

The ethics of conducting molecular autopsies in cases of sudden death in the young

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In an effort to identify the cause of sudden death, especially in the young (SDY), the National Association of Medical Examiners (NAME) recommends retaining samples for genetic testing in all cases where an autopsy is performed (Middleton et al. 2013). On September 30, 2014, the Centers for Disease Control and Prevention, in collaboration with the National Institutes of Health, launched an ambitious effort aimed at addressing the devastating impact of SDY by providing funding for 10 states to expand the existing Sudden Unexpected Infant Death Case Registry into a comprehensive SDY Registry and to enhance the value of that resource for public health and research purposes, chiefly through introduction of a standardized autopsy protocol and collection of biospecimens for DNA analysis (<http://www.nhlbi.nih.gov/news/press-releases/2014/nih-and-cdc-announce-grantees-sudden-death-young-registry>).

This collection of blood and tissue for DNA analysis, or the “molecular autopsy,” is an increasingly pervasive tool in investigating SDY cases, the majority of which fall within the category of sudden cardiac death (SCD) (Semsarian and Hamilton 2012; Farrugia et al. 2015; Wang et al. 2015). There are, however, several unresolved ethical and policy issues that must be addressed for the responsible conduct of molecular autopsies as part of a death investigation by medical examiner or coroner offices (ME/C). For example, under most state laws, the ME/C has a statutory obligation to investigate unexpected deaths and authority to proceed without informing the family about the scope of the investigation. In addition, autopsy reports may be subject to public disclosure requirements that take little or no account of implications for family members, while the protocols for disclosing the genetic results to potentially affected family members remain conflicted (Elger et al. 2010; Boers et al. 2015). As molecular autopsies become more widely integrated into public death investigations, guidance for how best to manage these issues is needed.

There are many nuanced jurisdictional differences in the law and how molecular autopsies are performed. We have published a

more detailed analysis of state laws and the implications of differences elsewhere (Moore et al. 2016). In this paper, we describe the experiences and reflections of the Molecular Autopsy Consortium of Houston (MATCH), a collaboration between the Harris County Institute of Forensic Sciences (an integrated operation including Medical Examiner services and Crime Laboratory services) and Baylor College of Medicine, which conducted genetic analysis on a large cohort of 351 deceased infants, children, and young adults (age range 0–37) in an effort to determine the cause and manner of death (Methner et al. 2016).

Although there are jurisdictional differences in how molecular autopsies are performed, we propose general recommendations to address the ethical and policy challenges raised (Box 1), based on our experience as a multidisciplinary consortium with expertise in pathology, medical genetics, genome science, genetic counseling, bioethics, and law (with consultation from experts in cardiology). The focus of this paper is on SDY because these cases are most likely to fall within the jurisdiction of the ME/C and because the absence of any physiologic finding on standard autopsy is more common in children, necessitating a molecular autopsy to determine the manner and cause of death. Nonetheless, the issues are similar for adults, and our own approach did not differ between the children and young adults in our cohort. We also limit the scope of this paper to molecular autopsies performed during a death investigation by a ME/C, while acknowledging that molecular autopsies may occur in different circumstances, such as in the context of private autopsies requested by family members.

Consent

In the clinical and research realms, the importance of obtaining informed consent before proceeding with genetic testing is widely acknowledged as a matter of law and ethics (with limited exceptions). This practice is based on respect for autonomy and consideration of the consequences of testing. However, if testing is performed to determine the cause and manner of death, consent

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BOX 1. Summary of recommendations

Before conducting molecular autopsies in cases of sudden death in the young, a multidisciplinary team of medical examiners or coroners, clinical geneticists, genetic counselors, and cardiologists should be established. The team should consult other specialized medical professionals, bioethicists, and lawyers when appropriate. All of the recommendations require communication and collaboration among this team.

Consent

Recommendation 1.1. Reasonable efforts should be made to notify the decedent's family before conducting genomic analysis as an aspect of a death investigation or when a positive result is obtained.

Recommendation 1.2. When notifying families about the planned analysis, members of the team (as appropriate) should (1) solicit consent to obtain samples from biological relatives, if available, for confirmatory testing, (2) offer family and biological relatives an opportunity to opt out of receiving genetic test results, and (3) discuss opportunities for research participation.

Confidentiality

Recommendation 2. Although genetic test results may become part of the cause of death statement and autopsy report, the public release of post-mortem genetic test results should generally be treated as an "unwarranted invasion of personal privacy" and exempted from disclosure under state and federal Freedom of Information Acts.

Analysis

Recommendation 3.1. Causality of any given gene variant should be determined through a process that includes (1) review of the literature, (2) careful manual curation of multiple databases, (3) validation of the finding by an independent method (usually Sanger sequencing), (4) if carried out in a research laboratory, confirmation of the result in a CLIA/CAP certified diagnostic laboratory, (5) multidisciplinary collaboration, and (6) other useful methods.

Recommendation 3.2. Validation testing of available first-degree biological relatives should be carried out whenever possible.

Disclosure

Recommendation 4.1. Positive results that are confirmed and determined to be causative or likely causative should be disclosed to the next-of-kin and first-degree biological relatives who have submitted samples for validation testing. The potential risk to other biological relatives should be clearly communicated.

Recommendation 4.2. When communicating negative findings, families should be counseled on the limitations of our current knowledge and technology to detect all genetic risk factors for SDY.

Recommendation 4.3. The disclosure discussion with the family and biological relatives should include a genetic counselor or clinical geneticist.

Recommendation 4.4. All first-degree relatives of the decedent with a presumed pathogenic variant should be referred to a genetic specialist familiar with issues in diagnostic DNA sequencing and the interpretation of the lab reports, and a clinical specialist who has familiarity with the specific disorder and expertise in evaluation, follow-up, and management of these rare disorders.

Recommendation 4.5. The ME/C should remain involved in the case even after disclosure because follow-up genetic testing of biological relatives could affect the determination of the cause and manner of death of the decedent.

is not required as a matter of law, and some suggest it may not be ethically required if genetic testing is crucial to a death investigation (MacLeod et al. 2013). Moreover, a ME/C may have legitimate concerns that allowing families an opportunity to veto an aspect of the death investigation would be at odds with both professional responsibility and the legal duty of a public official with a specific charge. These disparate legal and ethical frameworks collide when genetic testing is done as part of a death investigation but then used as the foundation for public health and research programs.

Although concerns about individual autonomy and privacy are either attenuated or absent in the context of post-mortem genetic testing, the results of an autopsy may be relevant to living biological relatives, with potential for third party benefit and harm (Forrest et al. 2007; Semsarian et al. 2015). The potential benefits of molecular autopsy may include peace of mind and early testing and treatment for biological relatives (Sexton and Metcalf 2008). Potential harms could include discovery of misattributed parentage, with possible ramifications for the family, as well as undue concern and anxiety about mutations in other children. Disclosure of plans to conduct a molecular autopsy is an acknowledgment of the family's interests and potential concerns. Disclosure can also help to secure buy-in early on, as proper interpretation of genetic test results often requires testing of biological relatives. Early inclusion may also prepare family members for genetic test results, allow them to pursue genetic counseling and recom-

mended clinical testing, and increase research participation (Sexton and Metcalf 2008).

Parental notification of genetic testing should not interfere with the death investigation conducted by the ME/C. Approximately 27 jurisdictions require a death investigation whenever a child (usually under age 18) dies, and the remaining states require an investigation when the death is suspicious or unexpected (<http://www.cdc.gov/phlp/docs/coroner/table1-investigation.pdf>). Merely notifying parents or guardians of a plan to conduct genetic testing would not provide additional information enabling parents to impede the investigation. Moreover, genetic testing could provide exculpatory evidence that supports parents' innocence and so should not engender a negative reaction on their part.

There is also potential for genetic testing conducted without family knowledge to undermine public trust, even when informed consent is not legally required, as illustrated by recent controversies. The Alder Hey Children's Hospital in Liverpool, England became a focus of criticism when its practice of performing genetic testing on retained tissues and organs from child autopsies came to light (Sexton and Metcalf 2008). In response to public outrage, the law was changed to restrict tissue retention for later testing or research (Sexton and Metcalf 2008). Similarly, in Minnesota and Texas, state health departments were sued for storing blood specimens collected for newborn screening indefinitely and using them for research and other purposes without parental knowledge or consent (Lewis et al. 2012). Millions of specimens had to be

destroyed, and both states now have laws that give parents the option of limiting sample storage and use (Lewis et al. 2012).⁸

In light of these considerations, although consent is not legally required to conduct a molecular autopsy, we recommend that, unless it would compromise the death investigation, reasonable efforts be made to notify the decedent's family before conducting genomic analysis as an aspect of a death investigation or when a positive result is obtained (Recommendation 1.1). This would increase transparency without unduly impeding achievement of the goals of ME/Cs, public health agencies, and researchers. Such a conversation should be used as an opportunity to (1) solicit consent to obtain samples from first-degree biological relatives, if available, for confirmatory testing, (2) offer family and biological relatives an opportunity to opt-out of receiving genetic test results, and (3) discuss opportunities for research participation (Recommendation 1.2).

Confidentiality

A notable consideration for molecular autopsies is the potential for genetic results to become part of the official autopsy report, which may ultimately be accessed by the public under the state's Freedom of Information Act (hereafter, collectively referred to as SFOIA). These state laws are patterned after the federal Freedom of Information Act (FOIA) and serve the purpose of maintaining transparency and accountability in government. Open government must be balanced with privacy interests, and every state law provides some version of the federal exception to disclosure for information contained in personnel, medical, or similar files when its release would constitute an "unwarranted invasion of personal privacy".⁹ Some states, such as New York, go further and specifically exempt autopsy reports from their SFOIA, with exceptions only for law enforcement, next-of-kin, and for public safety reasons.¹⁰

Other states, such as Texas, explicitly allow for the public disclosure of autopsy reports under their SFOIA.¹¹ In cases where a molecular autopsy is performed, genetic test results related to the cause of death will become part of the cause of death statement and the autopsy report. However, because genetic information is identifiable, can reveal predictive information about future disease risk, and is familial by its very nature, release of such information could cause harm (e.g., genetic discrimination, stigmatization) to families, which outweighs the public interest in disclosure.

Even in the absence of harm, families and biological relatives have a privacy interest that deserves protection. The United States Supreme Court recognized families' right to personal privacy with respect to their close relative's death-scene images in a case involving a request for death scene photographs of President Clinton's deputy counsel, Vincent Foster.¹² The Supreme Court agreed with the District Court that the autopsy photographs were exempt from disclosure under the federal FOIA because their release would constitute an "unwarranted invasion of personal privacy" that was

not outweighed by evidence of the public's interest.¹³ Even states with the strongest public policy favoring open government have excluded autopsy photographs from public disclosure, and many people consider genetic information to be just as private as graphic images, justifying similar protections.

Although genetic test results may become part of the cause of death statement and autopsy report, we recommend that the public release of post-mortem genetic test results generally be treated as an "unwarranted invasion of personal privacy" exempt from disclosure under state and federal FOIAs (Recommendation 2). In accordance with state autopsy laws, release to guardians and parents of the deceased child would not be affected by this exemption, and other limits to the exemption could be promulgated to account for the interests of extended family members and other biological relatives. Additional limited exceptions to nondisclosure could also be promulgated to permit disclosure of post-mortem genetic test results for research and to public health officials, an approach already adopted by some states with strong privacy protections.¹⁴ We are not proposing the case-by-case application of our recommendation by ME/Cs, as that would create an undue burden. Rather, we believe states should create statutory guidance on the release of molecular autopsy results, as has already been done with autopsy photographs.

Analysis

It has been estimated that genetic testing of decedents or their family members may identify inherited cardiac disease in as many as 30% of young sudden cardiac deaths (Tester and Ackerman 2006). However, there are no standards for genomic analysis or interpretation, resulting in unacceptably large numbers of false positives (MacArthur et al. 2014). SDY cases are particularly challenging because often there are no pathological findings on autopsy, parental samples may not be available for confirmatory testing, and ME/Cs may have limited family history information.

In order to mitigate the potential for false positives, we recommend a comprehensive process for determining the causality of any given gene variant that includes (1) review of the literature, (2) careful manual curation of multiple databases (e.g., OMIM, HGMD, dbSNP, ESP, ClinVar), (3) validation of the finding by an independent method (usually Sanger sequencing, if next generation sequencing was used), (4) if carried out in a research laboratory, confirmation of the result in a CLIA/CAP certified diagnostic laboratory, (5) multidisciplinary collaboration, and (6) other useful methods (Recommendation 3.1). Rigorous processes and evidentiary standards for causality are important because a positive genomic finding for a child with unexplained sudden death may lead to a costly and potentially harmful cascade of follow-up tests and screening for biological relatives (Deyo 2002).

Our group benefited from vigorous multidisciplinary discussion among MATCH members, including ME/Cs, anatomic pathologists, medical geneticists, genome scientists, bioethicists, lawyers, and genetic counselors, in deciding which variants to report to the family. We also met with a team of cardiologists to discuss the findings and any follow-up recommendations for the family before issuing a written report, and going forward, we would suggest that these specialists be engaged from the outset.

⁸Minn. Session Laws, chapter 203, S.F. No. 2047 [2014]; <http://www.leg.state.mn.us/>.

⁹U.S.C.A. title 5, section 552[b][6] [2000]; <https://www.gpo.gov/fdsys/pkg/USCODE-2011-title5/pdf/USCODE-2011-title5-part1-chap5.pdf>.

¹⁰N.Y. Ann. section 677[3][b]; <http://codes.findlaw.com/ny/county-law/cntsect-677.html>.

¹¹Tex. Gov. Code title 5[a], section 552.001; <http://www.statutes.legis.state.tx.us/>.

¹²*National Archives v. Favish*, 541 U.S. 157 [2003].

¹³*National Archives v. Favish*, 541 U.S. 157 [2003].

¹⁴*National Archives v. Favish*, 541 U.S. 157 [2003].

We are fortunate to be located in a large urban academic medical center and recognize that other ME/Cs may have to reach out to collaborate with individuals with relevant expertise.

In our study, we did not conduct validation testing of biological relatives, but as previous studies have confirmed, such validation testing and examination of family medical histories can help inform interpretation (Bagnall et al. 2014; Miles and Behr 2016). For example, findings of a genetic variant in a clearly unaffected relative might signal caution, although because there is variable penetrance with many of these genes, causality would not be ruled out. As the field moves toward whole-genome and whole-exome sequencing (WG/WES), we are seeing an increasing number of healthy individuals presenting with what were previously thought to be fully penetrant disease genotypes, making it more challenging to understand the causal relationship of genetic variants. Because understanding causation is so crucial to the death investigation, we recommend validation testing of available first-degree biological relatives whenever possible (Recommendation 3.2).

Disclosure to families

Positive results that are confirmed and determined to be causative or likely causative should be disclosed to the next-of-kin and first-degree biological relatives who have submitted samples for validation testing. The potential risk to other biological relatives should be clearly communicated (Recommendation 4.1). Relatives who submit samples for validation testing should also be told whether they carry the variant identified in the deceased. It may also be important to communicate negative findings, but families should be counseled on the limitations of our current knowledge and technology to detect all genetic risk factors for SDY (Recommendation 4.2). Molecular autopsies have the potential to reveal misattributed parentage, and depending on the technology used, even cases of consanguinity. Although there is some debate whether to disclose these findings (Palmer and Fiester 2014; Chandler 2015), current guidelines suggest avoiding disclosure unless “there is a clear medical benefit that outweighs the potential harms” (Botkin et al. 2015). When conducting genomic analysis, information about misattributed parentage may be crucial to the interpretation of findings and recommendations for follow-up clinical testing, which should be considered in weighing the risks and potential benefits of disclosure.

As the cost of sequencing declines, molecular autopsies will increasingly be performed using newer technologies such as WG/WES. This has the potential to reveal incidental findings unrelated to sudden death. In clinical genetics, it is recommended that laboratories report and clinicians communicate certain clinically significant incidental findings to patients who undergo WG/WES and have consented to disclosure (Green et al. 2013). However, because autopsies for SDY are state mandated for the purpose of identifying the manner and cause of death and the ME/C does not have a physician-patient relationship with the deceased or the relatives of the deceased, it would exceed the scope of their professional obligation to require them to report findings unrelated to the death investigation.

Even without disclosure of incidental findings, counseling families of SDY victims about the results of a molecular autopsy is complex and challenging. We therefore recommend that the disclosure discussion include a genetic counselor or clinical geneticist (Recommendation 4.3). Overall, the main goals of counseling should include explaining the finding in language the family will understand, identifying other at-risk relatives, and providing

referrals for follow-up as needed. Consideration should be given to obtaining a three-generation pedigree. Further, we recommend referral of all first-degree relatives of the decedent with a presumed pathogenic variant to a genetic specialist familiar with issues in diagnostic DNA sequencing and the interpretation of the lab reports, and a clinical specialist who has familiarity with the specific disorder and expertise in evaluation, follow-up, and management of these rare disorders (Recommendation 4.4).

Those involved in the post-test care of the surviving relatives should carefully consider the limitations of the results of the molecular autopsy in determining their significance and how to use them. The type of test that was performed (e.g., panel versus WG/WES), the context in which it was performed (e.g., research laboratory versus clinical laboratory), and the expertise of those performing the analysis should all be taken into account. Finally, this entire process should be a collaborative effort, with the ME/C remaining involved even after disclosure because follow-up genetic testing of biological relatives could affect the determination of the cause and manner of death of the decedent (Recommendation 4.5).

Conclusion

Genomic analysis has become increasingly important in clarifying the contribution of heritable conditions to SDY and potentially preventing sudden death in biological relatives. As molecular autopsies become integrated into death investigations conducted by ME/Cs, it is essential that they be conducted ethically and in accordance with relevant law. We hope that the recommendations generated by our multidisciplinary consortium will stimulate a more robust national discussion and contribute to the development of consensus standards for the more routine integration of molecular autopsies in cases of sudden death in the young.

Competing interest statement

A.L.M. is an unpaid Ethics Consultant for the SDY Registry.

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