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Cost Comparison of Genetic and Clinical Screening in Families With Hereditary Hemorrhagic Telangiectasia

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Endoglin (*ENG*) and *ALK-1* mutations cause hereditary hemorrhagic telangiecstasia (HHT), an autosomal dominant disorder leading to vascular dysplasia in the form of mucocutaneous telangiectasia and visceral arteriovenous malformations (AVMs). We proposed to compare two alternative strategies for management of HHT: screening HHT families with molecular diagnostic tests followed by targeted clinical screening versus conventional clinical screening. A decision analytic model was constructed to compare screening strategies for a hypothetical HHT family. The family consists of 1 index case and 13 relatives. The clinical screening protocol in use at the Canadian HHT Center in Toronto was assumed to be the standard of care. Unit costs for clinical screening (in Canadian dollars) were obtained from the 2003 Ontario Health Insurance Schedule of Benefits. Genetic screening costs were estimated for quantitative multiplex PCR and sequencing of *Endoglin* (*ENG*) and *ALK-1* genes, as performed at HHT Solutions, Toronto. The genetic screening strategy resulted in a net cost of $4,060 per individual versus $5,975 for the clinical screening strategy. The genetic screening strategy would save $1,915 per family member or $26,810 saved per family. Sensitivity analyses revealed that the genetic screening strategy was cost saving over all plausible ranges of input variables for all hypothetical families tested. We concluded that a genetic screening strategy with targeted clinical screening is more economically attractive than conventional clinical screening and results in a reduction in the number of clinical tests for family members who do not have HHT.

KEY WORDS: cost; cost-benefit; hereditary hemorrhagic telangiecstasia; genetic; endoglin; *ENG*; *ALK-1*

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder affecting approximately 1 in 8,000 individuals [Plauchu et al., 1989]. HHT is characterized by vascular dysplasia in the form of mucocutaneous telangiectasia and visceral arteriovenous malformations (AVMs). Telangiectases commonly occur on the skin, nasal, and gastrointestinal mucosa resulting in recurrent hemorrhage. Recurrent spontaneous epistaxis is the most common symptom of HHT [Guttmacher et al., 1995]. Visceral AVMs, which are direct artery to vein connections, are a particular source of morbidity and mortality [Gossage and Kanj, 1998]. Pulmonary AVMs (PAVMs) are present in approximately 30% of HHT patients [Nanthakumar et al., 2001] and cerebral AVMs (CAVMs) are present in 10%–15% [Haitjema et al., 1995; Maher et al., 2001]. If not detected and appropriately monitored and treated, PAVMs and CAVMs can lead to debilitating and life-threatening complications such as stroke, cerebral abscess, massive hemoptysis, massive hemothorax, and seizures [Gossage and Kanj, 1998]. Unfortunately, complications from PAVMs and CAVMs can occur before typical mucocutaneous telangiectasia or epistaxis appear, leaving seemingly unaffected family members at risk for life-threatening complications of AVMs [Guttmacher et al., 1995]. Therefore, the standard of care requires that patients with HHT and their relatives routinely undergo screening and long-term monitoring for PAVMs and CAVMs [Guttmacher et al., 1995].

Diagnostic genetic testing for HHT has very recently become available in North America and is expected to change the way HHT families are managed. In 1994 it was discovered that the endoglin gene (*ENG*), located on chromosome 9q33, was responsible for causing HHT type 1 (HHT1) and in 1996 the *ALK-1* gene, located on chromosome 12q, was found to be responsible for causing HHT type 2 (HHT2)) [McAllister et al., 1994; McDonald et al., 1994; Shovlin et al., 1994; Johnson et al., 1995, 1996; Vincent et al., 1995]. Since then, a total of 156 *ENG* and 123 *ALK-1* mutations have been reported, as recently reviewed [Abdalla and Letarte, 2005]. Most families carry a unique mutation [McAllister et al., 1995; Vincent et al., 1995; Berg et al., 1997; Pece et al., 1997; Shovlin et al., 1997; Gallione et al., 1998, 2000; Abdalla et al., 2000, 2003; Cymerman et al.,

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2000, 2003; McDonald et al., 2000; Kjeldsen et al., 2001; Lin et al., 2001; Paquet et al., 2001; Trembath et al., 2001; Olivieri et al., 2002; Lastella et al., 2003]. Mutations identified to date include nonsense mutations and missense mutations, insertions and deletions. Deletions vary in length from one base pair to multiple exons. Moreover, the mutations are distributed across the entire span of the two genes, so molecular screening is potentially labor intensive.

We hypothesized that the use of genetic testing in HHT families will reduce direct health care costs by eliminating the need for long-term clinical screening in family members found not to carry the familial mutation. Clinical screening is uncomfortable, inconvenient, invasive, and carries procedure-related risks. Molecular testing allows AVM screening to be limited to only the individuals found to carry an HHT mutation. Individuals who test negative for the familial mutation avoid unnecessary AVM screening and monitoring. This approach increases the quality of care for family members who do not carry the familial mutation and should reduce health care expenditures.

METHODS

Study Design

We performed a cost comparison of two potential screening strategies for family members of individuals with HHT using a decision analytic model. Our study estimated the costs of genetic and clinical testing until the cohort reached age 75. Costs were estimated from the perspective of a third-party payer. This analysis did not include costs associated with complications of HHT (e.g., stroke, epistaxis), clinical care other than screening, out-of-pocket costs, or time loss associated with screening or treatment. Costs were estimated in 2003 Canadian dollars. Future testing costs were discounted at a rate of 5% [CCOHTA, 1997].

Strategies

We modeled two screening strategies for a hypothetical HHT family: (I) conventional clinical screening; and (II) molecular diagnostic screening followed by targeted clinical screening.

The clinical screening strategy includes screening all family members at risk, regardless of their clinical diagnosis (known HHT or unknown HHT status), and does not include any genetic tests. The genetic screening strategy involves drawing a sample of blood from the index case (a family member with a definite diagnosis of HHT) and analyzing DNA to diagnose the family's mutation. If the familial mutation is identified, genetic screening tests continue for relatives at risk, by degrees of relatedness to the index case, until all relatives at risk have been identified as carriers or non-carriers. Family members shown to carry the familial mutation undergo clinical screening tests, whereas non-carriers will not.

CLINICAL SCREENING PROTOCOLS

We constructed a standard screening protocol for the index patient and family members based on review of the medical literature and consultation with expert physicians at the Canadian HHT Center in Toronto. The standard screening protocol for PAVM is detailed in Figure 1 and is based on the following: (1) screening tests include contrast echocardiography (echo) and chest radiography (CXR). (2) Diagnostic tests include thoracic computed tomography (CT) and pulmonary angiography. Oxygen shunt testing is included with the diagnostic testing as it is generally performed as a baseline prior to treatment. (3) Patients with PAVMs undergo treatment with transcatheter embolotherapy, though this is not included in the model. (4) Follow-up tests include oxygen shunt testing, echo, and CT.

It was assumed that the clinical screening protocol described, based on the Toronto HHT Center screening protocol and expert opinion, is the standard clinical screening protocol in specialized HHT Centers. Though some centers now accept CT thorax as the diagnostic standard for PAVM, the pulmonary angiogram remains the diagnostic standard in the medical literature, and therefore we retained it in our model.

The standard screening protocol for CAVMs is detailed in Figure 2. Adults undergo initial screening cerebral magnetic resonance imaging (MRI). If this is positive, the patient undergoes diagnostic cerebral angiography. Patients with CAVMs are referred for treatment, which is not included in the model. It was assumed that adults with an initial negative cerebral MRI do not undergo further screening for CAVM unless they become symptomatic. Children undergo an initial cerebral MRI, followed by repeat cerebral MRI every 5 years (and cerebral angiogram if necessary) until they reach adulthood (defined as age 20) (Fig. 2).

Probability Estimates for Positive Screening Tests

Baseline probability estimates for the decision model, as well as plausible ranges for these values, were derived from a literature review, and from expert opinion of physicians in the multidisciplinary Canadian HHT Center located at St. Michael's Hospital in Toronto, Canada (Table I). When possible, probabilities were calculated using the outcome of 500 patients seen at the HHT center. Permission to utilize information from the HHT Database was granted by the Research Ethics Board at St. Michael's Hospital.

The probability of detecting a mutation in the index case (pSens) was estimated at 0.70, based on recent unpublished experience at the HHT Solutions Laboratory (technology detailed below in costs section), as there is no published accuracy data for this newly available molecular test. In addition, we assumed the probability of detecting the familial mutation (identified in the index case), in a family member with HHT to be 1.0.

In addition to probability estimates for positive screening tests, this model also includes probabilities to represent the chances that family members will comply with testing recommendations. We assumed that the probability of compliance is 1.0 among family members for all screening tests, but explored a range of compliance rates in a sensitivity analysis.

Cost Estimates

Genetic testing for HHT, performed at HHT Solutions in Toronto, currently involves quantitative multiplex polymerase chain reaction (QMPCR) and DNA sequencing using the open gene automated DNA sequencing system (VGI) [Berg et al., 1997; Olivieri et al., 2002]. The cost for genetic testing was determined assuming the current state of technology and costs of labor and materials were included. The cost for conducting a molecular diagnostic screening test for the index case is $3,300, while the cost for screening additional family members for a known mutation is $500 (Table II). In determining costs for genetic testing, it was further assumed that each family member has a counseling session with a genetic counselor. The index case has a 2-hr consultation with a genetic counselor and all subsequent family members have a 1-hr session with a genetic counselor (Table II).

We estimated the costs of clinical screening by multiplying the number and type of resources consumed in screening protocols by the unit costs associated with those resources. The costs for physician visits, consultations, and outpatient diagnostic procedures were obtained from the 2003 Schedule of

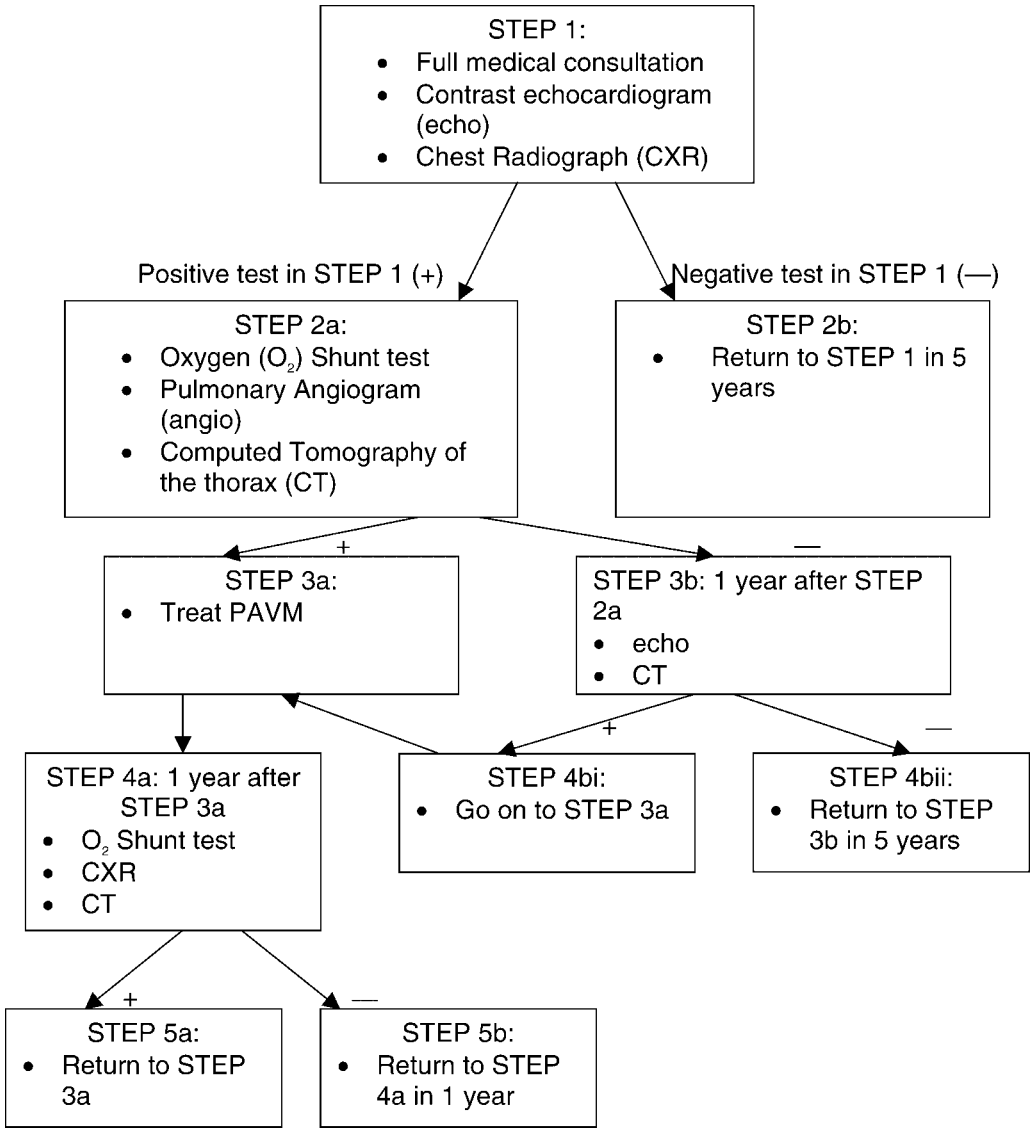

Fig. 1. Clinical screening protocol for pulmonary arteriovenous malformation (PAVM). The standard screening protocol for PAVM is outlined in Figure 1 and includes the following: Step 1: patients undergo a full medical consultation and undergo an agitated saline transthoracic contrast echocardiogram (echo) and chest radiograph (CXR). If either of these tests are positive (suggesting pulmonary AVMs), then the patient goes on to Step 2a, which includes an oxygen shunt test, pulmonary angiogram (angio), and computed tomography (CT) of the thorax. Step 2b: If all tests from Step 1 are negative, then patients return for follow-up (Step 1) in 5 years time. Step 3a: If the angiogram is positive in Step 2a, patients are treated for PAVM and return for follow-up (Step 4a) in 1 year's time. Step 4a: Patients have an oxygen shunt test, CT and CXR as follow-up 1 year after embolization for PAVM. If any of these tests are positive suggesting that all PAVM not successfully treated, then patient's return for further treatment (Step 3a). If the oxygen shunt test, CT and CXR are negative from Step 4a, patients return for follow-up (Step 4a) in 1 year's time. Step 3b: If the CT thorax and pulmonary angiogram from Step 2a are negative, then patients return for follow-up (Step 3b) in 1 year's time, with a CT. If the CT is positive from Step 3b, then patients go on to Step 3a for treatment. If the CT is negative from Step 3b then patients return for follow-up (Step 3b) in 5 year's time.

Benefits of the Ontario Ministry of Health and Long-Term Care [Ontario Health Insurance Schedule of Benefits, 2003], as reported in Table II.

Structure of the Decision Model

We constructed a decision model to evaluate the genetic screening strategy versus the clinical screening strategy for families in which the index case is defined as a family member with a definite clinical diagnosis of HHT. The genetic screening strategy is the upper first branch while the clinical screening strategy is the lower first branch (Fig. 3). The green circles in the figure represent events that may occur by chance and thus have an associated probability of occurrence. For the genetic screening strategy, the first chance event is the probability of compliance with molecular diagnostic testing (not shown in decision tree). The sensitivity of the genetic test, pSens, is defined as the probability that the genetic screening test will detect a mutation in the index case. If the mutation is found in the index case, then relatives at risk are screened for the mutation. If the mutation for HHT is not found in the index case, all family members undergo clinical screening.

Outcomes for family members are estimated separately for each of the three defined age categories based on age at onset of screening. Separate age strata are employed because mortality rates and duration of screening are age-dependent. The three

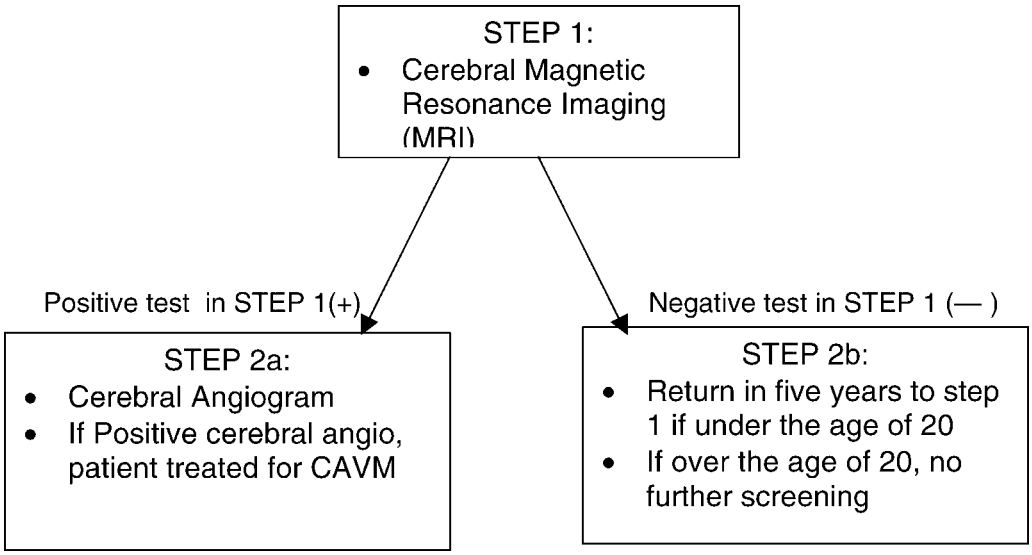

Fig. 2. Clinical screening protocol for cerebral arteriovenous malformation.

age categories are: Senior (age 60+), Adult (age 21–59), and Child (age 0–20).

The next chance event is the probability of family members having the HHT mutation (pCarry). If family members undergo genetic screening for HHT prior to clinical screening, then only those family members found to have HHT are monitored further via clinical screening. If family members do not undergo genetic screening, then all family members undergo clinical screening.

For the clinical screening strategy, clinical screening occurs immediately, and is indicated in the diagram by a red square.

Figure 3 does not depict details of the clinical screening trees as they are large and complex. The structure of the screening trees, however, closely follows the clinical screening algorithms shown in Figures 1 and 2 and as detailed above.

The stream of costs associated with screening for each individual are captured using Markov processes. Markov processes are of particular value in representing events that occur over long periods of time, and can easily represent cyclic events like screening. In our model, we used Markov states that, in general, corresponded to steps in the clinical screening protocol. For example, Steps 1–4b (Fig. 1) illustrating the clinical screening protocol for PAVM correspond to Markov states that are within the PAVM decision tree, with two exceptions. The PAVM decision tree has two additional Markov states consisting of the health state "death" and the health state "treatment." A small proportion of the cohort is expected to die each year based on population mortality rates. Members of the sub-cohort are sent to the treatment state when results of clinical screening tests indicate presence of a PAVM. Following treatment, the sub-cohort is either sent back to the first state, Step 1, to begin monitoring for PAVM again or the cohort is sent to the death state. The Markov tree continues cycling through all of its states until family members either die or reach 75 years of age. The outcomes from the decision analysis are the expected net present value of costs for both genetic and clinical screening strategies. When all of the trees are combined into one large decision tree representing outcomes for the entire family, the resulting cost is a weighted average of expected costs for screening the index case and their family members. These costs represent the average cost for HHT screening per family member.

TABLE I. Probabilities of Positive Clinical Screening Tests in Patients With and Without HHT

Variable	Definition of probability	Value	Range of values tested in sensitivity analysis
Probabilities for positive test results in patients with HHT			
P1	Echocardiogram or chest radiograph	0.73[a]	0.30–0.80[b]
P2	Thoracic CT scan or pulmonary angiogram	0.61[a]	0.40–0.90[b]
P3	Echocardiogram or thoracic CT scan	0.10[a]	0.01–0.20[b]
P4	Cerebral MRI	0.0056[a]	0.0100–0.2000[b]
P5	Cerebral angiogram	0.75[a]	0.50–0.95[b]
Probabilities for positive test results in patients without HHT			
P6	Echocardiogram or chest radiograph	0.15[b]	0.05–0.30[b]
P7	Thoracic CT scan or pulmonary angiogram	0.0003[b]	0.0000–0.0010[b]
P8	Echocardiogram or thoracic CT scan	0.0001[b]	0.0000–0.0002[b]
P9	Cerebral MRI	0.0100[b]	0.0001–0.0200[b]
P10	Cerebral angiogram	0.0001[b]	0.000–0.0002[b]
P11	Thoracic CT or chest radiograph	0.100[c]	0.000–0.200[b]

[a]Values obtained from the Toronto HHT Center Database.
[b]Values determined from expert opinion.
[c]Value for P11 is equivalent for patients that have and do not have HHT.

TABLE II. Unit Costs for Screening

	Cost (2003 $C)
CAVM screening[a]	
Cerebral MRI	95
Cerebral angiogram	675
PAVM screening[a]	
Chest radiograph, two views	21
Echocardiogram	95
Thoracic CT without contrast	66
Pulmonary angiogram	816
Oxygen shunt test	83
Respiratory consult (full)	112
Genetic screening index case	
Molecular diagnostic test	3,300
Genetic counseling[b]	238
Total	3,538
Family member	
Molecular diagnostic test	500
Genetic counseling[c]	119
Total	619

[a]Costs for clinical screening tests are obtained from the 2003 OHIP Schedule of Benefits.
[b]Cost for genetic counseling the index case included a full 2-hr consultation with a genetic counselor.
[c]Cost for genetic counseling family member includes a 1-hr consult.

In defining probabilities of positive test results by clinical screening, patients with and without HHT have different chances of having positive tests. Thus, there are different probabilities for family members depending on whether or not they have HHT (Table I). The time horizon for follow-up was modeled so that the index case and family members were screened until age 75. Thus children were screened for 65 years, adults for 35 years, and seniors were screened for 15 years. The primary outcome measure was direct costs of screening tests. The decision analysis was performed using DATA^{TM} 3.2 (TreeAge Software, Inc., Williamstown, MA).

Model Assumptions

Several assumptions were employed in constructing the decision tree: (1) a hypothetical HHT family consists of the index case and 13 family members. The family includes two parents (two Seniors), their four adult children (including the index case and three other Adults), and eight grandchildren (eight Children) as each "Adult" family member is assumed to have two children. (2) The index case is an Adult family member in his/her forties with a positive clinical diagnosis for HHT. (3) The average age of screening onset is 10 years for 8/14 relatives, 40 years for 4/14 relatives and 60 years for 2/14 relatives. (4) All family members fully comply with genetic and clinical screening protocols. (5) Since HHT is an autosomal dominant disorder, approximately 50% of Seniors, their children (Adult) and their children's children (Child) will develop HHT. Thus it was assumed that 50% of each generation has HHT. (6) Mortality rates for family members that do and do not have HHT are equivalent. (7) The clinical screening protocol described, based on the Toronto HHT Center screening protocol and expert opinion, is the standard clinical screening protocol in specialized HHT Centers.

Sensitivity Analysis

Probabilities of test results were examined over a wide range of values through a series of sensitivity analyses. The goal of the sensitivity analysis is to evaluate the robustness of the analytic results under alternate assumptions and values for parameter estimates. In order to perform a sensitivity analysis, ranges of values are substituted for individual probabilities in the model while holding the rest of the probabilities constant. The goal of the sensitivity analysis is

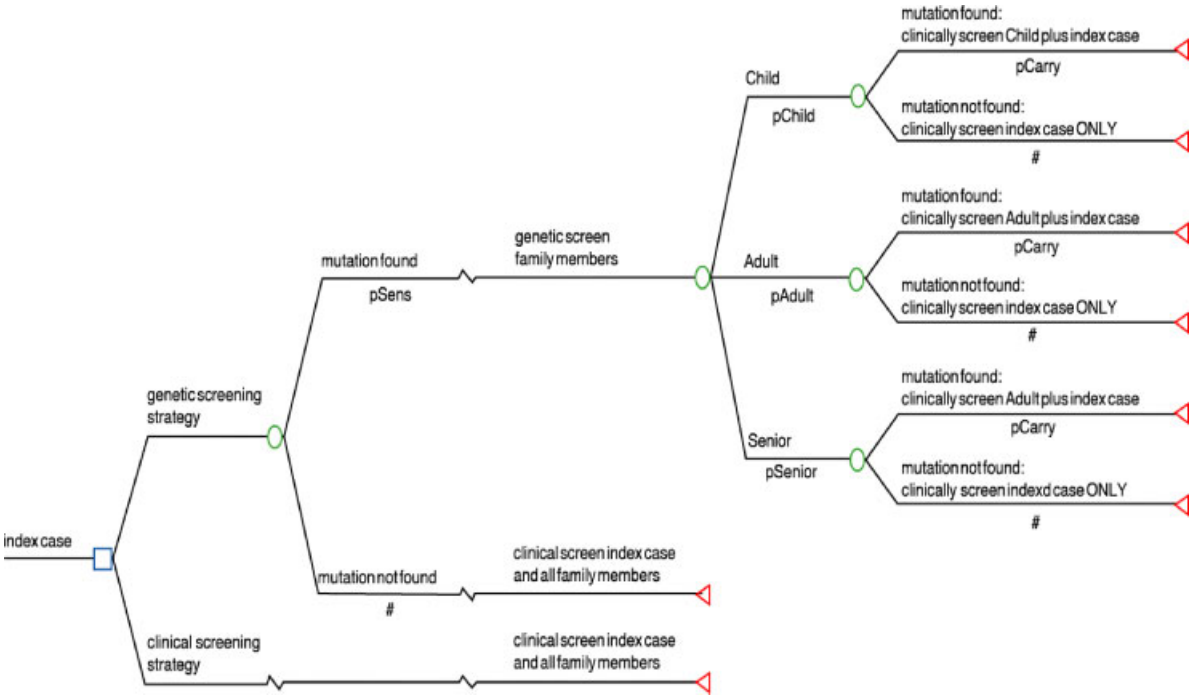

Fig. 3. Representation of the decision model used in the analysis. The two strategies, genetic and clinical screening, are separated by the blue square on the left. Each green circle represents chance events. The Markov process that includes clinical screening trees for CAVM and PAVM, is represented by red triangles in the rightmost portion of the decision tree. Complementary events are indicated by a "#" symbol. In the genetic screening strategy, if the mutation is not found in family members, then they are not clinically screened. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

to determine if there is any point at which the genetic screening strategy is no longer cost saving compared to the clinical screening strategy. This is referred to as the threshold value of a given variable in the model. The ranges for sensitivity analysis are detailed in Table I for probabilities of positive clinical screening tests. For the pSens sensitivity analysis, we used the full range of probabilities from 0 to 1, due to the uncertainty of this estimate.

In order to assess the effect of family composition on the decision analysis, a number of hypothetical family compositions were substituted into the decision model. We explored a number of scenarios regarding family size and age distribution in sensitivity analyses (Table III).

RESULTS

Lifetime Costs of Clinical and Genetic Screening Strategies

The net present value of costs associated with the genetic screening strategy, as described in Figure 1, was found to be $4,060 per family member. The net present value of costs associated with the clinical screening strategy (Fig. 1), in which all family members undergo clinical screening, is $5,975 per family member. The genetic screening strategy therefore costs on average, $1,915 less than the clinical screening strategy per family member screened. The hypothetical family consists of 14 family members, thus the total cost saving per family screened is $26,810.

Results from the sensitivity analysis for the hypothetical HHT family reveal that with the exception of the variable pSens (the probability of the genetic screening test being able to detect a mutation when it exists in a family member), the genetic screening strategy is cost saving over the full range of all variables in the model when compared to the clinical screening strategy. Thus, the model is robust to changes in costs of the genetic and clinical tests, and sensitivity and specificity of all clinical tests. With respect to the sensitivity of the genetic test, the genetic screening strategy is cost saving when the value of pSens remains above 0.1. When the value of pSens falls below 0.1, the genetic screening strategy is no longer cost saving.

We then proceeded to complete a sensitivity analysis on family composition. The various family compositions include: the original model/hypothetical HHT family of 14 members (2 Senior, 4 Adults, each adult has 2 Children for a total of 8 Children in the family), a family of 10 (consisting of 2 Senior members, 4 Adult members and 1 Child/Adult), a family of 18 (2 Senior members, 4 Adults and 3 Children/Adult), a family of 11 (2 Senior members, 3 Adults and 2 Children/Adult), and a family of 17 (2 Senior members, 5 Adults and 2 Children/Adult).

Results from the sensitivity analysis suggest that the genetic screening strategy is more economical than conventional clinical screening over the full range of all variables that were assessed for every combination of family composition with, again, the exception of the sensitivity of the genetic screening test (pSens). Among the other family compositions that were tested, it was determined that the overall range of the threshold of pSens varies from 0.10 to 0.20. Table III also includes the expected difference in cost per family member for the genetic screening strategy and the clinical screening strategy and the overall difference in expected cost per family screened.

DISCUSSION

This analysis compares direct health care costs for genetic screening followed by targeted clinical screening versus clinical screening for HHT.

We found that the genetic screening strategy costs $1,915 less on average than the clinical screening strategy per person screened, with an overall savings of $26,810 per family. Sensitivity analysis for family composition revealed that the overall difference in screening costs for genetic and clinical screening strategies per family ranges between $12 140 and $41, 490 with the average difference in the genetic screening strategy per family member compared to clinical screening strategy ranging from $1,214 to $2,305 (Table III). The only variable in the model in which the sensitivity analysis reached a threshold value was pSens. At the threshold value, the genetic screening strategy is no longer cost saving compared to the clinical screening strategy. This result did not raise concern as the sensitivity of the genetic screening test utilizing our methodology is estimated to be near 70% and thus, pSens is not expected to reach its threshold value.

One limitation of our analysis is that it does not consider the costs of treating HHT-related abnormalities or complications (e.g., pulmonary AV shunts, strokes) or cost savings incurred by avoiding negative outcomes due to preventive screening. However, this simplification does not change the analytic result. The overall sensitivities of both genetic and clinical screening strategies are near 100%. Because all individuals with HHT will be detected by either strategy, the downstream consequences of testing, including prevention of respiratory, neurological, and other complications of HHT will be similar in both testing strategies. Thus, the true marginal costs in a full economic evaluation that incorporates all costs flowing from a testing decision should be very similar to our reported marginal costs.

TABLE III. Sensitivity Analysis on Family Composition

Family members that remain fixed	Family members that are varied	Total # family members	Proportion of family that are adults	Proportion of family that are children	Proportion of family that are seniors	Expected cost difference per family member	Expected cost difference per family	Threshold value for pSens*
2 seniors, 2 children/adults	3 adults	11	0.27	0.55	0.18	$1,736	$19,096	0.1
2 seniors, 2 children/adults[a]	4 adults[a]	14[a]	0.29[a]	0.57[a]	0.14[a]	$1,915	$26,810[a]	0.1[a]
2 seniors, 2 children/adults	5 adults	17	0.29	0.59	0.12	$1,604	$27,268	0.1
2 seniors, 4 adults	1 child/adult = 4 children	10	0.40	0.40	0.20	$1,214	$12,140	0.2
2 seniors, 4 adults	3 children/adult = 12 children	18	0.67	0.22	0.11	$2,305	$41,490	0.1

[a]These are the values determined for the original hypothetical HHT family.
*pSens is the only probability within the decision model, which reaches a threshold value.

A comprehensive economic evaluation would include not only the costs of health interventions, but also their clinical effects. Thus, a test that resulted in cost saving might not be economically attractive if it resulted in adverse health effects. Although our analysis did not measure the clinical effects of HHT genetic testing, we believe that the net effect of screening on the health of screenees is likely to be positive. Genetic testing makes it possible to avoid a large number of echocardiograms, CT scans, and angiograms which are not only costly, but are also associated with complications and discomfort. Including the health benefits of foregoing unnecessary treatment in a full economic evaluation would make the genetic screening strategy appear to be even more economically attractive.

Our estimate of the cost of genetic testing may be an overestimate as the current costs available for genetic testing in the two American laboratories offering HHT testing are significantly lower than our reported cost. Thus, our analysis may underestimate the cost saving associated with genetic testing.

Projected cost savings may not materialize if patterns of practice change when new tests become available. For example, costs may actually rise if genetic testing is inappropriately used to test individuals without a known familial mutation who do not meet clinical diagnostic criteria. This suggests that, while genetic testing for HHT appears to be cost saving and therefore highly economically attractive, a careful use of screening guidelines will be required to ensure that the projected health and economic benefits associated with HHT genetic testing are realized in clinical practice.

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REFERENCES

Abdalla SA, Letarte M. 2005. Hereditary haemorrhagic telangiectasia: Current views on genetics and mechanisms of disease. J Med Genet (in press).

Abdalla SA, Pece-Barbara N, Vera S, Tapia E, Paez E, Bernabeu C, Letarte M. 2000. Analysis of ALK-1 and endoglin in newborns from families with hereditary hemorrhagic telangiectasia type 2. Hum Mol Genet 9:1227–1237.

Abdalla SA, Cymerman U, Johnson RM, Deber CM, Letarte M. 2003. Disease-associated mutations in conserved residues of ALK-1 kinase domain. Eur J Hum Genet 11:279–287.

Berg JN, Gallione CJ, Stenzel TT, Johnson DW, Allen WP, Schwartz CE, Jackson CE, Porteus MEM, Marchuk DA. 1997. The activin receptor-like kinase 1 gene: Genetic structure and mutations in hereditary hemorrhagic telangiectasia type 2. Am J Hum Genet 61:60–67.

CCOHTA. 1997. Canadian coordinating office for health technology assessment guide: Canada. 2nd edn. Ottawa: Canadian Coordinating Office for Health Technology Assessment.

Cymerman U, Vera S, Pece-Barbara N, Bordeau A, White RL Jr, Dunn J, Letarte M. 2000. Identification of hereditary hemorrhagic telangiectasia type I in newborns by protein expression and mutation analysis of endoglin. Pediatr Res 47:24–35.

Cymerman U, Vera S, Karabegovic A, Abdalla S, Letarte M. 2003. Characterization of several novel endoglin mutations associated with hereditary hemorrhagic telangiectasia. Human Mutation 21:482–492.

Gallione CJ, Klaus DJ, Yeh EY, Stenzel TT, Xue Y, Anthony KB, McAllister KA, Baldwin MA, Berg JN, Lux A, Smith JD, Vary CPH, Craighen WJ, Westermann CJJ, Warner ML, Miller YE, Jackson CE, Guttmacher AE, Marchuk DA. 1998. Mutation and expression analysis of the endoglin mutation in hereditary hemorrhagic telangiectasia reveals null alleles. Hum Mutation 11:286–294.

Gallione CJ, Sheessele EA, Reinhardt D, Duits AJ, Berg JN, Westermann CJJ, Marchuk DA. 2000. Two common endoglin mutations in families with hereditary hemorrhagic telangiectasia in the Netherlands Antilles: Evidence for a founder effect. Hum Genet 107:40–44.

Gossage JR, Kanj G. 1998. Pulmonary arteriovenous malformations: A state of the art review. Am J Respir Crit Care Med 158:643–661.

Guttmacher A, Marchuk D, White RI. 1995. Hereditary hemorrhagic telangiecstasia. New Engl J Med 14:918–924.

Haitjema T, Disch F, Overtoom TTC, Westermann CJJ, Lammers JWJ. 1995. Screening family members of patients with hereditary hemorrhagic telangiecstasia. Am J Med 99:519–524.

Johnson DW, Berg JN, Gallione CJ, McAllister KA, Warner JP, Helmbold EA, Markel DS, Jackson CE, Porteous ME, Marchuk DA. 1995. A second locus for hereditary hemorrhagic telangiectasia mapped to chromosome 12. Genome Res 5:21–28.

Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, Stenzel TT, Speer M, Pericak-Vance MA, Diamond A, Guttmacher AE, Jackson CE, Attisano L, Kucherlapati R, Porteous ME, Marchuk DA. 1996. Mutations in activin receptor-like kinase 1 gene in hereditary hemorrhagic telangiectasia type 2. Nature Gen 13:189–195.

Kjeldsen AD, Brusgaard K, Poulsen L, Kruse T, Rasmussen K, Green A, Vase P. 2001. Mutations in the *ALK-1* gene and the phenotype of hereditary hemorrhagic telangiectasia in two large Danish families. Am J Hum Genet 98:298–302.

Lastella P, Sabba C, Lenato GM, Lattanzi W, Gallitelli M, Cirulli A, Guanti G. 2003. Endoglin gene mutations and polymorphisms in Italian patients with hereditary hemorrhagic telangiectasia. Clin Genet 63: 536–540.

Lin WD, Wu JY, Hsu HB, Tsai FJ, Lee CC, Tsai CH. 2001. Mutation analysis of a family with hereditary hemorrhagic telangiectasia associated with hepatic arteriovenous malformation. J Formos Med Assoc 100:817–819.

Maher CO, Peipgras DG, Brown RDJ, Friedman JA, Pollock BE. 2001. Cerebrovascular manifestations in 321 cases of hereditary hemorrhagic telangiecstasia. Stroke 32:877–882.

McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrel J, McCormick MK, Pericak-Vance MA, Heutink P, Oostra BA, Haitjema T, Westerman CJJ, Porteous ME, Guttmacher AE, Letarte M, Marchuk DA. 1994. Endoglin, a TGF-ß binding protein of endothelial cells, is the gene for hereditary hemorrhagic telangiectasia type I. Nat Genet 8:345–351.

McAllister KA, Baldwin MA, Thukkani AK, Gallione CJ, Berg JN, Porteus ME, Guttmacher AE, Marchuk DA. 1995. Six novel mutations in the endoglin gene in hereditary hemorrhagic telangiectasia type I suggest a dominant-negative effect of receptor function. Hum Mol Genet 4:1983–1985.

McDonald MT, Papenberg KA, Ghosh S, Glatfelter AA, Biesecker BB, Helmbold EA, Markel DS, Zolotor A, McKinnon WC, Vanderstoep JL, Jackson CE, Iannuzzi M, Collins FS, Boehnke M, Porteous ME, Guttmacher AE, Marchuk DA. 1994. A disease locus of hereditary hemorrhagic telangiectasia maps to chromosome 9q33-34. Nat Genet 6:197–204.

McDonald JE, Miller FJ, Hallam SE, Nelson L, Marchuk DA, Ward KJ. 2000. Clinical manifestations in a large hereditary hemorrhagic telangiectasia (HHT) type 2 kindred. Am J Med Genet 14:320–327.

Nanthakumar K, Hyland RH, Graham AT, Robinson TI, Grande P, Pugash RA, Clarke JA, Hutchison SJ, Mandzia JL, Faughnan ME. 2001. The use of agitated saline contrast echocardiography in detecting pulmonary arteriovenous malformations. Am Heart J 141:243–246.

Olivieri C, Mira E, Delu G, Pagella F, Zambelli A, Malvezzi L, Buscarini E, Danesino C. 2002. Identification of 13 new mutations in the ACVRL1 gene in a group of 52 unselected Italian patients affected by hereditary hemorrhagic telangiectasia. J Med Genet; 39:39e

Ontario Health Insurance Schedule of Benefits. 2003. Ontario, Canada. Ottawa: Ministry of Health and Long Term Care.

Paquet ME, Pece-Barbara N, Vera S, Cymerman U, Karabegovic A, Shovlin C, Letarte M. 2001. Analysis of several endoglin mutant reveals no endogenous mature or secreted protein capable of interfering with normal endoglin function. Hum Mol Genet 10:1347–1357.

Pece N, Vera S, Cymerman U, White RIJ, Wrana JL, Letarte M. 1997. Mutant endoglin in hereditary hemorrhagic telangiectasia type I is transiently expressed intracellularly and is not a dominant negative. J Clin Invest 100:2568–2579.

Plauchu H, de Chaderevian JP, Bideau A, Robert J-M. 1989. Age-related profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 32:291–297.

Shovlin CL, Hughes JM, Tuddenham EG, Temperley I, Perembelon YF, Scott J, Seidman CE, Seidman JG. 1994. A gene for hereditary hemorrhagic telangiectasia maps to chromosome 9q3. Nat Genet 6:205–209.

Shovlin CL, Hughes JMB, Scott J, Seidman CE, Seidman JG. 1997. Characterization of endoglin and identification of novel mutations in hereditary hemorrhagic telangiectasia. Am J Hum Genet 61:68–79.

Trembath RC, Thomson JR, Machado RD, Morgan NV, Atkinson C, Winship I, Simonneau G, Nazzareno G, Loyd JE, Humbert M, Morrell NW. 2001. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. N Engl J Med 345:325–334.

Vincent P, Plauchu H, Hazan J, Faure S, Weissenbach J, Godet J. 1995. A third locus for hereditary hemorrhagic telangiectasia maps to chromosome 12q. Hum Molec Genet 4:945–949.