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Abstract
In families with genetic disorders due to a known genetic mutation, presymptomatic genetic testing can lead to early detection and treatment of inherited disorders that may manifest later in life. The health benefits for family members at increased risk, however, is limited by the predictive value of the genetic test, the availability of effective treatments, and individuals' and families' willingness to undergo genetic testing in the first place. This Issue Brief describes the case of a genetic condition for which genetic screening of family members is clearly useful, and just as clearly underused. It explores the barriers to the use of genetic screening and has implications for the future as genetic technologies become more complex and produce more uncertainty.

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Editor's note: In families with genetic disorders due to a known genetic mutation, presymptomatic genetic testing can lead to early detection and treatment of inherited disorders that may manifest later in life. The health benefits for family members at increased risk, however, is limited by the predictive value of the genetic test, the availability of effective treatments, and individuals' and families' willingness to undergo genetic testing in the first place. This Issue Brief describes the case of a genetic condition for which genetic screening of family members is clearly useful, and just as clearly underused. It explores the barriers to the use of genetic screening and has implications for the future as genetic technologies become more complex and produce more uncertainty.

Genetic testing is available for many genetic disorders

Scientists continue to discover specific genes responsible for heritable forms of cancer, cardiovascular diseases, and other single-gene disorders. Identifying a genetic mutation in a family can help diagnose an individual with symptoms, and reduce uncertainty for family members at risk for the disorder.

- In families where a genetic mutation is found, genetic screening of relatives may provide reassurance to those testing negative, and allow targeted treatment of those testing positive. When early treatment can prevent complications, genetic testing has clear benefits.
- Even when genetic testing has clear benefits, utilization is low. Studies involving people at risk for disorders such as hereditary breast cancer, hereditary nonpolyposis colon cancer, and hypertrophic cardiomyopathy show that less than half of at-risk relatives are tested for the familial mutation.
- In general, barriers to testing among at-risk relatives include difficulty communicating with relatives, lack of providers who offer the test or refer family members appropriately, concerns about confidentiality or genetic discrimination, wanting to avoid bad news, and believing that genetic testing would provide no important information.

Researchers study a prototypical genetic disorder to understand barriers to genetic testing

Hereditary hemorrhagic telangiectasia (HHT) is an example of a disorder for which a strong case can be made for routine genetic testing of relatives, so that effective interventions can be directed only to those carrying the familial mutation.

- HHT occurs in about 1 of every 5,000 individuals. In HHT, tangles of abnormal blood vessels called arteriovenous malformations (AVMs) can occur anywhere in the body, including the lungs, brain, and liver. These AVMs develop over time and often remain undetected until they result in a sudden and life-threatening complication such as a stroke or brain abscess. Most, though not all, individuals with HHT have recurrent nosebleeds.

- Early diagnosis of HHT in both symptomatic and asymptomatic individuals allows prophylactic treatment, usually through embolization—a deliberate blockade of the affected blood vessels.
- Because nearly all cases of HHT are due to a genetic mutation inherited from an affected parent, a family history will identify people at risk for HHT. It follows an autosomal dominant inheritance pattern, meaning that children of an affected parent have a 50% chance of inheriting HHT. Individuals at risk need to be screened by history, physical examination, and various imaging tests until the diagnosis is either established or the patient is old enough to be reasonably sure that features will not develop, indicating that the patient likely did not inherit the disease.
- Genetic testing can now identify an HHT-associated mutation in about 89% of clinically-diagnosed HHT families. If the family mutation is identified, at-risk relatives can be tested to determine, with certainty, whether they are affected. Family members not carrying the mutation can be reassured and no further screening for HHT is required. Family members carrying the mutation can be monitored and treated for HHT complications, resulting in decreased morbidity and mortality.
- Genetic testing for HHT in families of affected individuals is therefore very useful: family members are at high risk; the genetic screening test is highly accurate; family members testing negative for the familial mutation do not need to be followed for complications; the condition is expensive to detect otherwise; and early detection allows more effective treatment. These are the conditions that make screening worthwhile.
- Despite these advantages, uptake of genetic screening in HHT families is low. Bernhardt and colleagues studied HHT families to understand barriers to use.

Study assesses why genetic tests are underused in HHT families

The investigators conducted surveys and online discussion groups with people from HHT families. They recruited study participants online through the HHT Foundation International, an advocacy and support group.

- During the summer of 2009, 119 people with HHT and their first-degree relatives completed a baseline survey that included questions related to HHT status, attitudes towards genetic testing, and the results of genetic testing for HHT if it had been performed.
- A week after the surveys, participants were assigned to one of 12 online discussion groups. The groups responded to two scenarios: one in which a woman with symptoms must decide whether to have genetic testing, and the other in which the woman, having tested positive, talks to her siblings about getting tested, and no one follows her advice.

Surveys reveal concerns about cost and discrimination

Most participants had been diagnosed with HHT (91.6%) and 41% had genetic testing. The majority of tests had been ordered through a provider at an HHT Center of Excellence.

- The majority of respondents agreed that people who have had genetic testing should encourage their relatives to be tested. The majority also believed that relatives (both those with and without signs of the disease) should be tested if the family mutation is known.
- Although many participants did not know a lot about genetic testing, the majority believed that genetic testing is expensive and not covered by insurance. This is a misperception, as genetic testing is often covered by insurance. Costs vary for those without insurance: finding the mutation in the first affected person can cost $1,500-$3,000, but testing for a known familial mutation in other family members usually costs a few hundred dollars.

- About half of participants believed that people with a positive genetic test will have a hard time buying life insurance.
- In response to an open-ended question about barriers to genetic testing, the most frequently cited barrier was cost (57%). Access and inconvenience, including living far away from an HHT Center and not knowing where to go for testing, were also frequently mentioned, as were emotional issues (such as fear of diagnosis and guilt about putting children at risk) and concerns about discrimination in employment or insurance.

Online discussions point to knowledge, access and emotional barriers to genetic screening

The online groups allowed the investigators to bring participants together from a wide geographical area and to probe barriers to genetic testing in more depth. Each group consisted of 10-12 participants and lasted about one hour.

- In response to the first scenario, 76% of participants agreed that the woman with symptoms should have genetic testing, mostly to confirm the diagnosis or to help family members who might not be aware that they have HHT. Many participants believed that genetic testing could clarify for certain whether she was affected, and whether her children were at risk. In fact, the familial mutation cannot be found in about 11% of affected families, and for them, genetic testing of relatives will not be useful.
- The second scenario about genetic testing of family members once the familial mutation is found prompted much discussion and revealed three broad categories of barriers: inadequate knowledge and awareness of testing; inadequate access to testing; and emotional barriers. Genetic testing was frequently seen as part of a way to diagnose HHT, but not recognized as a way to exclude HHT and avoid further testing.
- Later in the discussion, participants were asked whether the woman's two-month-old child should be tested. Most agreed that the infant should be tested, although only about half understood that genetic testing in the context of a known familial mutation could exclude, with near certainty, the diagnosis in this infant.
- Lack of understanding of the rationale for genetic testing, misperceptions about screening and treatment, and a general perception that testing is complicated and expensive constitute major barriers to genetic testing. In addition, respondents perceived that primary care providers are reluctant or unable to order and interpret genetic tests, further reducing access to HHT testing for family members.

POLICY IMPLICATIONS

This study helps explain the low uptake of genetic testing for HHT, in the face of generally positive attitudes toward genetic testing and clear reasons for testing relatives. These barriers may have even greater significance as more genetic tests become clinically available.

- The results of this study can be used to clarify misperceptions about HHT and other autosomal dominant disorders and improve access to genetic testing. Voluntary disease organizations should develop and disseminate brief educational materials that describe the rationale for genetic testing and emphasize the benefits of early detection and treatment. In the case of HHT, materials should emphasize the following key points:
  - The most serious complications of HHT are invisible, but can be prevented through early diagnosis and treatment;
  - Someone in the family with symptoms of HHT should be tested first to identify the family's genetic mutation;
  - If a familial mutation is found, then genetic testing of relatives can determine who does and does not have HHT;

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POLICY IMPLICATIONS
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  - Testing of young at-risk children will spare 50% from evaluations and imaging and its radiation while identifying children who need screening and management;
  - Genetic testing can be done on a sample of blood or saliva and ordered through primary care doctors, HHT Centers of Excellence, or local genetics clinics;
  - Genetic testing is usually covered by insurance;
  - Legal protections prohibit genetic discrimination in health insurance and employment, but not life insurance.
- Primary care providers are key to improving access to genetic testing for at-risk relatives who may live far away from a specialized genetics center. Voluntary disease organizations should provide specific directions for patients to share with relatives and primary care providers about alternatives to accessing testing. Laboratories offering genetic testing should provide support for primary care providers to order and interpret genetic tests for family members. The four laboratories conducting HHT testing employ genetic counselors who can guide primary care providers.

This Issue Brief is based on the following article: B.A. Bernhardt, C. Zayac, R.E. Pyeritz. Why is genetic screening for autosomal dominant disorders underused in families? The case of hereditary hemorrhagic telangiectasia. Genetics in Medicine, vol. 13, published online June 1, 2011, doi:10.1097/GIM.0b013e31821d2e6d.

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