

Virtual Mentor

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Genetic Testing: Clinical and Personal Utility

Commentary by Rachel A. Mills, MS, Susanne B. Haga, PhD, and Geoffrey S. Ginsburg, MD, PhD

Dr. Orson is a family practice physician who has been treating Michael since he was born. He knows Michael's parents and siblings, having been their family doctor for nearly 30 years. He is also intimately familiar with Michael's family history: 3 members of his family in their 30s and 40s have suffered sudden cardiac death. Michael is now 22 years old, 10 years younger than his uncle was when he died of this cause. Michael is therefore vigilant about clinical surveillance of his overall health, but tends to avoid the subject of his family history altogether. He has, however, happily shared with Dr. Orson news of his recent marriage and his desire to start a family.

In preparation for Michael's first office visit since his marriage, Dr. Orson has done some research and found a genetic testing kit that examines a 5-gene profile of known inherited mutations that can lead to arrhythmias or death. Dr. Orson believes that the testing will either alleviate Michael's anxiety or allow him and his wife to prepare for possible cardiac complications.

Dr. Orson enters the exam room to find Michael accompanied by his wife Susan, who announces that they are expecting their first child. Dr. Orson congratulates them and inquires after the course of the pregnancy. Then he turns to Michael to continue the annual check-up. After giving Michael a clean bill of health, he brings up the topic of genetic testing and encourages Michael to submit a sample to test for the known channelopathies. Michael's mood changes; he becomes upset and angry about the suggestion.

"I'm about to become a father and you're telling me to take a test that might announce a death sentence?" Michael eventually says.

"I think it would be valuable information to know so we could initiate treatment or, at worst, prepare your family to anticipate...complications. We have ways of better predicting likelihoods of serious diseases now; why not use that information to prepare yourself appropriately?" Dr. Orson retorts.

"Why would I want to know that I might die soon? Can't I just live my life like everybody else, without thinking about my own mortality?" Michael responds.

Dr. Orson insists, “But the test could also provide reassurance, and think of your family and how they should prepare. I’m confident that if this testing had been available for others in your family, they would have gotten it. I really think you should consider it, for your good and the good of your family.”

Michael curtly thanks Dr. Orson for his time and the check-up and leaves the appointment. As Susan prepares to follow, Dr. Orson asks her to see if she can talk with him at home about the testing.

Commentary

In the past two decades, a number of genes have been found to be associated with dysfunctions of ion channels in cells (channelopathies) that can lead to sudden cardiac death. Testing is available when clinical symptoms, abnormal ECGs, or family history are present. Familion [1], GeneDx [2], and Correlagen [3] are commercially available genetic testing panels for mutations underlying channelopathies, cardiomyopathies, and other lethal cardiac disorders. Testing is also available through medical and research facilities [4].

With the identification of several causative genetic variants and testing platforms such as Familion, it is now the standard of care to discuss genetic testing for channelopathies, particularly for patients with a significant family history like Michael’s [5, 6]. However, the utility of genetic testing may be limited—only some genetic variations in one disorder, long QT syndrome (LQTS), can guide therapy [7], while the clinical recommendations are not yet well-defined for asymptomatic people with genetic mutations associated with other channelopathies, such as short QT syndrome or Brugada syndrome.

The case of Dr. Orson and his patient Michael raises questions about the management of patients with a family history of sudden cardiac death. One is the timing of Dr. Orson’s discussion about genetic testing. Given Dr. Orson’s long-time care of Michael and knowledge of the family history, a discussion about genetic testing might have best been had earlier. Though it is possible that Dr. Orson might have not had the knowledge or access to such testing, he could have referred Michael to a genetic specialist who would be more knowledgeable about familial channelopathies and options for genetic testing. Unfortunately, like many primary care physicians today, Dr. Orson may have been hindered by lack of education about genetics and genetic testing or lack of access to genetics professionals [8].

The primary ethical dilemma is that Dr. Orson is stuck between the duties of beneficence and nonmaleficence on the one hand and respect for patient autonomy on the other. These three principles are central to medical ethics. Beneficence means promoting good and nonmaleficence is the avoidance of harm; respecting patient autonomy is about honoring and promoting patients’ wishes, values, and preferences for health care. Dr. Orson recognizes that if Michael doesn’t have this testing, he may be missing the opportunity for treatment. Further, Dr. Orson is concerned about the health and well-being of Michael’s unborn child and any future children.

To find balance between these competing ethical duties, it is important that Dr. Orson and Michael consider the clinical utility, as well as the personal utility, of the test. Clinical utility is an intervention's usefulness in changing clinical outcomes, while personal utility takes into account things like psychosocial effects, family planning, lifestyle changes, future decision making, and the value of the information to the patient [9].

Dr. Orson's situation is not an uncommon one, especially concerning genetic tests with limited clinical utility. The potential "burden of knowledge" often influences a patient's perception of personal utility, as is commonly seen by geneticists and genetic counselors working with families affected by diseases like Huntington, Alzheimer, and some cancers. There are currently no treatment or preventative measures that patients at increased risk of these diseases can take; thus, genetic testing would not have significant clinical utility. The primary benefits of this testing would be personal: genetic testing can provide knowledge about disease risk for the patient and family members and inform life and end-of-life decisions. The risks associated with testing for diseases with no clinical utility include psychological burden and genetic discrimination—although the Genetic Information Nondiscrimination Act (GINA) protects patients from changes in health insurance or employment, it does not cover life insurance or disability [10].

It is difficult to compare the risks and benefits of genetic testing in cases like Michael's; each risk or benefit can have a different "weight" for every patient. Even people within the same family may make different decisions about testing based on how they weigh these risks and benefits.

Testing Michael for channelopathies may have some clinical utility, unlike testing for Huntington or Alzheimer diseases. With a genetic diagnosis of long QT syndrome, for example, there would be the possibility of treatment with beta blockers and risk reduction by lifestyle modification. However, in Michael's situation the benefits of genetic testing are uncertain. It is unclear which hereditary channelopathy is affecting Michael's family. Without this knowledge, one cannot know whether Michael's genetic test would yield clinically useful information. If a symptomatic family member were to undergo genetic testing to identify the underlying mutation, the type of channelopathy would be specified. Then Dr. Orson and Michael would have a better understanding of the clinical utility of genetic testing for him. However, as Michael is already "vigilant about clinical surveillance of his overall health," he would probably find that genetic testing has limited clinical usefulness if testing of another family member revealed the familial syndrome was not treatable.

Conclusion

Though it is important that Dr. Orson consider the implications of genetic testing, ultimately the decision is Michael's. A legal and ethical precedent has been set recognizing patients' right *not* to know their genetic risk for diseases [11]. The

decision about genetic testing is a personal one that is influenced by a number of factors that a health care professional may or may not be able to appreciate completely. The patient will likely take into account the perceived treatability and preventability of the disease as well as a perception of his or her own personal risk [12]. Given the possibility of minimal clinical utility, the decision hinges on Michael's view of the test's personal utility.

It may be beneficial for Dr. Orson to refer Michael to a genetic counselor or a geneticist who is trained to discuss such testing with patients. Genetic counselors have a central ethos of "nondirectiveness" [13]; counselors seek to provide the patient with the information necessary to make an informed decision. Genetics professionals may also be able to determine which channelopathy is affecting Michael's family by doing a thorough review of his family history, thereby informing the decision further.

Dr. Orson may also consider bringing up genetic testing to another family member, perhaps someone who has been affected with symptoms of a channelopathy like syncope or who has an abnormal ECG. Genetic testing is most informative when performed on someone affected by the disease in question [14]. Once a concrete diagnosis is made within the family, Michael may reconsider testing, particularly if treatment options are available or he is interested in the possibility of ruling out the presence of the mutation.

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Further Reading

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