Cardiogenetics in the MHS: Unraveling the Code to get to the Heart of the Matter

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Ms. Lydia Hellwig is a certified genetic counselor and assistant professor of pediatrics at the Uniformed Services University of the Health Sciences through the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. in support of the Center for Military Precision Health. Ms. Hellwig is a co-investigator and genetic counselor for many military genomic research projects, including genomic medicine implementation studies as well as studies that seek to better understand sudden cardiac death, cancer, and other hereditary diseases. Her clinical practice, research, and teaching efforts seek to improve the way in which genomic technologies are used to maximize health and psychosocial outcomes.

Disclosures

Ms. Lydia D. Hellwig has no relevant financial or non-financial relationships to disclose relating to the content of this activity.

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Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Describe how cardiogenetics can impact patient and family care.
2. Identify at least three cardiogenetics conditions.
3. Summarize the role of postmortem genetic testing.

Cardiogenetics Diseases

- 1/200 people have inherited cardiovascular disease.
- Inherited cardiovascular diseases are the leading cause of sudden death in young people.
- Identifying at-risk patients is often life-saving.
- **A cardiovascular genetics evaluation is recommended for families with hereditary heart conditions by Heart Rhythm Society (HRS), Heart Failure Society of America (HFSA), American Heart Association (AHA), American College of Cardiology (ACC), and others.**

www.jyi.org, 2017

Family History

Indications for referral to cardiovascular genetics

A personal or family history of:

Cardiomyopathy:
- Hypertrophic cardiomyopathy (HCM)
- Familial or idiopathic dilated cardiomyopathy
- Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC/D)
- Peripartum cardiomyopathy
- Left ventricular non-compaction
- Restrictive cardiomyopathy
- Familial amyloidosis

Arrhythmia:
- Long QT syndrome (LQTS)
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Familial atrial fibrillation
- Progressive conduction system disease
- Unexplained sudden death
- Unexplained cardiac arrest
- Short QT Syndrome

Vascular diseases:
- Aortic aneurysm and/or dissection (<50 years old)
- Marfan syndrome
- Loeys-Dietz syndrome
- Vascular Ehlers-Danlos (IV)

Other:
- Familial hypercholesterolemia
- Heritable heart defects (e.g. conotruncal defects, left ventricular outflow tract defects)
- Multiple relatives with congenital heart defects
- Familial or idiopathic pulmonary arterial hypertension

Family history suggestive of a hereditary cardiovascular condition:

- Unexplained cardiac arrest(s) or sudden death ★★★★
- Unexplained syncope, syncope with exercise or emotional distress ★★
- Unexplained seizures, seizures with normal neurological evaluation ★
- ICD/Pacemaker (<50 years) ★★
- Heart failure (<60 years) ★★
- Heart transplant (<60 years) ★
- Cardiomyopathy or "enlarged heart" ★
- Arrhythmia or "irregular heartbeat" ★
- Exercise intolerance ★
- Early "heart attack", coronary artery disease, or stroke (Males <55 years; Females <65 years) ★★
- Aortic aneurysm/dissection (< 50 years) ★
- Sudden infant death syndrome (SIDS) ★
- Unexplained accidents (i.e. drowning, single car accident, etc.) ★★★★
- Untreated LDL ≥190 ★

★ Cardiomyopathy ★ Arrhythmia ★ Vascular disease ★ Familial hypercholesterolemia

Inherited cardiovascular diseases are the leading cause of sudden death in young people

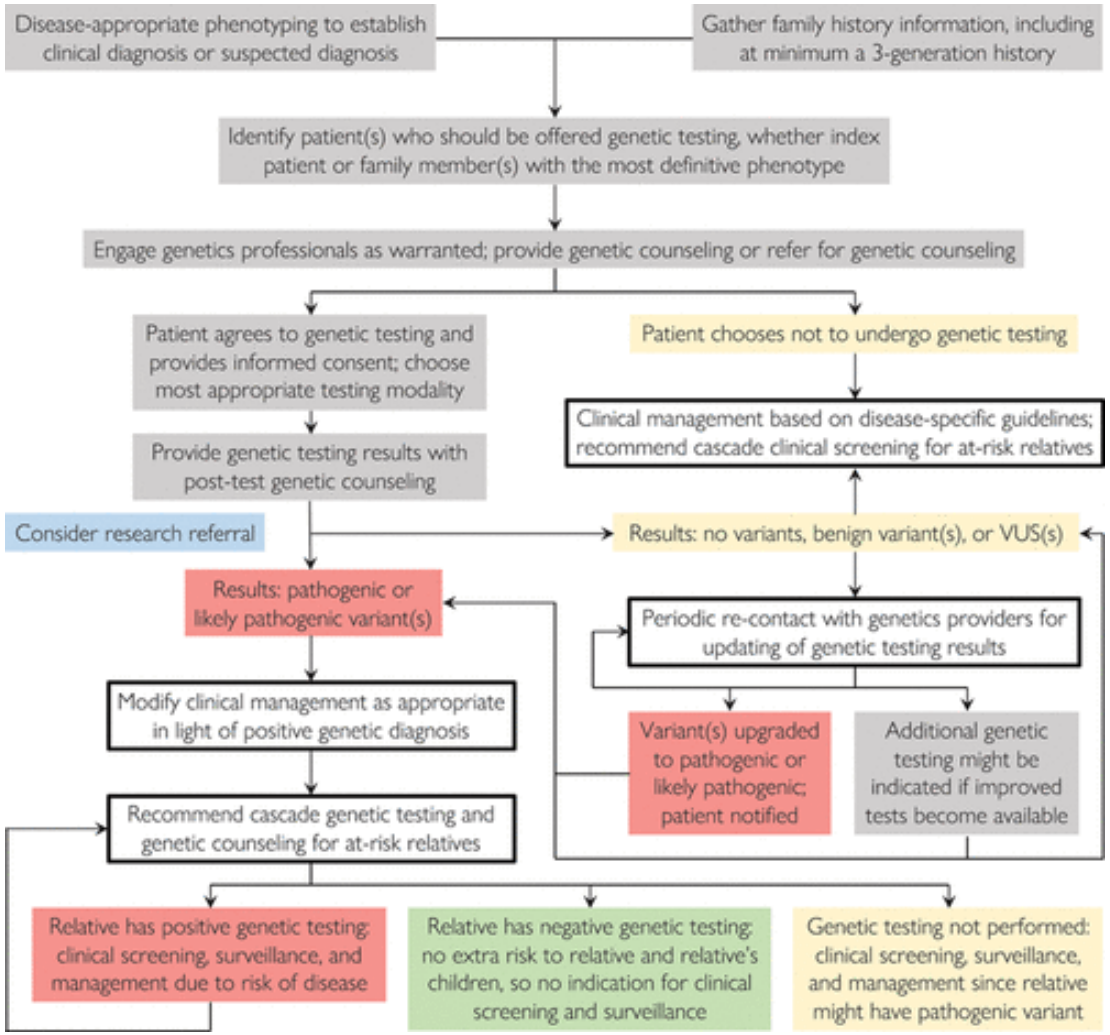
National Society of Genetic Counselors, 2022

Precision Medicine

"An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"

https://ghr.nlm.nih.gov/primer/precisionmedicine/definition , 2020
https://researcher.watson.ibm.com/researcher/view_group.php?id=1179, n.d.

Genetic Testing for Inherited Cardiovascular Disease



Musunuru et al., 2020

What does the cardiogenetics clinic do?

- Genetic Counseling and Genetic Testing
  - There are LOTS of genetic testing options including multiple labs offering panels that include different genes! Our team will order the most appropriate genetic test for clinically indicated patients
  - Pre-test and post-test genetic counseling
  - Follow up about uncertain genetic test results
- Interpretation and Follow Up
  - Follow up with patients and providers
- Family Member Screening
  - Recommended family member clinical cardiac evaluation and follow up

www.insideprecisionmedicine.com, 2022

Case Example 1

- 30 year old male referred due to high cholesterol: low-density lipoprotein (LDL) >200
- Family history of paternal relatives dying of heart attacks in their 50s-60s

Familial Hypercholesterolemia (FH)

- FH is a genetic disorder that causes high cholesterol levels in the blood.
- Increased risk for premature heart disease and sudden death if left untreated.
- Medical management recommendations for individuals with FH are different than for individuals who just have high cholesterol.
- Treated with medication and lifestyle changes
  - Statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors often necessary to achieve optimal LDL-Cholesterol (LDL-C) reduction.
- Initial screening of children at risk for FH should take place between and 8 years of age.

Results

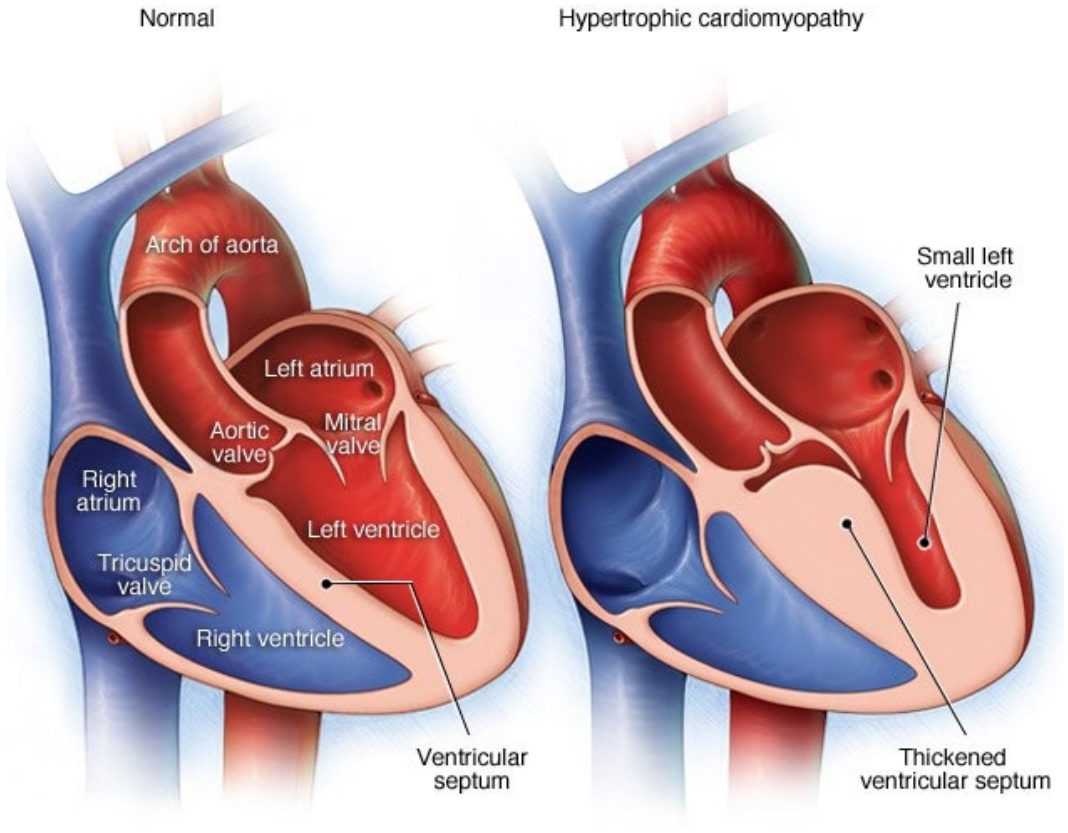
- Pathogenic (disease-causing) variant in the *APOB* gene
- Children had cholesterol levels checked and underwent targeted genetic testing
- 2/3 children have pathogenic variant and have increased cholesterol levels
  - Impacts current medical management

Case Example 2

- Father and 3 children referred to cardiogenetics clinic due to father's recent diagnosis of Hypertrophic cardiomyopathy.
- Clinical cardiac screening for children at the time of the visit was normal.
- Parents expressed constant worry about the children participating in any sort of physical activity given the uncertainty of their risk.

Hypertrophic Cardiomyopathy (HCM)

- Heart condition characterized by thickening of the heart muscle
- Symptoms can vary, even within the same family
- Some people may not have any symptoms, others may experience chest pain, shortness of breath, feeling fluttering or pounding in the chest, lightheadedness, dizziness, fainting, and sudden death
- HCM can develop at any time throughout life



Results

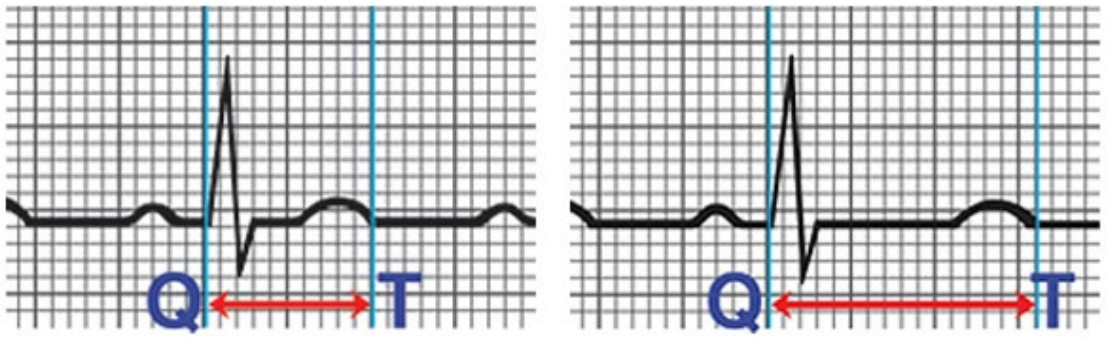
- Father found to have a pathogenic variant in the *MYBPC3* gene consistent with his diagnosis of HCM.
- Discussion of potential risks and benefits of genetic testing, including potential impact for military career.
- Targeted genetic testing showed that 2 of the children did not inherit the pathogenic variant.
- One child inherited the pathogenic variant and we discussed next steps together.
- Family expressed their relief given that they feel confident about the plan moving forward for the care of their family.

Case Example 3

- 12 year old female referred to cardiogenetics for prolonged QT interval.
- Family history notable for maternal uncle that drowned in shallow water in his 20's and one maternal uncle that died shortly after birth.

Long QT Syndrome

- Cardiac electrophysiological disorder characterized by QT prolongation and T wave abnormalities that are associated with tachyarrhythmia.
- Cardiac events can occur during exercise and emotional stress, less frequently during sleep, and usually without warning.
- Approximately 50% of untreated individuals with a pathogenic variant in an associated gene have symptoms, usually one to a few syncopal events.
- Cardiac events can occur from infancy through middle age and are most common from preteen years through the 20's.



Normal Q-T Interval *Long Q-T Interval*

https://healthjade.net/long-qt-syndrome/ , 2019

Results

- Pathogenic variant identified in the *KCNQ1* gene, associated with long QT syndrome type 1.
- Medical Management Implications:
  - Avoid QT-prolonging drugs
  - Medications
  - Follow Up
- Family Member Testing:
  - Sister does not have this variant.
  - Mom also has this variant and will be following up with cardiologist.
  - Importance for future children as well.

Cardiogenetics Clinic at Walter Reed

- Multidisciplinary clinic at Walter Reed National Military Medical Center (WRNMMC)
  - Providers from genetics, adult cardiology, and pediatric cardiology
- See patient and all eligible indicated family members at one time
  - Saves the family visits to multiple separate specialties AND family context often helps with medical management

Sudden Death

- AHA estimates that 92% of individuals who experience cardiac arrests each year died prior to reaching the hospital

- Young sudden cardiac death is 1.3-8.5/100,000 per year
  - This is MUCH higher in the Active Duty population

- Nearly 50% of sudden cardiac death victims under 35 have no warning signs or reported family history of sudden death
  - 30% of these cases have no heart abnormality on autopsy

Postmortem genetic testing: the "Molecular Autopsy"

Determine cause of death: For cases of unexplained death, genetic testing may provide a cause of death up to 40% of the time

Protecting surviving family members: If genetic testing identifies the cause of a sudden death, then at-risk family members can undergo targeted genetic testing to determine whether they inherited the same risk of sudden death and receive medical care to reduce their risk of sudden death

When to consider postmortem genetic testing?

Especially in these cases:

- Individuals 40 years old and younger
  - Sudden unexplained death, especially during exercise or during sleep
  - Possible cardiac etiology
    - Drowning
    - Single motor vehicle accident
    - Unexplained seizures
  - Cardiomyopathies (hypertrophic, idiopathic dilated, restrictive, arrhythmogenic)
  - Thoracic Aneurysm
  - Known genetic diagnosis
  - Family history of sudden death of inherited heart disease

Case Example 4

- 26 year old female collapsed while running on the treadmill.
- Just returned on a flight from US to Germany and cause of death attributed to pulmonary embolism [German Medical Examiner (ME) declined to perform an autopsy].
- Armed Forces Medical Examiner System (AFMES) assumed jurisdiction and performed autopsy. No evidence of pulmonary embolism or deep vein thrombosis (DVT). Evidence of borderline cardiomegaly with four-chamber dilatation.
- Referred for genetic counseling and genetic testing.

Case Example- Results

- Pathogenic (disease-causing) variants identified in two genes associated with cardiomyopathy and sudden death.

Why is this important?

- Family member screening and targeted genetic testing
- Significantly alters family member medical management
- If assumed to be pulmonary embolism, we would never have known about the risk to other family members

Systematic Evaluation of Sudden Death in the Military

- Currently does not exist.
- Autopsies
  - Not systematically done
  - Not all done through Armed Forces Medical Examiner
- Samples
- Counseling and Consent for Families
  - We provide counseling to families and obtain consent from primary next of kin (PNOK) so that results can appropriately be used/useful to families.
  - Postmortem genetic testing after a family member has died can be an overwhelming and emotional process for the family. The cardiogenetics team supports and assists the families throughout this sensitive time.

Systematic Evaluation of Sudden Death in the Military

- Standard procedures and educational tools developed for clinicians and families of individuals with sudden death

- Clinician guide for how to help with sudden, unexplained death of a patient
  - First thing to do would be immediately contact the ME to ask that they obtain a deoxyribonucleic acid (DNA) sample [Blood sample in purple top/Ethylenediamine tetraacetic acid (EDTA tube)] and then contact WRNMMC Cardiogen Team to help with the process
  - For historical cases, referral to Cardiogen is appropriate.

- Cardiogenetics team assists with the logistics of ordering genetic testing, informed consent for the family, psychosocial support, interpretation and return of results, and coordination of family evaluations.

Research

- Our knowledge of genetics and genomics is constantly changing!
- Gene-Disease Relationships
- Variant-Disease Relationships
- Guidelines for clinical care management
  - Affected and unaffected genotype-positive individuals
- Ethical, Legal, and Social Implications (ELSI)
  - Military-specific implications and policy
  - Challenges of genetic testing and appropriate us

www.gigagenomics.uliege.be , 2018

Conclusions

- Genetic counseling and genetic testing is critical to the care of patients and families in the MHS.
  - Diagnosis and Screening
- Multidisciplinary team approach
- Postmortem cases can be quite difficult
  - Logistically
  - For families
  - Results
- Our experience has shown that families find this really helpful, whether they decide to pursue testing or not.

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Questions?

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