Science at the heart of medicine

Ethical, Legal and Social Issues in Genetic Testing Following Unexpected Deaths: Translation of Cardiogenetic Knowledge to Clinical Practice

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- American Recovery and Reinvestment Act (ARRA) grant on Ethical Issues in the Translation of Genetic Knowledge to Clinical Practice
- Funded by National Heart, Lung and Blood Institute
- Research project began on January 1, 2010
Center for Cardiogenetics

- Patients referred by cardiologists or in follow-up to a SIDS death
- Pediatric & Adult Cardiology
  - Physical Exam, EKG, Echocardiogram, Stress Test, Holter
- Genetic Counseling & Clinical Genetics
  - Family History & Pedigree
- Psychology & Social Work
- Genetic Testing
- Translational Research
  - Gene discovery and channel characterization
- Research on subjective experience of patients via focus groups
- Personalized Medicine

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SIDS and SUDS

- SIDS: Sudden Infant Death Syndrome
- SUDS: Sudden Unexpected Death Syndrome

<table>
<thead>
<tr>
<th>SIDS/crib death</th>
<th>SUDS</th>
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<tbody>
<tr>
<td>Timing</td>
<td>Ages 1-35</td>
</tr>
<tr>
<td>Prevalence</td>
<td>54 per 100,000 births</td>
</tr>
<tr>
<td>Genetics</td>
<td>~10-20% associated with genetic mutations</td>
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Long QT Syndrome

- Uncommon genetic disorder
  - ~1:2,500
  - Mutations in potassium (K) and sodium (Na) channels
  - >90% autosomal dominant

- ECG findings: Prolonged QTc Interval

- Torsade de pointes (polymorphic ventricular tachycardia)

- Syncope or Sudden Death
QT interval can be prolonged by mutations in K (potassium) or Na (sodium) channels.

QTc is the QT interval corrected for heart rate.

KCNQ1, LQT1
Events often result from gene-environment interactions

Occurrence of Event Triggers

<table>
<thead>
<tr>
<th>Event Trigger</th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>62%</td>
<td>26%</td>
<td>3%</td>
</tr>
<tr>
<td>Emotion</td>
<td>13%</td>
<td>43%</td>
<td>29%</td>
</tr>
<tr>
<td>Sleep</td>
<td>39%</td>
<td>19%</td>
<td>13%</td>
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Personalized Genetic Medicine

- Based on family history, perform genetic testing

- KCNQ1, LQT1
- KCNH2, LQT2
- SCN5A, LQT3

- β-blocker
- Avoid competitive sports
- Remove alarms from bedroom
- Remove auditory ring from phone
- Pacemaker
- Mexiltiline (low dose)
Risk Stratification in LQTS patients

- **Very High Risk (Secondary Prevention):**
  - Occur in the context of LQTS
  - Spontaneous TDP

- **High Risk (Primary Prevention):**
  - Either one or more:
    - QTe > 500 ms
    - Prior syncope

- **Low Risk:**
  - QTe ≤ 500 ms
  - No prior syncope

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Personalized Genetic Medicine

- **Gene**
  - KCNQ1
  - KCNH2
  - SCN5A

- **LQTS Subtype**
  - LQT1
  - LQT2
  - LQT3

- **Treatment:**
  - β-blocker
  - Avoid competitive sports
  - β-blocker
  - Remove alarms from bedroom
  - Remove auditory ring from phone
  - Pacemaker
  - Mexilitine (low dose)
Grant Specific Aims

1. Evaluate and systematize ethical and social issues associated with SIDS and SUDS that reveals a molecular cardiogenetic cause with implications on clinical care for surviving family members.

2. Analyze potential tensions and conflicts that might arise from the transfer of genetic knowledge to clinical practice in cardiogenetics.

3. Develop recommendations, guidelines and tools specifically for use by multidisciplinary cardiogenetics centers and more generally for disease-specific centers offering personalized genomic medicine, and disseminate these through a series of articles and conference publications.

Questions?
Ethical Issues Illustrated

Mr. Wasserman

Case 1

- 15 year old female, asymptomatic adolescent
- Long QT Syndrome, Type 2
- Older sibling died unexpectedly, posthumous diagnosis of LQTS made by Medical Examiner’s Office
- Parents initially refused to disclose medical condition to adolescent
- Adolescent refused to give up her participation in competitive athletic activity
  - “I’d rather die than stop running.”
- Parents advocating for implantable cardioverter defibrillator (ICD)
Case 2

- Adult male, experienced cardiac life-threatening event
- Diagnosed with Long QT Syndrome, Type 3, and mutation identified
- Refuses, with wife, to allow their 16 year old daughter be tested for the mutation
- Parents understand that this condition is autosomal dominant and daughter has a 50% risk of having the same mutation
- Parents believe daughter is asymptomatic and health risk is not as threatening as potential psychological harm from testing, including depression
- Physicians bear the burden of withholding from patient information they consider potentially lifesaving
- Parents consider this to be protecting their child from the same information

Case 3

- 17 year old adolescent, experiences anxiety and palpitations
- Father died suddenly in his early 30s from a fatal arrhythmia
- Paternal uncle had an ICD placed shortly after father’s death – presumed diagnosis was Brugada Syndrome
- Pediatrician advised mother not to pursue a cardiac workup until adolescent turned 18 years old
- During patient’s workup, this uncle is contacted by family, but he now refuses to disclose any further medical information or release any of his medical records to relatives or health professionals
- Cardiology workup reveals no abnormalities and genetic testing is negative, however, testing is only positive in about 30% of patients who have the condition
- Teenage patient is taking a commonly prescribed psychotropic medication which may be proarrhythmic and should be avoided by patients with Brugada syndrome
Ethical Considerations

Three sets of issues raised by these cases:

1. Does the clinician have a duty to disclose the patient’s genetic test results to at-risk family members, even if those results are "personal health information?"

2. Should adolescents have the same rights as adults to receive and act on genetic information from family members?

3. What duties do parents have to discover and mitigate genetic risks to their children?

First Issue: Disclosure vs. Confidentiality

• From Tarasoff to Safer. Is the genetically-based risk of sudden cardiac arrhythmia "imminent" enough to trigger a duty to disclose positive test results without the patient’s consent to family members with a significant probability of having the same mutation?

• How should the duty to warn be weighed against the duty not to disclose "personal health information?" Is disclosure of test results permitted because it is "necessary to prevent or lessen a serious and imminent threat to the health or safety" of family members?

• If there is a duty to disclose, how far does it extend? For example, to distant relatives with less than a 50% chance of having the deleterious mutation?
First Issue: Disclosure vs. Confidentiality, Cont.

- Whose genetic information is it, anyway?
- Is it a mistake to see these cases as presenting conflicts between disclosure and confidentiality, rather than an issue about whom genetic information is really “about?”
- Is genetic information about any or all of biological relatives of the individual tested, so that they are also entitled to it?
- If genetic information is really about the family, is there a duty not to be tested if other family members do not want to know?

Second Issue: Adolescent Decision Making

- Do adolescents have a right to know about their family’s genetic risk information and make their own decisions about genetic testing and medical compliance?
  - Mixed picture of adolescent competency and maturity from social, behavioral, and neuroscience standpoints
  - Different competence for different kinds of decisions?
  - Different competency standards for different decisions?
  - Different standards for adolescents versus young children?
Third Issue: Parental Responsibility

• Do parents have a duty to have their adolescent or younger children tested for controllable genetic risks?

• How much latitude do parents have to decide what risks to their children are acceptable and to trade off health risks against other risks, benefits and values?

• How can clinicians assess the reasonableness of their patients’ decisions about risk? In particular, how can they distinguish disagreements in risk estimation, on which they are likely to have superior knowledge, from differences in risk preferences, on which they have no special authority?

Questions?
Psychosocial Issues in Cardiogenetics

Dr. Stolerman

Project Overview

• Total of 47 people interviewed

• 5 focus groups and 24 family or individual interviews

• All of the participants had:
  • A cardiac problem themselves, or
  • A relative with a cardiac problem, or
  • Experience with the sudden death of a family member
Project Overview

• Qualitative Methodology; Family Perspective

• 1-2 hour long unstructured interviews

• Open ended questions
  • “Tell us the story of what happened in your family.”
  • “How did ___’s death affect how you think about the health of your family?”
  • “How did the availability of genetic testing affect your family?”

Emergent Psychosocial Issues

• How can cardiogenetic information be useful to families as they grieve?

• How do family experiences shape parental decision to permit their adolescent children to undergo genetic testing?

• How do families manage the disclosure of genetic information to other family members?
Utility of Cardiogenetic Information

- Explanation of Death
  - “We knew why she died! It wasn’t a mystery anymore.” (White woman, 51)
  - “It gives me some closure, knowing the cause of death.” (African Caribbean woman, 57)
- Exonerates from suspicion of risky behavior
  - “We found out that he was married but the same day we found out that he passed. So I guess for a long time especially in the beginning it was not only dealing with his death but it was dealing with a new wife and the suspicion was all around what really caused his death…and my husband was still focused on the whole Red Bull and alcohol thing.” (African-American woman, 52)

Utility of Cardiogenetic Information

- Validation and improved treatment by medical professionals.
  - “People know you’re for real, they believe you! The doctors even.” (White woman, 56)
- Security for surviving family members
  - “My main focus was trying to figure out what happened so I could figure out how to prevent it with our second child.” (White woman, 42)
- Some were not ready
  - “I definitely wouldn’t have [been ready to hear about genetic testing]…I would have felt like, I need to process, I need to grieve…So for me it would have been an intrusion early on.” (White woman, 45)
Decision Making

• Intersection of sports and healthcare:
  
  • “She didn’t tell me until the coach said two weeks ago [she collapsed]…it made me worry even more because it wasn’t realistic to her.” (Mother, White woman, 48)
  
  • “Didn’t wanna come…, I was just annoyed [these tests are] a waste…I’ve been running like since I could walk. And I’m really athletic, and nothing has ever happened to me before…It’s not the end of the world.” (Her daughter, 17)
  
  • “We needed [results] ASAP because we have four athletes in the family.” (Mother)

• Reassurance for future planning, i.e. use of medical device; restrictions. Justification for life change.
  
  • “It has given me confidence that we can deal with whatever comes up…the eventuality that he will probably have to have a defibrillator…I don’t know that we would have been able to accept it as readily if we had not had genetic testing available and had it done.” (White woman, 51)
  
  • “Since I’ve gone through genetic testing now, we know I have LQT 1…my cardiologist feels more comfortable with my choice [not to get an ICD].” (White woman, 35)
Sharing Genetic Information in Families

• Developmentally appropriate
  - “Your heart takes a little bit longer to re-start than most people’s. So they want to give you this (ICD) so if something happens, you’ll be OK.” (African-American woman, 29)
  - “They know they [children ages 5 and 8] have to have their heart checked because mommy passed away from the heart. I just keep it simple with them.” (Latino, 31)

• Clinician’s assistance
  - “Dr. A. helped me explain it to the school and the family.” (White woman, 46)

• Variability within families
  - “My sister hasn’t gotten herself of her kids tested. I think she’s in denial.” (White woman, 51)
  - “I would make it a law if I could!” (White woman, 48)
  - “There is a moral obligation, but you can’t obligate someone legally.” (White woman, 46)
  - “If this comes back positive, I don’t want my cousins to get tested now…it would have been awful to be the bearer of bad news.” (White adolescent, 17)
Study Limitations

- Sample bias
  - Sources of recruitment were patients of Cardiogenetics Center and advocacy groups.
  - Majority of participants interested in genetic testing and experienced it as helpful and often as a source of “relief.”
  - High percentage (80%) of participants are women.

Questions?
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Thank you!