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# Guideline

Subject: **Genetic investigation of cause of death in coronial autopsy cases**
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## Purpose of these guidelines

These guidelines relate to coronial cases in which genetic testing is proposed to assist the investigation of a deceased person's cause of death. For example, in the case of presumed cardiac sudden death in which the initial post-mortem examination has not ascertained a cause of death.

There will also be cases in the coronial system where the cause of death has been determined and could be heritable or where pathology with possible genetic basis has been found. However, these cases are outside the scope of these guidelines.

## Key considerations for forensic pathologists

Determining the cause of death of a deceased person can provide closure to that person's next of kin. Finding a genetic basis for a death can have significant implications for the deceased's family members.

There are numerous published case reports and papers that record finding a genetic abnormality to explain the sudden death of a deceased person. However, these do not provide a true indication of the potential success of molecular autopsies, as under-reporting of negative findings does occur (1). Nonetheless, large prospective studies may provide useful information regarding the incidence of genetic abnormalities to account for sudden death (2).

International guidelines in the form of expert consensus statements relating to the conduct of genetic testing are available, for example in relation to channelopathies and cardiomyopathies (3). However, forensic pathologists must ensure they always comply with the relevant laws, policies and practices in their own jurisdiction.

Considered below are some key matters relating to genetic testing of a deceased person in the coronial context:

### 1. Variations of Unknown Significance – 'Genetic Purgatory"

Bagnall and colleagues (2) and many others, report the finding of a number of Variations of Unknown Significance (VUS). The common finding of mutations of uncertain significance has been termed "Genetic Purgatory" (4).

The presence of 'background genetic noise' renders it likely that the more closely a genome is examined the more likely an abnormality will be found, with the average person's genome containing in the order of 400 potentially damaging mutations in their DNA (5). However, abnormalities are not necessarily linked to outcome (4). This observation is an extension of the consideration that a post-mortem examination has the potential to find abnormalities that the

person died *with*, not *from* (6).

In determining if genetic abnormalities are significant in relation to a deceased's cause of death, the dictum '*pre-test odds influence post-test outcome*' (7) should be observed. Thus, it is not surprising that the involvement of genetic counsellors (8) to identify families with a history of sudden death compatible with a genetic basis increases the rate of positive outcomes in subsequent genetic testing (9).

**2. Phenotype – Genotype discordance**

Genetic heterogeneity can underlie deaths that were previously assumed to result from specific mutation (10). The manifestation of a genetic cardiac abnormality can be modified by environmental factors or other gene variations including 'modifier genes' (11-13). An end phenotype may be caused by a number of genetic abnormalities, (14) and conversely a single genetic abnormality can result in more than one phenotype (15). Sudden death relating to genetic abnormalities may have more than one manifestation and genetic mutations associated with channelopathy deaths have been detected in cases of sudden death attributed to epilepsy (16). Furthermore, somatic genetic testing ignores the potential role for inherited mitochondrial disorders (17).

In this complex field, counsellors specialising in the investigation of sudden death have been shown to have a valuable role in selecting the appropriate genetic test, (18) and it has been suggested that it is preferable to avoid 'fishing' for an abnormality in genotype until the phenotypic abnormality is established (4). However, care has to be taken not to be misled by family screening, and attention has to be paid to the findings in the deceased (19).

**3. Legal/Ethics**

The coronial legislation in each Australian state and territory provides that coroners may direct that certain post mortem investigations be conducted (usually by a specialist forensic pathologist) to assist in the investigations into a deceased person's cause of death.

The health departments or coroners' courts in some jurisdictions have issued policies or guidelines regarding the types of tests or examination that may be conducted as part of coronial post mortem investigations.

The issue of consent does not arise in the context of coronial cases as the coroner may direct the conduct of a genetic test to determine the deceased's cause of death without being required to obtain consent (though this may not be the case for genetic testing outside the coronial context, or where a test is not directed by the coroner. There may also be other implications in these situations, eg funding for the tests, but these are outside the scope of these guidelines). However, most jurisdictions have provisions that, to a varying degree, allow for specified family members to object and/or appeal against a determination by a coroner that a post-mortem be carried out.

The laws regarding genetic testing to assist in the investigation of the cause of death in coronial cases differ across the various Australian jurisdictions, and medical practitioners should ensure they are aware of, and comply with, the requirements in their own state or territory.

**4. Samples**

A prerequisite to conducting a genetic test is the availability of a suitable sample for testing.

Where genetic analysis to assist the determination of the cause of death might be undertaken, it is recommended that a 5ml sample of blood in EDTA preservative is retained for this purpose. Frozen EDTA blood may be used for DNA analysis for up to approximately one year.

For longer storage it would be preferable to extract and either store the DNA in suspension at -70°, or desiccate the DNA and store it at room temperature.

However, please note that the laws regarding the retention of such samples may vary across the states and territories.

**5. Engagement with family of the deceased**

Post-mortem genetic testing to assist the investigation of the cause of death may require or result in some engagement with the family of the deceased person, depending on the circumstances and any applicable laws or policies in the relevant jurisdiction.

**6. Guideline recommendation**

It is recommended that prior to undertaking genetic testing of the deceased there is:

1. engagement of the family of the deceased with a genetic counselling service; and
2. confirmation of a family history compatible with a heritable disorder; and
3. (ideally) identification in the living relatives of a putative genetic defect (or defects) or phenotype for which testing is available.

Genetic testing of the deceased in the absence of points 1 and 2 (above) is not endorsed.

***NOTE**:*
*Please be aware that these guidelines are intended only to be a high level and general guide to appropriate practice in Australia, to be followed subject to a medical practitioner's own judgement and the circumstances of each individual case. It does not and cannot refer to all considerations that may be relevant to the subject matter of these guidelines and is not intended to be comprehensive or prescriptive in all circumstances. Where specific examples are included, these are intended to be indicative only.*

*These guidelines are not intended to provide legal advice. It is outside the scope of these guidelines to refer to all laws, policies or operating procedures that may apply in a particular case.*

*These guidelines do not address genetic analysis of a deceased person in the case of sudden death for research purposes (as this is outside the scope of these guidelines). However, provided it conforms to the applicable ethical and legal regulations, such research is encouraged.*

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