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Cost-Effectiveness of Population-Based Genetic Hemochromatosis Screening

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Key Words

Economic evaluation · Decision tree · Hemochromatosis · Costs · Screening

Abstract

Objective: Evaluation of the costs of a population-based genetic hemochromatosis (HH) screening. ***Methods:*** We performed a decision tree analysis and subsequently quantified the screening and treatment costs and the effect on life expectancies. Assumptions were based on literature data and expert opinions. ***Results:*** Under the very conservative assumptions of a 10% penetrance, a carrier frequency of 10%, a mean age of onset of complications of 54 years, and a 90% compliance with treatment (phlebotomy), we calculated the cost to be 7.26 EUR per tested person versus 1.62 EUR per nontested person (1 EUR ≈ 1 USD). The life expectancies for a 25-year-old male are 48.99843 years (if not tested) versus 48.99970 years (if tested). Although increased life expectancy for the entire population as a result of screening is negligible, for the 1 in 4,000 men who could benefit from it, an average of 2,000 extra days will be gained. By dividing the difference of cost by the difference of life expectancy, we calculated the cost for one life year gained to be 4,441 EUR. Under less stringent conditions (higher penetrance, higher carrier frequency) the costs decrease substantially. ***Conclusion:*** Costs of population-based genetic HH screening are very acceptable compared to the costs of other health care measures. We conclude that genetic HH screening is feasible under economic aspects of health care.

Introduction

Hemochromatosis (HH; MIM 235200) is a particularly attractive candidate for a population screening program and its economic evaluation, due to its safe, effective and inexpensive treatment and its high frequency. The frequency of HH homozygosity in Caucasians is estimated at 2–5 per 1,000 [1–3] and recent studies revealed homozygosity for the Cys282Tyr mutation (G to A substitution at nucleotide 845) [4] in the HFE gene in 80–100% of Caucasian HH patients [4–9]. Early diagnosis and treatment are likely to prevent iron overload and severe complications, such as liver cirrhosis, liver cancer, cardiomyopathy and diabetes mellitus. The implementation of a genetic HH screening program is expected to be generally advantageous for the public health [10], although several issues, including the appropriate age for

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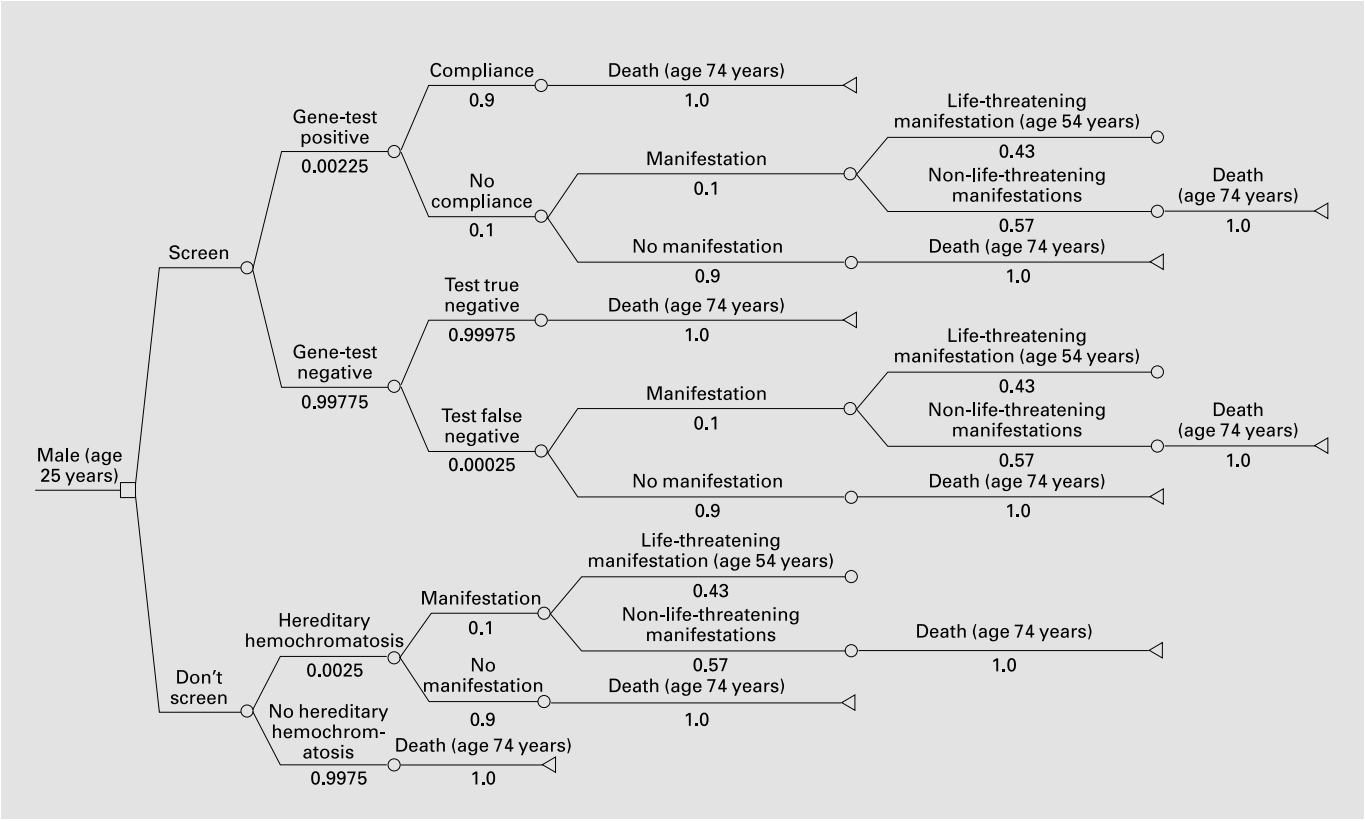

Fig. 1. Evaluation of the decision tree branches 'genetic screening and no genetic screening of a healthy 25-year-old male'. Life expectancies are given in table 1. Probabilities within the decision tree are given in table 2 . The tree was constructed with TreeAge (data).

screening, the exact prevalence and penetrance of HH as well as psychosocial and economic factors of health care have to be addressed by research and pilot studies before establishing a population-wide screening program. In addition, there is wide discussion whether the initial HH screening test should be transferrin saturation or DNA testing. Uncertainties regarding penetrance may argue in favor of transferrin saturation, while the need for repeated transferrin saturation testing argues in favor of DNA testing, which has to be done only once.

This study was initiated to answer the question whether a genetic HH screening program is an efficient health care measure. Therefore, we carried out a cost-effectiveness analysis for a genetic HH screening program by using the decision tree technique. We were able to base our considerations on some previously published studies on HH screening, especially those by Phatak et al. [11] and Adams et al. [12], who also performed decision tree analyses. HFE-gene mutation analysis was not available when these calculations were carried out, and therefore the structure of the decision trees regarding the diagnosis was much more complicated than our model. Previous results of economic analyses of HH screening were favorable [11–15], although mutation testing was not possible before the cloning of the HFE gene in 1996 [4].

In our study only the direct costs and the direct benefits are calculated. Indirect costs and benefits (e.g. induced or avoided productivity losses) are not considered.

Methods

The decision tree starts off with a cohort of men aged 25 [13]. As the extent of organ damage caused by HH varies between men and women, a general evaluation cannot be given. The effects of the HH gene mutation have an impact on men 4–5 times more often than on women [16]. Consequently, the model is restricted to males only. Both the branches 'genetic testing' (screen) or 'no genetic testing' (don't screen) are evaluated (fig. 1), based on the assumptions given in tables 1 and 2.

The evaluation is based on the very conservative estimate of a homozygote frequency of 1:400. First, the alternative 'don't screen' is

Table 1. Life expectancy of 25-year-old males with organ damage due to HH, with organ damage appearing at the age of 54 years

Organ damage	Life expectancy at the age of 54
Normal life expectancy	20
Cirrhosis with hepatocellular carcinoma (liver transplantation)	2
Cirrhosis with hepatocellular carcinoma (conservative treatment)	1
Cirrhosis without hepatocellular carcinoma (liver transplantation)	0 resp. 8[1]
Cirrhosis without hepatocellular carcinoma (conservative treatment)	4
Diabetes (all types)	10
Cardiomyopathy (improved by treatment)	14
Cardiomyopathy (not improved by treatment)	1

[1] Patients may die during or shortly after liver transplantation (0). Patients who survive transplantation have a life expectancy of 8 years.

presented. In the USA as well as in Germany, the average life expectancy is 74 years of age for a 25-year-old male [17, 18]. Organ damage usually manifests at an average age of 54 years in HH patients [12]. In our model, HH is diagnosed and treatment is initiated at this age in the 'don't screen' group.

As mentioned above, the penetrance of HH is the least known variable in the whole decision tree [16]. In the basic structure it is calculated that the disease phenotype manifests in only 10% of the homozygotes, which may exhibit life-threatening or non-life-threatening manifestations.

In case of screening, the tree divides into the two branches, 'gene test positive' and 'gene test negative', the latter containing true- as well as false-negative results. Approximately 90% of HH patients are homozygous for Cys282Tyr. With a prevalence of 1:400, there are 250 HH homozygotes among 100,000 people, of whom 225 are identified by the test. The probability that the test is positive is thus 0.00225 and 0.99775 that it is negative. The probability for the 25 false-negative results is then 0.00025 (rounded up) and in 0.99975 of the negative tests this result will be correct. If the test is false-negative, however, manifestations can either occur or not.

If the genetic screening test has turned out positive, it is almost certain that the result is correct, since false-positive results are very unlikely to occur. The compliance of those persons who were tested

Table 2. Probabilities within the decision tree

Conditions	Probability	References
HH	0.0025	experts
Gene test positive	0.00225	experts
Gene test true negative	0.99975	experts
Compliance (if gene test positive)	0.9	experts
Manifestation of organ damage due to HH	0.1	experts
Life-threatening manifestations	0.43	12
Cirrhosis	0.303	12
Diabetes	0.182	12
Cardiomyopathy	0.045	12
Cirrhosis and diabetes	0.273	12
Cirrhosis and cardiomyopathy	0.045	12
Diabetes and cardiomyopathy	0.045	12
Cirrhosis, diabetes and cardiomyopathy	0.107	12
Hepatocellular carcinoma	0.25	12
Liver transplantation with hepatocellular carcinoma	0.01	experts
Liver transplantation without hepatocellular carcinoma	0.3	experts
Insulin-dependent diabetes	0.6	11
Insulin-dependent diabetes improved by phlebotomy	0.45	11
Non-insulin-dependent diabetes improved by phlebotomy	0.5	11
Cardiomyopathy improved by phlebotomy	0.8	experts
Death after liver transplantation without hepatocellular carcinoma (age 54)	0.1	experts
Death after liver transplantation without hepatocellular carcinoma (age 62)	0.9	experts

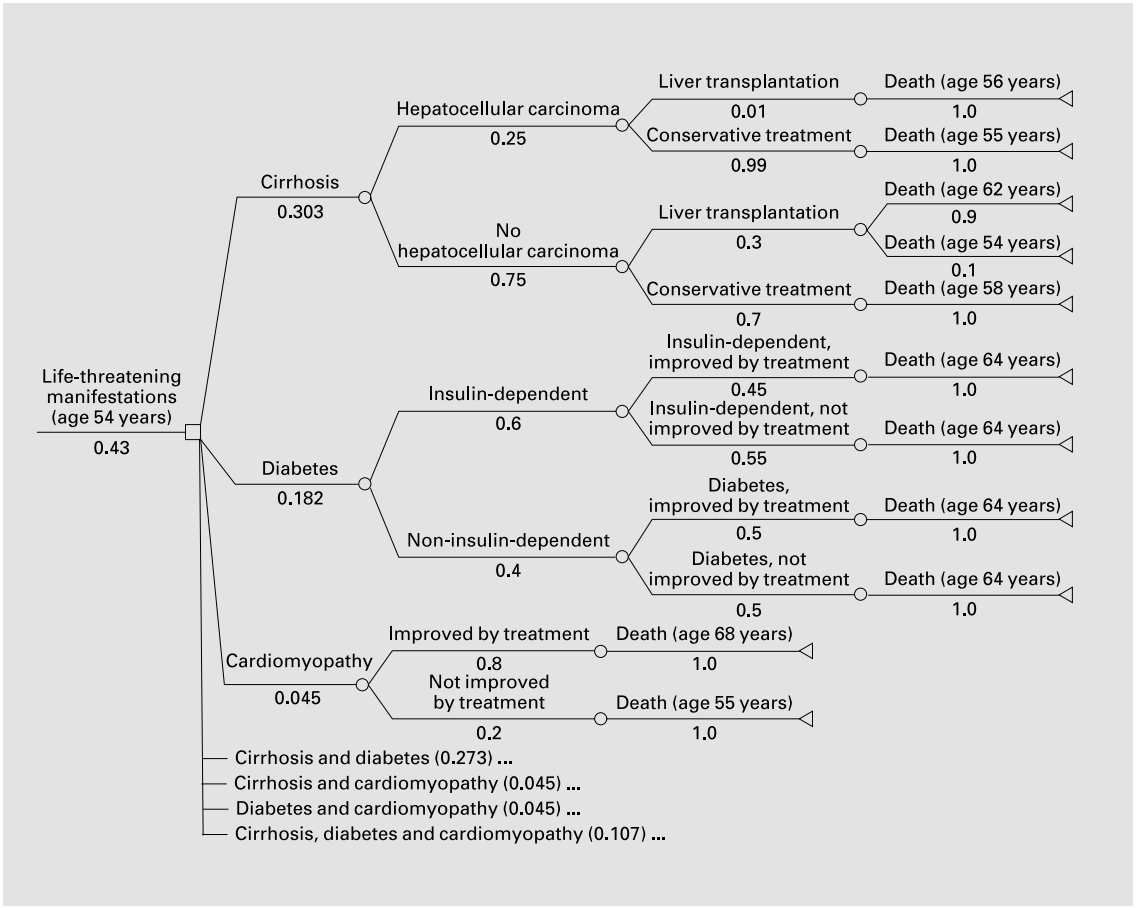

Fig. 2. Evaluation of the decision tree branches 'life-threatening manifestations'. The evaluation was carried out separately for the manifestations cirrhosis, diabetes and cardiomyopathy, as well as for the different combinations of these three symptoms (bottom; detailed data not shown). More detailed information on the branches of the combined symptoms are available from the authors on request. Life expectancies are given in table 1. Probabilities within the decision tree are given in table 2. The tree was constructed with TreeAge (data).

positive was assumed to be 90%. Positive individuals who have blood taken regularly over many years will probably be spared from organic manifestations and are expected to have a normal life expectancy [19]. In noncompliant homozygotes, the HH phenotype can either manifest or not, and the manifestation can again be either life-threatening or non-life-threatening.

The life-threatening manifestations complicate the decision tree considerably. Three different organ manifestations are observed (liver cirrhosis, diabetes, cardiomyopathy), which can also occur in combination [19, 20]. This results in a sevenfold division of the branch 'life-threatening manifestations' (fig. 2). The probability for the occurrence of the individual organ manifestations and the corresponding life expectancies were taken from Phatak et al. [11] and Adams et al. [12]. In the case of cirrhosis, the model differentiates whether a liver carcinoma is present or not and whether or not the patient receives a liver transplantation. Diabetes may be insulin-dependent or not. Furthermore, it was taken into consideration that, due to the phlebotomy treatment, the condition can either improve or not. This has particular consequences for the cost of treatment because drugs can be reduced if necessary (assumption: reduction of costs by 40%) [11]. Also in cardiomyopathy the condition can improve with therapy, or not, leading to a different life expectancy.

When combined organ manifestations occurred, it was assumed that the treatment costs would be added together and that the shorter of the two life expectancies would be achieved. Therefore, regarding the life expectancy, no cumulative effect was assumed. In addition, several other assumptions had to be made so that the decision tree structure corresponds to the clinical reality (e.g. it was assumed that when liver manifestations occur simultaneously with cardiomyopathy the alternative of liver transplantation does not exist). Altogether, the decision tree consists of 159 individual branches.

The age of death is different in each individual branch of the tree. The cost of the test accrues at the beginning of the screening. In the case of a positive-testing person, counseling is provided and phlebotomy is commenced in the same year and is continued for the rest of the life. In the basic evaluation, costs of 50 EUR per year are assumed

Table 3. Costs of diagnosis and treatment

Treatment	Costs, EUR (1 EUR ≈ 1 USD)
Genetic testing (once)	5.00
Treatment of testing positive (year 0, once)	50.00
Phlebotomy (year 1 to death, once per year)	50.00
Treatment of non-life-threatening manifestations (per year)	500.00
Treatment of insulin-dependent diabetes (no amelioration, per year)	2,500.00
Treatment of insulin-dependent diabetes (amelioration, per year)	2,000.00
Treatment of non-insulin-dependent diabetes (no amelioration, per year)	500.00
Treatment of non-insulin-dependent diabetes (amelioration, per year)	400.00
Conservative treatment of cirrhosis without carcinoma (per year)	7,500.00
Conservative treatment of cirrhosis with carcinoma (per year)	20,000.00
Liver transplantation (once)	125,000.00
Treatment after liver transplantation (per year)	7,500.00
Treatment of cardiomyopathy (per year)	1,500.00
Treatment of heart failure (once, last year)	35,000.00

which should cover the costs of blood extraction four times a year, and the serum ferritin control once a year. In the case of noncompliant persons, these costs do not occur. From the 54th year treatment costs occur with persons who are affected by organ damage due to HH. By discounting each individual payment and by weighting each branch with its probability, the average present costs of both alternatives 'screen' and 'don't screen' are determined by a recursive calculation. The costs of diagnosis and treatment are summarized in table 3. Additionally, the average life expectancy for both alternatives can be calculated by establishing the sum of life years for each branch of the tree and weighting it up with the respective probability onset. The cost per additional life year is calculated by dividing the extra costs of the screening measure by the life years gained.

Computer Programs

The decision tree presented above was constructed using the program TreeAge data, version 3.0 (TreeAge software Inc., Williamstown, Mass., USA). In order to quantify the treatment costs and the effects on the life expectancy, an Excel calculation version 5.0a (Microsoft Corp., Redmond, Wash., USA) was conducted in parallel to the former.

Results

According to the basic assumptions presented above, discounted present costs of 7.26 EUR arise for the alternative 'screen' per person tested. This value comprises the costs of the test, the treatment of each person testing positive (as far as he is compliant), the disease costs due to HH of persons with false-negative results and also the costs for noncompliant persons.

In the alternative 'don't screen' average HH-induced disease costs of 1.62 EUR per untested person arise. This figure comprises the cost of treatment for organ damage from the age of 54 years onwards. This results in a cost difference between the two alternatives of 5.64 EUR, which must be borne for each person who takes part in the screening program. It is the discounted value which results according to the decision tree and all its assumptions and not the pure cost of screening (which is 5 EUR per person).

Due to the screening measure, apart from the costs, positive effects on the life expectancy of the tested population arise. The remaining life expectancy in the untested population of 25-year-old males is, on average, 48.99843 years. This value increases to an average of 48.99970 years after carrying out the screening measure. A positive difference in the remaining life expectancy of 0.00127 years (0.46 days) per tested person is derived.

The costs and the benefits of a HH screening can thus be compared. By dividing the difference of the costs of both branches (screen or don't screen) by the difference of life years we calculated the costs per life year gained to be 4,441 EUR.

In addition, we evaluated the number of tests which are necessary to avoid one case of symptomatic HH. According to the very restrictive basic assumptions of the model, about 444.4 tests are necessary to identify a Cys282Tyr homozygote male. With the assumed penetrance and noncompliance of 10%, 4,444 tests are necessary to identify a (future) HH phenotype and 4,938 tests to successfully prevent manifestations. If only life-threatening manifestations are considered, 11,484 tests are necessary. The number of tests becomes considerably lower if the very restrictive assumptions are modified. A preva-

Table 4. Sensitivity analyses

Variable (basic assumption)	Variation of cost (compared to basic assumption), EUR	Costs per year of life gained (variation of baseline result)[1], EUR
Costs of genetic testing (5.00 EUR)	4.50 (–10)	4,047 (–8.9)
	10.00 (+100)	8,377 (+88.6)
Costs of treatment of individuals testing positive (year 0) (50.00 EUR)	45.00 (–10)	4,431 (–0.2)
	100.00 (+100)	4,529 (+2.0)
Costs of phlebotomy (year 1 to death) (50.00 EUR)	45.00 (–10)	4,296 (–3.3)
	100.00 (+100)	5,889 (+32.6)
Costs of non-life-threatening manifestations (500.00 EUR)	450.00 (–10)	4,456 (+0.3)
	550.00 (+10)	4,426 (–0.3)
Costs of all life-threatening manifestations (see table 3)	(–10)	4,529 (+2.0)
	(+10)	4,352 (–2.0)
Homozygosity rate for hemochromatosis (1/400)	1/200 (+100)	2,472 (–44.3)
	1/500 (–20)	5,425 (+22.2)
Penetrance (0.1)	0.05 (–50)	9,914 (+123)
	0.2 (+100)	1,704 (–61.6)
	0.6 (+500)	–120 (–102.7)
Compliance (0.9)	0.5 (–44.4)	7,664 (+72.6)
	0.95 (+5.6)	4,229 (–4.8)
Discount rate costs (0.05)	0.03 (–40)	4,159 (–6.3)
	0.06 (+20)	4,511 (+1.6)
Discount rate benefits (life years) (0.00)	0.03	15,094 (+240)
	0.05	33,078 (+645)

Figures in parentheses are percentages.
[1] Baseline result refers to the costs for one year life gained (4,440 EUR)

lence of 1/200 and a penetrance of 50% result in 5,742 tests for a prevented life-shortening HH manifestation.

Many of the data used in the model cannot be definitively verified, making it necessary to vary them and to show their influence on the complete result. Normally, this is calculated with the ceteris paribus assumption, i.e. one variable is varied and all remaining variables are constant. Particularly, when a model consists of many assumptions a single variable has frequently very little influence. So, for example, when cost for a liver transplantation is rated at 137,500 EUR instead of 125,000 EUR (+10%), the complete result of the model is reduced by 0.6%. It makes hardly any difference whether the individual costs have been incorrectly estimated (at least concerning the quantity order of the result). This is why it is sometimes necessary to draw up certain scenarios in which more than one variable is simultaneously changed. Both procedures are applied in the following sensitivity analyses (table 4).

One can recognize that the gene test has a particularly prominent influence on the complete result of 4,441 EUR. The cost of the gene test in the basic evaluation is rated at 5.00 EUR. The complete result is reduced by 8.9%, if the test can be carried out 10% cheaper. If the price of the gene test doubles, the relation between costs and life years is 88.6% more unfavorable. Individual testing for mutation Cys282Tyr costs between 100 and 200 EUR, to date. This cost will considerably decrease soon. For example, one German company (Origen Biotechnology, Berlin) is already selling a Cys282Tyr detection kit for approximately 10 EUR per test, which is amenable to automation. In a recent study, Yuan et al. [21] calculated the costs of detecting a mutation in the FBN1 gene (the fibrillin 1 gene, mutated in Marfan syndrome) and reported the costs of one PCR reaction including reagents and labor to be 3.35 USD in a routine diagnostic setting. However, these costs can be reduced in mass screening programs, where working time per sample is much less (thereby substantially reducing labor costs). There is no

need for (relatively expensive) DNA extraction from blood, since the polymerase chain reaction can be performed directly from buccal cells obtained by a simple mouthwash procedure. This cheap procedure is very specific as well as sensitive, as exemplified by the determination of the mutation ΔF508 of the cystic fibrosis gene in over 11,000 mouthwashes [22]. Large-scale buccal testing for HH has also been reported [23]. In addition, costs for supervision, collection and administration will amount to only 2–3 EUR in mass screening programs, as known from newborn screening programs. For example, the total cost (including overhead costs) for tandem screening of several disorders (incl. phenylketonuria, PKU) in newborns is approximately 5 EUR [E. Mönch, Berlin, pers. commun.] and it is highly predictable that the cost of DNA-based HH testing will be similar in a mass screening setting.

False estimations of the costs of treatment of life-threatening and non-life-threatening manifestations of HHs, however, have little influence on the overall result. A 10% reduction of the treatment costs in non-life-threatening manifestations leads to an alternative result which is 0.3% higher than the basic calculation. The cost of the treatment of life-threatening organ damage was only varied as a whole since the influence of an individual variable is minimal. If all costs are set 10% lower, the result increases by 2.0%, i.e. a value of 4,529 EUR. The treatment costs which were assumed in the basic evaluation must doubtless be seen as very indefinite as they are only based on experts' estimates and are not differentiated according to severity and duration of the illness. In addition, they may also vary between different countries. However, guided by the sensitivity analysis, it can be shown that with these variables even extremely false estimates have hardly any influence on the result.

Errors in the assumptions concerning prevalence, penetrance and compliance influence the total result substantially. By halving the prevalence, the result increases by 44.3%, i.e. a screening program is considerably less attractive. If a penetrance figure of 0.2 instead of 0.1 is assumed, the costs per life year gained are reduced by 61.2% to 1,704 EUR. With a penetrance of only 0.05 (i.e. –50% compared to the basic assumption), the result worsens by 123.0%. In the economic studies on HH which have already been published, values from 0.4 or even 0.5 were calculated [13]. This would then bring this study towards a range where no more costs arise, but rather a profit is made per test performed, which would be the case in the model with a penetrance of about 0.6. However, it has to be taken into account that the proportion of life-threatening manifestations (with cost-intensive treatments) will most likely be lower in case of a higher penetrance. With a reduction of the compliance from 0.9 to 0.5, the costs of the screening program increases by 72.6%. A minor compliance rate may not only be due to noncompliant patients, but also to providers who may not place a high priority on the indicated phlebotomy for asymptomatic homozygotes.

In the guidelines on the performance of economic evaluations of health issues, a discounting of all costs and monetary benefits is generally required and an applied rate of 0.05 is stipulated [24]. The higher the discounting, the worse the result produced because expensive treatments at the end of the decision tree have less significance. With a discounting of 6%, the total result of 4,441 EUR increases by 1.6%. The influences on the result keep in bounds with any fluctuation of the discounting factor around the chosen figures of the basic valuation. In contrast, the consideration of discounting the life years gained (intangible effects) is problematic. It was suggested that discounting nonmonetary measures is not required although it should be conveyed in an additional account [25]. In contrast to the recommendations in most European countries, discounting of costs as well as (monetary and nonmonetary) benefits is suggested in US guidelines [26]. Discounting life years would have extremely negative effects on the result. With a discounting rate of 0.03 a result of just over 15,000 EUR per life year gained would arise, i.e. more than three times the result of the basic valuation. A discount rate of 5% would lead to 33,000 EUR.

Discussion

Health care systems are often dominated by 'instinctive' or 'intuitive' decisions when trying to solve the problem of spreading limited resources across individual measures in the health service. Economic evaluations can be employed here to make the health service more efficient [27]. Our study aimed to evaluate whether genetic hemochromatosis screening represents an efficient health care measure.

Hemochromatosis screening will lead to a 0.46 days increase in the remaining life expectancy per tested 25-year-old male. This result is at first glance not impressively high. However, this figure presents the average gain of *each tested person,* although only 1 in 400 will be Cys282Tyr homozygous and according to assumptions organ damage manifests in every 10th homozygote only.

Only about 1 in 4,000 men profits from the test (if he is compliant), but then he receives about 2,000 extra days of life expectancy, on average.

The value of 4,441 EUR per life year gained gives little indication as to whether or not the cost of HH screening is in an acceptable range. However, if one compares the result with the results of other cost-effectiveness studies (e.g. annual breast cancer screening, costs between EUR 9,400 and 12,650 in Germany [28] or USD 10,000 and 190,000, world-wide; hypertension screening; costs between USD 5,000 and 87,000) [reviewed in ref. 29], which equally show the cost per life year gained, one can recognize that this result actually lies in a good range and therefore, from an economic point of view, the screening program should be applied in public health [29]. This is particularly valid when one points out that very restrictive assumptions are put forward in the model (e.g. regarding penetrance) and the result improves considerably with somewhat more favorable assumptions. Cost-effectiveness studies very often use the 'cost per life year gained' value as an endpoint which enables the comparison of different studies. Of course, for gaining public acceptance of HH screening, the potential health benefits are more important than the economic evaluations. Whether such screening is undertaken by state or federal health agencies in the frame of the national health insurance or by private companies, economic aspects will also contribute to the decision whether or not such screening should be implemented.

Several aspects of HH screening have not been addressed by our study, but will be discussed in the following:

(1) We did not consider the costs of advertisement of the screening program. Such costs may greatly differ from country to country, and the best way (and its costs) for reaching 25-year-old males (information on TV or in newspapers; through sickness funds; through companies or during military drafting) has to be defined within further research.

(2) Costs of pretest counseling were not assessed because it is totally unknown how this counseling would be performed within a population screening setting. Such a pretest counseling will presumably differ considerably in extent from genetic counseling usually performed because of either family planning before or during pregnancy, or presymptomatic testing because of a specific familial risk situation. Although pretest counseling should in principle be available for any person undergoing genetic HH testing, this counseling may be similar to the less intensive one usually given in newborn-screening programs. However, further research is mandatory to prove this notion. Posttest counseling costs are included in the treatment costs of year 0 after screening. Again, this counseling differs from usual genetic counseling, since it is focussed on clinical rather than on family aspects.

(3) Quality of life effects were not evaluated for several reasons. Due to the numerous possible organ manifestations, an empirical study on the ascertainment of quality of life effects can hardly be financed. Apart from that, only consistent average quality of life values for each condition can be integrated in the model, i.e. a differentiation of quality of life effects over time is not possible (corresponding values cannot be completely obtained from the literature). Furthermore, it is unknown how the quality of life is affected when several organ manifestations come together, i.e. if there is a cumulative effect. If one takes a quality of life value of 1 for all the years without manifestations from HH and gives the affected years any value smaller than 1, it can be established that the costs per quality-adjusted life-year are less than the costs per life year, since here, the affected years are seen as equal to the unaffected years and the screening turns affected years into unaffected years.

(4) The indirect costs or benefits which arise within the decision tree were not considered, for example the productivity loss, which arises through premature death or the incapability to work. Technically, it would be relatively arduous but unproblematic to integrate these effects into the model. However, this was dispensed with for the following reasons. With a time horizon of 30–40 years, the quantification of productivity loss is subject to considerable uncertainties. With a high rate of unemployment, a consideration of the total unproductive time is no longer seen as acceptable in economic evaluation studies [30]. On the other hand, the indirect benefit of using the blood removed for transfusion was not included in the calculations, since this issue is a moot point. While the American Medical Association does not recommend the unrestricted unlabeled use of therapeutically drawn blood for direct transfusion [31], it is possible to use blood drawn from otherwise healthy HH homozygotes for transfusion in other countries like Canada or Germany.

(5) In the basic model it was assumed that a population screening was limited to men only. Using the same assumptions for females, the results of a HH screening program would be approximately EUR 21,000 for one life year gained. For a detailed economic evaluation of a screening program for a female population the decision tree would have to be extensively adjusted specifically to suit women (e.g. longer life expectancy, later manifesta-

tions of organ damage, different proportion of life-threatening and non-life-threatening manifestations). If a gender-unspecific screening program is initiated, the costs per life year have to be weighted according to the gender proportion of those screened.

(6) Consideration of the screening of family members.

HH is normally diagnosed at the age of 54 when the organ damage becomes evident. It is possible to make the patient an 'index case' and then from there to test his relatives for HH ('cascade screening'). This is particularly important for male children who will reach an age where damage to the organs can be totally avoided with regular venesection. By calculating the effects it is possible to fall back on many of the assumptions of the decision tree, as a similar entry age (25 years) is likely for such a child. Only the prevalence of the disorder in this case is presented in a different way to that of the normal population.

Cascade screening has been performed in cystic fibrosis, where it was 10 times more efficient in detecting carrier couples than unfocused screening [32]. However, in a model calculation, it was assumed that less than 25% of all carrier couples could be detected in a given population by cascading to the second-cousin level [33]. Although the situation is different in HH (detection of homozygotes versus heterozygous carrier couples, different disease prevalences), it seems appropriate to assume that far more HH homozygotes are detectable by population screening than by cascade screening. We anticipate that at the beginning of the population screening program, many of the detected homozygotes will inform their relatives and a backward cascade screening with somewhat different costs (and benefits) will take place in these families. Our overall calculations reflect the situation after this initial stage with a combined population/cascade screening.

Even if fewer ethical problems can be anticipated when screening for HH compared to other hereditary diseases, the possible occurrence of problems cannot be totally disregarded. For example, problems with insurance companies and employers may arise. Anxiety could be generated in those men identified as homozygotes, although with only a 1 in 10 chance of developing disease, many men will unnecessarily undergo phlebotomy, which, by itself, may be less deleterious than organ damage, which could have been prevented by screening and compliant treatment. Alternatively to starting phlebotomy immediately after mutation screening, periodic transferrin saturation or serum ferritin measures may be performed in men identified as Cys282Y homozygotes and phlebotomy would only be initiated when evidence of increased iron stores appears. In this case, the costs of HH screening would even be more favorable.

Since most homozygotes will be asymptomatic at 25 years of age, compliance may be less than 90%. Ethical problems as well as other issues, like the appropriate age for screening, the compliance rate, the question when to start phlebotomy and the prevalence and penetrance of HH should be assessed in research and pilot studies. Such studies will also help refine the assumptions made in our economic analysis of health care. Finally, research and pilot studies will also be necessary to answer the question how to handle heterozygosity. The biochemical phenotype of heterozygotes slightly differs from that of normal subjects, but organ damage due to iron overload is extremely rare [34]. Under the concept of an autosomal-recessive disease, heterozygotes will not be at risk of HH, but have a higher risk of HH in their offspring. However, some Cys282Tyr heterozygotes may in fact be compound heterozygotes for Cys282Tyr and a second mutation in the HFE gene (e. g. His63Asp) [4]. In case of compound heterozygosity for Cys282Tyr and His63Asp, the risk of developing HH is much lower than for Cys282Tyr homozygotes, but higher than for heterozygotes. Taking into account the presumably very low penetrance in compound heterozygotes, it is not known whether – or how much – one should pay attention to compound heterozygotes. The aim of HH screening lies in the detection of individuals with a high risk of developing symptomatic HH, which does not apply for compound heterozygotes and heterozygotes. Pending the outcome of further studies, we assume that delivery of test results to Cys282Tyr heterozygotes will not be necessary in an HH population screening program.

In summary, we conclude that a genetic screening program for HH produces convincing economic results. Therefore, one major requirement for the introduction of a screening program is met.

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