Virtual Mentor
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Clinical Case
Presymptomatic Genetic Testing for ALS
Commentary by Leo McCluskey, MD, MBe

Mr Smith is a fit 35-year-old without any major health complaints. He recently moved, and, during his first visit with his new physician, Dr Sanders, he revealed that his older brother had died of amyotrophic lateral sclerois (ALS, also called Lou Gehrig's disease) at age 47. Dr Sanders acknowledged that this must have been a staggering loss for Mr Smith, who disclosed that what his brother went through was terrible and quite traumatic. He told Dr Sanders that he could not imagine going through that disease course and doesn't know how his brother coped.

Dr Sanders remembered having read that about 10-15 percent of ALS cases are familial. She inquired whether any other family members had developed the disease, and Mr Smith said that a great-uncle had died of an unknown disease at a young age, but no one ever thought it might have been ALS. Other than that, there was no reason to think ALS ran in his family.

Dr Sanders thought about offering genetic screening to Mr Smith but wanted to consider further the risks and benefits to her patient. She wondered whether telling Mr Smith that he had the genetic markers for this deadly disease before he became symptomatic would only distress him and not yield an offsetting benefit, since the age of onset was unpredictable.

Commentary
ALS is a rare, presently incurable neurodegenerative disorder that annually affects 2-2.5 persons per 100 000. Ninety percent of ALS, known as sporadic ALS, is not inherited. Five to 10 percent of ALS is familial, and only 20 percent of familial ALS (FALS) is caused by a recognized dominant mutation in the so-called SOD1 gene for which testing is currently available. Only one drug, Riluzole, has been found to affect the progressive clinical course of ALS, but there is no evidence to support the use of this drug to prevent or to delay the onset of clinical symptoms in individuals with FALS. Palliation of symptoms is currently the main focus of ALS clinical care, and clinical management is the same, regardless of the patient's genetic status [1, 2].

Dr Sanders has much to contemplate about whether to discuss the potential for familial ALS with Mr Smith. Many ethical principles are in tension in this case—autonomy (respecting the patients' rights), truth-telling, beneficence (helping patients), and nonmaleficence (not harming patients). Let's consider the possible outcomes.

It is ultimately Mr Smith's right to decide whether he wants to discuss with Dr Sanders the inheritance of ALS and the availability of genetic testing.

Mr Smith is a new patient for Dr Sanders. Even though he told her that "what his brother went through was terrible and quite traumatic," and "he could not imagine going through that disease course," and "he doesn't know how his brother coped," it will be difficult for Dr Sanders to accurately predict the reactions this new patient will have to discussing the pros and cons of genetic testing, undergoing testing, and learning of the (potentially positive) results. Lying by omission, that is, withholding information about the availability of genetic testing from Mr Smith, is justified only if Dr Sanders concludes that Mr Smith will be significantly and irreparably harmed by the information he receives. Absent this conclusion, Dr Sanders' paternalistic response may harm the trust necessary for a good patient-physician relationship. While Dr Sanders may be justified in delaying the discussion until she can assess its probable effects on her patient, it is most likely that she or a genetics counselor will eventually have to have this conversation with Mr Smith.

Mr Smith may benefit from a discussion of the genetics of ALS and the availability of genetic testing, whether or not he decides to be tested.

Dr Sanders should consider the benefits Mr Smith could derive from talking with her about FALS. For example, he may not have known of his potential risk. A frank conversation about the realities of genetic testing for the SOD1 gene would almost certainly help Mr Smith weigh the pros and cons of going ahead with the test for himself. At the same time, Dr Sanders could inform him about the current status of ALS care, the potential for disease-modifying therapy via Riluzole, and the palliation of even the most distressing symptoms via medical therapy. If she wants to go beyond the topic of treatment, Dr Sanders can inform Mr Smith of ongoing ALS research, the potential for clinical trials, the benefits of disease-specific advocacy, and the potential benefits of organizations, such as the ALS Association and the Muscular Dystrophy Association, that provide specialty care. Such a discussion may provide Mr Smith with some measure of hope despite the serious and life-threatening reality of the disease.

Mr Smith may benefit from being informed even if he decides to forgo testing. The possibility that he may have the harmful mutation might influence Mr Smith's choice of health care insurance coverage. For example, he may elect insurance that has ample coverage for pharmaceuticals (the current cost of Riluzole is about $900 a month), durable medical equipment, and home care. He may also decide to obtain long-term care insurance and alter his current life and disability insurance status.

If Mr Smith proceeds with testing he may discover that, although he is presently asymptomatic, he does have the mutant SOD1 gene. While this would certainly be a devastating result, he may view even this knowledge as having some benefit for him. For example, while Mr Smith's marital status or his plans for having a family are not discussed in the case, knowledge of his genetic status would almost certainly influence his family planning. He may choose not to conceive children but to adopt or pursue other options such as artificial insemination from an anonymous donor. He may opt to

use in vitro fertilization with preimplantation screening of the embryos for SOD1 and implantation of only those embryos that do not carry the mutant gene.

Mr Smith may be harmed by a discussion of the genetics of ALS, the availability of genetic testing, and by proceeding with the testing.

Dr Sanders should consider that Mr Smith might become distressed and suffer significant psychological harm as a result of even a discussion of FALS. While Mr Smith's concern may be limited to himself, Dr Sanders must also consider that he may have genetic guilt or worry about the possibility of transmitting the SOD1 mutation to his offspring. It is not possible to calculate the likelihood that Mr Smith carries the mutation, but Dr Sanders can assure Mr Smith that ALS is rare (only 2 or 2.5 cases per 100 000), and familial or inherited ALS is an even more unusual disorder (with an average of 2 or 2.5 cases per million). The variety of familial ALS for which testing is available is more rare still (4 or 5 cases per 10 million). But the instance of familial ALS for which testing is *not* available is 8-12 cases per 10 million. Thus, while Dr Sanders may introduce the specter of FALS with Mr Smith, genetic testing is unlikely to predict definitively whether Mr Smith will or will not get ALS. A negative test may, in fact, provide Mr Smith little solace.

If Mr Smith decides to be tested, he may also be adversely affected by the month-long waiting period before the results become available. While he may eventually be relieved by a negative result, he may be dejected by a positive test result.

If he tests positive, it is very likely that Mr Smith will experience significant fear, anxiety, and, potentially, depression triggered by concern for both himself and his offspring. He may even contemplate suicide. A positive test result status may adversely affect Mr Smith's ability to maintain his present health insurance or procure new coverage; if he retains coverage, his carrier may raise his rates. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 provides some protection for people who have employer-based health insurance by prohibiting group health plans from using genetic information as a basis for denying coverage if a person does not currently have a disease. However, the act does not prohibit employers from refusing to offer health coverage as part of their benefits, nor does it prevent insurance companies from requesting genetic information from potential buyers. Moreover, HIPAA does not provide protections for those who are self-employed.

If Mr Smith's employer learns about the positive test result, Mr Smith may experience genetic discrimination in the workplace. Although there are currently no federal laws specific to genetic nondiscrimination, some protection from discrimination by employers is offered through the Americans with Disabilities Act of 1990 (ADA). In 1995, the Equal Employment Opportunity Commission expanded the ADA definition of "disabled" to include individuals who carry genes that put them at higher risk for genetic disorders. The extent of this protection, however, has not yet been tested in the courts. Several states have laws that address genetic discrimination by employers and health insurance companies. The degree of discrimination protection varies from state

to state. Therefore, the decisions that Mr Smith makes about genetic testing while living in one state may have repercussions in the future if he moves to another area.

If Mr Smith tests positive for a SOD1 gene mutation, he may not be able to obtain private life, disability, or long-term care insurance. He is likely to be more successful in obtaining such coverage if it is offered by his employer, but it is possible that the employer may refuse to offer such benefits to him.

Conclusion

Weighing the potential benefits and harms of testing for FALS in this way, it is safe to conclude that Mr Smith would benefit from a discussion of the genetics of ALS through which he would become better informed and therefore empowered to make decisions regarding insurance coverage, family planning, and the pros and cons of proceeding with testing. While he may encounter some psychological stress and anxiety, it is unlikely that he would suffer depression or even contemplate suicide as a result of the discussion. Dr Sanders, therefore, is ethically responsible for initiating this conversation with Mr Smith. Since the discussion is likely to take a considerable amount of time and has many facets that may well be beyond the expertise of Dr Sanders, it would be appropriate for her to refer Mr Smith to a genetic counselor or to a neurologist with expertise in the genetics of ALS. Like most patients who weigh the benefits and burdens of presymptomatic testing for FALS, Mr Smith may elect to forgo genetic testing. Nonetheless, an informed Mr Smith is better prepared to make life choices that might be influenced by the possibility of FALS.

References

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Leo McCluskey, MD, MBe, is an assistant professor of neurology at the University of Pennsylvania. He is also the medical director of the ALS Association Center at the Penn Neurological Institute.