Published in final edited form as:
Genet Med. 2011 September ; 13(9): 812–820. doi:10.1097/GIM.0b013e31821d2e6d.

Why is genetic screening for autosomal dominant disorders underutilized in families? The case of hereditary hemorrhagic telangiectasia (HHT)

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Abstract

Purpose—Appropriate management of autosomal dominant disorders reduces morbidity and mortality, but relies on identifying which family members are affected. Genetic testing may identify relatives needing follow-up, but is underutilized. We conducted this study to identify barriers to genetic testing for one disorder, hereditary hemorrhagic telangiectasia (HHT).

Methods—Surveys and on-line discussion groups with people from HHT families.

Results—Multiple barriers to HHT genetic testing were identified including lack of knowledge about genetic testing, problems with access, and emotional barriers. Many participants: did not understand the rationale for HHT testing or benefits of early detection; believed that genetic testing is expensive and not covered by insurance; believed that primary care providers don't know how to order genetic testing. Access to HHT testing is limited by distance from an HHT Center or a genetics clinic. Emotional barriers include fear of insurance discrimination; denial of having HHT or being at risk; guilt and stigma.

Conclusion—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 addition, laboratories offering genetic testing should provide support for primary care physicians to order and interpret genetic tests.

Keywords

Hereditary hemorrhagic telangiectasia; genetic testing; barriers; utilization; on-line discussion

INTRODUCTION

Identifying the genes responsible for a variety of single gene disorders has led to the ability to do genetic testing in families in order to identify which family members have inherited that familial disorder, and which have not. This testing is especially useful for autosomal

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Conflict of interest

The authors report no conflict of interest

dominant disorders with variable expressivity and later age of onset where there may be difficulty in making a diagnosis based on clinical involvement, especially on younger at-risk relatives.[1]

The expectation is that such testing provides reassurance for those testing negative, saves health care dollars, and leads to early screening or treatment for those testing positive, resulting in reduced morbidity and mortality, and an improved quality of life[2, 3]. Despite the obvious utility of such genetic testing, there is some evidence that utilization of genetic testing in appropriate families is low. Much of the research exploring test utilization has focused on the extent to which at-risk relatives are tested after the family's mutation has been identified. Studies involving people at risk for disorders such as hereditary breast cancer, hereditary non-polyposis colon cancer and hypertrophic cardiomyopathy showed that fewer than 50% of at-risk relatives are tested for the familial mutation[4–6]. Utilization of testing is higher among individuals presenting for genetic counseling[7] and among relatives who are informed by researchers of the availability of testing[8]. Limited data are available regarding barriers to testing among individuals who do not attend genetic counseling sessions, as well as among those who are not contacted directly by researchers and offered testing. Some general barriers to genetic testing among at-risk relatives include difficulty communicating with relatives[9–12], lack of providers who are able to test or refer family members[13], concerns about confidentiality or genetic discrimination[14, 15], wanting to avoid bad news[12], believing that genetic testing would not provide any important information[16] and disliking blood draws[15].

To further explore barriers to genetic testing with an eye to developing recommendations for reducing barriers, we have chosen to focus on genetic testing for one relatively common single-gene disorder, hereditary hemorrhagic telangiectasia (HHT) (OMIM # 187300). HHT is prototypic of the type of disorder for which a strong case can be made for routine genetic testing of relatives so that effective interventions can be targeted at relatives carrying the familial mutation[1].

HHT is an autosomal dominant disorder of vascular development occurring in at least 1 in 5,000 individuals[17]. Manifestations, which develop over time and are rarely present at birth, include epistaxis, hypoxemia from pulmonary arteriovenous malformations (PAVM), stroke from cerebrovascular arteriovenous malformations (CAVM) or paradoxic embolism through PAVM, mucocutaneous telangiectases, liver dysfunction from hepatic arteriovenous malformations (HAVM), gastrointestinal bleeding, and high-output cardiac failure[18]. Large AVMs can occur in the lungs, brain and liver, and these AVMs often remain clinically silent until they result in a sudden and life-threatening complication such as stroke or brain abscess. Cerebral AVMs are present in approximately 10% of affected individuals, and are congenital. Intracranial hemorrhage secondary to AVM has been reported as the presenting symptoms of HHT in some infants and children with HHT. Current approaches to management, including identification and embolization of arteriovenous malformations in the lung and brain, can prevent much morbidity and mortality[19], but most rely on early detection of potential problems.

Because nearly all cases of HHT are due to a mutation inherited from an affected parent[20], taking a family history will identify individuals at risk for having HHT. Individuals who are at up to 50 percent risk need to be screened by history, physical examination, and various imaging modalities repetitively until the diagnosis is either established[17], or the patient is old enough to be reasonably sure that features will not develop. This latter age has not been established firmly, which leads to considerable uncertainty for health professionals and patients alike. Because the most easily identified manifestations of HHT such as telangiectases and epistaxis often do not appear until adolescence or later, it is particularly

difficult to determine whether young at-risk individuals have inherited HHT from an affected parent. Moreover, some of the manifestations of HHT such as epistaxis, cutaneous telangiectases and gastrointestinal bleeding are common in the general population, complicating diagnosis.

Genetic linkage studies suggest that mutations in at least six loci can cause HHT[17, 21]. In the three HHT-associated genes that have been discovered, many pathologic mutations have been identified. A number of clinical molecular diagnostic laboratories around the world provide mutation detection for the genes encoding endoglin (*ENG*), activin receptor-like kinase 1 (*ACVRL1*) and SMAD-related protein 4 (*SMAD4*) by direct sequencing and assaying for deletions and duplications. For a person who meets the so-called Curaçao criteria for diagnosis of HHT[18], genetic testing by first sequencing *ENG* and *ACVRL1*, followed by duplication and deletion testing should detect a mutation in approximately 87% of those tested[22]. If testing of *ENG/ACVRL1* is negative, testing of *SMAD4* identifies a mutation in an additional 2% of cases diagnosed with HHT[23].

Because genetic testing only identifies a disease-associated mutation in about 89% of families, predictive testing for at-risk asymptomatic family members requires prior identification of the disease-causing mutation in an affected person in the family. Once the family mutation is identified, asymptomatic relatives, or those with only one or two clinical features can be tested to determine if they are affected. For those relatives who do not carry the familial mutation, reassurance can be provided and no further HHT screening undertaken. Screening for complications of HHT can be directed only to those relatives who did inherit the familial disease-causing mutation.

Utilizing genetic testing to determine which family members need to be followed for signs and complications of HHT provided the justification for the development of laboratories offering this service. After the two genes involved with the majority of cases of HHT were discovered in 1994 and 1996, the patent for analyzing the genes for HHT was held by Duke University and the University of Toronto which were the universities where the genes were discovered. These patents impeded the development of a clinical test that could be offered for HHT[24]. Through efforts of the advocacy group HHT Foundation International, the patents were released in 2003 and clinical molecular testing became available through two laboratories in the United States later that year. The HHT Foundation then announced the availability of testing at their annual meeting, in their newsletters and on their website, and encouraged all families with HHT to seek testing[24]. In addition, centers designated by the HHT Foundation International as HHT Centers of Excellence all advocate genetic testing. Currently, there are 12 HHT Centers of Excellence in the United States, and new Centers are periodically established in order to increase access to expert comprehensive care for people with HHT and their at-risk relatives.

Despite the clinical utility of genetic testing for HHT and the endorsement of genetic testing through the HHT Foundation, we and other providers at HHT Centers of Excellence have observed that genetic testing in families is infrequently performed. To investigate this, we conducted this project to identify barriers to genetic testing for HHT with the intention of developing recommendations to address some of the identified barriers.

MATERIALS AND METHODS

The overall methodology included on-line discussion groups and surveys of people with HHT and their first degree relatives, conducted over the summer of 2009. Subjects were recruited through the HHT Foundation International. We chose an on-line approach because we wanted input from a relatively large number of subjects from a wide geographical area.

Use of on-line discussion groups makes it possible to bring together discussants that would otherwise not be able to communicate with each other due to geographical constraints[25]. Such groups are being used increasingly as a research tool for gathering opinions relating to health-related issues[25, 26].

The Foundation sent out an email to all members informing them of the discussion groups and asking them to contact researchers at the University of Pennsylvania if they were interested in participating. They were told that participation, for which they would be paid $25, would involve completing a baseline survey, participating in a one-hour online discussion a week later, and completing a post-discussion survey 10 days after the discussion. The study was approved by the Institutional Review Board of the University of Pennsylvania.

The baseline survey was completed one week before the online discussion. Informed consent to participate in the study was obtained before participants completed the survey. The baseline survey included questions related to sociodemographics, HHT status, whether the participant had genetic testing and the result, and attitudes towards genetic testing for HHT. We also included an open-ended question asking participants to list up to three barriers to genetic testing for HHT. The post-discussion survey reassessed attitudes about genetic testing for HHT. Five-point Likert scales (strongly agree to strongly disagree) were used for responding to attitudinal items. For purposes of data analysis, responses were trichotomized agreed (response 1 or 2), neutral/disagree (response 3–5) or don't know. Responses to the open-ended item were grouped into broad categories.

We assigned subjects to discussion groups so each group would have between 10 and 12 participants. In order to protect the identity of subjects, aliases were assigned. Subjects were instructed to log on to the discussion group at the scheduled time. Each discussion was led by a moderator who followed a prepared script. Follow-up questions were asked by the moderator to clarify responses.

During the online discussion, participants were presented with two scenarios. In one scenario, a patient experiencing symptoms of HHT sees her primary care provider who must manage her care, referrals, and screening. In another scenario, the same patient receives a positive HHT genetic test result and suggests to her family members that they have genetic testing for HHT. After each scenario, participants were also presented with polling questions to assess opinions about the utility of genetic testing. Following these opinion polls, participants were probed about their poll responses. Participants also were asked follow-up questions regarding their opinions of the patient's and physicians' choices and how they would have acted in these situations.

Transcripts of the online discussions were edited to remove identifying information that may have been shared during the discussion, and typographical errors, and then imported into the qualitative data analysis software package, NVivo. Using this software, all transcripts were first coded for broad themes based on an a priori coding scheme that followed the discussion guide. These themes included: (a) primary care providers and genetic testing, (b) other specialist ordering genetic tests, (c) testing the proband, (d) testing the at-risk child, (e) implications of test results, (f) barriers to getting tested, (g) approaching family members about genetic testing and their response. Within these themes, each coder created sub-codes as new themes emerged in the data. The research team met periodically to revise the codebook and, to discuss the significance of emerging themes. Such coding allowed us to determine the relative frequency of each theme, for example, specific barriers to genetic testing, and to retrieve quotations illustrating the themes.

RESULTS

246 people completed a brief screening survey to determine eligibility for the discussion. Of those respondents, 204 were eligible and were assigned to one of 12 discussion groups. Respondents were classified as ineligible if they indicated that they did not have a confirmed diagnosis of HHT or a first degree relative with a confirmed diagnosis. 119 people participated by completing pre-and post-discussion surveys and participating in discussion groups.

Surveys

Nearly all participants had been diagnosed with HHT, and the majority were female, Caucasian, parents and well-educated (Table 1). The majority had been seen at some point at an HHT Center of Excellence, and 41% had genetic testing, primarily full sequencing. The majority of genetic tests had been ordered through a provider at one of the HHT Centers.

Data from the pre-discussion survey regarding attitudes towards HHT and genetic testing are outlined in Table 2. Nearly all participants agreed that HHT is a very serious condition, and agreed that getting good medical care can make a difference in morbidity. While many participants did not know a lot about genetic testing, the majority believe that genetic testing is very expensive and not covered by insurance. Nearly one-half of participants believed that people with a positive genetic test will have a hard time buying life insurance. The majority of those surveyed agreed that people who have genetic testing should encourage their relatives to be tested, and the majority agreed that both relatives with signs of HHT and those without signs should be tested if the family mutation is known. Finally, the majority of participants agreed that primary care doctors do not know how to arrange for genetic testing.

Responses to the open-ended question asking participants to list barriers to genetic testing for HHT are included in Table 3. The barrier to testing cited most commonly related to the cost of testing and lack of insurance coverage for testing. Access and inconvenience, including not living close to an HHT Center, not knowing where to go for testing or how to get it done, or not wanting to have blood drawn were also frequently mentioned as barriers. Concerns about discrimination, including insurance and employment discrimination were also frequently mentioned. Emotional issues including fear of being diagnosed, denial of being at risk and guilt about putting children at risk were also frequently named as barriers.

On-line discussions

At the beginning of the discussion groups, we presented a Scenario (Table 4a). We polled participants about whether Colleen should have genetic testing and 76% of participants agreed that Colleen should have the genetic test. We then asked participants to explain why they voted as they did. Most thought she should be tested either to confirm the diagnosis: *“The genetic test would be a reliable way to determine if she has HHT” - Ruth 3 6,* or to help the family: “*Genetic testing will also help family members who may have HHT and are not yet aware of it”- Barbara2 6.*. Many participants incorrectly believed that genetic testing could clarify for certain whether she was affected: *“a negative test means that she doesn’t have it and none of her children are at risk” -Lucy 2 5.* In addition to believing that she doesn’t have HHT if she tested negative, many participants believed that it meant that her children were not at risk for HHT: *“They should not have HHT, at least not from her” - Molly 3 6.*

Barriers to genetic testing

We presented a second scenario aimed a stimulating a discussion about barriers to genetic testing among family members (Table 4b). This scenario prompted a great deal of discussion

about why siblings might not get testing, and people who themselves had genetic testing shared personal stories. Through the course of this discussion, we were able to identify three broad categories of barriers to genetic testing: inadequate knowledge and awareness of testing; inadequate access to testing; and emotional barriers.

Inadequate knowledge

The primary knowledge/awareness barrier related to poor understanding of the rationale for genetic testing in families. Nearly all participants had heard of genetic testing for HHT, and many were informed about it through the HHT Foundation website or through providers at one of the HHT Centers of Excellence. Even though people overwhelmingly thought someone like Colleen should have genetic testing, many participants when discussing her situation further questioned Colleen's need to be tested since it seemed clear that she had HHT, and there didn't seem to be any purpose in getting the genetic test since she could be diagnosed clinically: *"I don't know how much it will help her, since it seems that she doesn't need it for a diagnosis" -Becky2 10; "If you have the signs - spider marks - nose bleeds, why should you get genetic testing done?" -Chris 4 10; "I have not had testing and I voted not sure. I have signs of HHT and it has already been diagnosed in my family so I don't see what the purpose of genetic testing is"- Abby 3.*

Later on in the discussion, we asked whether Colleen's 2-month old child should be tested. Most participants appeared to understand autosomal dominant inheritance and knew that the children of an affected parent may or may not be affected. In addition, the majority of participants agreed that the infant should be tested. Additional discussion revealed that only about one-half of the patient/family member participants understood the rationale for testing family members for a known familial HHT mutation. These participants, most of whom had genetic testing themselves, understood that testing negative for a familial HHT mutation meant that the person wasn't affected: *"Yes [test the child] to rule it out so every time he has a nosebleed, she doesn't have to worry" -Lucy 2 5; "I had genetic testing and it allowed me to have my son tested early enough to avoid having to put him through other more costly and difficult tests. He had nosebleeds, but tested negative for HHT"-Diane 2 2; "Three of our four kids came up positive, meaning one never had to get the diagnostic tests--and the other three could be evaluated and treated right away"-Pat.*

Many other participants did not appear to understand that genetic testing of relatives could exclude the diagnosis of HHT and instead equated getting the genetic test, regardless of the result, as the first step toward an HHT work-up: *"I was tested so that I could do the proper screenings on my own children. They have not done the genetic testing. Since I know that I have HHT, I know to watch for the signs of HHT in my kids" –Ellen 8 9.* A number of participants indicated that they would assume a child could be affected after a negative genetic test: *"[if the child tested negative] I still would screen, the genetic testing is not perfect yet"-Nathan 2 5; " If the gene does not show up in her son, she still needs to keep a close watch on him for any symptoms and then take care of them as soon as they show up"-Barbara 2 6.*

Several participants clearly indicated that they saw no role for genetic testing at all to determine whether a relative was tested with HHT because they were convinced that the diagnosis could always be established or ruled out based on clinical involvement: *"What's to be gained? Why not just check them regularly for symptoms, perhaps have chest/brain scans and keep watch?" -Derek 4.*

Many participants were confused about benefits of diagnosing HHT early so as to reduce complications from untreated arteriovenous malformations: *"I think often family members don't get tested b/c they don't realize screening can reduce complications"-Brittany*. This

lead some participants to see no role for genetic testing because a positive result would simply label a child as having a disorder with no medical benefit: *"Why burden a child with the knowledge they could just suddenly drop dead?"-Michael 7*.

Participants also made statements suggesting that many people with HHT or at risk for HHT believe that a diagnosis of HHT can be based simply on the presence or absence of nosebleeds without understanding variability and reduced penetrance. Several people in each discussion group referred to their own relatives, many whom were teenagers or young adults, who were considered to be unaffected because they had no history of significant nosebleeds or telangiectases: *"My brother has not been tested – he is completely asymptomatic and I don't question his decision not to be tested at all"-Susan 4 6; "They might just not think that they have it so why bother. If they've never been screened for AVMs and don't have bad nosebleeds they probably assume they didn't inherit the mutation"-Jennifer 5*.

Some participants indicated that misinformation about HHT and genetic testing is reinforced by physicians: *"Family doctors won't encourage testing if they're not fully aware of how serious HHT can be."-Kelly 7 10; "My own granddaughters are not being tested because their PCP doesn't think it will be of any benefit."-Natalie 3 8*. One participant with HHT pointed out that the relatives' failure to act could relate to what was actually told to the relative: *"We also don't really know how the conversation with the sibs went. What was actually said?? What information was given and in what way? They may not realize how important it is."-Jennifer V*.

Inadequate access to testing

Most patients who were themselves tested had testing done through an HHT Center of Excellence. They were knowledgable about barriers through discussions they had with their relatives about getting tested themselves. Access issues revolved around the belief that genetic testing for HHT is expensive and not covered by insurance, and difficulty with finding a provider to order the test. The majority of participants in all groups raised cost as the most important barrier to testing. Among people who had themselves been tested, about half indicated cost and lack of insurance coverage as a barriers. Several participants were annoyed by insurance companies who would cover most HHT-related costs, but not genetic testing: "*Insurance….mine wouldn't pay for testing but they would pay for a lung scan and MRI"-Laura 2 7*.

A number of participants expressed frustration with not being able to have access to an HHT Center of Excellence or an informed genetic service provider who could help facilitate testing. Distance and lack of insurance coverage were cited as barriers to these sources of care. Most participants were also aware that only a handful of labs in the country did genetic testing for HHT, and the inability to access testing through their own local or capitated lab was considered a barrier: *"If you live in Florida and the testing centers are in Georgia….you have to drive at least 10 hours to a testing facility…but you need to be at work because you can't pay your bills?" – Natalie 3*.

When the moderator asked participants if primary care providers are able to order genetic testing, a number of patient participants shared the experiences of their relatives as they attempted to get testing for their familial mutation through their primary care provider or a local laboratory. Many of the participants were also concerned that primary care providers might not be adequately prepared to interpret test results or to provide counseling or education about the test: *"In my experience, the primary care folks don't understand HHT and certainly don't understand how to interpret the genetic tests" –Pat 4*.

A number of patient participants shared the experiences of their relatives as they attempted to get testing for their familial mutation through their primary care provider or a local laboratory. Most of the time, the relatives were not successful in getting tested because of confusion about what test or order, or about where a sample should be sent. As one participant said: *"Unless you educate them, the doctors don't know about the tests and where genetic testing is done" – Dina 6*. Another participant summarized: *"Yes - they don't know where to begin…so I've heard from one of my siblings wanting to get tested." – Sharon 2*. One participant referred to her own experience with genetic testing in the community in which the wrong type of testing was ordered for her son: *"In my experience, if the (HHT-testing) lab did not call me, they would have done the identification of which gene was affected in my son's blood rather than the test to look for our family's gene which would have been a much more expensive test, because the hospital up here that took the blood did not send the right paperwork – Shelly 2 8*.

Emotional barriers

During the on-line discussion, the moderator asked: "what are some of the barriers to getting genetic testing for HHT?" In addition to cost, the majority of participants first mentioned a variety emotional barriers to testing. Most frequently mentioned were denial and fear, especially fear of insurance and employment discrimination:*"The confidentiality of the results is a worry to me for insurability (life) and discrimination in other ways if disclosed" – Laura 4*. The fear of insurance discrimination was raised in each group, and only five participants made comments indicating that they were aware of legislative protections against insurance discrimination, but none of them mentioned GINA by name: *"I believe a bill was passed that outlaws bias based on any genetic disease now". – Alex 6 9*.

Additional insight into these barriers emerged when the moderator asked "for those of you who have had genetic testing, what was the response of your relatives when you approached them about testing?" All participants who were tested had shared results with relatives and felt an obligation to urge them to get tested. Although there were a number of participants who reported that their relatives responded positively and had genetic testing for their familial mutation, the majority of participants reported less positive responses. Just under half of the patient/family member participants mentioned that people are afraid to hear that they have HHT, and also that their children might be at risk. Several participants spoke of the stigma that can be associated with being labeled as having a genetic disorder like HHT: *"They refuse because they don't want to be labeled or admit they have some imperfection" – Tom 3; "I recently sent e-mails with the HHT link to my brother and sister - not one response - my sister has new grandbabies - you think she would want to know more about it… They refused because no one likes bad news so if they don't know they can remain in denial" – Jenna 2 10; "Sounds just like my siblings. There are 7 of us and only one other has been genetically tested. The others think that if they don't know, then they don't have anything to worry about" – Richard 2 10*.

Several participants reported that their relatives were annoyed by persistent requests that they get tested: *"My entire family is completely in denial. They even started resenting me for e-mailing them general info about HHT" – Michael 7*. However, for a few participants, constant nagging eventually resulted in relatives being tested: *"My kids tried to ignore me. I wouldn't let them. It took almost a year, but they finally went" Ruth 3 6*. Other participants reported that their family members did eventually get genetic testing, but that it took a while for it to happen: *"You can only give them the information and allow them to make the decision. With my siblings it took two years for one sister to get tested… my younger sister was in denial and worried about her twins. Now she wished she had done it at the same time as her other siblings. She worried her self to death for two years" – Julia 2 4*. This experience illustrates the tendency of relatives to avoid genetic testing out of fear of learning

bad news without acknowledging that testing could exclude the disease. Still other participants reported that family members only considered getting genetic testing after a serious HHT-related event in the family: *"In my family it took my father to die and my son to nearly die before anyone did anything about it" – Julia 2 4; "All but one of my siblings ignored me. The other was tested only after he had a stroke and I reminded him of HHT – John 1 2"*.

DISCUSSION

Consistent with other studies involving different genetic disorders[7, 11, 16], we found that people with HHT held the belief that relatives, whether or not they had symptoms, should have genetic testing. Genetic testing was frequently viewed as a part of a work-up for HHT, rather than as a test that can be used to determine which family members in fact need further evaluation for possible complications of HHT. Despite the positive attitudes towards genetic testing, most relatives did not pursue genetic testing for a variety of reasons that we were able to identify through the on-line discussions and surveys.

As previously demonstrated in studies involving people with other genetic conditions such as HNPCC[10, 11] and inherited breast/ovarian cancer[6, 27], it appears that people who have had genetic testing identifying an HHT-associated genetic mutation do discuss their results with many at-risk family members and urge them to get testing. The low uptake of testing among family members is therefore not due to lack of notification. The content of the information communicated, however, could affect test utilization. Difficulty explaining medical and genetic aspects of a genetic disorder has been documented as a barrier to testing family members by others[12]. One recent study[28] documented that DNA test result information communicated by probands, and the interpretation of the information by relatives, bears little resemblance to the actual information given to probands by medical professionals. Participants in the present study often were confused about the rationale for genetic testing in both probands and at-risk family members. This implies that relatives may be given a garbled message that fails to persuade them to seek out testing. This possibility is supported by the frequency of misperceptions about testing we have documented, including the notion that health insurance would be lost if someone has a positive genetic test, the failure to recognize that genetic testing can exclude a diagnosis of HHT if the familial mutation has been identified, and the belief that testing is complicated and not covered by health insurance. Information about genetic testing that is made available through the HHT Foundation website reinforces the notion that testing is complicated by beginning their explanation of genetic testing with the statement "genetic testing for HHT is quite complex" (HTTP://hht.org/living-with-hht/genetic-testing-procedures, visited 12/23/10).

Although providing information to at-risk relatives about a genetic disorder can serve to increase awareness of being at risk and of genetic testing, such information may not always be welcome, and can precipitate stress and anxiety, especially when children are involved[16, 28]. Others have shown that resistance to genetic testing may also be linked to an overestimate of the emotional response to a positive test result[29, 30]. Among our discussion participants, many at-risk relatives reportedly wanted to avoid being diagnosed with HHT. Many reasons to avoid diagnosis were identified including concern about insurance discrimination, wanting to avoid being labeled as having an illness, and denial of being at risk for serious disease complications. Many of these relatives had few symptoms, and would likely test negative for a familial mutation if they were to be tested. Such definitive results could provide certainty about being unaffected, and could be used to reassure their children that they were not at risk. Some of these relatives with no or few symptoms, however, could be affected, and should have been getting screened for pulmonary AVMs, which could predispose to complications such as stroke or brain abscess if left untreated. In

these families, for relatives who assume they are affected on the basis of nosebleeds alone (even though the nosebleeds could be spurious), genetic testing is thought to be unnecessary because a positive result would only confirm what is already known, and a negative result might be received with skepticism, leading to uncertainty about the diagnosis.

If at-risk relatives decide to seek out testing for the HHT-associated mutation that has been identified in their family, some of these relative will consult with their primary care provider about being tested. Primary care providers in fact can play a variety of roles to facilitate testing of at-risk family members. First, research has documented that providers feel an ethical obligation to encourage their patients to discuss genetic risk with family members[31, 32]. In doing so, they may review with patients what should be told to relatives, and provide written information to share[33]. Providing information to probands to share with at-risk relatives may increase utilization of genetic testing, but results are mixed[7, 34]. Ongoing contact with patients regarding communication of information to relatives can increase notification within families[35]. In addition, given evidence that discussions with family members are often emotionally demanding and technically and logistically challenging, providers can be helpful by allowing a patient to identify potential barriers and facilitators that may be relevant to their family[33].

Despite their important role, as we heard during our discussion groups, engaging the primary care workforce to play a larger role in ordering and interpreting genetic tests is challenging[36]. Indeed, based on the experience with genetic tests for HHT performed at the Genetic Diagnostic Laboratory at the University of Pennsylvania from 2004–2008, only 10.3% of the 1022 tests performed were ordered by a primary care provider (personal communication, Dr. Arupa Ganguly). Knowledge of genetics and genetic testing by non-geneticist providers is low[37, 38]. Physicians have inadequate knowledge of genetics in general[36, 39], of specific genetic disorders[40, 41], and of guidelines for genetic testing or referral[42, 43]. In addition, recent research has shown that many physicians are unaware that genetic testing is generally covered by insurance[13], and they may also have inappropriate concerns about potential harms of genetic testing, such as unfair insurance discrimination[44, 45]. Potential insurance discrimination has been frequently cited by primary care physicians as a barrier to incorporating genetic testing into their practice[46], even though many non-geneticists have limited awareness of protections against insurance discrimination, and believe that patients' concerns about discrimination is a barrier to genetic testing[47].

This inadequate knowledge may lead to unwillingness or uncertainty about offering a genetic test, as well as lack of confidence in discussing tests with patients[48–50]. Some of providers' uncertainly relates to concerns about the potential lack of clinical utility of genetic tests in terms of modifying patient management[44, 46, 51]. Other uncertainty arises because physicians, especially those caring for adult populations, have the perception that genetic services are irrelevant and unimportant for the vast majority of their patients[39, 52].

Limitations

Because of the methodology used in this study, our findings need to be interpreted cautiously. We recruited participants for our discussion groups through the HHT Foundation. People who are on the HHT Foundation listserve may differ in important ways from those who do not receive emails from the Foundation. They may be better informed about HHT, or more knowledgeable about HHT than others with HHT. Because our qualitative data consisted of simultaneous written responses by multiple participants to the moderator's questions, we were unable to probe all individual responses for clarification. So, for example, while many participants cited "denial" as a barrier to genetic testing, we were not able to consistently seek clarification as to the meaning of denial unless the participant

spontaneously provided an explanation. Finally, although most participants responded to each of the moderator's questions, not all did. We therefore did not have responses to all questions from each participant.

Recommendations to reduce barriers to genetic testing

Despite the limitations of our study, based on our findings, we believe we can offer some recommendations to address barriers to genetic testing for autosomal dominant conditions such as HHT for which early screening and intervention can reduce morbidity and mortality. First, given barriers due to lack of information or misperceptions about genetic testing or genetic disorders (in this case HHT), additional education for patients and families is needed. We recommend that the needed education be provided through voluntary organizations devoted to specific genetic disorders. In the case of HHT, we recommend that the organization Hereditary Hemorrhagic Telangiectasia Foundation International include on their website a brief bulleted summary of the rationale for genetic testing that spells out precisely why and how genetic testing is done in families. These points include: 1) most serious risks of HHT are invisible (pulmonary and cerebral AVMs); 2) disability can be prevented through early diagnosis and treatment; 3) genetic testing in families can determine who does and who does not have HHT; 4) when testing is done early in childhood, one-half of children with an affected parent will be spared the need to undergo evaluations/imaging because genetic testing will find they are not at risk; 5) young adults who don't have nosebleeds can still be affected and can have affected children; 6) genetic testing can be ordered through primary care doctors, HHT Centers of Excellence or local genetics clinics; 7) genetic testing can be done on a sample of saliva and mailed to a testing lab; 8) someone in the family with obvious HHT needs to be tested first to identify the family's genetic marker for HHT; 9) genetic testing is usually covered by insurance; and 10) there are protections in place to prohibit genetic discrimination in health insurance and employment. We recommend against stating that genetic testing is complex or complicated. Much of the information families need to appreciate the rationale for genetic testing could be incorporated into a 2-minute video that could be available through the HHT.org website. This video could highlight the experiences of families whose children were determined to be unaffected and spared further screening, and of families whose affected children were identified early and provided needed treatment such as embolization of pulmonary AVMs.

In terms of barriers to testing due to issues with access, we recommend that the HHT Foundation take steps to make both providers and HHT families aware of alternatives to accessing testing outside of HHT Centers of Excellence. Brief information for primary care providers related to genetic testing can be made available through the HHT website. Providers can be directed to the four genetic testing labs offering genetic testing, all of which employ genetic counselors who are willing and able to assist providers with test ordering and the interpretation of results. Families and providers can also be made aware of the availability of genetic testing through genetic counselors that can be identified through the National Society of Genetic Counselors (www.nsgc.org). In addition, genetic counseling is increasingly available through companies offering telephone genetic counseling. Such services, in conjunction with genetic testing that can be done on a sample of saliva mailed to a testing lab, can increase access to genetic testing services to people residing in rural or underserved areas, and to those who may fear having blood drawn.

Overcoming emotional barriers to testing could be addressed through educating relatives about protections against insurance discrimination through the Genetic Information Nondiscrimination Act (GINA) of 2008, about the rationale for testing and about the danger of leaving pulmonary or brain AVMs untreated. Much of this education could be done through the HHT Foundation website. In addition, peer counseling by people with HHT who understand the reasons why people are reluctant to seek out testing could be helpful. Finally

a series of testimonials available through the HHT website that highlight empowerment through genetic testing could address some of the reasons why family members are reluctant to seek out genetic testing.

Conclusions

To date, much of the research identifying barriers to genetic testing for single gene disorders in families has focused on communication, or lack of communication, in families. Through our discussion groups, we discovered that lack of communication is rarely the main barrier to testing. We discovered that lack of understanding of the rationale for genetic testing, misperceptions about screening and treatment, as well as the general perception that testing is complicated and expensive, constitute major barriers to genetic testing for a relatively common treatable autosomal dominant genetic disorder. In addition, the reluctance or inability of primary care providers to order genetic testing reduces access to genetic testing for those who serve to benefit from it. Much of the education about genetic testing and the disorder itself can be taken on by voluntary disease organizations with the assistance of genetics professionals or members of the medical advisory boards of individual organizations[53]. Further research is needed to determine if the relatively simple recommendations we have made improve uptake of testing, and ultimately, whether genetic testing can lead to reductions in morbidity and mortality associated with a genetic disorder such as HHT.

Acknowledgments

This study was funded by the National Institutes of Health grant 1P50HG004487-01

We would like to thank members of the Hereditary Hemorrhagic Telangiectasia Foundation who participated in our study, as well as Nicole Schaefer from the HHT Foundation for her assistance with recruitment. We also thank Dr. Joseph Cappella, Georgia Griffin, Brittany Milliner and Shimrit Keddem for their help with setting up the discussion groups and analyzing data. We are grateful to Marianne Clancy, Executive Director of the HHT Foundation for her review of our data and our recommendations for addressing barriers to genetic testing.

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Table 1

Characteristics of participants (N=119)

		N	%
Female		87	73.1
Caucasian		110	92.4
Educational attainment			
High School		9	7.6
Some college		37	31.1
Bachelor's degree		41	34.5
Post-graduate education		32	26.9
Has children		94	79.0
Age			
Mean	52.3 years		
Range	25 – 80 years		
Diagnosed with HHT		109	91.6
Seen at HHT Center of Excellence			
Within last 5 years		60	50.4
More than 5 years ago		23	19.3
Never		36	30.3
Has had genetic testing			
Yes, full sequencing		37	31.1
Yes, single site		9	7.6
No		69	58.0
Unsure		4	3.4
Type of provider ordering genetic testing (if tested)			
Primary care provider		3	6.5
Provider at HHT Center of Excellence		31	67.4
Genetic counselor/medical geneticist		12	26.1

Table 2

Attitudes toward HHT and genetic testing (N=119)

	Agree		Neutral/Disagree		Don't Know	
	N	%	N	%	N	%
HHT is a very serious disease	115	96.6	4	3.4	0	0
Getting good medical care can make a big difference in how HHT will affect a person	118	99.2	1	0.8	0	0
I know a lot about genetic testing for HHT	49	41.2	61	51.3	9	7.6
Genetic testing for HHT is very expensive	67	56.3	15	12.6	37	31.1
Medical insurance usually covers the cost of genetic testing	24	20.2	59	49.6	36	30.3
People who have a positive genetic test for HHT will have a hard time keeping their health insurance coverage	32	26.9	51	42.9	36	30.3
People who have a positive genetic test for HHT will have a hard time buying life insurance	58	48.7	25	21.0	36	30.3
If the genetic marker for HHT is known in a family, relatives with signs of HHT should get tested for the marker	105	88.2	11	9.2	3	2.5
If the genetic marker for HHT is known in a family, relatives without signs of HHT should get tested for the marker	93	78.2	21	17.6	5	4.2
People who have genetic testing for HHT should encourage their relatives to get tested	110	92.4	7	5.9	2	1.7
Primary care doctors don't know how to arrange for genetic testing for HHT	80	75.6	19	7.6	20	16.8

Table 3

Responses to open-ended question regarding barriers to genetic testing for HHT

Barrier	# citing barrier
Cost of testing	68
Access/inconvenience	39
Discrimination	35
Emotional concerns	33
Lack of knowledgeable providers	21
Lack of awareness/understanding	17
Potential for error/misdiagnosis	12
Uncodeable	19

Table 4

Scenarios

a.	*Colleen is a 35 year old woman with nosebleeds since childhood and a family history of stroke. She has recently started to feel short of breath. Her family doctor refers her to a lung doctor. The lung doctor runs many tests and discovers that Colleen has pulmonary arterio-venous malformations (AVMs), which are treated by an interventional radiologist. The radiologist suggests to Colleen's primary care doctor that Colleen probably has HHT and that she should have genetic testing.*
b.	*Colleen has the genetic test that shows that she a genetic mutation which causes HHT. Before she was tested, the family doctor told Colleen that her family members are also at risk. As soon as she finds out that she carries a mutation, Colleen immediately talks to her siblings and urges them to get testing. No one follows her advice.*