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CURRENT PRACTICES IN POST-MORTEM CARIOGENETIC TEST-ORDERING
AND GENETIC COUNSELING IN CASES OF SUDDEN CARDIAC DEATH (SCD)

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Current Practices in Post-Mortem Cardiogenetic Test-Ordering and Genetic Counseling in Cases of Sudden Cardiac Death (SCD)

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KEYWORDS

Sudden cardiac death, Sudden unexpected death, SCD, SUD, Post-mortem genetic testing, Medical examiners, Genetic counselors, Genetic counseling, Genetic testing, Insurance coverage

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ABSTRACT

This study aims to provide current insights into practice variation among genetic counselors (GC's) and medical examiners (ME's) with regards to post-mortem genetic testing in the context of Sudden Cardiac Death (SCD). Ninety total respondents (37 GC's, 47 ME's, 3 cardiologists, and 3 forensic pathologists) were surveyed, with questions addressing: who initiates testing and for what indications; what types of tests are ordered and how are they paid for; and what areas of the post-mortem genetic testing process need to be addressed in future studies for potential improvement. Significantly more GC's ordered post-mortem genetic testing for SCDs than ME's, with financial constraints being the main obstacle for ME's and sample type/amount being the main determining factor for GC's. The majority of respondents who ordered testing used arrhythmia panels with both cardiomyopathies and channelopathies. Most GC's (64.9%) reported families paying out-of-pocket, whereas many ME's (48.9%) reported their ME Office covering testing costs. Experience with insurance coverage was highly varied across GC's, while ME's were generally unsure about coverage. Seventeen ME's (36.2%) reported no provision of pre-test counseling to families affected by SCD; 14 (29.8%) reported referring families to other providers or research organizations for determination of testing. When cost was not a barrier, grief was reported to be the greatest obstacle to testing. Overall, there were notable differences in practice, knowledge, and opinions between GC's and ME's with regards to pre-test counseling, financial responsibility, and key determining factors for testing, respectively. Future research is needed to help establish a uniform and enforceable protocol that healthcare professionals (including ME's) and insurance companies can adhere to for post-mortem genetic testing in SCD cases, so that all affected families may receive the same standard of care during one of their most difficult times.

INTRODUCTION

Sudden unexplained death (SUD) describes any death that occurs as a natural and fatal event within an hour of symptoms onset, or within 24 hours after the affected individual was witnessed as completely healthy (Adabag, Luepker, Roger, & Gersh, 2010; Lim, Gibbs, Potts, & Sanatani, 2010; Srinivasan & Schilling, 2018). In some SUD cases, a completed autopsy can determine no identifiable cause or can suggest a potential genetic cause of death (Middleton et al., 2013). Sudden cardiac death (SCD), by comparison, refers specifically to a subset of SUDs with a definitive cardiovascular cause, or can be applied to any death or cardiac arrest that occurs outside of the hospital or in the emergency room, presumably due to coronary/ischemic heart disease (Adabag et al., 2010; Hayashi, Shimizu, & Albert, 2015).

Worldwide SCD accounts for 15-20% of all deaths, and over 60% of all deaths from cardiovascular disease (Adabag et al., 2010; Hayashi et al., 2015). In the U.S., a 2018 report from the American Heart Association cited SCD prevalence in the U.S. as 13.5%, or 1 in every 7.4 people (Benjamin et al., 2018). Risk factors for SCD can include certain behaviors (poor eating, heavy alcohol use), sex, age, ethnicity (African-American or non-Asian), past medical history (hypertension, diabetes), family history of SCD, and specific genetic variants (Wong et al., 2019). The majority of SCDs (75%) are caused by coronary heart disease (CHD) (also called coronary artery disease and ischemic heart disease), followed by cardiomyopathies (15%), valvular heart disease (5%), inherited arrhythmia syndromes (2%), and other causes (3%) (Srinivasan & Schilling, 2018).

The prevalence of arrhythmias ranges from 1/1,000 to 1/10,000, and 1/250 to 1/1,000 for cardiomyopathies (Lin et al., 2017). Primary arrhythmic disorders (long-QT syndrome, Brugada syndrome, and catecholaminergic polymorphous ventricular tachycardia) are defined as

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conditions where improper functioning of ion channel proteins in the heart muscle cells causes irregular heartbeats. On the other hand, cardiomyopathies (hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy) are a heterogeneous group of diseases affecting the structure and/or function of the heart muscle. Both channelopathies and cardiomyopathies can be inherited or acquired (some cardiomyopathies can also be idiopathic), and both can have sudden death presenting as the first symptom.

Many experts have emphasized the importance of post-mortem genetic testing for SCD cases that are categorized as autopsy-negative, and recommend including it as a required component for adequate postmortem assessment of SCD (Semsarian & Hamilton, 2012; Gollob et al., 2011; Tester et al., 2012). The purpose of postmortem genetic testing is to identify whether the deceased carried a pathogenic variant that explains their SCD, and to initiate genetic testing in family members of the deceased (symptomatic or not) whenever a pathogenic variant is detected, as they may also carry the variant and be at increased risk for SCD. Knowing the specific causative variant(s) can allow for risk stratification and phenotype prediction in carriers. This is useful because most cardiomyopathies and inherited arrhythmias have variable expressivity and low penetrance (Bezzina, Lahrouchi & Priori, 2015). Besides providing genotype-phenotype correlations, genetic test results can also highlight suitable treatments, medications, and enhanced screening options for eligible individuals. For example, some individuals with a specific variant have an optimal response to beta blockers, while those with other variants experience symptom recurrences despite full-dose beta blockers. In the future, individuals diagnosed with HCM who carry a specific SNP that can be targeted by an adeno associated virus-9-mediated RNAi may be eligible for gene therapy, which will suppress the expression of the mutant allele of the gene (Bezzina, Lahrouchi & Priori, 2015).

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Overall, pathogenic variants found in this context are actionable, and positive result disclosure necessitates the following discussion points: receiving follow-up, surveillance, making lifestyle changes, taking medications, and even having cardioverter defibrillators implanted for prophylaxis (especially if they are adults). All of these interventions can provide patients with a normal life expectancy (Ackerman et al., 2016; Garcia-Elias & Benito, 2018; Jacoby & McKenna, 2012; Miles et al., 2019; Tan et al., 2005).

Major genetic testing companies now offer next generation sequencing (NGS) panels that encompass a great majority of the genes associated with arrhythmias, cardiomyopathies, or both. These large panels have both advantages and disadvantages relative to more targeted testing. On the one hand, the scale of such testing increases the yield of positive results. Tan et al. (2005) used molecular genetic testing on 43 families and reported 8.9 asymptomatic carriers of inherited disease per family. However, larger panels open the door for an increase in variants of unknown significance (VUS). Additionally, larger panels expand to include genes with weaker associations that may be influenced by modifier genes or environmental factors, further complicating variant interpretations (Kapplinger et al., 2011). These genes may have small or uncertain clinical utility. The need for lengthy counseling, the emotional and psychological stress associated with uncertainty, and the risk of misinterpretation by healthcare providers are all challenges to the usage of large panels. Despite these disadvantages, the ease and coverage of large diagnostic panels is often more appealing to providers.

To date, the ability to conduct post-mortem genetic testing has been limited due to the absence of resources and insurance coverage. Lack of resources is a potential explanation for why post-mortem genetic testing is not standard practice at most medical examiners' offices. A body is brought to a medical examiner's attention under any of the following circumstances:

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death by criminal violence, by accident, by suicide, suddenly and when in apparent health, when unattended by a physician, in a correctional facility, or in any suspicious or unusual manner. The role of a medical examiner includes the following responsibilities: investigate the circumstances surrounding the deaths, perform an autopsy and external examination, order or complete needed lab tests and review results, determine cause and manner of death, complete death certificate, and compile all findings into a report. In a 2013 position paper, the National Association of Medical Examiners (NAME) presented recommendations for medical examiners to follow when retaining postmortem samples for genetic testing in the context of sudden unexpected death (Owen et al., 2013; Semsarian & Hamilton, 2012). The level of care outlined in this position paper is hard to ensure, given that the infrastructure and funding systems of Medical Examiner Offices vary from state to state, and feasibility of sample collection, storage, transport, and communication for each location may differ. (Tester et al., 2012)

Besides limited resources, who or what institution is responsible for covering the cost of post-mortem genetic testing is another area with inconsistencies. In a study by Mohammed et al. (2017), 54% of individuals with a diagnosis applied for insurance, and 60% of them reported being denied coverage on the basis of “sudden arrhythmia death syndromes” (SADS) as a pre-existing condition. The authors addressed that these changes in coverage and premium rates predated the full enforcement of protective provisions in the Affordable Care Act of 2010; they anticipated that such forms of discrimination would be reduced after January 1, 2014, when the provisions came into full effect. The Heart and Rhythm Society created a poster at the 2014 conference titled *Review of Postmortem Clinical Genetic Testing Sample Success Rates and Payors from Commercial Labs*, which can now be found to the National Society of Genetic Counselors (NSG) website. Out of the 313 postmortem cases surveyed, the majority were self-

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pay (42%), but other payor types included medical examiner and/or forensic pathologist (14%), Canadian Ministries of Health and Pathology Services (24%), US medical Institution (11%), commercial insurance (6%), and other (3%). There have been virtually no studies on insurance coverage of genetic testing for postmortem analysis of suspected SCD, or for testing of family members of victims with suspected SCD. Studies are needed to assess current postmortem practices for sudden death, which may provide insight for outlining detailed and feasible site-specific protocols.

For family members concerned about the financial burden of pursuing post-mortem genetic testing (especially in light of its diagnostic uncertainty), alternative options have been explored. An example is DNA banking, which may be more affordable and would allow families to pursue testing at a later point when scientific knowledge in this area has advanced (Middleton et al., 2013). Another option is using commercially available genetic testing services that provide cardiac panels targeting genes associated with sudden death in those under age 40 (Methner et al., 2016); these still involve an out-of-pocket expense, but may be less expensive (Tester et al., 2012). Finally, another option discussed by Tester et al. (2012) is enrolling the deceased's sample into research-based genetic testing; here, the price is free, but the process can be painfully slow. At this point in time, there is a shortage of available literature on current genetic testing trends in the context of sudden cardiac death. This study surveys healthcare professionals (medical examiners, genetic counselors, and cardiologists) who are involved in ordering post-mortem genetic testing, to gain insight into their opinions on the following: who is ordering post mortem testing, what specific tests are being ordered, what specific medical events necessitate postmortem testing, and how coverage for postmortem testing varies by region.

METHODS

This study was designed to capture the experience and perspective of medical providers likely to have interacted with families following SCD, including GC's, ME's, and cardiologists. Much of this study borrows from and expands upon Liu et al.'s (2018) exploration on genetic counselors' approach to postmortem genetic testing after sudden death. GC's were recruited via an email list of full members maintained by the National Society of Genetic Counselors (NSGC), a professional organization for GC's and other healthcare professionals involved in genetic counseling. To recruit ME's, the survey was sent to the National Association of Medical Examiners (NAME) and to the International Association of Coroners and Medical Examiners (IACME). Attempts at recruiting cardiologists were largely unsuccessful, although the survey was distributed to colleagues by several cardiologists reached through personal contacts. For NSGC, NAME, and IACME, a total of two emails were sent by each organization—one initial email, and one reminder email.

A survey was developed, evaluated by our advisors, and piloted by one cardiologist before being distributed using surveymonkey.com (a pilot was not conducted with GC's or ME's due to time constraints). The introduction to the survey included informed consent and specified inclusion criteria limiting participation to individuals directly or indirectly involved with postmortem genetic testing for cases of sudden cardiac death (SCD). The survey consisted of a maximum of 27 questions and utilized skip logic. All responses were anonymous. Respondents were asked about their professional roles and demographics at the beginning of the survey. The study was approved by Institutional Review Boards at Sarah Lawrence College and the NYC Office of the Chief Medical Examiner.

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All data was downloaded from [surveymonkey.com](https://www.surveymonkey.com). Statistical analysis was conducted using Microsoft Excel (part of the MS Office Professional Plus 2016 Suite). Responses for all questions were summarized using the PivotTable function to create frequency distributions and contingency tables. Responses were coded and collapsed to facilitate interpretation. In particular, states in the USA were collapsed into the four Census-Bureau-designated regions:

Northwest: CT, ME, MA, NH, RI, VT, NJ, NY, PA

Midwest: IN, IL, MI, OH, WI, IA, KS, MN, MO, NE, ND, SD

South: DE, DC, FL, GA, MD, NC, SC, VA, WV, AL, KY, MS, TN, AR, LA, OK, TX

West: AZ, CO, ID, NM, MT, UT, NV, WY, AK, CA, HI, OR, WA

Results were analyzed using Pearson Chi-square tests and Fisher's exact tests. Statistical significance was defined as a p -value equal to or less than 0.05. As sample size was low for cardiologists and forensic pathologists, their responses were not used as a separate group for statistical analysis, but were included when considering the total number of responses.

The online survey was sent to approximately 3,090 full members of the National Society of Genetic Counselors (NSGC); 1000 members of the National Association of Medical Examiners (NAME); and 900 members of the International Association of Coroners and Medical Examiners (IACME). Some overlap is possible between the NAME and IACME memberships. The survey was also distributed to a limited number of cardiologists, with the potential to reach approximately 120 eligible participants. According to the 2019 NSGC Professional Status Survey, approximately 279 genetic counselors (GC's) worked in cardiology, 79 of whom reported cardiology as their primary area of practice. Given that the response rate on the PSS was 49%, these numbers are conservative estimates for the number of GC's eligible to take our survey.

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A total of 99 participants accessed the survey between July 8th, 2019 and December 1, 2019; these included 41 GC's, 51 ME's, 4 cardiologists, and 3 forensic pathologists (while there is overlap in the roles of an ME and a forensic pathologist, we distinguish here those who described their role as a pathologist and not an ME in this study). Nine individuals indicated that they have never considered or ordered postmortem genetic testing and skipped a majority of the questions; these 9 participants were removed. Six other participants completed the full survey but skipped multiple questions in between; their responses were included for the questions they answered and omitted for the ones they skipped. In total, the final sample size was 90 individuals, with 37 GC's, 47 ME's, 3 cardiologists, and 3 forensic pathologists. Thus, the genetic counselor response rate was approximately 13.3%, assuming responses came from GC's who work either primarily or entirely in cardiology, and 1.2% for all GC's on NSGC's student survey email list. The response rate for medical examiners and cardiologists was 2.5% each.

RESULTS

Respondent Demographics

Of the 37 GC's, 12 (32.4%) were from the Midwest, 9 (24.3%) were from the West, 8 (21.6%) were from the Northeast, 5 (13.5%) were from the South, 2 (5.4%) were from Canada, and 1 (2.7%) did not specify their location. Of the 47 ME's, 14 (29.8%) were from the West, 12 (25.5%) were from the South, 7 (14.9%) were from the Midwest, 7 (14.9%) were from the Northeast, 3 (6.4%) were from Canada, 2 (4.3%) were from Australia, 1 (2.1%) was from Singapore, and 1 (2.1%) did not specify their location. For cardiologists, 2 were from the South (both NC) and 1 was from the Northeast (NY). For forensic pathologists, 2 were from the South (FL; DC) and 1 was from the West (WA). In general, no significant regional trends or

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discrepancies were identified, but there were several outliers, and these have been identified when relevant throughout the results section.

Volume of SCD Cases Encountered Annually

Table 1. Volume of SCD cases encountered annually by survey participants in their respective roles. Table displays categories of numerical ranges, and the number and percentage (n (%)) of participants that selected each range as capturing their annual SCD case load.

# Cases/Year	GC's	ME's	Cardiologists	Pathologists	Total
All SCDs					
0-20	32 (86.5)	11 (23.4)	2 (66.7)	3 (100)	1
20-40	2 (5.4)	13 (27.7)	1 (33.3)	-	48
40-60	1 (2.7)	5 (10.6)	-	-	16
60-80	-	6 (12.8)	-	-	6
80-100	-	5 (10.6)	-	-	6
>100	1	7 (14.9)	-	-	5
Skipped	1 (2.7)	-	-	-	8
Total	37	47	3	3	90
Channelopathy-Suspicious SCDs					
0-20	33 (89.2)	47 (100)	3 (100)	3 (100)	86
20-40	3 (8.1)	-	-	-	3
Skipped	1 (2.7)	-	-	-	1
Total	37	47	3	3	90
Cardiomyopathy-Suspicious SCDs					
0-20	33 (89.2)	39 (83)	2 (66.7)	3 (100)	77
20-40	2 (5.4)	3 (6.4)	-	-	5
40-60	1 (2.7)	2 (4.3)	-	-	3
60-80	-	2 (4.3)	-	-	2
>100	-	1 (2.1)	-	-	1
Skipped	1 (2.7)	-	1 (33.3)	-	2
Total	37	47	2	3	90

Participants were asked to select a numerical range that captured the number of SCDs they encounter annually, as well as SCDs suspicious of an arrhythmia, and SCDs suspicious of a cardiomyopathy. See Table 1 for complete responses. The majority of participants reported seeing 0-20 annual cases for all types of SCDs. Some significant differences were noted based on participants' roles. Collectively, ME's encountered a significantly higher number of annual SCD

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cases than GC's ($p < 0.001$). GC's encountered a significantly higher number of arrhythmia-suspicious SCDs per year than ME's ($p = 0.044$).

Laboratory Types and Commonly Used Labs or Organizations for Referral

Laboratory Types

Participants were asked which type or types of lab they used to order testing, and to specify names of the labs/organizations used if possible. The majority of participants (57/90, 63.3%) reported using a third-party commercial lab. Overall, significantly more GC's reported direct ordering from third-party commercial labs, and significantly more ME's reported referring cases to other organizations or studies for genetic testing ($p < 0.001$). Among GC's, most (32/37, 86.5%) reported using a third-party commercial lab, and other responses were inconsistent. One GC in Canada who reported using a third-party organization specified that testing is "arranged through the Ontario coroner system".

Of 47 ME's, 7 (14.9%) said they do not order or deal with genetic testing; of these, 1 ME in Oakland, CA specified that they attempted to send one specimen to Northwestern University, but were stopped by their administrators as their "office wants the lab to indemnify the office for liability that results from the testing". Four ME's out of the 7 who do no testing specified that they were financially restrained, or that protocols for genetic testing were cost prohibitive. Only 1 ME (2.13%) at the New York City OCME reported using an in-house lab.

All 3 cardiologists reported using a third-party commercial lab, and 2 of the 3 forensic pathologists reported the same. The other forensic pathologist reported using an in-house lab. Complete results are listed in Table 2.

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Table 2. Types of Laboratories Used for Postmortem Genetic Testing in SCD Cases.

Lab Types Used	n (%)				
	GC's	ME's	Cardiologists	Pathologists	Total
Third-party commercial lab	32 (86.5)	20 (42.6)	3 (100)	2 (66.7)	57 (63.3)
Third-party providers or research organization	1 (2.7)	14 (29.8)	-	-	15 (16.7)
Family is responsible for arranging third-party genetic testing	-	5 (10.6)	-	-	5 (5.6)
In-house lab	1 (2.7)	1 (2.1)	-	1 (33.3)	3 (3.3)
Infrequently/never order genetic testing	-	7 (14.9)	-	-	7 (7.8)
Infrequently/never order genetic testing for SCDs	1 (2.7)	-	-	-	1 (1.1)
Other (unspecified)	1 (2.7)	-	-	-	1 (1.1)
Skipped	1 (2.7)	-	-	-	1 (1.1)
Total	37	47	3	3	90

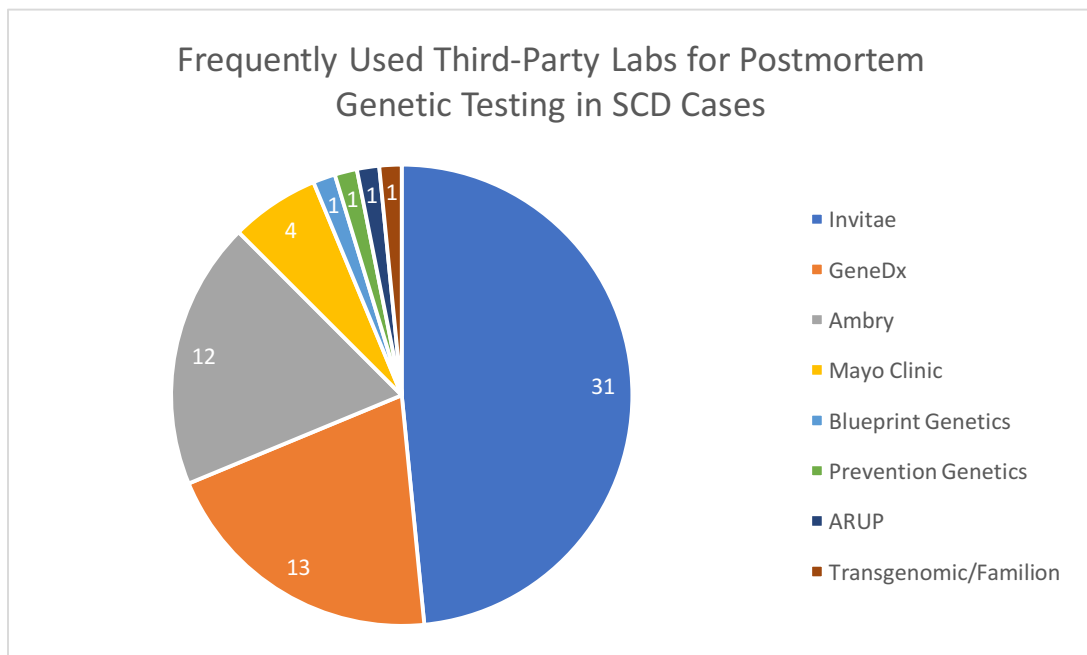


Figure 1. Pie chart of reported third-party commercial laboratories used for postmortem genetic testing in SCD cases (includes data from all participants).

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Frequently Used Third-Party Commercial Labs

Participants that reported using third-party commercial labs were asked in an open-ended question to specify which labs they use most often. The lab named most frequently was Invitae (31/57, 54.4%). See Figure 1 for a complete list. It is important to note that several of the 57 providers reported use of multiple labs, so there was overlap. For those mentioning multiple labs, Invitae was most frequently described as the preferred choice.

Third-Party Organizations or Studies to which ME's Refer SCD Cases for Testing

Of the 14 ME's that referred families to other organizations, 9 (64.3%) referred them to university or research groups, and 5 (35.6%) referred them to cardiologists, genetic counselors, or teams of both. Three university/research groups were specified by the 9 ME's who refer cases to them: 4 mentioned the Webster Cardiac Genetics Group at Northwestern University; 3 mentioned the Sudden Death Genomics Laboratory at Mayo Clinic; and 2 mentioned UCSF's San Francisco Postmortem Systematic Investigation of SCD clinical research program.

Testing for SCDs Suspicious of Underlying Channelopathy and Cardiomyopathy

Participants were asked about their practice and preferences regarding the ordering of genetic testing for channelopathy-suspicious and cardiomyopathy-suspicious SCDs with 4 multiple choice questions. See Table 3 for a comprehensive list of questions and responses, with comparisons of test ordering practice by specialty. An open-ended comment box was included for respondents to provide further explanation if they reported not ordering genetic testing.

Choosing to Test for Channelopathy-Suspicious SCDs

When asked if they would order genetic testing for channelopathy-suspicious SCDs, the majority of participants responded Yes (75/90, 83.3%). Significantly more GC's responded Yes than ME's ($p < 0.001$). Fourteen (29.8%) ME's responded No; all cited financial constraints by

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the state or their workplace as the reason. A disproportionately higher number of ME's who do not order testing were from the South; Southern ME's were 43% (6/14) of the "do not order" group, but only 25% (12/47) of total ME respondents.

Types of Genetic Tests Used for Channelopathy-Suspicious SCDs

Of the participants who said that they ordered testing for channelopathy-suspicious SCDs, the majority (54/75, 72%) selected "arrhythmia panel with both cardiomyopathies and channelopathies." Of respondents who selected "channelopathy panel" or said testing is case-dependent, most were ME's. One ME and one forensic pathologist selected "whole exome sequencing" for both channelopathy and cardiomyopathy-suspicious SCDs; neither commented on the circumstances or motivations for doing so.

Choosing to Test for Cardiomyopathy-Suspicious SCDs

When asked if they would order genetic testing for cardiomyopathy-suspicious SCDs, the majority of participants responded Yes (71/90, 78.9%). Significantly more GC's responded Yes than ME's ($p < 0.001$). Eighteen (38.2%) ME's responded No; of these, 9 (50%) cited financial constraints or lack of funds as the reason; 4 (22.2%) stated the testing is unnecessary as cardiomyopathy can be distinguished morphologically (some added that they would test only if morphological anomalies were absent or borderline); 4 (22.2%) stated that they don't test because cases are referred elsewhere (to studies or genetics teams); 1 (5.6%) stated they don't order testing unless requested to do so by the family.

As with channelopathy-suspicious SCDs, a disproportionate number of ME's who don't order testing for cardiomyopathy-suspicious SCDs were located in the South; Southern ME's were 33% (6/18) of the "do not order" group, but only 25% (12/47) of all ME respondents.

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Table 3. Respondents' practice and preferences regarding the ordering of genetic testing for SCDs suspicious of either channelopathy or cardiomyopathy. Percentages for specific tests ordered are calculated out of the total number of participants in each role who responded Yes to testing (for example, 36 GC's responded Yes for testing; 3 reported using channelopathy panels; thus, percentage of GC's ordering channelopathy panels = $3/36 = 8.3\%$).

	n (%)				
	GC's	ME's	Cardiologists	Pathologists	Total
<i>Do you/would you order genetic testing for channelopathy-suspicious SCDs?</i>					
Yes	36 (97.3)	33 (70.2)	3 (100)	3 (100)	75 (83.3)
No	0 (0)	14 (29.8)	0 (0)	0 (0)	14 (15.6)
Skipped	1 (2.7)	0 (0)	0 (0)	0 (0)	1 (1.1)
Total (n)	37	47	3	3	90
<i>What specific test do you order for channelopathy-suspicious SCDs?</i>					
Channelopathy panel	3 (8.3)	6 (18.2)	0 (0)	1 (33.3)	10 (13.3)
Arrhythmia panel with both cardiomyopathies and channelopathies	30 (83.3)	21 (63.6)	2 (66.7)	1 (33.3)	54 (72)
Whole exome sequencing	0 (0)	1 (3)	0 (0)	1 (33.3)	2 (2.7)
Varies/depends on case	3 (8.33)	5 (15.2)	1 (33.3)	0 (0)	9 (12)
Total (n)	36	33	3	3	75
<i>Do you/would you order genetic testing for cardiomyopathy-suspicious SCDs?</i>					
Yes	37 (100)	28 (59.6)	3 (100)	3 (100)	71 (78.9)
No	0 (0)	18 (38.3)	0 (0)	0 (0)	18 (20)
Skipped	0 (0)	1 (2.1)	0 (0)	0 (0)	1 (1.1)
Total (n)	37	47	3	3	90
<i>What specific test do you order for cardiomyopathy-suspicious SCDs?</i>					
Channelopathy panel	0 (0)	2 (7.1)	0 (0)	0 (0)	2 (2.8)
Cardiomyopathy panel	17 (46)	3 (10.7)	1 (33.3)	1 (33.3)	22 (31)
Arrhythmia panel with both cardiomyopathies and channelopathies	17 (46)	18 (64.3)	1 (33.3)	1 (33.3)	37 (52.1)
Whole exome sequencing	0 (0)	1 (3.6)	0 (0)	1 (33.3)	2 (2.8)
Varies/depends on case	3 (8)	4 (14.3)	1 (33.3)	0 (0)	8 (11.3)
Total (n)	37	28	3	3	71

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Types of Genetic Tests Used for Cardiomyopathy-Suspicious SCDs

Of the participants who said that they did order testing for cardiomyopathy-suspicious SCDs, the majority (37/71, 52.1%) selected “arrhythmia panel with both cardiomyopathies and channelopathies.” Of the 22 participants who selected “cardiomyopathy panel”, GC’s significantly outnumbered ME’s ($p = 0.007$).

Other Indications for Genetic Testing on the Deceased

Participants were asked in an open-ended question to specify any other reasons for which they would consider postmortem genetic testing. Of 90 participants, 63 (70%) responded to this question, some of whom provided multiple other indications. All responses were grouped and coded into 11 categories based on concerns with similar themes. For each response, all applicable categories were given a count. See Figure 2 for all categories and the number of responses that fell into each.

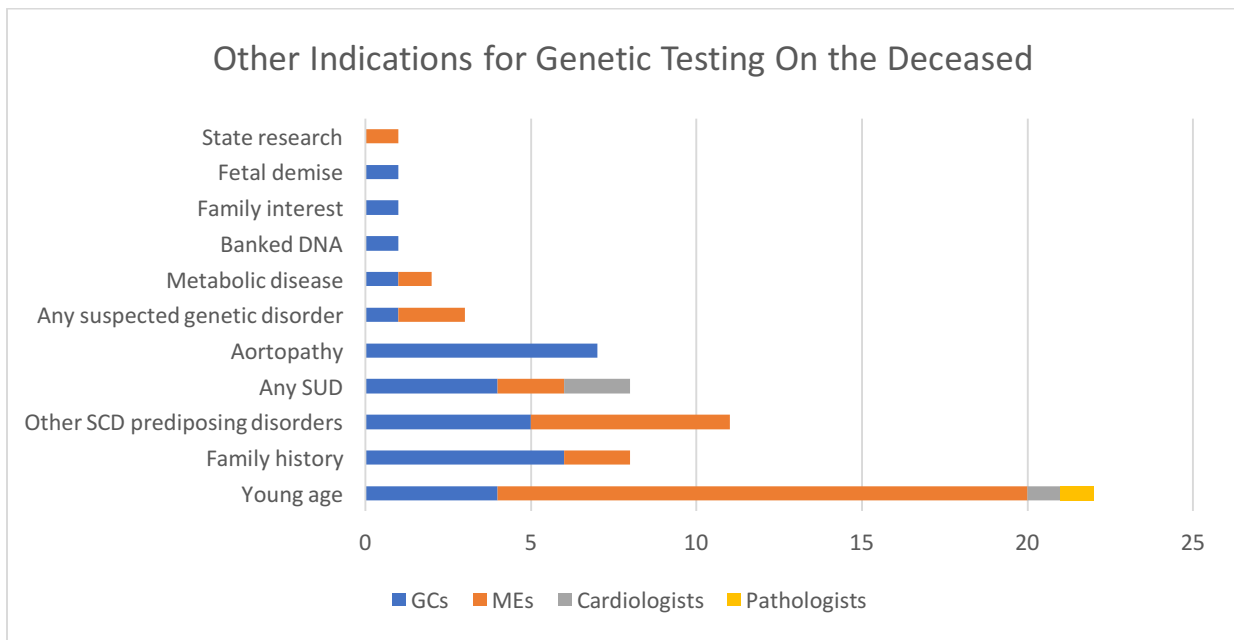


Figure 2. Horizontal stacked bar graph showing other indications for genetic testing of the deceased as reported by respondents, with their roles distinguished by color. The category “Other SCD predisposing disorders” includes SUDEP, SIDS, SCAD, RASopathies, congenital heart diseases, coagulopathies, seizure disorders, and early dementia.

Genetic Testing of At-Risk Family Members Absent Information on Genetic Status of Deceased

Participants were asked, “Do you order genetic testing on at-risk family members when you do not have information on the genetic status of the deceased?”. Of 37 GC’s, 20 (54.1%) selected No and 17 (45.9%) selected Yes. Three (17.7%) of the 17 GC’s who responded Yes specified that they would provide extensive genetic counseling before testing unaffected family members and would ideally want the relatives to receive cardiac screening first to identify symptomatic individuals. Of the 20 GC’s who responded No, 8 (40%) specified that they only recommend cardiac screening and not genetic testing, and would consider testing in very rare circumstances of strongly symptomatic individuals or extreme family histories. One such GC wrote, “Have only ordered on asymptomatic fam members of a deceased once. This was an extreme family history and no living relatives. We got a lot of VUSs. Was unfortunately uninformative.” With regards to the type of tests ordered on family members by GC’s, 6/17 GC’s checked “channelopathy panel”, 6/17 GC’s checked “cardiomyopathy panel”, 15/17 GC’s checked “arrhythmia channel with both cardiomyopathies and channelopathies”, 1 checked “whole exome sequencing”, and 2 checked “other” but did not specify.

Of 47 ME’s, 40 (85.1%) responded that they would not order genetic testing on family members when genetic status of the deceased is unknown, 4 (8.5%) ME’s responded that they would, and 3 (6.4%) skipped the question. Most of the ME’s who responded No specified that ordering such testing is not part of their job; 5 ME’s specified that they refer families to genetic counselors or cardiologists if a genetic etiology is suspected. With regards to the type of tests ordered on family members by ME’s, 2/4 ME’s indicated “channelopathy panel”, 2/4 ME’s indicated “arrhythmia channel with both cardiomyopathies and channelopathies”, 1 indicated “whole exome sequencing”, and 2 indicated “other”, one of whom indicated prodrome-specific

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testing (for symptomatic family members who already undergo cardiac screening), and the other indicated following a physician's recommendations.

Among cardiologists, 2/3 responded Yes to testing for family members, 1/3 responded No. Both cardiologists who responded Yes indicated using the "arrhythmia panel with both cardiomyopathies and channelopathies"; one of them also indicated "whole exome sequencing". All 3 forensic pathologists responded No, stating that testing relatives is not part of their job.

Contributing Factors for Postmortem Genetic Testing

Participants were asked to choose which factors contribute to whether or not postmortem genetic testing is completed (they could select as many factors as they desired). Six potential factors were listed, along with an "Other" option. When asked which factor is the most important, "financial" was chosen by the greatest number of participants (38/90, 42.2%). However, the most important factor for GC's alone was "sample type/amount", while "financial" came second (Table 4, Figure 3). The number of ME's who selected "financial" as the most important factor was significantly greater than the number of GC's who did so ($p = 0.009$). Significantly more GC's selected "sample storage/retention" as a determining factor of postmortem genetic testing than ME's ($p < 0.001$). See Table 4 for all responses.

Financial Responsibility of Genetic Testing for the Deceased

Participants were asked "Who is responsible for the cost of genetic testing?" with regards to testing the deceased. Approximately a third of participants (31/90, 34.4%) said that families paid out-of-pocket; 26 (28.9%) said the ME office paid; 10 (11.1%) said it was highly variable and depended on each case; 5 (5.6%) said the cost was covered by research funds/grants; 2 (2.2%) selected "decedent's insurance"; 2 (2.2%) selected "family member's insurance"; 4 (4.4%) said they are unsure and don't know; 3 (3.3%) skipped the question. (continued page 21)

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Table 4. Obstacles to Postmortem Genetic Testing

Potential Contributing Factors	GC	ME	Cardiologist	Pathologist	Total
Financial	30	33	3	2	68
Sample type/amount	34	21	1	2	58
Sample storage/retention	30	8	-	-	38
Shipping Process	7	4	-	-	11
Turnaround time	2	9	1	-	12
Informed consent	14	9	1	-	24
“Index of suspicion”	2	4	-	-	6
Family involvement	5	3	-	-	8
ME Office liability	-	1	-	-	1
ME knowledge	2	-	-	-	2
Difficulty of whole process	1	-	-	-	1

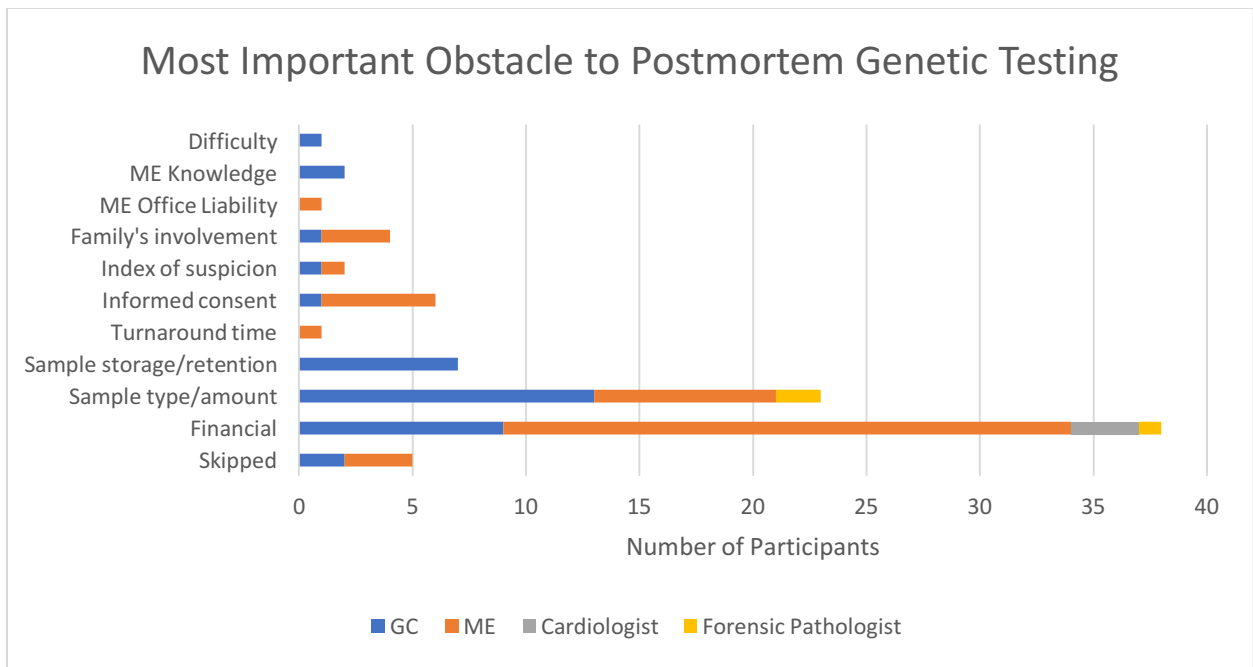


Figure 3. Horizontal stacked bar graph showing the number of participants in each role and their response for which contributing factor is most important to whether or not postmortem genetic testing is completed.

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The remaining 7 (7.8%) participants reported that costs were covered by hospitals, attorneys, or government healthcare (these respondents were ME's or GC's in Australia or Canada). When correlating responses with participants' roles, there was a significant difference between GC and ME responses ($p < 0.001$); the majority of GC's reported families paying out-of-pocket for postmortem genetic testing (24/37, 64.8%), while ME's most commonly reported costs being the Medical Examiner Office's responsibility (23/47, 48.9%) (See Figure 4). No significant regional variation was detected.

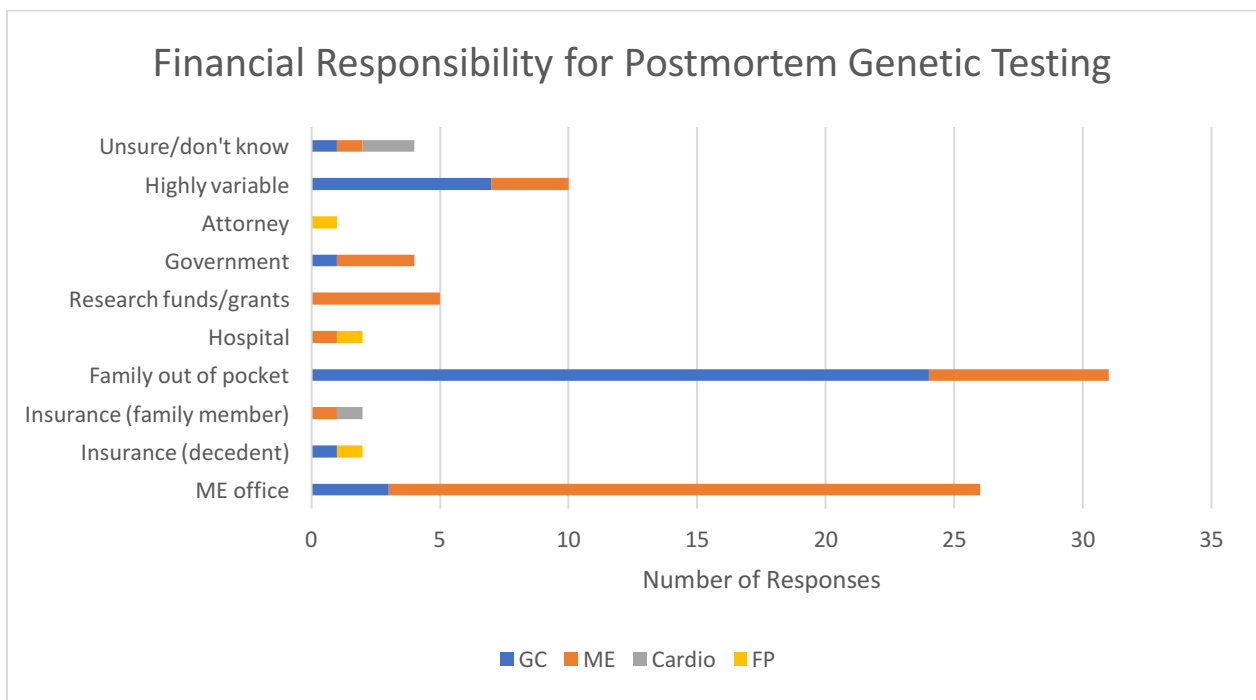


Figure 4. Horizontal stacked bar graph showing the number of participants in each role and their response for which parties are responsible, in their experience, for the cost of postmortem genetic testing. GC's and ME's were significantly different in their responses ($p < 0.001$).

Turnaround Time (TAT) for Postmortem Genetic Testing

Participants were asked, "When post-mortem genetic testing is ordered, what is the average turnaround time in months (from autopsy to disclosing genetic results to families)?"

Responses were grouped into categories of 3-month increments. The largest group of participants

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(32/90, 35.6%), regardless of whether they were GC's (13/37, 35.1%) or ME's (16/47, 34%), reported the average TAT for postmortem genetic testing as 1-3 months.

Referral to Direct-to-Consumer/Consumer-Initiated Testing Options

Participants were asked, "For family members who don't qualify for/can't afford clinical genetic testing, do you refer them to DTC (direct-to-consumer) genetic testing options?". The majority of participants (69/90, 76.7%) said they would not. Of 37 GC's, 2 (5.4%) said they would offer DTC options for testing the deceased. One of them specified: "I know families that have paid for genome trios through Perkin Elmer, which I am comfortable with". The other GC said they offer Color or testing through Invitae's DETECT program. One GC said they do not currently offer DTC options, but will offer Color or Invitae in the future. Of 47 ME's, 5 (10.6%) said they offer DTC options for testing family members. Two ME's and 2 of the 3 forensic pathologists said they would offer DTC options for testing both the deceased and their relatives.

Pre-Test Counseling for Postmortem Genetic Testing

Participants were asked, "Before the deceased is tested, who provides pre-test counseling to the deceased's family? Select all that apply." Six participants (6/90) skipped this question. Of all the options, "Genetics" was reported by the most participants in total (47/90), followed by "No pre-test counseling is provided" (25/90), "Cardiologists" (22/90), "Medical examiners" (14/90) and "PCP (primary care practitioner)" (9/90). See Figure 5 for the full distribution of responses. There were significant differences between GC's' and ME's' responses ($p < 0.001$); more ME's reported that no pre-test counseling is provided.

Points Discussed During Pre-Test Counseling

Those participants who did pre-test counseling were asked to select which topics were covered. Five potential topics were listed, along with an "Other" option. Participants could select

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all that applied. The majority of participants who responded were GC's (36/37, 97.3%), as many ME's (33/47, 70.2%) and all three forensic pathologists were not involved with pre-test counseling. "Potential results" was the most selected topic by both GC's and the ME's who responded. Two GC's reported discussing testing logistics and coverage; one ME reported discussion of referral to PCP for follow-up. Table 5 lists the topics selected and displays the number of respondents who reported each topic as being included in pre-test counseling.

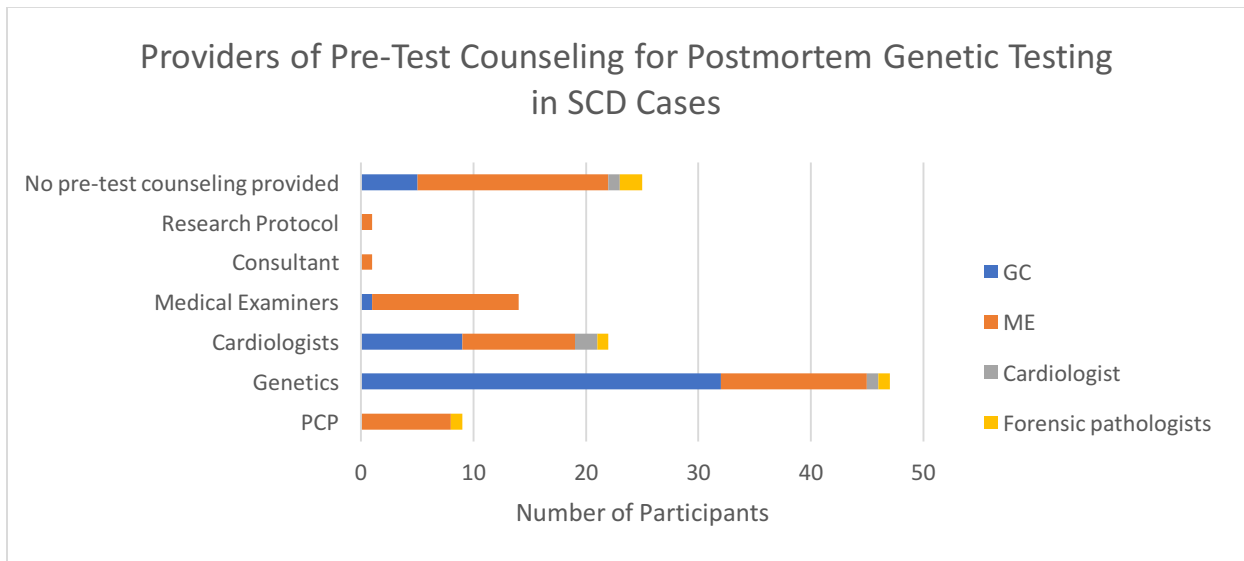


Figure 5. Horizontal stacked bar graph showing the number of participants that reported which types of providers are in charge of providing pre-test counseling to families for postmortem genetic testing of SCD cases.

Table 5. Topics Covered in Pre-Test Counseling for Postmortem Genetic Testing in SCDs. Table shows the number of participants (by role) who indicated coverage for each topic.

Topics Covered	GC's	ME's	Cardiologists	Total
Potential Results	30	8	2	40
Management	26	5	1	32
Insurance coverage	18	2	2	22
Family Planning	26	2	2	30
Educational Resources	20	4	-	24
Referral	-	1	-	1
Logistics	2	-	-	2

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Post-Test Counseling for Postmortem Genetic Testing

Participants were asked, “After the deceased is tested, who provides post-test counseling to the deceased's family? Select all that apply.” Seven participants (7/90) skipped this question. Of all the options, “Genetics” was reported by the most participants in total (61/90), followed by “Cardiologists” (28/90), “Medical examiners” (16/90), and “PCP (primary care practitioner)” (11/90). Six participants (5 ME’s, 1 forensic pathologist) reported that no post-test counseling is provided. See Figure 6 for the full distribution of responses.

Points Discussed During Post-Test Counseling

Participants who do post-test counseling were asked to select which topics were covered. Five potential topics were listed, along with an “Other” option. Participants could select all that applied. The majority of participants who responded were GC’s, as many ME’s and 2/3 forensic pathologists were not involved with post-test counseling and wrote “not applicable”. “Actual results” was the most selected topic by both GC’s and ME’s. Four ME’s reported referring families to other providers, two of whom mentioned referral to PCPs, and two referred to genetic counselors/geneticists. Table 6 shows the number of participants who indicated that each topic is covered in post-test counseling.

Table 6. Topics Covered in Post-Test Counseling for Postmortem Genetic Testing in SCDs. Table shows the number of participants (by role) who indicated coverage for each topic.

Topics Covered	GC’s	ME’s	Cardiologists	Pathologists	Total
Actual results	32	14	2	1	49
Management course	30	3	1	-	34
Insurance coverage	22	-	1	-	23
Family planning	29	1	1	-	31
Educational resources	27	10	1	-	38
Referral to others	-	4	-	-	4

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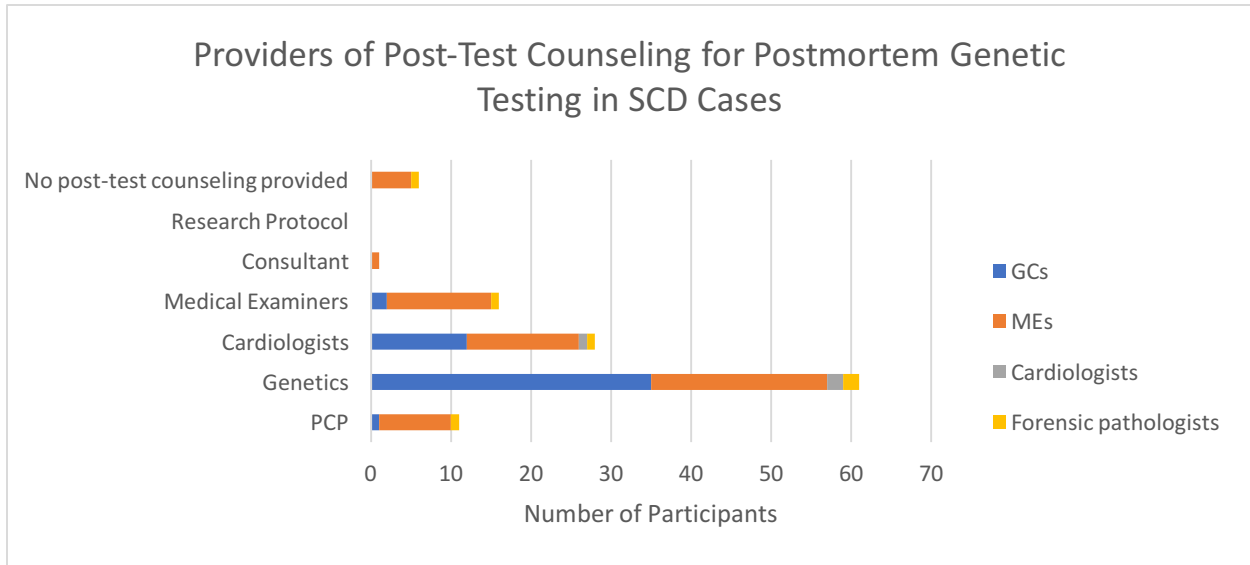


Figure 6. Horizontal stacked bar graph showing the number of participants that reported which types of providers are in charge of providing post-test counseling to families for postmortem genetic testing of SCD cases.

Factors for Denying Postmortem Genetic Testing When Cost is not a Barrier

Participants were asked, “In your experience, which of the following factors has prompted a family to deny post-mortem testing when the cost of testing is not a barrier? Check all that apply.” They could choose from “grief”, “misinformation”, “miscommunication”, and “cultural/religious reasons”. Thirty-one respondents (31/90, 34.4%)—8 GC’s and 23 ME’s—skipped this question. For those who responded, “Grief” was the most selected reason (34/59), followed by “misinformation” (28/59), “cultural/religious reasons” (21/59), and “miscommunication” (18/59). As a group, ME’s were more likely to choose “misinformation” (12/24, 50%) than “grief” (8/24, 33.3%).

Insurance Coverage of Genetic Testing for the Deceased and for Living Family Members

Participants were asked about their experience with insurance coverage of postmortem testing for the deceased (62/90, 68.9% responded). Responses were coded into 5 categories; see Figure 9 for all responses. Among those that said they often see insurance cover costs of testing,

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two ME's indicated that the UCSF genetic counselors they refer families to are "good at getting insurance companies to pay" and one cardiologist said "With proper documentation and medical records, the majority of cases are covered." One notable regional trend was that Southern practitioners made up 55% (11/20) of "never" responses, but only 23% (21/90) of all participants. Participants were also asked about insurance coverage for genetic testing of family members when test results are not available for the deceased proband (67/90, 74.4% responded). See Figure 7 for all responses. No regional trends were noted.

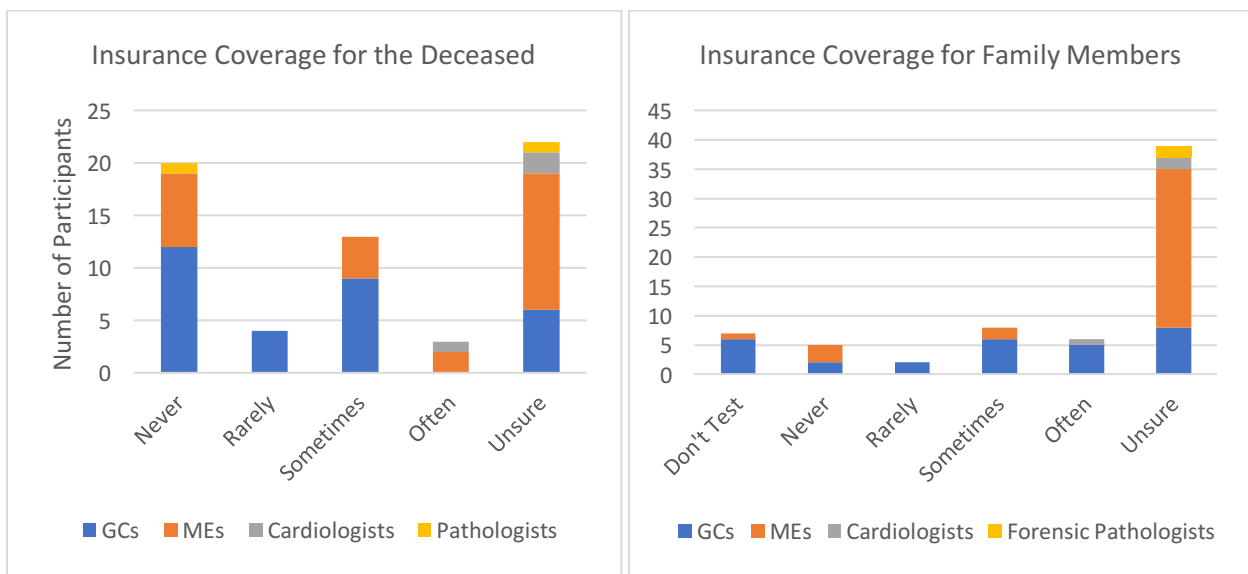


Figure 7. Frequency of insurance coverage of postmortem genetic testing for the deceased (n=62), and for family members when genetic status of the deceased is unknown (n=67).

DISCUSSION

This study's main focus was to gain insight into the perspective of healthcare professionals (medical examiners, genetic counselors, and cardiologists) on postmortem genetic testing, particularly with regards to SCDs suspicious of underlying channelopathy or cardiomyopathy. The survey included a series of questions to address the following: what specific medical events necessitate postmortem genetic testing; who is ordering postmortem testing; what specific tests are being ordered; and how does insurance coverage for postmortem

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testing vary by region. The majority of respondents were GC's and ME's who either have a primary role or background in cardiology, and only three cardiologists and three forensic pathologists completed the survey.

With regard to postmortem genetic testing, our survey suggests that there are differences in what GC's and ME's regard as their role in the process; there are also inconsistencies in insurance coverage of postmortem genetic testing, none of which appear to be attributable to regional variation.

Inconsistencies in the Postmortem Genetic Testing Process

The discrepancy between how ME's approach postmortem genetic testing and how GC's approach postmortem genetic testing is significant. In general, all respondents emphasized that both pre-test and post-test counseling for postmortem genetic testing should be done by genetic professionals. However, more ME's than GC's reported that no pre-test counseling is provided when postmortem genetic testing is offered. This suggests that the amount of information available to patients prior to consenting to postmortem genetic testing is inconsistent.

Discrepancies Pertaining to Which Factors Prevent Postmortem Genetic Testing from Happening

One significant discrepancy between the two main groups of respondents was in what each group identified as the principle contributing factor preventing postmortem genetic testing. A majority of the ME's surveyed reported that financial constraints are the main reason why postmortem genetic testing is not facilitated, and that the financial responsibility for such testing falls onto the medical examiner's office rather than the family or insurance companies. On the other hand, GC's were significantly more likely to select "sample type/amount" as the main obstacle to postmortem genetic testing ($p < 0.001$). It is unclear why this difference in GC and ME perspective exists. Possible explanations include: ME's lack a comprehensive understanding of

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sample type/amount requirements for postmortem genetic testing during the autopsy and don't retain appropriate samples; ME's are removed from follow-up and are unaware if testing is actually achieved; financial constraints behave as the primary obstacle and influence adequate sample collection; and a general lack of communication exists between GC's and ME's.

Our results are inconsistent regarding whether or not insurance companies will cover postmortem genetic testing on SCD cases. Responses indicate that some families are paying for postmortem genetic testing, and some have insurance cover the testing, while other cases are covered by the ME's office. Another potential area of focus for future studies is influenced by GC involvement; it is possible that certain GC activities, such as writing letters of medical necessity, play a crucial role in securing insurance coverage, making it less of an impediment for GC's. Overall, inconsistency when it comes to who is financially responsible and what insurance will cover raise a red flag, indicating that cost may impact availability of testing in many cases.

Alternative Postmortem Genetic Testing Options Discussed by Healthcare Professionals

Respondents proposed the following methods to help families obtain postmortem genetic testing:

- Providing proper documentation and medical records as evidence to insurance companies as to why postmortem genetic testing is necessary
- Direct-to-consumer/Consumer Initiated testing (Color or Invitae) for families with financial constraints
- Enrolling in clinical research programs offered at specific institutions (Webster Cardiac Genetics Group at Northwestern University, San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) clinical research program, and Sudden Death Genomics Laboratory at Mayo Clinic)
- Selecting a lab that is cost effective (e.g., Invitae versus GeneDx)
- Molecular autopsy labs within medical examiners' offices

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Direct-to-consumer/consumer-initiated testing (DTC/CIT) allows families interested in postmortem genetic testing on to have it done at a more affordable price. About 5% of GC's said they would offer DTC/CIT options for testing the deceased. About 11% of ME's, 5 (10.6%) said they offer DTC/CIT options for testing family members. Two ME's and 2 of the 3 forensic pathologists said they would offer DTC/CIT options for testing both the deceased and their relatives.

Studies mentioned by individual respondents vary in terms of inclusion criteria in terms of what they require to determine cause of death and other eligibility restrictions. Some are open to referrals from physicians nationwide, while others are regional programs. The San Francisco Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) clinical research program is unique in that it is a partnership between cardiac electrophysiology specialists and the County Medical Examiner. The cases eligible for this program are only out-of-hospital sudden death within the County of San Francisco meeting WHO criteria.

Selecting specific lab companies can help reduce cost to families as well. One respondent cited an Invitae program called Detect, which provides free-of-charge genetic testing for conditions in which testing is underutilized and can improve diagnosis and treatment. These conditions include cardiomyopathy and arrhythmia, as well as lysosome storage diseases and amyloidosis in the Cardiology category. In addition to testing, the Detect programs offer participants post-test genetic counseling to help them understand their test results and make more informed decisions about their health. Some programs also offer follow-up testing to family members of patients with genetic variants associated with disease to better understand their disease risks. In general, Invitae covers family follow-up testing for patients with a relative who was tested at Invitae (within 90 days of order) and was found to have a pathogenic/likely

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pathogenic variant or a variant of uncertain significance (VUS resolution at no additional charge). Therefore, if the family has to pay out of pocket for postmortem genetic testing, the follow-up testing for family members (if ordered within the specific time frame) is covered. Unlike Invitae, GeneDx states that once a pathogenic or likely pathogenic variant is identified in the proband, targeted testing of family members is recommended and can be performed at a reduced cost of \$99 USD for those meeting certain criteria (as of March 2020).

Most ME offices around the world lack the technology and finances to routinely perform molecular testing on every autopsy-negative natural death case (Sampson and Tang, 2017). In New York City, the Office of Chief Medical Examiner has its own Molecular Genetics Laboratory that started in 2003, which is the only such laboratory based in a medical examiner's office nationwide. The laboratory provides postmortem molecular diagnostic testing to search for gene changes that explain sudden deaths, and to alert surviving family members. There are no charges for this service to the family.

Implications for Practice

In general, the results showed that there are inconsistencies in how ME's function in postmortem genetic testing. For example, 14.9% of the ME's emphasized that they do not order or deal with genetic testing, 29.8% refer families to a third-party organization for test-related decision-making, and 42.6% facilitate postmortem genetic testing themselves. It may be that ME's would benefit from continuing education or guidelines to establish a baseline understanding of their role in postmortem genetic testing. This, potentially, could facilitate adherence to a uniform testing and counseling protocol for families affected by SCD

Another subject for discussion that could be evaluated is whether or not medical examiners' offices should incorporate GC's into their practice to help ensure that all families

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who are thinking of undergoing postmortem genetic testing receive appropriate counseling prior to testing. Again, this might help establish a uniform level of care for all families who have experienced the loss of a family member due to SCD. More GC's employed by medical examiner offices might also improve communication and reduce the likelihood of an inadequate sample type/amount, which GC's in this study had pointed to as a primary obstacle to postmortem genetic testing.

In Middleton et al (2013), they discuss the collaborative efforts of genetic counselors and NAME to improve postmortem genetic testing protocols. The authors concluded, "medical examiners not only have the responsibility of determining cause and manner of death, but also function as stewards of public health promotion and monitoring". The results from this study indicated that not all ME's are incorporating best practices for pre- or post-test counseling in the postmortem. In Bagnall et al. (2020), they emphasize that "the molecular autopsy is not without challenges" and "can be time-intensive". These specific types of cases make up a small percentage of the total caseload brought to an ME's attention, since they are also highly involved in cases of homicide, accidents, other natural deaths, etc. Therefore, this makes having a multidisciplinary team approach (medical examiners, cardiologists, genetic counselors and geneticists) very valuable when selecting the optimal panel of genes and interpretations of genetic results. Efforts to promote uniformity in how ME's and GC's work together may benefit families in need of postmortem genetic testing.

With regards to cost, an appeal to insurance companies may help to generate improvements in insurance companies' policies so that a fair and predictable process is available for families considering postmortem genetic testing. While research studies and payment through ME's offices remain an option for many families today, they have restrictions and cannot be

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relied on to provide access on a consistent basis. As has been seen, labs may also be willing to absorb some cost if necessary.

Research Recommendations

Further research is needed to understand the role of ME's in postmortem genetic testing and to what extent that role necessitates additional training. The benefits and limitations of the following ideas should be explored: (1) Having GC's employed by ME's offices or (2) ME offices having universal referral programs where appropriate samples are sent to Genetics for any SCD case, and all genetic information pertinent to the cause of death is communicated back. It should also be evaluated whether or not each idea: reduces misinformation and miscommunication; improves TAT; increases the number of cases that get pre-test and post-test counseling; and alters the percentage of families that agree to postmortem genetic testing.

Our study showed several regional trends, with ME's in the Southern region of the U.S. more likely to report financial constraints affecting the availability of testing and a majority of southern healthcare professionals reporting that postmortem genetic testing to is "never" covered by insurance companies. Future studies might explore if these differences can be replicated, and investigate possible factors creating regional differences in policy or practice

Study Limitations

The survey was distributed through listservs as well as through personal contacts; there is potential for ascertainment bias, as those who click and proceed to take the survey are most interested in the topic. Our study originally aimed to compare responses between GC's, ME's, and cardiologists, but due to unsuccessful attempts at recruiting cardiologist respondents, we were unable to conduct such comparisons. Another limitation is the low sample size for each state, leading us to collapse respondents by region and possibly missing certain location-based

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trends or patterns. Also, there was potential for human error when coding and categorizing qualitative responses. The last question in the survey was open-ended and phrased as such: “In what situations will insurance companies cover cascade genetic testing for family members if the deceased has not been tested?”. This question involved incorrect usage of the term “cascade testing”, as cascade testing refers specifically to testing of family members after a genetic variant has been discovered in the proband. This error could have potentially led to misinterpretation and inaccurate responses. Future studies exploring the same topic should take additional care with question design. A better alternative would have been similarly phrased with the word “cascade” omitted.

Conclusion

In conclusion, while this study identified some cost-reductive and cost-free methods of how to approach postmortem genetic testing, it also highlighted inconsistencies in how postmortem genetic testing is practiced and paid for, and the roles played by healthcare professionals. More effort is needed to establish a uniform understanding among healthcare professionals and insurance companies of the importance of postmortem genetic testing and the necessary components of pre-test and post-test counseling, as well as coverage of postmortem genetic testing, and the relevance of postmortem genetic testing in management of family members with a family history of SCD. This topic requires further research and interdisciplinary consideration to help establish guidelines and protocols that healthcare professionals can follow in order to provide uniform care to patients.

CONFLICT OF INTEREST

Miranda Di Biase and Kiran Gangwani declare that they have no conflict of interest.

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