowchart



* Mandatory if < 40y; Consider if >40 and <65 y; Case by case > 65y

¥ Standards: minimal criteria; histological examination; sampling for toxicology, genetics, other lab tests; collection of health history/records

Professionals and policy makers are encouraged to distribute and discuss the following recommendations to improve practices relating to post mortem genetic testing for cardiac disorders, and stimulate the development of national and European guidance. This task requires the sustained and collaborative effort by the various professional groups involved.

Draft Recommendations

1. Sudden cardiac death at a young age should be considered as a public health priority because of the high prevalence of inherited cardiac diseases and the impact for the family. Therefore, public funding should be allocated for related relevant investigations.

2. Increase the rate of both medicolegal and medical autopsy in case of sudden, unexpected natural death should be a major objective. This should be mandatory for deaths under the age of 40, it should be considered for deaths between ages 40 and 65, and evaluated on a case by case basis after age 65.

3. Educate primary care physicians, coroners/district attorneys and (forensic) pathologists on when an autopsy should be performed.

4. Medicolegal autopsies should have a dual aim: (i) to establish if a death was natural or caused by a criminal act or accident; (ii) to establish the cause of a natural death, and allow results to be used for health care purposes for the surviving relatives.

5. In cases of sudden (cardiac) death a full autopsy should be performed including heart dissection, sampling for possible genetic and toxicological analysis, and examination shall adhere to minimal standards as per European guidelines. European guidelines should be made mandatory in member countries by seeking support from Ministries of Health and Justice.

6. Access to second opinions of teams with expertise in cardiovascular pathology (reference network) should be promoted to support routine workup.

7. In the course of an autopsy, blood or tissue samples(e.g. spleen, muscle, skin, kidney) should be taken and stored frozen together with detailed phenotypic information for future genetic analysis. This sample should be accessible for medical purposes. After completion of the forensic proceeding, the sample should be stored in healthcare embedded biobanks according to national regulations. Family members should be informed about the availability of the sample and asked for consent to storage. It should be clear how long a sample will be stored.

8. Organize local multidisciplinary teams or reference centers to connect different domains in health care and the judiciary system in order to co-design pathways and procedures, clarify who is responsible for storage during and after the forensic investigation, clarify the source of funding to implement this policy, design information letters or leaflets for patients and family members, and designate the case manager who can be contacted by health care and forensic professionals as a point of reference.

9. Information on genetic testing and communication of genetic test results should be given in compliance with standard procedures in clinical genetics and with the appropriate national legislation.

Familial communication and appropriate cascade testing should be approached in a systematic fashion using genetic services where possible. We consider that there can be no duty to warn all relatives but that a responsible system will make attempts to alert relatives where possible.

10. A multidisciplinary cardiogenetic team should conduct the family investigation. The appropriate genetic test should be considered according to a combination of pathology findings, family history and results of cardiac family screening. The genetic test shall be performed on the DNA of the deceased in first instance, and testing of relatives should then be offered if a clear pathogenic mutation is identified.

11. Professionals, professional organizations, relevant national institutions and policy makers should make a collaborative effort to further discuss the respective responsibilities of the different professionals involved, the allocation of funding for autopsies and postmortem genetic tests, the procedures required to connect the domains of forensics and healthcare in the context of hereditary cardiac disorders identified in suddenly deceased individuals, and how best to address the ethical issues arising when informing family members and possible psychological harms associated with disclosure.

12. There is a need for an economic and public health evaluation of the use of genetic testing in post mortem investigations, in order to validate the process from a public health point of view and to clarify the situations for which post mortem genetic testing is a useful tool.

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