

ETHICAL PERSPECTIVES IN NEUROLOGY

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The practice of neurology presents a series of ethical challenges for the clinician. These rarely have simple or straightforward solutions, but require careful consideration by the neurologist. This section of *CONTINUUM*, written by colleagues with particular interest in the area of bioethics, provides a case vignette that raises one or more ethical questions related to the subject area of this issue. The discussion that follows should help the reader understand and resolve the ethical dilemma.

NOTE: This is a hypothetical case.

A 24-year-old woman seeks genetic testing for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). She has migraines and asthma but is otherwise healthy. She states that her mother died from the condition, but she does not know whether genetic testing was performed. A maternal grandmother was also diagnosed with the disorder, and she is also deceased. Two maternal great aunts had features of the disorder but were never formally diagnosed.

She has read that genetic testing for CADASIL is now available and requests testing for this condition because she has a great deal of frustration with the uncertainty she faces about her future. This frustration is making it difficult for her to function in her daily activities.

As her neurologist is completing the laboratory requisition forms for DNA sequencing of *NOTCH3*, the gene associated with CADASIL, he mentions the case to his colleague. His colleague replies, “You know, there is a lot more to genetic testing than simply completing the paperwork. You should make sure that you have provided genetic counseling before you obtain the sample.”

COMMENT

- ▶ Genetic testing is rapidly becoming an integral component of the diagnostic armamentarium of the clinical neurologist. DNA sequencing, fluorescent in situ hybridization (FISH) probe analysis for deletions and duplications, differential methylation testing for epigenetic abnormalities, chromosomal microarray analysis, and other molecular genetic tests are revolutionizing the practice of neurology in the 21st century. Molecular genetic testing can provide a rapid and relatively inexpensive method to confirm a diagnosis. Identification of a pathologic mutation can guide future screening and medical treatment, prevent additional and unnecessary diagnostic testing, and empower patients by increasing their understanding of their medical condition. However, genetic test results also frequently have far-reaching implications for the patient’s future and for the patient’s other family members. Thus, it is essential that clinicians recognize that genetic testing is fundamentally unlike other testing that may be performed for a patient.

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Despite the exciting promises that genetic testing affords, it also has several limitations. Perhaps the most significant limitation is that no molecular genetic test is 100% sensitive. In the case of CADASIL, the sensitivity is quite good—95% of individuals with a diagnosis of this condition will have a pathologic mutation in *NOTCH3*. For other neurologic conditions the sensitivity can be much lower. The basis for decreased sensitivity is multifactorial. DNA sequencing will not usually identify pathologic mutations in noncoding regions (promoters, enhancers) and cannot typically detect deleterious deletions in a gene. Furthermore, many conditions can be due to pathologic mutations in more than one gene (locus heterogeneity). But when clinical testing is available for a genetic disorder, sometimes only a subset of the genes associated with the disorder is known and can be sequenced. Another limitation of genetic testing is that currently the result rarely alters the specific medical treatment. For example, a pathologic mutation in *SCN1A* does not help predict which anticonvulsant will be most effective in managing epilepsy in a patient.

Because of the unique implications and limitations of genetic testing, several ethical issues are raised by this testing. The case highlights many of these issues, including:

- (1) What is the informed consent process for molecular genetic testing?
- (2) What are the ethical considerations in presymptomatic genetic testing for adults?
- (3) What are the unique ethical considerations of presymptomatic genetic testing for minors?

INFORMED CONSENT FOR GENETIC TESTING

► One of the practical applications of the principle of respect for patient autonomy is that patients provide their informed consent for medical tests and procedures. For genetic testing, informed consent is classically obtained through the process of pretest genetic counseling (Ensenauer et al, 2005). Genetic counseling is the communication process that addresses the concerns associated with occurrence or risk of occurrence of a genetic disorder in a family. A clinical geneticist, a genetics counselor, or a health care professional (HCP) who understands the genetic basis for a particular disease can provide genetic counseling.

The components of the informed consent process for genetic testing include a discussion of the following:

- Medical indications for a test
- Risks and benefits of performing the test
- Risks and benefits of not performing the test
- Alternatives, if any, to genetic testing
- Process of obtaining the sample and performing the test
- Potential results of the genetic test

During the informed consent process, I recommend using the shared decision-making model. In this model the HCP addresses each of the above components of the informed consent process. The HCP also helps the patient work through the decision to obtain genetic testing based on the patient's values and goals. Thus, the HCP ought to take the time to understand the patient's motivation for obtaining genetic testing. In this clinical vignette, the patient states that the psychological stress of an uncertain future makes it difficult for her to function in her activities of daily living. Through additional

conversations with the patient, the HCP learns that she will make different decisions regarding her college education and career goals if she has a pathologic mutation in *NOTCH3*. Thus, genetic testing for the patient could help address uncertainty about her future and help her make lifestyle choices. In the shared decision-making model, the HCP can offer a recommendation about obtaining genetic testing if it is made in the context of the patient's goals and values. Such an approach honors the patient's autonomy as long as it is truthful, honest, and derived explicitly from the patient's perspective and goals of care.

Perhaps the most important and unique aspect of the informed consent process for genetic testing is the discussion of the potential results of the genetic test prior to obtaining the sample for the test. Typically, there are four possible results from a molecular genetic test: (1) test is normal, (2) pathologic mutation is identified, (3) benign polymorphism or rare variant is identified, and (4) variant of unknown significance (VUS) is identified.

If a pathologic mutation is identified, then the diagnosis has been confirmed. If the test is normal, the diagnosis has not been confirmed. However, a normal result rarely excludes the diagnosis because of the limitations in the sensitivity of molecular testing discussed earlier. A benign polymorphism or rare variant is a harmless change that is known to not cause disease. It is regarded as the clinical equivalent of a normal test result.

A VUS is a change that may or may not be pathologic. Usually there is simply inadequate information for the laboratory to determine if the change is deleterious. A VUS is not rare in cancer genetic testing (Harris et al, 2005). As genetic testing becomes more widely available, VUS will also become more common. In these situations, testing additional affected and unaffected family members can help determine whether the genetic change is pathologic by determining if the change segregates with disease within the family. The possibility of a VUS and the possible requirement to test additional family members ought to be discussed in a few brief sentences during pretest counseling. Although this may seem unnecessary, it is much better than trying to explain a nebulous and complicated result to anxious and confused patients and families after the testing has been completed. From an ethical perspective, failure to discuss the possibility of a VUS is equivalent to obtaining consent without fully informing the patient because all potential outcomes of the testing were not disclosed.

PRESYMPTOMATIC GENETIC TESTING IN ADULTS

- ▶ It is becoming common for neurologists to see presymptomatic adults at risk for developing symptoms of a familial genetic disease, also known as consultands. Consultands might request genetic testing for a variety of reasons, including initiation of presymptomatic medical treatment, alleviation of fear of not knowing, preparation for the future, and planning for future pregnancies.

The informed consent process for presymptomatic testing in adults builds on the general genetic counseling principles outlined above; additional factors should also be discussed with the consultands. First, genetic testing should be performed in a symptomatic relative whenever possible. This will help determine the diagnostic

sensitivity of the test within the family. Thus, in this case vignette, the physician should first determine if the patient's mother had genetic testing performed. When genetic testing of the affected individual is not possible, then testing of the consultand can be performed after the sensitivity limitations of the test are discussed.

The neurologist should also discuss the penetrance and treatment options for the particular disease with the consultand (Burke et al, 2001). The risks and benefits of presymptomatic genetic testing of a disease that is highly penetrant and treatable (eg, Wilson disease) are significantly different than for a disease that is highly penetrant but not treatable (such as CADASIL or Huntington disease). For example, in untreatable neurodegenerative diseases, psychological distress can occur either when a pathologic mutation is identified and or when a pathologic mutation is not identified ("survival guilt"). Finally, the risk for genetic discrimination in determining insurability should be reviewed. Although there are case reports of genetic discrimination, most states have laws that prohibit the use of genetic information when determining eligibility for health insurance, and some states have laws against using such information when determining life insurance rates (Clayton, 2003; Ensenauer et al, 2005; Harris et al, 2005). The Health Insurance Portability and Accountability Act (HIPAA) bans the use of genetic information when determining eligibility for health insurance but does not prohibit rate adjustments for insurance plans on the basis of genetic information. HCPs should review the laws in their particular states. In general, most geneticists recommend that presymptomatic individuals obtain health, life, and disability insurance policies prior to completing genetic testing.

PRESYMPTOMATIC GENETIC TESTING IN MINORS

- Presymptomatic testing in minors at risk for a genetic condition is considerably more complicated. If the condition is treatable and can present before the individual reaches the age of majority, then testing is indicated. In these situations, the risks and benefits of treatment should also be reviewed. For example, the treatment for Wilson disease is considerably different than enzyme replacement therapy or bone marrow transplantation for Hurler syndrome. On the other hand, most ethicists discourage genetic testing in a minor if the disease is treatable but the condition does not present until adulthood and treatment or screening does not need to begin until adulthood (Duncan et al, 2005; Ross, 2002). Breast cancer due to mutations in *BRCA1* or *BRCA2* is an example of a condition in this category. However, in a mature older teenager with a family history of breast or ovarian cancer, I would consider offering the testing as long as the individual clearly understands the risks and benefits of testing and of not testing. CADASIL and Huntington disease fall into yet another category in which treatment is unavailable and the symptoms do not usually begin until adulthood. Most ethicists agree that genetic testing is impermissible because testing minors in these situations violates their right to choose not to know. Some ethicists argue that respect for the parents' desire to have their minor children tested outweighs the autonomy of the minor, but this is a minority perspective (Duncan and Delatycki, 2006). In any case, for untreatable conditions that present in adulthood, I do not offer presymptomatic testing in all children or in teenagers who lack the maturity to understand the implications of the testing.

CONCLUSION

- ▶ We have the opportunity to provide medical care in an exciting era in which genetic testing is rapidly changing the paradigm of clinical practice. But genetic testing is fundamentally different from the other tests and studies that neurologists order. Consequently, the informed consent process for genetic testing must include pretest genetic counseling. For those neurologists who routinely offer genetic testing, deliberate planning and practice will help facilitate thorough and efficient counseling. Alternatively, neurologists who perform genetic testing less frequently should consider referring their patients to centers with expertise in genetic testing to ensure that the genetic counseling and testing are completed appropriately.

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