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Cost savings through molecular diagnosis for hereditary hemorrhagic telangiectasia

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Purpose: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of vascular development resulting in direct connections between the arterial and venous systems, bypassing capillaries. Symptoms and signs can appear throughout life and marked intrafamilial variability confounds diagnosis based purely on clinical criteria. We set out to determine the impact of genetic testing on the cost of screening for HHT in at-risk relatives.

Methods: We performed economic modeling of idealized pedigrees following two scenarios: repeated clinical screening until an HHT diagnosis could be either affirmed or excluded, and mutation testing in the proband, followed by genetic testing of at-risk relatives and clinical monitoring of only those relatives who test positive for the familial mutation.

Results: Based on actual reimbursement data from our region's largest health insurer, the molecular diagnostic model saved over $22,000 for a family with four relatives at risk for the initial diagnostic work-up. For a cohort of 100 probands, the total savings for the molecular diagnostic model over a reasonable period of follow-up was greater than $9 million.

Conclusion: In this idealized setting in which all probands and at-risk relatives accepted molecular testing, the economic advantages of genetic screening over repeated clinical screening are substantial.

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Key Words: cost-effectiveness; economic analysis; genetic screening; genetic testing; hereditary hemorrhagic telangiectasia

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder of vascular development. Manifestations, which develop over time and may be present at birth, include epistaxis, hypoxemia from pulmonary arteriovenous malformations (PAVMs), stroke from cerebrovascular arteriovenous malformations (CAVMs) or paradoxic embolization through PAVM, mucocutaneous telangiectases, liver dysfunction from hepatic arteriovenous malformations, gastrointestinal bleeding, and high-output cardiac failure.[1,2] Current approaches to management can prevent much morbidity and mortality, but most rely on early detection of potential problems.[1,3,4] Because the overt manifestations often do not become evident until adolescence or later, clinical screening is essential to detect those in a family who are at risk. Moreover, given that some of the manifestations either are common in the general population (e.g., epistaxis, cutaneous telangiectases, gastrointestinal bleeding) or occur in isolation in people without HHT (e.g., PAVMs, CAVMs), determining who has inherited HHT in a family is often difficult. Individuals who are at up to 50% risk need to be screened by history, physical examination, and various imaging modalities repetitively until either the diagnosis is established[5] or the patient is old enough to be reasonably sure that features will not develop.[1,3] This latter age has not been established firmly, which leads to considerable uncertainty for health professionals and patients alike. The repeated clinical evaluations are costly, may involve radiation exposure, and often provoke anxiety about indecision as to affected status.

Genetic linkage studies suggest that mutations in at least six loci can cause HHT.[1,6] In the three genes that have been discovered, many pathologic alleles have been identified.[6,7] 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,[5] the probability of finding a clearly pathologic mutation in one of these three genes is 80–87%.[6–8] If a pathologic mutation can be identified in someone clearly affected by HHT, then all the relatives at potential risk can be offered assessment for whether or not they carry the mutation. If a relative does have the familial mutation, then the clinical screening protocol can be maintained and tailored to the particular signs and symptoms. If a relative does not have

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the mutant allele, then reassurance can be provided and no further HHT screening undertaken.

We have been studying a number of aspects of clinical molecular genetic screening in our center for HHT and in collaboration with others.[7,9–11] One consideration is the economic implications of the several approaches to assessing individuals at risk for this condition. Our hypothesis in this study is that clinical molecular screening in the United States will save health-care dollars as compared with our current protocol for clinical assessment. A previous study examined this issue in Canada and concluded that clinical molecular screening has clear economic benefit.[12] However, the differences between the health-care systems in the United States and Canada are substantial, especially with regard to their economics.

In our analysis, we modeled standard families with a proband clearly affected by HHT. For each of the two diagnostic scenarios, clinical and molecular plus clinical, we enumerated the costs, over two periods of time for follow-up, based on actual charges in our geographic region. The first time period involves clinical screening into adulthood for relatives at risk for HHT. The second time period was three years because private health insurance providers in the United States focus on a relatively brief time frame due to the mobility of consumers from one plan to another.[13]

The results clearly demonstrate an economic benefit for clinical molecular screening, whether the clinical screening is conducted into adulthood or for a relatively brief period.

MATERIALS AND METHODS

We performed a cost comparison, using a decision analytic model, of two diagnostic screening methods for at-risk relatives of a proband clearly affected with HHT. We termed these the clinical evaluation model and the genetic testing model. In each case we began with 100 probands, all clinically diagnosed with HHT by current diagnostic criteria.[1] We chose 100 probands because this approximates the number of new patients we and some other HHT centers see annually. For purposes of modeling, any number of probands could be chosen. For each proband, we modeled costs of screening four at-risk but undiagnosed children or sibs, under the two different models. The choice of four at-risk relatives is again arbitrary but approximates the average in our clinic. Although some newly ascertained probands have families with a dozen at-risk relatives (as modeled in the study by Cohen and colleagues[12]), many have families in which only a few relatives will be available for screening in our center.

Clinical evaluation model

The clinical evaluation model involves screening all 400 children or sibs for HHT. Each of the probands with HHT does not get genetic testing, and therefore all at-risk relatives, who each have an a priori 50% chance of being affected, must be screened. Initial screening of relatives consists of a history and physical examination that focuses on signs and symptoms consistent with HHT; a cerebral magnetic resonance imaging (MRI) study with and without contrast to screen for CAVMs, infarcts, or abscess; and a transthoracic contrast echocardiogram to screen for PAVMs.[3] If the contrast echocardiogram is considered positive for a shunt at the level of the lungs by virtue of late right-to-left passage of contrast, a computed tomographic (CT) scan of the thorax with and without contrast is performed.[14] We estimate the percentage of relatives who actually have HHT requiring a thoracic CT at 58%,[15] so 29% of all at-risk relatives will require a thoracic CT scan. Studies prompted by a detection of a PAVM or a CAVM are not considered in this model because they represent therapy and not diagnosis. We ignore the costs and potential clinical benefit of the identification and further evaluation of incidental findings. In the hundreds of people at risk for HHT who have had clinical screening, one had a cerebral glioma that required surgery, less than half a dozen had lung nodules for which they were referred to their primary-care physicians, one had a Chiari malformation for which neurologic referral was made, and three had dilatation of the ascending aorta for which they were referred for cardiologic consultation. The last finding may not be incidental but an uncommon manifestation of HHT (R.E. Pyeritz, unpublished data).

Relatives who warrant a diagnosis of HHT on the basis of this first clinical screening drop from further consideration in this model. Relatives who do not meet diagnostic criteria (negative or uncertain) require follow-up at regular intervals until the diagnosis is established or considered excluded. Based on our experience, if there are no hard findings of HHT by the age of 40, we consider the diagnosis excluded. (By "hard findings" we mean CAVM, PAVM, persistent gastrointestinal bleeding, epistaxis producing anemia, and many mucocutaneous telangiectases. By contrast, soft findings include a history of occasional epistaxis and a few telangiectases, which are known to increase with age in people who do not have HHT.) This end point differs from that of the model used by Cohen and colleagues,[12] who continued following relatives to age 70. Follow-up evaluations consist of an interval history and physical examination, contrast echocardiogram, and a thoracic CT scan if a pulmonary shunt is suspected. In practice, we recommend diagnostic screening every 5 years, which is in concert with clinical guidelines.[1,3] There is no consensus on the need to repeat brain imaging for the appearance of CAVM if the initial examination is negative, even in infancy. Some recommend repeating a brain MRI when a person at risk for HHT reaches adulthood. As this is not our practice, we have not included a brain MRI in our model of follow-up evaluations.

For purposes of our models, we assume that two of the four at-risk relatives are 20 years old and two are 5 years old. If HHT cannot be diagnosed clinically, the adults would need to be screened every 5 years until age 40, for a total of one initial and four follow-up evaluations. We assume that one of these adult relatives will have the diagnosis ascertained at age 30, and therefore will require only two follow-up evaluations. Similarly, the young relatives would require one initial screening and a total of seven follow-up evaluations if the diagnosis is not established. We assume that one of these children will be diagnosed clinically, at age 20, and therefore will require only

three follow-up evaluations. For the initial screening at the age of 5 years, sedation is often required for the cerebral MRI and the transthoracic echocardiogram (we perform the studies in sequence, so only one sedation is necessary), but we did not include this cost in the analysis.

Genetic testing model

The genetic testing model assumes that all 100 probands diagnosed with HHT agree after genetic counseling to undergo genetic testing. For those probands in whom no deleterious mutation is found, they and their undiagnosed at-risk family members will proceed with a screening protocol identical to the clinical evaluation model, where all at-risk relatives will undergo clinical evaluation until a definitive diagnosis can be made or excluded. We estimate the fraction of probands in this category at 13%.[6,7] This includes probands who are found to have a variant of uncertain significance in one or more genes, but no clearly pathogenic mutation. For probands who do carry a deleterious mutation, all at-risk relatives are offered genetic counseling and genetic testing. We assume that all of those relatives offered testing agree to it. For those who have genetic testing that shows that they do *not* carry the familial deleterious mutation, no further evaluation is necessary because the diagnosis has been excluded. The at-risk relatives who are found to carry the deleterious mutation undergo clinical screening for signs of HHT, but because the diagnosis of HHT has already been established, we do not include these clinical costs in the analysis.

Estimation and collection of data

Probability estimates for the decision models were derived from the medical literature, expert opinions from providers at the University of Pennsylvania HHT Center for Excellence, and the University of Pennsylvania's HHT Clinic Database. Permission to utilize information from the HHT Clinic Database was granted by the institutional review board at the University of Pennsylvania.

We collected insurance costs for procedures in the decision analytic models. Current Procedural Terminology codes for the clinical screening procedures were used to obtain charge and payment data for FY2010 negotiated rates in US dollars for the three health insurers in the local region that combined cover 55% of patients served by the Department of Medicine of the University of Pennsylvania Hospital System. We collected data for both technical and professional payments for each Current Procedural Terminology code through operational reimbursement and managed care analysis at the University of Pennsylvania Hospital System. We summed the technical and professional fees to obtain total payment data for each Current Procedural Terminology code (**Table 1**). We obtained the charges for genetic testing and genetic counseling from the Genetic Diagnostic Laboratory at the University of Pennsylvania and the University of Pennsylvania Hospital System, respectively. Because these charges are paid out-of-pocket by patients, we equated charge with payment for these items. Most patients will submit these costs to their insurer and be reimbursed, net of deductibles and co-pays, which we ignored for the analyses.

We conducted a cost-minimization analysis to demonstrate possible cost savings by genetic testing. Costs for each procedure, utilizing reimbursement data for insurer 2 in **Table 1**, were multiplied by the number of tests done based on a probability that the test would be needed (**Table 2**). The totals for each procedure were summed to provide total cost estimates for each model. We considered two scenarios. In the first, at-risk relatives would be screened once. In the second, at-risk relatives would be screened at 5-year intervals until the diagnosis was affirmed or considered excluded. The first scenario is relevant because of the tendency of people in the United States to change health insurance providers frequently, which we estimated as an average of every 3 years. Therefore, we assume that some insurance providers will be interested in the economic analysis of only the initial screen.

RESULTS

Costs of the first attempt to establish a diagnosis

In the clinical evaluation model, all 400 at-risk relatives require clinical screening, after which we estimate 160 (40%) will either show enough signs to warrant a diagnosis of HHT or no signs and, because of their age, can be reassured that they are very unlikely to have inherited HHT. The former group, which we estimate at 110 relatives, will require lifelong management, and perhaps immediate treatment, but these costs are not factored into our analysis, which focuses only on costs of diagnosis. The 50 who are reassured that they are unlikely to be affected require no further screening, unless some worrisome clinical problem emerges, but we eliminate them from the economic analysis. The remainder, 240 relatives, do not warrant a diagnosis on the basis of the initial screen, but because of their a priori risk and variable expression, especially age-dependency, they do require routine diagnostic screening, and these costs

Table 1 Payments for each diagnostic procedure

CPT codes	Description	Insurer 1	Insurer 2	Insurer 3
70553	Brain MRI, with and w/o contrast	$5,381.57	$1,643.32	$1,313.64
93306	Echo with contrast	$2,850.15	$4,750.15	$845.95
71275	CT angiogram of chest	$2,820.14	$4,688.68	$955.44
99205	Comprehensive evaluation (history and physical examination)	$50.19	$231.11	$259.91

CPT, Current Procedural Terminology; CT, computed tomographic; MRI, magnetic resonance imaging.

Table 2 Insurance payments comparing the clinical and genetic models for attempting to diagnose HHT in one at-risk relative (insurer 2)

		Clinical model		Genetic model	
Procedure	Payment for service	Probability of performing service	Payment per person	Probability of performing service	Average payment per person
Genetic counseling of proband	$75	0	$0	1.0	$75
ENG/*ACVRL1* testing of proband	$1,720	0	$0	1.0	$1,720
SMAD4 testing of proband	$560	0	$0	0.15	$84
Genetic counseling of at-risk relative	$75	0	$0	0.87	$65
Genetic testing of at-risk relative	$340	0	$0	0.87	$296
History and physical	$231	1.0	$231	0.13	$30
Brain MRI	$1,643	1.0	$1,643	0.13	$214
Contrast echo	$4,750	1.0	$4,750	0.13	$618
Chest CT	$4,689	0.29	$1,360	0.04	$177
Total payments		$7,984		$3,575	

ACVRL1, gene encoding activin receptor-like kinase 1; CT, computed tomography; *ENG*, gene encoding endoglin; MRI, magnetic resonance imaging.

are summed going forward as described in the Materials and Methods section.

In the genetic testing model, the cost of finding a pathogenic mutation in the proband (with a probability of 0.87) is $1,879 (cost of genetic counseling before mutation screening, cost of screening *ENG* and *ACVRL1*, and the cost of screening *SMAD4* in 15% of probands initially negative for mutations in *ENG* and *ACVRL1* by both sequencing and deletion/duplication analysis). The probability that a relative will test positive for a mutation, and thus require no further clinical screening for diagnostic purposes, is 0.435 (87% chance of finding a pathogenic mutation in the proband times 0.5, the likelihood that any first-degree relative will inherit HHT). Based on insurance payments for services by one payer, the cost to confirm or exclude the diagnosis of HHT in the first at-risk relative (regardless of age) is $361 (cost of genetic counseling before mutation screening plus the cost of single mutation screening) plus the cost of finding the proband's mutation, for a total of $2,240. For each subsequent at-risk relative, the cost of confirming or excluding the diagnosis is $361. The pathogenic mutation will not be identified in 13% of probands, and they and all of their at-risk relatives require diagnostic work-up as in the clinical evaluation model.

Table 2 compares the two models for the initial diagnostic screening, based on data for the most frequent payer in our region (payer 2 in Table 1). For an at-risk relative, following the clinical evaluation model costs $7,984. As we assume that each proband has four at-risk relatives, the cost of screening these four by the clinical evaluation model is $31,936. Following the genetic evaluation model, it costs $1,879 to determine if the proband has a mutation. If the proband does have a pathogenic mutation, screening the four at-risk relatives costs $75 for counseling and $340 for molecular testing, for a total of $415 per relative or $1,660 for all four. However, as a pathogenic mutation will be found only 87% of the time, this total becomes $1,444 plus the cost of finding the mutation, which equals $3,323. The 13% of families lacking a pathogenic mutation are screened by the clinical evaluation model and the cost totals $4,152 plus the cost of searching for the mutation (i.e., $1,879), for a total of $6,031. This value plus $3,323 equals $9,354, the total cost of the initial screening of one family by the genetic testing model.

Thus, the savings for one "average" family is $31,936 minus $9,354, or $22,582. For our hypothetical 100 probands, using genetic screening saves over $2.2 million. Repeating the analyses for payers 1 and 3 in Table 1 shows similarly large savings through the genetic screening model. For payer 1, the cost of screening four at-risk individuals by the clinical evaluation model is $36,400 and by the genetic evaluation model is $9,100. For payer 2, the cost of screening four at-risk individuals by the clinical evaluation model is $10,788 and by the genetic evaluation model is $4,279. These calculations for a single screening visit are relevant to insurance providers in the US health-care market, where consumers change insurers, on average, less than every 5 years.[13]

Costs of screening until the diagnosis is established or excluded

We also calculated diagnostic costs over a lifetime of screening, assuming the at-risk relatives maintained the same insurer (payer 2 in Table 1). We screened every 5 years until the at-risk relative reached age 40 (in the absence of a diagnosis) or until the diagnosis was made. This analysis better reflects the cost to payers on the whole, regardless of how those costs are distributed across different insurers over time. For simplicity, neither did we include an inflationary factor nor did we discount costs back to their present value—two simplifications that offset each other to the extent that discount rates will be reasonably close to any inflation.

In the clinical model, the cost of the initial diagnostic evaluation is $7,984 (Table 2). In our "average" family, one-half of the at-risk relatives are of age 20 and one-half of them will require four follow-up screenings until the diagnosis is assumed to be

excluded at age 40. One-half of these 20-year-olds will have the diagnosis established at age 30, requiring two follow-up screenings. Each follow-up screening costs $5,375, so the six follow-up visits will cost our 20-year-olds $33,250 plus the $7,984 each cost for initial screening, for a total of $48,218. The other two at-risk relatives are 5 years old. For the average of one of them who will not have inherited HHT, this will require seven follow-up visits to age 40. For the one who has inherited the condition, we assume this will be recognized by age 20, requiring three follow-up screenings. The 10 follow-up screenings cost $53,750 plus the $7,984 each for initial screening, for a total of $69,718. Thus, the total cost for one family is $117,936.

In the genetic testing model, the costs for the initial screening are shown in **Table 2**. Thirteen percent of the at-risk relatives will require clinical screening because the mutation in the proband was not found. Given the same age structure and follow-up schedule as described in the preceding example, the cost of clinical screening is 0.13 times $117,936 or $15,332 for the four at-risk relatives. This figure must be added to the cost of affirming or excluding the diagnosis in 87% of the families, which totals $3,323 per family. Subjecting the average family of four to the genetic testing model therefore costs $18,655. Thus, the net savings of the genetic testing model over the diagnostic lifetime is $99,281 for one family and $9.9 million for our cohort based on 100 probands insured by payer 2. Similar large savings would occur if the family were insured by payers 1 or 3 in **Table 2**.

DISCUSSION

New genetic technologies with potential clinical applications are emerging at a rapid pace.[16] Each new technology requires assessment by the ACCE criteria: analytic validity, clinical validity, clinical utility, and societal implications, including ethical, legal, and economic concerns.[17] The evaluation of some aspects of clinical utility of a genetic test can be approached through various investigations that include costs. Cost–benefit, cost-effectiveness, cost–utility, and cost-minimization analyses are all methods that have relevance.[18,19] The study we report here is primarily one of cost-minimization, but elements of benefit and utility also pertain. For example, the relatives identified by molecular testing as being not at risk for HHT derive the benefit of avoiding the inconvenience, indirect costs, and small but real risks (e.g., radiation) of clinical screening. However, our primary reason for conducting this modeling analysis was to test the hypothesis that clinical molecular testing for Mendelian disorders such as HHT will reduce overall health-care costs in a typical health-care setting in the United States.

This cost-minimization analysis compares direct payer costs for clinical screening alone versus genetic screening followed by targeted clinical screening for diagnosing HHT. We found that for one payer the genetic testing model saves more than US$2.4 million in screening 100 probands and four at-risk relatives of each proband once. The savings over the diagnostic lifetime of these same individuals is $9.4 million. Results for the other two major health insurers in our region were similar. The major cost savings is seen in at-risk relatives who can be eliminated from having to get costly imaging studies every 5 years by ruling out HHT with genetic testing. As the ability to detect pathogenic mutations in probands with HHT increases beyond 87%, the magnitude of the savings will increase.

Through sensitivity analysis, the costs of the diagnostic tests can be varied to anticipate future trends. The cost of DNA analysis continues to fall, eventually to be replaced by whole exome or whole genome screening, with a target cost of $1,000 or less in the near future. This trend will exaggerate the discrepancy further in favor of the genetic testing model, assuming the costs of imaging, physician evaluation, and counseling stay stable or rise, as they tend to do.

Apart from its cost savings, the genetic testing model is associated with other benefits. As a substantial proportion of the at-risk relatives will be found unaffected after genetic testing, they and their offspring will be spared unnecessary radiation and sedation to perform screenings. The genetic testing model will alleviate the uncertainty for at-risk relatives where HHT can be excluded with a simple genetic test. One potential disadvantage of genetic testing when whole exome or whole genome sequencing is utilized in the near future is the many incidental findings of possible clinical relevance that may need attention.[20,21]

Cohen and colleagues examined some of these same issues based on their experience in an HHT center in Canada.[12] Important differences, in both methodology and the national health-care systems, distinguish our study from theirs. As compared with the Canadian HHT laboratories at the time of that study, genetic testing for HHT in the United States is half as costly. In distinction, the costs for imaging tests and consultations are considerably more expensive in the United States. The Canadian researchers modeled clinical screening to age 75 in all those at risk, whereas we took the more realistic approach of terminating screening at age 40, by which time the patient who shows no signs of HHT can be reassured that he or she likely did not inherit the mutant allele. As reproductive fitness is little affected by HHT, some pedigrees are quite large. The Canadian study assumed each family consisted of a proband and 13 at-risk relatives of widely varying ages. Such families are uncommon in our clinical experience, which is why we modeled only four at-risk relatives of relatively young age. Since the early part of this century, pulmonary angiography has been completely supplanted by high-resolution chest CT, so we did not include that expensive test in our model, whereas Cohen and colleagues did. Similarly, in the Canadian model, cerebral MRI was repeated every 5 years into adulthood, whereas, in our center, we perform a baseline examination when the diagnosis is first considered and if that is negative, we do not repeat it. Despite these differences, our two studies of the value of screening relatives for HHT using mutation analysis arrive at the same broad conclusion. In purely economic terms, clinical molecular screening is advantageous. Importantly, neither study considered indirect costs associated with either genetic or clinical screening. As the costs of travel and lost wages are

considerable for repeated clinical testing, including indirect costs would certainly skew the economic analysis further in favor of molecular screening.

The past decade has seen an upsurge in interest in evaluating the economic impacts of new genetic technologies, from both the theoretic and empiric perspectives.[22–25] Many of the studies that involve modeling or data analysis have examined genes that, when mutant, predispose to disease at considerably less than 100% penetrance. For example, people at higher than age-adjusted risk for colorectal cancer, based on family history or genetic testing of tumor tissue in relatives, benefit clinically from earlier institution of colonoscopic monitoring.[25] The cost-effectiveness of various models of screening for colorectal cancer for more aggressive management compared with the general population has been examined in several studies.[26–30] As improved data on effectiveness of testing, prevalence of mutations, and costs of testing and screening accrued, the cost-effectiveness of targeting therapy for colorectal cancer based on genetic screening has been judged reasonable (in terms of earlier diagnosis of tumors and reduced costs) for both individuals and the population.[27,30]

At the same time, it is important to recognize the cost savings that we observe with genetic screening for HHT or that may be likely with other single-gene disorders such as Lynch syndrome or long QT syndrome result because these tests offer sufficient negative predictive value that we can exclude individuals from further screening or surveillance, or at least reduce their later testing to levels appropriate for the general population. Screening for mutations in other contexts may not be similarly cost reducing, particularly where negative results do not warrant substantial decreases in surveillance.

Implications from our study of screening for HHT based on mutation analysis are important for policy makers, insurers, health-care providers, and consumers alike.[31,32] Regardless of which of the three major health insurers in our region cover the proband and the relatives, costs are saved.

One limitation of our analysis is that it assumes full compliance with screenings. It is a normative model, not a descriptive one. We know from recent online deliberations with people with HHT and their relatives that not all probands see a value in determining their mutation and that not all at-risk relatives want to confirm by DNA testing whether they have inherited the condition or not.[9] Some of the same at-risk relatives who are not interested in DNA diagnosis will not comply with recommendations for regular clinical screening. In addition, our analysis reflects costs from only three payers; payment rates varied substantially across these three payers and may vary even more across the nation. For example, Medicare pays less than the payers we used in our examples. However, given that we were modeling the costs of screening young relatives, Medicare would only infrequently be involved as a payer for HHT-related services. Furthermore, our analysis relies on the assumption that most relatives are of young age and require long-term follow-up if mutation status is unknown. Our analysis modeled only the costs involved with diagnosing or excluding the diagnosis of HHT in family members. We did not consider the costs of screening for clinical involvement in at-risk relatives who test positive for the familial pathogenic mutation, we did not consider the cost or cost savings of further evaluating and managing incidental findings in the course of imaging studies, and we did not consider the cost or cost savings of treating HHT-related complications, such as occluding PAVMs to prevent stroke or heart failure, or treating severe nosebleeds to prevent anemia and transfusion-dependence. For example, the long-term success rate of occluding PAVMs to prevent stroke, cerebral abscess, and heart failure is greater than 95%.[4,33] The health-care costs of caring for any of these chronic complications of untreated arteriovenous malformations, over a lifetime, are substantial. Despite these limitations, these results reveal that a strategy of genetic screening of relatives at risk for HHT eliminates the need for conventional clinical screening in nearly half the at-risk population, thereby greatly reducing clinical and economic costs.

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DISCLOSURE

The authors declare no conflict of interest.

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