

A GUIDE TO POSTMORTEM GENETIC TESTING

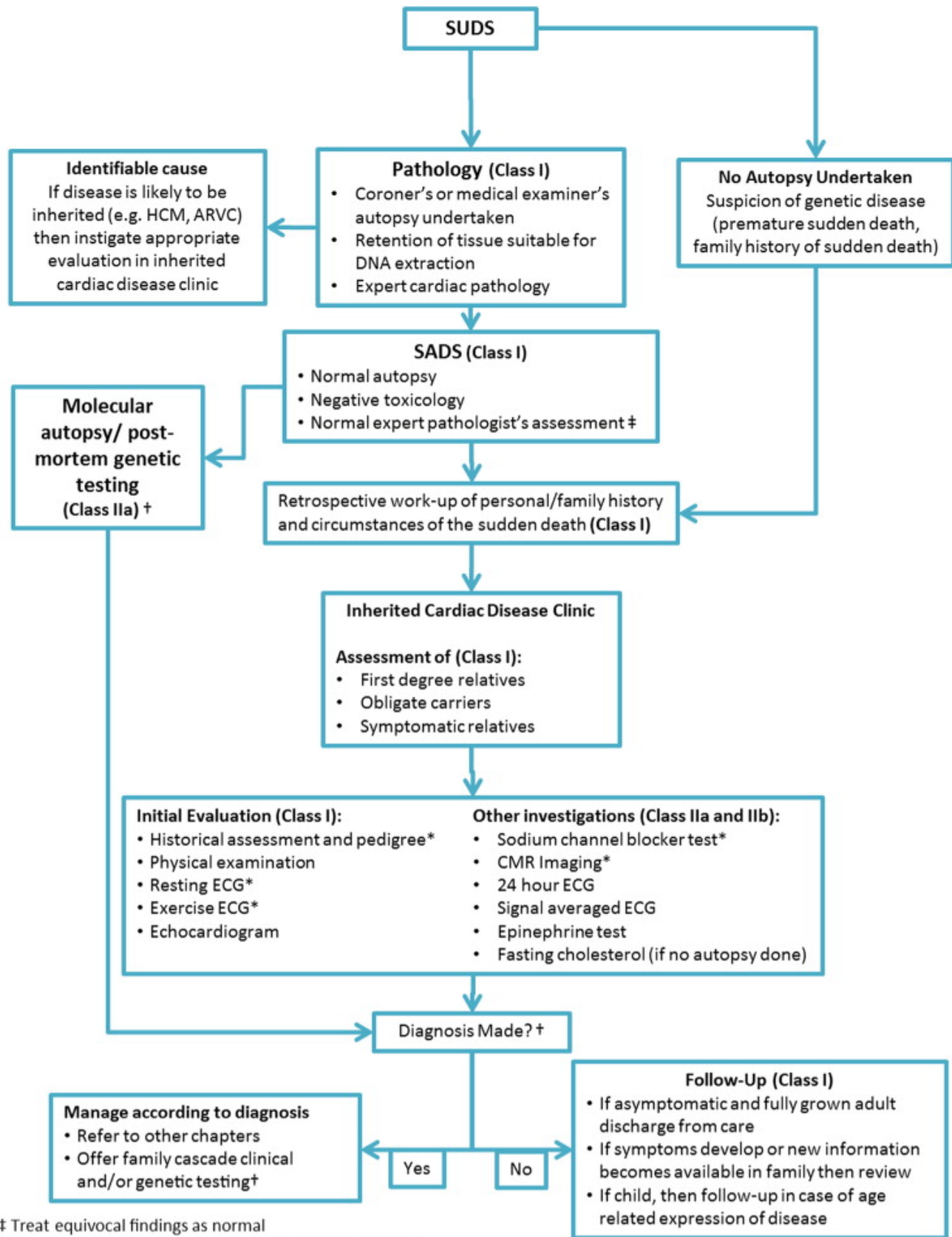
RACHEL CAMPAGNA

GENETIC COUNSELING MASTERS CANDIDATE | INDIANA STATE UNIVERSITY

Table of Contents

| | |
|---|----------|
| WHEN TESTING IS RECOMMENDED: | 3 |
| COLLECTION OF SAMPLES: | 4 |
| How to Store Blood & Tissue Samples | 4 |
| How to Store Blood Spots | 4 |
| REFERRALS AND FOLLOW UP: | 4 |
| COMMUNICATION WITH NEXT OF KIN: | 5 |
| PAYMENT FOR TESTING: | 5 |
| DNA/SAMPLE BANKING: | 5 |
| CONSENT: | 5 |
| APPENDIX A: Letter of Medical Necessity Sample | 6 |
| APPENDIX B: More Banking Information | 7 |
| APPENDIX C: Barriers to Postmortem Testing | 8 |
| APPENDIX D: HRS/EHRA Genetic Testing Recommendations | 9 |

WHEN TESTING IS RECOMMENDED:



‡ Treat equivocal findings as normal

† Refer to HRS/EHRA Genetic Testing recommendations

* Investigations with greatest yield

Figure 1: Adapted from NSGC Postmortem Recommendations For HRS/HER Recommendations, see [APPENDIX D](#)

COLLECTION OF SAMPLES:

- When to save samplesⁱ
 - All Sudden & Unexplained Deaths (SUD) under **40yo**
 - Death remains unexplained after autopsy
 - Collect extra blood sample (preferably in an EDTA tube) to be saved until completion of autopsy
 - Should be stored for at least 3 months after completion of autopsy in case sample is needed
 - Suspicious (non-violent) circumstances such as:
 - Drowning (especially if decedent was sober or a good swimmer)
 - Single Motor Vehicle Accident (MVA) with “no mitigating factors” (i.e. toxicology report negative)
 - Unexplained seizure(s) contributing to death
 - Cardiomyopathy or thoracic aneurysm identified on autopsy
 - Sudden & unexplained death of individual with **family history** of SCD or inherited heart disease
 - Sudden & unexplained death when cause of death is not clear
- Sample Typesⁱⁱ (may vary by lab):
 - Blood: 1-2 tubes preserved in EDTA (preferred)
 - Flash frozen tissue using dry ice or liquid nitrogen
 - Blood spots on standard filter paper cards
 - NSGC Sample recommendations: <https://www.nsgc.org/page/postmortem/samples>
- Remaining samples obtained during standard autopsy procedures for other evaluations (i.e. toxicology screen) should be released for genetic testing if deemed necessary or if family indicates that they would like to pursue testing on their own
 - All foreseeable required autopsy-related testing must be completed prior to sample release
- Samples saved for potential genetic testing should only be used for clinical testing and should **NOT** be used for research purposes
- Storage time should provide “ample opportunity for families and their health care providers to initiate genetic testing and/or banking”

How to Store Blood & Tissue Samples

- Short Term Storage (up to 4wks after autopsy): should be kept in a refrigerator (4°C)ⁱ
- Long Term Storage (months to years): should be moved to a -20°C to -70°C until they can be shipped to an appropriate laboratory or banking facility or properly disposed of after 3-month retention

How to Store Blood Spotsⁱⁱⁱ

- Filter paper should be in a single, gas-impermeable zipper bag, containing 1 to 2 desiccant sachets to protect the specimens from moisture
 - Optionally, add a humidity indicator card.
- Card & bag should be in freezer at -20°C or lower asap
 - Storage at -4°C or ambient temperatures is feasible for up to 14 days

REFERRALS AND FOLLOW UP:

- If death is suspected to be cardiac in nature, then for the next of kin:
 - Find a genetic counselor:
 - Go to NSGC.org and click “Find a Genetic Counselor”
 - Click “In Person” or “By phone” depending on family preference
 - In the search Filters, select your state and/or enter your zip code
 - Under “Types of Specialization”, select “Cardiology”
 - Select a GC that is closest to decedents family or whom is available by phone if that is preferred
 - Information needed for referral:
 - ICD-10 Codes
 - For more ICD-10 Codes: <https://www.icd10data.com/>
 - Release of Information from next of kin
 - Referral paperwork
 - A copy of the autopsy report is useful upon completion

| ICD-10 Code | Meaning |
|-------------|--|
| I46.2 | Cardiac arrest due to underlying cardiac condition |
| I46.9 | Cardiac arrest, cause unspecified |
| P29.81 | Cardiac arrest in newborn |
| Z86.74 | Personal history of sudden cardiac arrest |
| Z82.41 | Family history of sudden cardiac death |

- Similar referrals may be made if cause of death is suspected to be **neurologic** in nature

COMMUNICATION WITH NEXT OF KIN:

- Important to maintain contact with next of kin throughout process ^v
 - Ensure families have a single point of contact at your office
 - **Best practice:** a post-autopsy meeting should be offered at the beginning of death investigation ^{iv}
 - If needed, use an **interpreter** that is not a child or family member
 - An interpreter and a translator are not synonymous
 - Make sure interpreters have healthcare specific training
 - The American Translators Association has a “Find an interpreter” function that can be used if you do not have an established relationship with one
 - https://www.atanet.org/onlinedirectories/search_advanced.php
- Information to be shared with surviving next of kin ^v
 - What sample(s) are available, how long they will be stored
 - Information about possible referrals, testing, and/or banking
 - Estimations of costs, though noting every lab prices differently
 - Depending on what is identified, medical follow up may be indicated

PAYMENT FOR TESTING:

- Variety of payment methods implemented in the past ^v
 - Self-pay (42%) – payment made by next-of-kin
 - Commercial Insurance (6%)
 - For an example letter of medical necessity, see [APPENDIX A](#)
 - Medical Examiner and/or Forensic Pathologist (14%)
 - Consider including price of testing within autopsy fee ⁱⁱ
 - US Medical Institution (11%)
 - Canadian Ministry of Health and/or Pathology Services (24%)
- Consider applying for a grant at <https://grants.gov>
 - Enter in keywords such as “genetics,” “cardiology,” “postmortem,” etc.
- Look for research collaborations with established medical practices or universities

DNA/SAMPLE BANKING:

- Preserves a sample for extended period of time
- Permission from next of kin is required to send to a banking facility
- Typically, 10ml blood in EDTA is required, but may accept other sample types and amounts
- Cost varies depending on location and time of storage
 - Ranges from \$50-300
 - Storage from 5 years to indefinitely
- Reasons to bank
 - Provides time to consider pros and cons of genetic testing
 - Advances in genetic knowledge, technology, and affordability continue to improve
- For patient/family-friendly information on DNA banking, see [APPENDIX B](#)

CONSENT FOR TESTING:

- If results crucial to the accurate outcome of death investigation:
 - ME/C may be able to pursue testing without consent *according to local statutory authority*
- If not initiating genetic testing for death investigation:
 - Family should be alerted to the potential for genetic disease and recommend a consult with PCP or **refer to genetics**

APPENDIX A: Letter of Medical Necessity Sample

Name: XXX YYY

DOB:

Insurance ID:

Ordering physician:

Ordering NPI:

Test name: Molecular autopsy also known as post-mortem genetic testing

CPT codes:

Diagnosis code:

To Whom It May Concern:

Although the following predetermination request for insurance coverage is not a traditional one, please review this in detail as the implications of this testing may be lifesaving for the **YYY** family who are members of Health Insurance Company Name.

On **date**, **XXX YYY** suffered a cardiac arrest shortly after **INSERT TRIGGERS/SYMPTOMS/CIRCUMSTANCES**. **He/She** had an extensive post-mortem examination that did not determine why **he/she** died. **His/Her** cause of death is suspected to be due to cardiac arrhythmia. Fortunately, **XXX's** medical examiner retained a blood sample that can be used for DNA extraction and post mortem molecular genetic testing (aka molecular autopsy).

Genetic testing for genetic arrhythmias will determine the cause of death for up to 35% of victims of sudden death who have normal autopsies, toxicology testing, and expert pathology assessments just like **XXX**.^{vi} Therefore, the Heart Rhythm Society (HRS) recommends a molecular autopsy in cases of unexplained sudden death in two separate clinical guidelines.^{vii, viii}

Without genetic testing, the **YYY** family's doctors must rely on extensive cardiovascular testing to detect asymptomatic heart disease in at-risk family members. **Error! Reference source not found.** shown on page **Error! Bookmark not defined.** is taken directly from the 2013 HRS clinical guidelines and describes the algorithm for evaluating the surviving family members, like the **YYY** family. These medical evaluations are necessary because research has shown up to half of the families of victims of unexpected sudden death will have at least one close family member with an underlying genetic heart condition such as long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and arrhythmogenic right ventricular dysplasia (ARVD). A molecular autopsy may determine whether this cardiovascular testing is necessary and who in the family truly needs it.

If **XXX** is in the 35% of cases where genetic testing identifies her cause of death, then each of **his/her** surviving family members will be offered targeted and inexpensive genetic testing to determine whether they inherited the same risk of sudden death. If **XXX** tests positive for a disease-causing mutation, then each of his/her first-degree relatives will be at 50% risk for the same mutation. Any of **XXX's** family members who also test positive for the gene mutation will receive cardiovascular surveillance and specific medical treatment to protect them from the risk of cardiac arrest. Any of **XXX's** siblings or parents who test negative for the gene will not be at increased risk for life-threatening arrhythmias; therefore, extensive cardiovascular testing will no longer be necessary for them.

Dr. **ZZZ** and I recognize the unique nature of this insurance request as the genetic testing will be performed on an extracted DNA sample from someone who has recently died; therefore, **he/she** is not technically covered by Health Insurance Company Name at this moment. However, the implications of the testing are for the direct benefit of **XXX's** surviving siblings and parents who are currently covered by Health Insurance Company Name.

Please contact us with any questions or concerns you have about this request. My direct phone number is **(###)-###-####** and my email address is **INSERT EMAIL**.

Sincerely,



DNA Banking

Brought to you by National Society of
Genetic
Counselors

DNA banking allows genetic material from an individual to be saved for future use. It lets families pursue genetic testing at a later time and take advantage of future technology.

When might DNA banking be appropriate for me or my family?

- Current technology is unable to find a genetic cause for a suspected hereditary condition.
- No testing is available yet.
- Cost of current testing is too high.
- There is not enough time for traditional genetic testing (e.g. terminal illness).
- There has been a sudden, unexplained death.

How can my family participate in DNA banking?

- Discuss the option with your family and healthcare provider.
- A genetic counselor can help to determine whether DNA banking is appropriate and coordinate this service. If you don't have a genetic counselor, your provider can refer you, or you can find one at findageneticcounselor.com

How and where is my DNA banked?

- DNA can be obtained from blood, saliva or other tissue samples.
- The sample is sent to a laboratory where DNA is extracted and stored.
- Storage times may vary from a few years to no time limit.
- DNA banking is offered by various commercial and academic labs. Your genetic counselor will discuss the options and help determine the most appropriate one for you.

How much does DNA banking cost?

- Cost varies depending on the laboratory, but is typically under \$200 per individual.
- Most labs do not charge an annual fee, but there may be a charge to release the sample for testing.
- Generally, DNA banking is not covered by health insurance, but individual plans may vary
- Future genetic testing cost is not included in DNA banking costs.

Is DNA banking secure?

- Only the person who banked their DNA (the depositor) or a legally authorized person (designee) has the authority to request the DNA bank to release, transfer, test or destroy the sample.
- The sample cannot be accessed or used without permission from the depositor or their designee.

For more information about DNA Banking and Genetic Testing, visit www.findageneticcounselor.com

Barriers to Post Mortem Genetic Testing



APPENDIX D: HRS/EHRA Genetic Testing Recommendations

Recommendations from Ackerman et al., 2011.

Determining appropriate guidelines may require a referral to a genetics or cardiology specialist or extensive review of available clinical information.

STATE OF POSTMORTEM GENETIC TESTING FOR SUDDEN UNEXPECTED DEATH CASES

- Class I – **is recommended**
 - For all SUDs and SIDS cases, collection of a tissue sample **is recommended** for subsequent DNA analysis/genetic testing
 - Mutation-specific genetic testing **is recommended** for family members following the identification of a SUDs causative mutation
 - Mutation-specific genetic testing **is recommended** if circumstantial evidence points toward a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death)
- Class IIb – **may be considered**
 - In the setting of autopsy negative SUDs, comprehensive or targeted (RYR2, KCNQ1, KCNH2, and SCN5A) ion channel genetic testing **may be considered** in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives

STATE OF GENETIC TESTING FOR OUT OF HOSPITAL CARDIAC ARREST SURVIVORS

- Class I – **is recommended**
 - In the survivor of an unexplained out-of-hospital cardiac arrest, genetic testing **should be** guided by the results of medical evaluation and is used for the primary purpose of screening at-risk family members for asymptomatic disease
- Class III - **is not indicated/recommended**
 - Routine genetic testing, in the absence of a clinical suspicion for a specific cardiomyopathy or channelopathy, **is not indicated** for the survivor of an unexplained out-of-hospital cardiac arrest

STATE OF GENETIC TESTING FOR LONG QT SYNDROME (LQTS)

- Class I - **is recommended**
 - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing **is recommended** for any patient in whom a cardiologist has established a strong clinical index of suspicion for LQTS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype
 - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing **is recommended** for any asymptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc .480 ms (prepuberty) or .500 ms (adults)
 - Mutation-specific genetic testing **is recommended** for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case
- Class IIb - **may be considered**
 - Comprehensive or LQT1-3 (KCNQ1, KCNH2, and SCN5A) targeted LQTS genetic testing **may be considered** for any asymptomatic patient with otherwise idiopathic QTc values .460 ms (prepuberty) or .480 ms (adults) on serial 12-lead ECGs

STATE OF GENETIC TESTING FOR SHORT QT SYNDROME (SQTS)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the SQTS-causative mutation in an index case
- Class IIb - **may be considered**
 - Comprehensive or SQT1-3 (KCNH2, KCNQ1, and KCNJ2) targeted SQTS genetic testing **may be considered** for any patient in whom a cardiologist has established a strong clinical index of suspicion for SQTS based on examination of the patient’s clinical history, family history, and electrocardiographic phenotype

STATE OF GENETIC TESTING FOR BRUGADA SYNDROME (BrS)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case
- Class IIa - **can be useful**
 - Comprehensive or BrS1 (SCN5A) targeted BrS genetic testing **can be useful** for any patient in whom a cardiologist has established a clinical index of suspicion for BrS based on examination of the patient’s clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative drug challenge testing) phenotype
- Class III - **is not indicated/recommended**
 - Genetic testing **is not indicated** in the setting of an isolated type 2 or type 3 Brugada ECG pattern.

STATE OF GENETIC TESTING FOR CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)

- Class I - **is recommended**
 - Comprehensive or CPVT1 and CPVT2 (RYR2 and CASQ2) targeted CPVT genetic testing **is recommended** for any patient in whom a cardiologist has established a clinical index of suspicion for CPVT based on examination of the patient’s clinical history, family

history, and expressed electrocardiographic phenotype during provocative stress testing with cycle, treadmill, or catecholamine infusion

- Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CPVT-causative mutation in an index case

STATE OF GENETIC TESTING FOR PROGRESSIVE CARDIAC CONDUCTION DISEASE (CCD)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the CCD-causative mutation in an index case
- Class IIb - **may be considered**
 - Genetic testing **may be considered** as part of the diagnostic evaluation for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially when there is documentation of a positive family history of CCD

STATE OF GENETIC TESTING FOR ATRIAL FIBRILLATION

- Class III - **is not indicated/recommended**
 - Genetic testing **is not indicated** for atrial fibrillation at this time
 - SNP genotyping in general and SNP rs2200733 genotyping at the 4q25 locus in particular for AF **is not indicated** at this time based on the limited outcome data currently available

STATE OF GENETIC TESTING FOR ARRHYTHMOGENIC CARDIOMYOPATHY (ACM)/ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY (ARVC)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the ACM/ARVC causative mutation in an index case
- Class IIa - **can be useful**
 - Comprehensive or targeted (DSC2, DSG2, DSP, JUP, PKP2, and TMEM43) ACM/ARVC genetic testing **can be useful** for patients satisfying task force diagnostic criteria for ACM/ARVC
- Class IIb - **may be considered**
 - Genetic testing **may be considered** for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 task force criteria (European Heart Journal).
- Class III - **is not indicated/recommended**
 - Genetic testing **is not recommended** for patients with only a single minor criterion according to the 2010 task force criteria.

STATE OF GENETIC TESTING FOR HYPERTROPHIC CARDIOMYOPATHY (HCM)

- Class I - **is recommended**
 - Comprehensive or targeted (MYBPC3, MYH7, TNNI3, TNNT2, TPM1) HCM genetic testing **is recommended** for any patient in whom a cardiologist has established a clinical diagnosis of HCM based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of the HCM-causative mutation in an index case

STATE OF GENETIC TESTING FOR DILATED CARDIOMYOPATHY (DCM)

- Class I - **is recommended**
 - Comprehensive or targeted (LMNA and SCN5A) DCM genetic testing **is recommended** for patients with DCM and significant cardiac conduction disease (i.e., first-, second-, or third-degree heart block) and/or a family history of premature unexpected sudden death
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case
- Class IIa - **can be useful**
 - Genetic testing **can be useful** for patients with familial DCM to confirm the diagnosis, to recognize those who are at highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning

STATE OF GENETIC TESTING FOR RESTRICTIVE CARDIOMYOPATHY (RCM)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of an RCM-causative mutation in the index case
- Class IIb - **may be considered**
 - RCM genetic testing **may be considered** for patients in whom a cardiologist has established a clinical index of suspicion for RCM based on examination of the patient's clinical history, family history, and electrocardiographic/ echocardiographic phenotype

STATE OF GENETIC TESTING FOR LEFT VENTRICULAR NONCOMPACTION (LVNC)

- Class I - **is recommended**
 - Mutation-specific genetic testing **is recommended** for family members and appropriate relatives following the identification of a LVNC-causative mutation in the index case
- Class IIa - **can be useful**

- LVNC genetic testing **can be useful** for patients in whom a cardiologist has established a clinical diagnosis of LVNC based on examination of the patient's clinical history, family history, and electrocardiographic/echocardiographic phenotype

ⁱ Middleton, M. O., Baxter MS CGC, S., Demo MS CGC, E., Honeywell MSc CCGC, C., Jentzen MD, J., Miller MD, F., . . . MacLeod MS CGC, H. (2013). National Association of Medical Examiners Position Paper: Retaining Postmortem Samples for Genetic Testing. *Academy of Forensic Pathology*, 3(2), 191-194.

ⁱⁱ National Society of Genetic Counselors. (2018). *Postmortem Genetic Testing FAQs*. Retrieved from National Society of Genetic Counselors: <https://www.nsgc.org/p/cm/ld/fid=488>

ⁱⁱⁱ Gruner, N., Stambouli, O., & Ross, R. S. (2015). Dried blood spots - preparing and processing for use in immunoassays and in molecular techniques. *J Vis Exp*, 97, 52619.

^{iv} Scientific Working Group on Medicolegal Death Investigation, Guidelines for Communication with Next of Kin During Medicolegal Death investigations, June 13, 2012. <http://swgmdi.org/images/nokguidelinesforcommunicationwithnok6.14.12%202.pdf>

^v MacLeod, H., Leighton, J., Lynch, K., Kelly, M., Dolinsky, J., Singleton, A., & Baxter, S. (2014). Review of Postmortem Clinical Genetic Testing Sample Success Rates and Payors from Commercial Labs. Heart Rhythm Society, (<https://www.nsgc.org/d/do/4063>).

^{vi} Tester DJ, Ackerman MJ. The role of molecular autopsy in unexplained sudden cardiac death. *Curr Opin Cardiol* 2006;21:166–172.

^{vii} Ackerman, M.J., Priori, S.G., Willems, S., Berul, C., Brugada, R., Calkins, H., Camm, A.J., Ellinor, P.T., Gollob, M., Hamilton, R., et al. (2011). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Heart Rhythm* 8, 1308–1339.