In-BRIEF

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What Medical Examiner's and Coroner's Offices Should Know about Molecular Autopsy

"Molecular autopsies, exemplifying precision in forensic medicine, saves lives"

—Yingying Tang, M.D., Ph.D., DABMGG | New York City OCME Molecular Genetics Laboratory

Objectives

- Identify opportunities and benefits of using molecular autopsy techniques in casework.
- Define action items MEC offices should take to implement molecular autopsy techniques in casework.
- Explain the challenges of and provide potential solutions for implementing molecular autopsy techniques in casework.
- Showcase advancing research and molecular autopsy capabilities at MEC offices.

Introduction

A molecular autopsy consists of "postmortem genetic testing of decedents who died naturally, suddenly, and unexpectedly at young ages."[1] Molecular autopsies can enable a more accurate determination of cause of death in cases where the scene investigation, medical records review, toxicological analysis, and autopsy procedures have yielded negative or inconclusive results or positive results that may indicate a genetic cause. The 2020 Asia Pacific Heart Rhythm Society (APHRS) and the Heart Rhythm Society (HRS) Consensus Statement recommended incorporating molecular autopsies into the investigation of sudden unexplained deaths, and its utility has been demonstrated in determining pathogenic variants in cases of cardiovascular system conditions (e.g., thoracic aortic aneurysms, pulmonary embolisms), epilepsy and other seizures disorders, and sudden unexpected infant deaths.[2] Genetic testing panels can provide medical examiners and coroners (MECs) with an etiologically specific cause of death, provide more precise answers for surviving family members, and be a point of intervention for survivors to pursue further testing and prevent future sudden deaths. Knowing which variants are detected in the decedent can help guide genetic counselor recommendations for future testing,

including which relatives may be highest at risk because of the variants' inheritance patterns, and assist physicians in providing more precise medical care and monitoring recommendations for patients who have a higher predisposition of developing conditions that cause sudden death.

Traditionally, the cost of postmortem genetic testing ranged in the $1,000s per sample (i.e., a cost too high for most MEC offices or surviving family members to consider). Although some laboratories performed postmortem genetic testing, suitable samples were not always retained at autopsy for instances when surviving family members decided to pursue follow-up testing.[3] However, advancements in DNA technology have reduced costs and increased laboratory testing capabilities. Furthermore, with MEC offices following proper sampling procedures established by the National Association of Medical Examiners (NAME), these traditional deterrents of postmortem genetic testing are becoming less of a hurdle and more MEC offices are looking to implement molecular autopsy into their standard operating procedures.

Expansion of the Molecular Genetics Laboratory at the New York City Office of Chief Medical Examiner

Supported by four National Institute of Justice (NIJ) grant-funded research projects[a], the New York City Office of Chief Medical Examiner (OCME) Molecular Genetics Laboratory, led by Dr. Yingying Tang, developed and validated massively parallel sequencing/next-generation sequencing testing panels on various postmortem sample types and provided support for functional and family studies when results returned a variance of uncertain significance.[4] The New York City OCME recruited its first board-certified genetic counselor in 2015 (i.e., the first genetic counselor to be employed at an MEC office) and is currently compiling the results of a retrospective analysis of over 1,000 cases looking at the yields of cardiac genes testing and genotype-phenotype correlations.[4] Approximately 6,000 cases each year are autopsied at the New York City OCME, of which around 10% have samples submitted to the Molecular Genetics Laboratory for postmortem genetic testing or to be held for future genetic testing following autopsy and ancillary testing results. Cases with positive and negative autopsy findings suspicious for genetic contribution are tested to provide genetically specific information for cause of death determination. The results generated may be relevant to surviving family members who can benefit from possible follow-up testing and effective clinical care guided by their genetic counselor.

To help the MEC community better understand the current state of and implementation considerations for molecular autopsy, the Forensic Technology Center of Excellence (FTCOE) conducted interviews and assembled a "Molecular Autopsy Implementation Expert Panel" discussion on September 26, 2023. The panel provided guidance on molecular autopsies from a wide range of multidisciplinary experts, including forensic pathologists, cardiologists, geneticists, cardiac geneticists, genetics counselors, and surviving family members who have experienced the molecular autopsy process at the New York City OCME (**Exhibit 1**). Additionally, to complement the expert panel, the FTCOE coordinated a five-part virtual resource, entitled "Molecular Autopsy Implementation at the New York City OCME," to showcase workflows, relationships, and key considerations for MECs when implementing these techniques.

[a] NIJ Award Numbers: 2011-DN-BX-K535, 2014-DN-BX-K001, 2015-DN-BX-K017, & 2018-DU-BX-0204

Exhibit 1: List of the individuals involved in the FTCOE "Molecular Autopsy Implementation Expert Panel" held on September 26, 2023.

Molecular Autopsy Implementation Expert Panelists

Name	Title	Organization
Dr. James Gill	Forensic Pathologist, Chief Medical Examiner	Connecticut Office of the Chief Medical Examiner
Dr. Jason Graham	Forensic Pathologist, Chief Medical Examiner	New York City Office of Chief Medical Examiner
Dr. Celine Gounder*	Epidemiologist, Clinical Associate Professor of Medicine and Infectious Diseases	New York University Grossman School of Medicine
Dr. Susan Liebman*	Geneticist, Research Professor of Pharmacology	University of Nevada, Reno
Dr. Robert Marion	Medical Geneticist	Children's Hospital at Montefiore/Albert Einstein College of Medicine
Dr. Kathryn Pinneri	Forensic Pathologist, Director	Montgomery County (Texas) Forensic Services
Dr. Barbara Sampson	Forensic & Cardiac Pathologist, Vice Chair & Professor	Icahn School of Medicine at Mount Sinai
Sarah Saxton	Genetic Counselor	New York City Office of Chief Medical Examiner Molecular Genetics Laboratory
Monisha Sebastin	Senior Genetic Counselor	Montefiore Medical Center
Dr. Michelle Stram	Forensic Pathologist, Senior Medical Examiner	New York City Office of Chief Medical Examiner
Dr. Yingying Tang	Medical Geneticist, Director	New York City Office of Chief Medical Examiner Molecular Genetics Laboratory

*Denotes surviving family member who have experienced the molecular autopsy process at the New York City Office of Chief Medical Examiner.

Eight Things MEC Offices Should Know About Molecular Autopsy

Through the virtual resources and roundtable discussion, molecular autopsy implementation panelists provided comprehensive considerations for implementing molecular autopsy in casework. Eight key takeaways for MECs to consider are as follows:

1. The consideration of underlying genetic conditions for sudden deaths begins at the scene investigation and continues with an in-depth medical, familial, and social history evaluation.

Scene information and thorough interviews with witnesses of the sudden event, individuals closely associated with the decedent, and first responders can provide vital insight into perimortem indicators (e.g., recent or concurrent physical activity, witnessed physical symptoms, original body positioning) that may suggest that a molecular autopsy may be appropriate. When collecting the scene information and the medical and social histories of the decedent and their family members, it is important for medicolegal death investigators (MDIs) to ask questions broadly and in different ways, rather than asking about specific conditions, and to establish biological relationships to the decedent. MDIs should note family history of sudden cardiac death, cardiac conditions manifesting before middle age, traumatic deaths related to swimming or vehicle accidents (which can be triggered by cardiac events), or any sudden deaths of young and otherwise healthy individuals in the death investigation report.[2,5] Episodes of shortness of breath; rapid, skipping, or irregular heartbeats; and fainting, especially if they are related to a particular physical activity, are common, but not exclusive, symptoms children and adults may experience prior to a sudden death event. These symptoms, and details about what situations may have led to them, may not be available or documented in the decedent's medical history but can help point toward cardiac or non-cardiac-related conditions.

In cases of epilepsy or seizure disorders, MDIs should establish a detailed history of the seizure events through interviews and medical records review, noting whether the seizures are natural or post-traumatic, their age of onset and frequency, and if there is an association with illicit substances and alcohol use or recent withdrawal. On-scene MDIs should focus on any located medications, or lack thereof, document the decedent's compliance (i.e., comparing pill counts to prescription fill dates) in the death investigation report, and complete thorough scene photography. "Sudden unexplained deaths of an individual with epilepsy can pose a challenge to death investigators, as most deaths are unwitnessed, and the individual is commonly found dead in bed."[6] When sudden deaths are unwitnessed, it is important for MDIs to thoroughly examine and document the body positioning and related breathing obstructions, as the prone position has been associated with sudden unexpected death in epilepsy.[6,7]

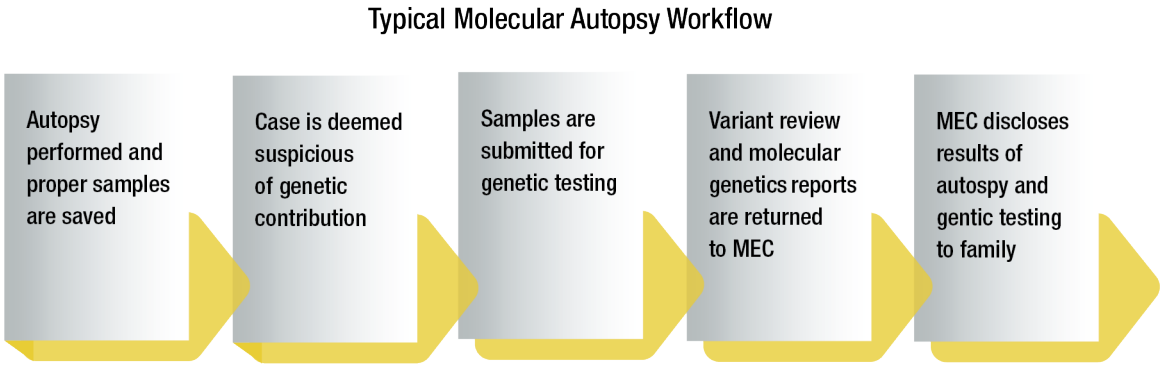
Sudden unexpected infant death investigations can be challenging cases and can also benefit from molecular genetic testing. MDI interviews and medical records requests should focus on the infant's age, gestational age at birth, birth history, and complete medical history. Additionally, MDIs should gather information and medical records pertaining to the mother's pregnancy history and medical history, as well as any family member(s) who also experienced infant or pediatric deaths when possible. MDI interviews and scene documentation, when infant deaths may be related to sleep, should focus on body positioning, breathing obstructions, and sleeping conditions. MDIs should also be sure to document any changes to the scene or decedent's position by family members, witnesses, or emergency personnel.

MECs should work closely with their MDI team to create standardized forms of investigation questions, as well as establish standard operating procedures for scene documentation and medical records search and acquisition in cases of sudden cardiac death, sudden unexpected death in epilepsy, and sudden unexpected infant death.[5, 6, 8, 9, 10, 11]

2. Molecular autopsy may provide the most value for a certain subset of cases (as outlined by NAME); however, MEC offices should ensure proper sample acquisition and storage for all cases.

Death investigation is a complex, multi-step process in which the initial scene investigation, witness statements, and medical records review play an integral role in subsequent autopsy procedures, sample retention, consultation needs, and the decision to pursue ancillary testing. This includes identifying cases that could benefit from additional sampling at autopsy in case a molecular autopsy is needed (**Exhibit 2**).[12] The 2013 *NAME Position Paper: Retaining Postmortem Samples for Genetic Testing* stated "ideally, a specimen should be saved in all MEC cases in which an autopsy is performed; however, many offices function within systems where space, equipment, and financial considerations will prohibit achieving this practice."[13] NAME minimally recommends retaining an additional blood sample for genetic testing from "individuals 40 years of age and younger who die suddenly and unexpectedly and whose deaths remain unexplained at the completion of the autopsy."[13] Findings from the scene investigation, medical records review, autopsy, and ancillary testing "that should be considered suspicious for a possible genetic etiology include, but are not limited to 1) drowning, particularly in the case of a sober or experienced swimmer; 2) single motor vehicle accidents when no mitigation factors are present (e.g., toxicology negative, favorable road conditions); 3) an unexplained seizure in a young person; 4) cardiomyopathy or aneurysm identified on autopsy; 5) an unexplained death of an individual with a family history of sudden death or inherited heart disease, such as a cardiomyopathy, thoracic aneurysm or known genetic cardiac diagnosis; 6) a death that is sudden and unexplained where the cause of death is unclear at autopsy."[13] Often due to the cost of postmortem genetic testing, the decision to pursue this specialized testing only occurs after the investigation, autopsy, and toxicology results leave the pathologist with an undetermined cause of death. Therefore, it is imperative that proper sample acquisition and long-term storage needs are considered at time of the autopsy.

Exhibit 2: Typical workflow of death investigation cases suspicious of genetic contribution and involving postmortem genetic testing.



3. An additional 5-10 mL blood sample in K2-EDTA anticoagulant should be retained at autopsy for future genetic testing. When possible, fresh heart, liver, spleen, and skeletal muscle tissue samples should be retained and frozen in a nucleic acid stabilization solution. A bloodstain card should be saved for all cases.

The 2013 *NAME Position Paper* recommended an additional 5-10 mL blood sample in K2-EDTA (dipotassium ethylenediaminetetraacetic acid) anticoagulant be retained at autopsy for future genetic testing.[13] The sample should be stored at 4°C for short-term storage (<1 month) and moved to –20°C or –70°C freezers for long-term storage (months to years).[13] In addition to the K2-EDTA blood sample, the New York City OCME recommends that when possible, fresh heart, liver, spleen, and skeletal muscle tissue samples be retained and frozen in a nucleic acid stabilization and storage solution, which stabilizes and preserves RNA and DNA.[4] In cases of decomposition, or when blood and specified tissue samples cannot be retained, a collection of soft red bone marrow (preferred over soft yellow marrow) should be retained and stored in a stabilization solution.[4]

Ancillary testing results can take a significant amount of time to return, and the decision to pursue genetic testing often occurs only after other ancillary testing has produced negative results. Many MECs do not have access to –20°C or –70°C freezers necessary for long-term storage, so pathologists are often left with formalin-fixed-paraffin-embedded (FFPE) tissues to pursue further testing. However, research conducted by the New York City OCME Molecular Genetics and Forensic Biology Laboratories noted that formalin fixation impacts genetic sequencing by creating DNA cross-linking, binding, and fragmentation issues.[14] These complications increase with greater fixation times and produce high false negative errors and artifact variants that can increase the risk of false positive variant calls; therefore, they advise caution on reporting results from FFPE samples.

Ideally, dried bloodstain cards provide a stable DNA sample suitable for genetic testing and should be retained in all cases. Although dried bloodstain cards may require an additional extraction step prior to submission for genetic testing, they do not require a lot of space, refrigeration, nor stabilization solutions for long-term storage. Since 1994, the New York City OCME has implemented an agency-wide policy of retaining bloodstain cards for DNA testing.[3]

4. Targeted panel testing is recommended as first-tier testing, whereas unfocused whole-genome sequencing is reserved for second-tier testing because of possible misinterpretation of known variants and variants of uncertain significance.[2]

Genetic laboratories organize their tests into panels, which look at a specific set of genes whose variations are known to cause specific pathological conditions. Which genes are tested and how many are included may vary across testing laboratories and may change as novel pathogenic variants are discovered. In cases of sudden unexplained deaths, the medical history of the decedent and up to three generations of their family members should be considered when trying to determine which genetic panel to pursue.

As next-generation sequencing becomes more widely available, MEC offices with academic partnerships and in-house molecular testing laboratories have created panels specific to the needs and capabilities of their office and laboratory. The Harris County Institute of Forensic Sciences and Baylor College of Medicine in Houston, Texas, developed and tested a single panel of 64 genes associated with multiple diseases linked to sudden death both from cardiac and non-cardiac causes.[15] The New York City OCME and their Molecular Genetics Laboratory have developed seven molecular analysis testing options for the investigation of sudden death cases (**Exhibit 3**).

Exhibit 3: Current molecular genetic testing available at the New York City OCME Molecular Genetics Laboratory.

Test Name	Description of Tested Genes
Cardiac-Focused Sudden Death Molecular Analysis – Panel A	132 genes associated with cardiovascular system conditions (cardiomyopathies, cardiac channelopathy, pulmonary arterial hypertension), and non-cardiac channelopathy (Bartter/ Gitelman's syndrome, familial hyperinsulinism)
Epilepsy-Focused Sudden Death Molecular Analysis – Panel B	159 genes associated with epilepsy (14 channel genes are from Panel A)
Cardiac & Epilepsy Sudden Death Molecular Analysis – Panel C	277 genes associated with a combination of Panel A and Panel B conditions
Aortopathy Analysis	20 genes associated with aortic aneurysms and dissections
Malignant Hyperthermia Susceptibility Analysis	3 genes associated with malignant hyperthermia susceptibility
Thrombophilia Analysis	3 genes for anticoagulants (SERPINC1, PROS1, PROC) and 2 mutations (FVL and FII G20210A)
Sickle Cell Disease Analysis	Hemoglobin S and Hemoglobin C

5. MEC offices that do not have partnerships with academic medical centers or in-house molecular testing laboratories can find genetic testing laboratories by searching through the Genetic Testing Registry (GTR®).

The GTR®, managed by the National Institutes of Health (NIH), is a searchable database of over 74,000 tests at over 400 laboratories.[16] It can provide MEC offices with a starting point when looking for possible genetic testing laboratories, which genetic testing panels are available (i.e., searchable by specific conditions), how to order the tests, and specimen source requirements. It is important to note that the GTR® is not exhaustive, as participation from genetic testing laboratories is voluntary and the GTR® is not independently verified by the NIH.

6. The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) have created a joint consensus recommendation for standards and guidelines for interpreting sequence variants.[18]

Genetic reports should include the variant's name, gene location of the variant, the conditions and inheritances associated with the gene or variant, its zygosity (i.e., how many copies of a variant were detected), and the laboratory's classification of the variants into one of five categories: (1) pathogenic variant, (2) likely pathogenic variant, (3) variant of uncertain significance, (4) likely benign variant, and (5) benign variant. These classifications can help MECs determine if the variant is known to be disease-causing and provide recommendations for family risk and follow-up testing (**Exhibit 4**).[17]

Following recommendations by the ACMG and the AMP, the evidence-based variant interpretation process at the New York City OCME involves (1) searching ClinGen[19] and Omim[20] to understand the gene's role in the disease, (2) searching the variant in clinical databases (e.g., ClinVar[21], HGMD[22], ARVD[23]) and literature searches (e.g., PubMed) to know whether the variant was reported or published, (3) searching population databases (e.g., gnomAD[24]) to estimate minor allele frequencies, (4) performing multiple in silico predictions (e.g., PP2, SIFT/proven, MutationTaster[25]) for missense variants to understand their functional effects, and (5) correlating the medical history and autopsy findings with the variant.[4]

Exhibit 4: Genetic variant classifications can help determine the likelihood that the variant contributed to the cause of death and can help determine follow-up testing for surviving family members.

Variant Classification	Test Result	Recommendations
Pathogenic or Likely Pathogenic	Positive and diagnostic, is or likely is disease-causing, and contributing to cause of death.	Family should be alerted of the variant and pursue genetic counseling and testing.
Variant of Uncertain Significance	Positive but not diagnostic, may or may not have contributed to death or is disease-causing.	Family may still be at an increased risk and may want to consider genetic counseling and testing.
Benign or Likely Benign	Negative, no disease-causing variant found.	Family may still be at increased risk; clinical evaluations and surveillance should be based on decedent/family history.

7. Molecular testing results should be integrated with all other information to have a cohesive explanation for a decedent's cause of death.

Determining the cause of death integrates all the information from the scene investigation, the medical records review, the social history review, the autopsy, and the results of ancillary studies. This information must be integrated and considered with any molecular testing results in order to have a cohesive explanation for a decedent's cause of death. Additionally, pertinent molecular genetic findings should be included in the autopsy report and on the death certificate as well as in a separate molecular genetics report.

A structured autopsy report includes a list of final diagnoses and documents the ancillary studies. In cases where the molecular results fundamentally underpin the cause of death, there is a strong case to be made for including the molecular genetic results in the final diagnostic list on the autopsy report in addition to a separate molecular genetics report. A separate molecular genetics report serves two main purposes: (1) communicating the molecular genetic results in lay language which is meaningful for the family, and (2) communicating to clinicians and other providers the specifics of what testing was performed, how the interpretation was rendered, and what the results mean.

The gene responsible for the death should also be included on the death certificate. In the event that the family only has a death certificate, having the molecular genetic results conveyed with the cause of death is tremendously informative for any clinician. Additionally, it can provide important information for vital statistics.

8. Although clinicians help families interpret autopsy findings, genetic counselors help them navigate implications of testing results and next steps.

In sudden or unexpected death cases, clinicians provide families with clear explanations of findings and ongoing studies, focusing on making molecular genetic results easily understandable and conveying test specifics to healthcare providers. As part of a thorough process, clinicians ideally reconnect with families following the completion of the entire autopsy. During this phase, detailed reviews of autopsy ancillary testing and molecular genetics results take place. This stage serves as an opportune moment for offering families the option to consult with a genetics counselor, especially in cases where identified molecular results indicate a pathogenic or likely pathogenic variant.

Genetic counselors assist families in navigating the intricacies of postmortem genetic testing, offering objective insights into the procedure and its implications, and highlighting risks associated with identified variants. Additionally, due to inheritance patterns and gene expressivity, genetic counselors can help determine whether certain family members may be at higher risk of specific variants or may not need to pursue follow-up testing at all. Genetic counselors follow a communication strategy to ensure comprehensive and clear explanations are provided to families **Exhibit 5**) and families must provide pertinent information, including medical history, dysmorphic features, and family history, specifically noting early deaths and signs or symptoms, for effective communication. Genetic counselors offer emotional support and counseling to help families cope with the impact of genetic testing results. Furthermore, they acknowledge potential financial challenges, particularly related to insurance coverage, and provide financial options for family members. Their overall objective is to offer comprehensive assistance in navigating the intricate implications of genetic testing results.

To find a genetic counselor, individuals can start by consulting their primary care physician or healthcare provider. These professionals often have networks and can provide referrals to reputable genetic counselors. Additionally, online directories provided by professional organizations, such as the National Society of Genetic Counselors (NSGC), can be a helpful resource for identifying certified genetic counselors in specific regions.

Conclusion

Molecular autopsy and detection of inheritable pathogenic variants provide the MEC community with a unique opportunity to prevent future deaths by combining genetic test results with genetic counseling and proper follow-up care. Future initiatives at the New York City OCME are being directed towards their Genetic Intervention Family Testing Services (GIFTS), which would provide in-house genetic testing for affected surviving family members. Knowledge of genetic risk is only step one, as there are many financial and social barriers (e.g., insurance considerations, language barriers, scheduling factors) that may prevent a family member from pursuing follow-up care. GIFTS, which is currently pending New York State approval, would provide equal access to genetic testing to disadvantaged families that may otherwise not be able to pursue testing and will help streamline coordination of family testing for earlier medical interventions.[3] Additionally, the New York City OCME hopes to share their over 20 years of experience performing and interpreting genetic testing results by becoming a National Reference Laboratory for postmortem genetic testing. Through fee-for-service agreements or funding through federal grants, the Molecular Genetics Laboratory could offer DNA extraction services for bloodstain cards and blood and tissue samples for submission to other testing laboratories; assist MECs by providing directed, targeted testing based on autopsy findings and support the understanding, interpretation, and communication of those results; and aid in identifying a local clinical genetic network to connect with family members.

Exhibit 5: Common questions genetic counselors can address with surviving family members.

What is genetic testing, and why was it done?	The primary objective of genetic testing is to ascertain the cause of death, which may also shed light on any genetic factors that might have contributed to the deceased individual's condition. This process aims to provide both answers regarding the cause of death and potential insights into hereditary conditions.
How did genetics play a role in the autopsy findings and cause of death of the deceased individual?	By analyzing the genetic material results, genetic counselors can identify any underlying genetic predispositions or mutations that contributed to the medical conditions observed during the autopsy, providing a more comprehensive understanding of the cause of death.
What do the results mean for me and surviving family members?	Genetic testing results provide closure by revealing the cause of death and addressing any lingering questions and uncertainties. It also signifies the potential for hereditary implications, enabling early medical interventions to prevent the occurrence of similar medical conditions in family members.
How can my family move forward knowing these genetic testing results?	Following genetic testing, genetic counselors may recommend specific courses of action for the family to navigate the future. This could include further medical evaluations, lifestyle adjustments, or periodic screenings for family members identified as potentially at risk.

Resources

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