

Genotype-based Screening for Hereditary Hemochromatosis: II. Attitudes Toward Genetic Testing and Psychosocial Impact—A Report from a German Pilot Study

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ABSTRACT

In collaboration with the German Sickness Fund (Kaufmännische Krankenkasse-KKH), we conducted a pilot study on DNA-based population screening of hereditary hemochromatosis (HH) in Germany. The health insurance organization KKH briefly informed their members about the possibility to participate voluntarily in this pilot project. A total of 5882 KKH members contacted us and received detailed information on the aim of the project and clinical and genetic aspects of HH. Of these individuals, 3961 requested HFE genotyping. After genotype results had been communicated to the participants' general practitioner, we sent a self-administered questionnaire to all homozygous ($n = 67$) and heterozygous ($n = 485$) as well as 448 wild-type study participants ($\Sigma = 1000$) to assess the psychosocial impact of HFE genotyping. In addition, questionnaires were sent to 8000 randomly selected members of the KKH to investigate their attitude toward genetic testing. Six hundred thirty-one (63.1%) of the test participants and 2141 (26.8%) of the randomly chosen KKH members responded. A total of 59.1% of the members would generally accept predictive genetic testing and 3.7% objected to such tests in principle. Individuals with higher educational status accepted predictive testing significantly more often than individuals with less education. Of the tested individuals, 69.9% thought that participation in the pilot study was probably beneficial for them and 1% (5 heterozygotes and 1 wild-type) thought that it was probably harmful. Of the participants, 94.6% judged their decision to have participated in the pilot study as right and 0.3% (2 heterozygotes) as probably wrong. Only very few of the tested individuals underwent pretest (1 case) or posttest (11 cases) genetic counseling. We conclude that genotype-based screening for HH is generally accepted and was perceived as beneficial. Negative psychosocial consequences are rare and could presumably have been prevented by delivering appropriate pretest and posttest information.

INTRODUCTION

HEREDITARY HEMOCHROMATOSIS (HH [MIM 235200]) is an autosomal recessive disorder, characterized by increased iron absorption and iron overload affecting liver, heart, pancreas, joints, and other organs. Early diagnosis is desirable, because iron removal by serial phlebotomy is highly effective, safe, and inexpensive, leading to a normal life expectancy when started before the development of complications such as cirrhosis or diabetes (Niederau *et al.*, 1996; McDonnell *et al.*, 1999).

In Germany (Graf and Stuhmann, 2000), 90% of HH patients are homozygous for a G to A transition at nucleotide 845 of the HFE gene, resulting in a cysteine to tyrosine substitution at amino acid 282 (C282Y) (Feder *et al.*, 1996).

The frequency of HH homozygosity in Caucasians is estimated to be 2–5 per 1000 (Simon *et al.*, 1977; Edwards *et al.*, 1988; Leggett *et al.*, 1990). Because of this high frequency, the availability of simple test methods and effective prevention and treatment, HH is a candidate for the implementation of a DNA-based population screening. Because of uncertainties regarding prevalence and penetrance of HFE mutations, and the optimal

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care of asymptomatic people carrying *HFE* mutations, it has been proposed to conduct population-based research to study the genotype–phenotype correlation in HH and to investigate the ethical, social, and psychological effects of DNA-based testing (Burke *et al.*, 1998).

Between January 2001 and August 2002, we conducted a pilot study in collaboration with the German sickness fund Kaufmännische Krankenkasse (KKH), to investigate the validity and costs of different genetic test methods, as well as clinical relevance, acceptance, uptake rates of consultations, counseling and testing, and the potential ethical and psychosocial impact of DNA-based HH screening in Germany.

The first part of our pilot study has recently been published (Stuhrmann *et al.*, 2005). Here, we focus on the attitudes regarding genetic testing and the psychosocial impact of *HFE* genotyping. Our aim was to compare the self-reported psychosocial consequences of genetic testing among those individuals who turned out to be homozygous, heterozygous, or who did not carry C282Y (wild-type genotype). We assessed the uptake rates of pretest and posttest medical consultations and genetic counseling of the study participants, as well as their knowledge of clinical and genetic aspects of HH. In addition, we explored the attitudes regarding genetic testing among members of the KKH by drawing a random sample to assess whether attitudes toward genetic testing are influenced by sociodemographic variables.

MATERIALS AND METHODS

Study design and participants

The overall study design has already been described in detail (Stuhrmann *et al.*, 2005). In brief, the study was performed in collaboration with the KKH, which is a nationwide sickness fund for 1.4 million adult individuals (63% female, 37% male). With the exception of gender, KKH membership does not differ from the German population at large. Sickness funds are insurance organizations, which establish and collect the health care contributions of employers and employees. The overall scheme of sickness funds provides full coverage for all medically necessary services, including ambulatory and inpatient care, prescribed drugs, medical appliances, dental care, and the early detection of and screening for diseases (Nippert *et al.*, 1997). In Germany, approximately 89% of the population are covered by compulsory health insurance, the Gesetzliche Krankenversicherung (GKV), a system run by sickness funds under strict state oversight, and about 9% by private health insurance (Nippert *et al.*, 1997).

Brief information on the pilot project was given to all KKH members via the magazine *KKH Journal* in all four issues in the year 2001, as well as by displaying flyers in KKH regional offices. This initial information focused on the offer to participate free of charge in a pilot study on the early detection of an iron overload disorder by genetic testing. A very short description of the clinical aspects of HH, the possible treatment, and the genetic test was given. Those adult members of the KKH who wanted to receive more information on the project were invited to contact the Institute of Human Genetics at Hannover Medical School (MHH). Between January 2001 and Au-

gust 2002, 5882 KKH insureds contacted the Institute of Human Genetics of the MHH and requested more information on the pilot project and test material. A detailed information leaflet about the aim of the pilot study and the clinical and genetic aspects of HH was sent to these individuals, including the information that it is unknown how many of the homozygotes will develop disease if left untreated. Additionally, a consent form, a filter paper, the invitation to attend the monthly information meetings at the MHH and to receive pretest counselling (personal or by telephone), and the invitation to discuss this issue with their respective general practitioner (GP) at the next regular visit were sent together with the information leaflet. A total of 3961 individuals (67.3% of those who had established contact) gave their written informed consent, and capillary blood was taken by the GP, spotted on the filter, and sent to the MHH. Genetic testing was performed between January 2001 and August 2002. After completion of each test, the result was immediately sent to the GP, together with the offer of genetic counselling in all cases of homozygosity or heterozygosity. Neither the names of the participants nor individual results were given to the KKH.

The study was approved by the Institutional Review Board (IRB) of the MHH and by the Bundesversicherungsamt (BVA), the independent federal commission overseeing the nationwide German health insurance system. An external independent advisory board, consisting of Prof. Bayertz (Ethics, University of Münster), Prof. Stremmel (Internal Medicine, University Hospital Heidelberg), and Prof. Vogel (Human Genetics, University of Ulm) supervised the project.

Information obtained from tested individuals: the MHH survey

In January 2003, a structured questionnaire (MHH survey) was sent to all individuals for whom a homozygous (67) or a heterozygous (485) result was obtained, as well as to 448 study participants with wild-type genotype ($\Sigma = 1000$). Our questionnaire was adopted in part from a questionnaire that was previously administered to the participants of the Australian Haem-Creen program (Nisselle *et al.*, 2004) and contained 20 questions regarding previous knowledge of or experience with HH, the sources of pretest and posttest information, the time frame between test result disclosure and completing the questionnaire, the anxiety levels experienced immediately after test result disclosure and at the time of completing the questionnaire, clinical and/or laboratory investigations after the genetic test, the self-perceived benefit gained or adverse effects caused by participating in the pilot study, the current knowledge of clinical and genetic aspects of HH, and sociodemographic parameters. Questionnaires, together with a prepaid return envelope, were sent by the Institute of Human Genetics at the MHH to all 1000 individuals by regular mail. Because the questionnaires could be filled out anonymously (by choice), they were color-coded depending on genotype, in order to be able to correlate genotypes with answers.

Information on the attitude of KKH members toward genetic testing: the KKH survey

To assess the attitude of the KKH members toward predictive testing, a self-administered questionnaire (KKH survey)

was initially pretested by personnel of the KKH main office and the institute of human genetics of the MHH, and then sent by the KKH to a randomly drawn sample of 8000 members in September 2002. The concept of predictive testing was explained in the context of hemochromatosis and questions were asked about the acceptance of such genetic testing and the circumstances and prerequisites under which such tests should be offered. In addition, data were obtained on personal and/or familial experience with HH and on sociodemographic parameters to assess whether or not any of these variables are influencing attitudes toward predictive testing. In order to evaluate the proportion of KKH members who knew about the pilot project and how many would report participating in the project, a specific set of questions was included. The questionnaires were sent by regular mail together with a prepaid return envelope. The survey was anonymous.

Statistical methods

Statistical evaluations (odds ratio, confidence intervals, Fisher's exact test, Wilcoxon signed rank test) were performed using the SPSS package version 12.0 (SPSS Inc., Chicago, IL).

RESULTS

General results

A total of 3961 individuals provided blood samples for testing of the *HFE* mutation C282Y. Of these, 3930 samples were successfully tested with two independent tests. In all, 67 of the tested individuals were homozygous for C282Y, 485 individuals were heterozygous and 3378 of the tested persons did not carry the C282Y mutation. A total of 42.6% of the homozygotes already knew their clinical diagnosis HH before sending the blood sample. Iron accumulation with further signs or symptoms of HH was present in eight of 34 newly diagnosed C282Y homozygous individuals.

Survey of individuals who underwent testing (MHH survey)

Sources of information. A total of 88.6% of the test participants (79.6% of homozygotes, 87.5% of heterozygotes and 91.8% of individuals with wild-type, $p < 0.05$) received initial information about the pilot project on genetic testing for HH through the KKH journal. The second most important source was mass media (6.2%), which was mentioned by 13.0% of homozygotes, 7.3% of heterozygotes, and 3.7% of individuals with wild-type ($p < 0.05$). The other sources were stated in a few cases only.

Of the tested individuals, 32.9% mentioned that they received additional information about HH after initially learning about the pilot study and, before sending the test strips, through the MHH information leaflet (12.8% of homozygotes, 30.7% of heterozygotes, and 39.6% of the wild-type individuals, $p < 0.001$). The GP was given as a source of additional information in 25.6% of cases (40.4%, 24.5%, and 23.8%, respectively, $p = 0.05$), a specialist (mainly of internal medicine) in 5.7% (25.5%, 5.8%, 1.7%, $p < 0.001$), a telephone inquiry with the

MHH Institute of Human Genetics in 10.2% (10.6%, 13.7%, and 5.9%, respectively, $p < 0.05$), and an Internet investigation in 8.4% of cases (not significantly different between the three genotypes). Educational sessions at the MHH were stated as the source of information by five individuals and genetic counseling by one individual only.

Explanation of the test result was mainly by the family doctor (56.9%, no significant differences between the three genotypes). Homozygotes were significantly more often (26.4%) informed via other specialists (mainly for internal medicine) than heterozygotes (10.4%) or wild-type individuals (4.4%; $p < 0.001$). Both homozygotes and heterozygotes underwent counseling by phone with the MHH significantly more often than individuals without C282Y (17.0%, 17.7%, versus 0.8%; $p < 0.001$). A consultation with a genetic counsellor to explain the result was stated by 2 homozygotes (3.8%) and 9 heterozygotes (3.1%) only. A total of 26.9% of all participants (15.1% of the homozygotes, 20.5% of the heterozygotes, and 36.8% of the individuals with the wild-type genotype, $p < 0.001$) answered that the test result had not been explained to them at all.

Additional information on HH was sought by 62.0% of the homozygotes, 30.7% of the heterozygotes, and 15.4% of the wild-type individuals ($p < 0.001$). The major source of additional information was the Internet in 55.1% of cases, followed by written material for professionals in 26.6%, written material for laypersons in 20.9%, and the German hemochromatosis patient support organization in 5.7% (no statistically significant differences in these additional information sources between the three genotype groups). Homozygotes learned their test result significantly earlier than heterozygotes or wild-type individuals and stated less frequently that they had not yet learned about it (Fig. 1).

After receipt of the test result, further laboratory tests or clinical examinations were performed in 79.6% of homozygotes, 28.0% of heterozygotes, and 6.1% of individuals without C282Y ($p < 0.001$). A total of 62.0% of homozygotes, 19.1% of heterozygotes, and none of the wild-type individuals believed that a clinical diagnosis of hemochromatosis had been carried out on them in the context of the pilot study ($p < 0.001$).

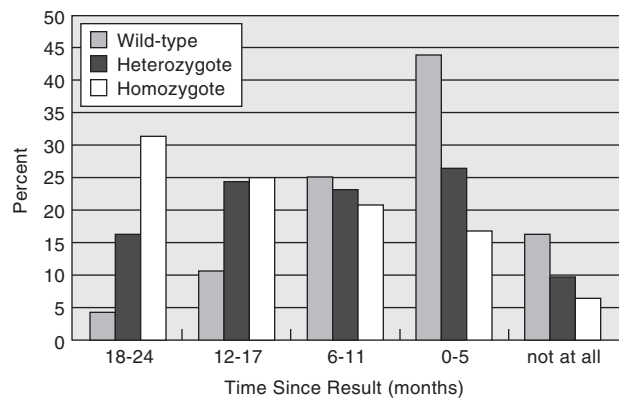


FIG. 1. Relation between genotype and time between disclosure of test result and survey. "Not at all" means that the test result was sent to the referring doctor (general practitioner [GP]) but not forwarded by the GP to the participant in the study, which occurred in 12.2% of all cases.

TABLE 1. EMOTIONAL REACTIONS ABOUT THE TEST RESULTS IN THE FIRST FEW DAYS AFTER RECEIPT AND THE TIME OF SURVEY

Emotional reaction	Genotype	Time 1 (the first few days after receipt of the results)					Time 2 (now)				
		Very much or moderate (%)	Somewhat or not at all (%)	Odds ratio	Confidence interval (95%)	p	Very much or moderate (%)	Somewhat or not at all (%)	Odds ratio	Confidence interval (95%)	p
Tense	Wild-type	2.8	97.2	1			2.9	97.1	1		
	Heterozygote	13.9	86.1	5.667	1.269-25.296	0.012	1.9	98.1	0.650	0.089-4.730	0.649
	Homozygote	25.0	75.0	11.667	2.170-62.726	0.003	9.5	90.5	3.526	0.465-26.718	0.231
Upset	Wild-type	1.4	98.6	1			0	100	1		
	Heterozygote	14.9	85.1	12.093	1.572-93.026	0.002	0	100	0.701	0.043-11.403	1.000
	Homozygote	21.7	78.3	19.167	2.105-174.51	0.003	10.0	90.0	7.556	0.648-88.086	0.125
Worried	Wild-type	0	100	1			1.4	98.6	1		
	Heterozygote	23.8	76.2	22.147	2.965-165.440	< 0.001	11.7	88.3	9.159	1.184-70.884	0.012
	Homozygote	30.0	70.0	30.429	3.643-254.158	< 0.001	26.1	73.9	24.353	2.746-215.975	0.001
Afraid	Wild-type	1.4	98.6	1			0	100	1		
	Heterozygote	7.4	92.6	5.520	0.675-45.139	0.091	1.0	99.0	0.719	0.044-11.690	1.000
	Homozygote	17.4	82.6	14.526	1.532-137.735	0.013	10.0	90.0	7.667	0.658-89.367	0.123
Calm	Wild-type	78.1	21.9	1			79.0	21.0	1		
	Heterozygote	45.2	54.8	0.232	0.142-0.377	< 0.001	59.8	40.2	0.395	0.242-0.645	< 0.001
	Homozygote	39.3	60.7	0.182	0.078-0.423	< 0.001	56.3	43.7	0.342	0.154-0.759	0.012
Relaxed	Wild-type	65.8	34.2	1			72.3	27.7	1		
	Heterozygote	39.6	60.4	0.340	0.185-0.628	0.001	53.7	46.3	0.445	0.241-0.820	0.011
	Homozygote	27.8	72.2	0.200	0.064-0.619	0.007	54.6	45.4	0.460	0.175-1.210	0.127
Content	Wild-type	72.7	27.3	1			77.5	22.5	1		
	Heterozygote	31.0	69.0	0.168	0.091-0.311	< 0.001	50.9	49.1	0.301	0.169-0.538	< 0.001
	Homozygote	23.5	76.5	0.115	0.035-0.385	< 0.001	50.0	50.0	0.291	0.113-0.749	0.016
Relieved	Wild-type	66.1	33.9	1			68.9	31.1	1		
	Heterozygote	37.7	62.3	0.311	0.181-0.534	< 0.001	50.0	50.0	0.451	0.259-0.784	0.006
	Homozygote	36.4	63.6	0.293	0.113-0.759	0.015	40.0	60.0	0.300	0.122-0.741	0.01

Differences in answer frequencies between individuals with wild-type and heterozygotes or homozygotes were tested using Fisher's exact test. Values in boldface italic type are nominally significant p values ($p < 0.05$). Odds ratio refers to the wild-type genotype. Where the frequency was 0, the odds ratio has been computed under the assumption that a single individual reported the respective feeling.

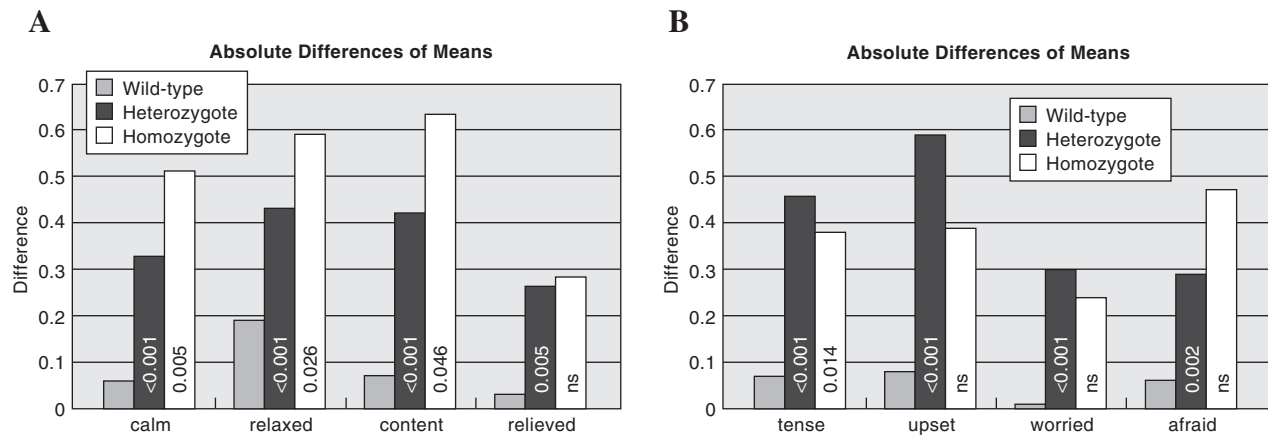


FIG. 2. Changes in feelings about the test result over time. Feelings were rated from 1 (very much) to 4 (not at all). Means were calculated for each feeling. Absolute differences of feelings at the time of disclosure of the test result (time 1) and at the time of the survey (time 2) were assessed by dividing the means of time 1 by the means of time 2 (positive feelings, **A**) or by dividing the means of time 2 by the means of time 1 (negative feelings, **B**). Differences of the means at the two time points are significant for all feelings in the case of heterozygosity and for most feelings in the case of homozygosity. No significant differences were seen in wild-type cases. Calculations of asymptotic two-tailed significance levels were made according to the Wilcoxon signed rank test. *p* values are given in the columns. ns, not significant.

Psychosocial consequences

Emotional reactions. Significantly more homozygotes and heterozygotes reported that they felt very much or moderately tense, upset, and worried for the first few days (T1) after receipt of the test results, compared to individuals with the wild-type (Table 1). Additionally, significantly more heterozygotes reported to be afraid and significantly less homozygotes and heterozygotes were calm, relaxed, content, and relieved at T1 than wild-type individuals. At the time of the survey (T2; up to 24 months later), no significant differences remained with respect to feeling tense, upset, and afraid (negative feelings), while still significantly more homozygotes and heterozygotes felt worried and significantly less felt calm, content, and relieved about the test result at T2 than individuals with wild-type. Additionally, significantly less heterozygotes reported that they felt relaxed at T2, compared to wild-type individuals (Table 1). However, at T2, a higher proportion of positive feelings and a lower proportion of neg-

ative feelings were present among homozygotes and heterozygotes, while no significant differences were seen between T1 and T2 among the group of wild-type individuals (Fig. 2A and 2B).

Benefit/harm. Of the participants, 69.9% thought that participation in the pilot study was probably beneficial for them and 1.0% thought that it was probably harmful (Table 2).

Five of the six individuals who considered their participation as being probably harmful, were heterozygous for C282Y, while one was wild-type. One of these heterozygous individuals did not give a reason why he considered his participation as probably harmful, nor did he answer the question how he now judged his decision to have participated. The other four heterozygotes gave the following reasons, “The desire to have children will probably not be fulfilled, because my husband has the same diagnosis.”; “The anxiety that there is something there with which I don’t know how to cope. I haven’t yet been able

TABLE 2. PERCEIVED BENEFIT OR HARM REPORTED BY INDIVIDUALS, WHO ACTIVELY PARTICIPATED IN THE PILOT STUDY

Statement	Answer	Individuals who had been tested Number (%)			
		Wild-type	Heterozygote	Homozygote	All
Do you think that participation in the model trial was probably beneficial for you?	“Yes”	179 (71.6)	193 (67.2)	39 (76.5)	411 (69.9)
	“No”	22 (8.8)	24 (8.4)	6 (11.8)	52 (8.8)
	“Don’t know”	49 (19.6)	70 (24.4)	6 (11.8)	125 (21.3)
Do you think that participation in the model trial was probably harmful for you?	“Yes”	1 (0.4)	5 (1.7)	0 (0.0)	6 (1.0)
	“No”	233 (93.2)	257 (88.9)	49 (94.2)	539 (91.2)
	“Don’t know”	16 (6.4)	27 (9.3)	3 (5.8)	46 (7.8)

Differences in the number of responders with regard to genotype were not significant, as calculated using χ^2 test (first statement, benefit) or Fisher’s exact test (second statement, harm).

to decide to undergo bloodletting. You see, I have rolling veins. I am not sure whether I can donate blood in the hospital in E.”; “I am worried because my father suffered from a liver disease (cirrhosis or cancer?), and died at 41 years of age. I did not know that iron deposits could lead to that.”; “I am not sure whether my GP did the right thing. He told me that treatment was not necessary.” The first three of these heterozygous individuals judged their decision to have participated in the pilot study as probably right; the fourth stated that it was neither right nor wrong to participate. The only individual with wild-type, who considered her participation as probably harmful, gave the following reason, “Harmful is an exaggeration but this survey did not allow an explanation of the answer ‘no’ in question 12. I did not benefit from the model trial and therefore it was harmful, because I do not have haemochromatosis, but it has not been medically clarified, why I have elevated concentrations of bilirubin and iron (and that as a vegetarian) so that the search is not over, as hoped, but will continue.” Nevertheless, this individual judged her decision to have participated as definitely right.

Overall, 82.2% judged their decision to have participated in the pilot study as definitely right, 12.4% as probably right, 5.0% as neither right nor wrong, 0.3% (two heterozygous individuals) as probably wrong, and none as definitely wrong. The latter two individuals did not detail reasons for their judgement. One of these responded “don’t know” and the other answered “no” to both of the questions whether they thought that participation in the model trial was probably beneficial or harmful to them.

Knowledge about hemochromatosis. Overall, homozygotes and heterozygotes had a better knowledge about clinical and genetic aspects of haemochromatosis than individuals with the wild-type genotype. Correct answers were given significantly more often by homozygotes and heterozygotes, while individuals without C282Y stated significantly more often that they did not to know the answer (Table 3).

Survey among members of the KKH sickness fund (KKH survey)

Sources of information. A total of 2141 KKH members responded to the survey. Two hundred eighty-three individuals (13.2% of the survey responders) knew about the pilot project on genetic testing for HH, mostly through the KKH journal (92.4%). In 31 cases, knowledge about the pilot study was gained through mass media (in 11 cases exclusively and in 20 cases in addition to the information in the KKH journal). All other potential sources were mentioned only rarely. Of those individuals who knew about the pilot study, 17 (6.0%) talked about it with their GP, and 14 (5%) asked the Institute of Human Genetics at the MHH for more information and eventually participated in the pilot study. The most frequently mentioned reasons for not participating were “lack of time” and the “need for more information about the disease” (59 times each). Other frequently given reasons were, “I am healthy and do not feel I need this test” (52), “other reasons” (reasons not proposed by questionnaire, (40), “participation would have been too much effort” (31), and “I am at an ad-

TABLE 3. KNOWLEDGE ABOUT CLINICAL AND GENETIC ASPECTS OF HEMOCHROMATOSIS OF INDIVIDUALS WHO ACTIVELY PARTICIPATED IN THE PILOT STUDY

Statement	Answer	Individuals who had been tested			
		Wild-type	Heterozygote	Homozygote	All
Timely blood-letting will prevent symptoms of hemochromatosis in homozygous carriers, i.e., individuals with two copies of the C282Y mutation.	“Yes” (correct) ^b	141 (61.6)	190 (70.9)	42 (80.8)	373 (67.9)
	“No” (wrong)	12 (5.2)	14 (5.2)	3 (5.8)	29 (5.3)
	“Don’t know” ^b	76 (33.2)	64 (23.9)	7 (13.5)	147 (26.8)
All homozygous carriers of the C282Y mutation will develop symptoms of hemochromatosis at some stage in their life if untreated	“Yes” (wrong)	85 (37.4)	87 (32.0)	21 (42.0)	193 (35.2)
	“No” (correct) ^c	34 (15.0)	87 (32.0)	15 (30.0)	136 (24.8)
	“Don’t know” ^c	108 (47.6)	98 (36.0)	14 (28.0)	220 (40.1)
All offspring of homozygous carriers of the C282Y mutation inherit at least one copy of this mutation	“Yes” (correct) ^c	70 (30.7)	126 (47.0)	25 (53.2)	221 (40.7)
	“No” (wrong) ^a	9 (3.9)	30 (11.2)	4 (8.5)	43 (7.9)
	“Don’t know” ^c	149 (65.4)	112 (41.8)	18 (38.3)	279 (51.4)
Heterozygous carriers, i.e., individuals with one copy of the C282Y mutation, have a high risk of developing symptoms of hemochromatosis	“Yes” (wrong)	72 (31.6)	74 (27.8)	14 (29.2)	160 (29.5)
	“No” (correct) ^c	34 (14.9)	105 (39.5)	18 (37.5)	157 (29.0)
	“Don’t know” ^c	122 (53.5)	87 (32.7)	16 (33.3)	225 (41.5)

Differences in the number of responders with regard to genotype were assessed by comparing the numbers of each line with the added numbers of both other lines for the same question. Statistically significant differences are given in bold, significance levels were calculated using χ^2 test or Fisher’s exact test, when appropriate.

^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$.

vanced age and do not think I could still develop hemochromatosis" (27).

Attitudes of KKH members toward predictive genetic testing

Most of the responders (59.1%) would generally accept predictive genetic testing if a medical benefit were proven. The acceptance rates were 57.6% among 1841 individuals who did not know about the pilot study and 68.2% among 264 individuals who knew about the pilot study but who did not participate ($p = 0.001$). A small minority (3.7%) of the responding KKH members objected to such genetic tests in principle, and 37.2% thought that they knew too little about predictive testing. The rate of acceptance and the difference in the proportions of people who are undecided are significantly affected by the educational status: the higher the educational status, the higher the acceptance rate and the lower the proportion of people who are undecided (Fig. 3, Table 4A). The rate of objection was not significantly influenced by the educational status and ranged between 3.3% (highest education) and 4.3% (lowest education). The highest rate of principal objection (8.3%) was seen in the youngest age group (18–24 years old).

Overall, 57.1% of the KKH members agreed that predictive genetic testing of a disease that can be prevented should be done specifically only after comprehensive genetic counselling with a specialist in clinical genetics; 15.0% answered that such a test should be freely accessible in a medical setting also without genetic counselling, whereas 2.1% thought that such a test should be freely accessible outside a medical setting; the remaining 25.8% felt they knew too little to make any statement in this regard.

When asked what the level of probability of manifestation of a serious disease should be in order that a predictive test should be covered by sickness funds, 40% answered that the level of probability should be at least 10%. A level of disease probability of at least 25%, 50%, 75%, or 100% was stated by 14.8%, 22.1%, 9.6%, and 12.8%, respectively.

A total of 64.3% of the survey responders were confident that a laboratory experienced in predictive genetic testing would

produce a correct test result, whereas 10.3% did not trust the correctness of the result.

Overall, 78.9% agreed and 4.2% disagreed with the statement that predictive genetic tests on preventable disease allow ones health to be positively influenced by prophylactic measures.

To the question whether the costs of predictive genetic tests should be covered by the sickness funds if there is a proven medical benefit, 88.4% answered with yes and 5.6% with no. A total of 72.5% stated that their willingness to participate in predictive testing would be enhanced if employers and insurers were legally forbidden to ask for genetic test results, and 76.3% found it important that their health insurance promote the implementation of innovative genetic tests.

Educational level and age are the sociodemographic parameters which explain most variances (Table 4A), followed by the marital status and the fact of having children (Table 4B). None of the other sociodemographic parameters revealed any differences.

Comparison of the two surveys

A comparison between the two surveys (Table 5) shows—as could have been expected—that individuals who had actively participated in genetic HH testing (MHH survey) responded significantly more often than the randomly chosen KKH members (KKH survey). MHH survey responders reported significantly more often on cases of HH in their family and on their own previously established diagnosis of HH. In addition, MHH survey responders were significantly older, were more often married or living in a partnership, were more highly educated (more university degrees, fewer than 9 years of school), and had a higher professional status (more employees and civil servants, fewer manual workers or unemployed individuals). The parameters of gender or having children were not significantly different between the two groups.

Among the tested individuals (MHH survey), significantly more homozygotes than expected on the basis of known allele frequencies in the population responded to the survey and stated that they knew previously that they were affected by HH. HH in family members was known significantly more often by homozygotes and heterozygotes than by individuals with the wild-type. No statistically significant differences between the three genotype groups were seen in any of the other sociodemographic parameters.

DISCUSSION

We performed a pilot study to evaluate technical performance, costs, and clinical relevance of genotype-based screening for HH (Stuhrmann *et al.*, 2005), as well as to investigate attitudes regarding genetic testing and the psychosocial impact of *HFE* genotyping. A major aim of this study was to examine the acceptance rate of DNA-based HH screening among German individuals who had received such an offer by their sickness fund. From the KKH survey we conclude that the acceptance rate is high and significantly influenced by the educational status. However, we must take into account that the response rate of 26.8% of the surveyed KKH members is too low for be-

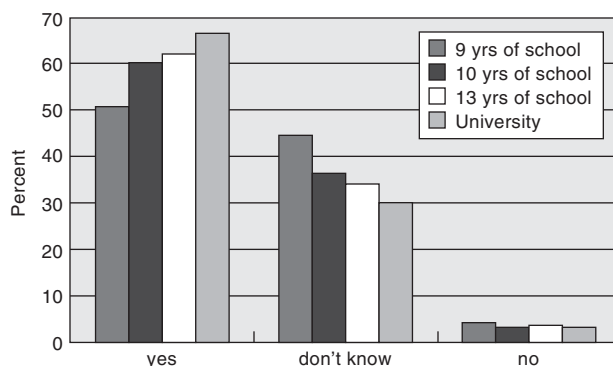


FIG. 3. Correlation between acceptance of genetic testing and educational status. 9 years of school (Volksschule or Hauptschule, basic German school form), 10 years of school (Realschule, medium German school form), 13 years of school (Gymnasium, highest German school form).

TABLE 4A. ATTITUDES OF KKH MEMBERS TOWARD GENETIC TESTING: EFFECT OF EDUCATION AND MARITAL STATUS

Items	Education				Marital status			
	Individuals with lower educational levels (% agreeing)	Individuals with higher educational levels (% agreeing)	Odds ratio	Confidence interval (95%)	Single/divorced/widowed (% agreeing)	Married/partnership (% agreeing)	Odds ratio	Confidence interval (95%)
Acceptance								
I accept predictive genetic testing, if a medical benefit is proven	55.9	64.6	0.69	0.58–0.83^c	56.3	60.5	0.84	0.70–1.01
Genetic counseling								
If a disease can be predicted by a genetic test and if its manifestation can be prevented specifically, this test should be done only after genetic counselling by a geneticist	53.7	63.2	0.67	0.56–0.81^c	58.0	56.7	1.05	0.88–1.26
Disease penetrance								
The probability of manifestation should be 50% or more	49.0	37.7	1.59	1.32–1.91^c	43.7	45.2	0.94	0.78–1.14
Confidence								
I trust that a laboratory experienced in predictive genetic testing will produce a correct test result	66.0	61.6	1.21	1.01–1.46^a	61.3	66.1	0.81	0.68–0.98^a
Prevention								
Predictive genetic tests on preventable diseases allow one's health to be positively influenced by prophylactic measures	78.7	79.3	0.97	0.78–1.21	75.9	80.6	0.75	0.61–0.94^a
Public insurance								
Should public insurance regularly offer predictive genetic tests if there is a proven medical benefit?	89.5	86.6	1.31	1.00–1.72	86.4	89.6	0.74	0.56–0.97^a
Legislation								
Would it enhance your willingness to participate, if employers and insurers were legally forbidden to ask for genetic test results?	70.2	76.2	0.73	0.60–0.90^b	69.5	74.2	0.79	0.65–0.97^a
Innovation								
Is it important for you that your sickness fund actively participates in the implementation of innovative genetic tests?	79.3	71.2	1.55	1.26–1.91^c	71.3	79.1	0.65	0.53–0.81^c

Statistically significant differences are given in bold, significance levels were calculated using χ^2 test.

^a $p < 0.05$; ^b $p < 0.01$; ^c $p < 0.001$.

KKH, Kaufmännische Krankenkasse.

TABLE 4B. ATTITUDES OF KKH MEMBERS TOWARD GENETIC TESTING: EFFECT OF HAVING CHILDREN AND AGE

Items	Children			Age				
	Without children (% agreeing)	With children (% agreeing)	Odds ratio	Confidence interval (95%)	Individuals 18–44 years of age (% agreeing)	Individuals 45 years and older (% agreeing)	Odds ratio	Confidence interval (95%)
Acceptance								
I accept predictive genetic testing, if a medical benefit is proven	60.5	58.4	1.09	0.90–1.32	58.8	59.5	0.97	0.82–1.15
Genetic counseling								
If a disease can be predicted by a genetic test and if its manifestation can be prevented specifically, this test should be done only after genetic counselling geneticist	60.1	56.0	1.18	0.98–1.43	59.1	55.4	1.16	0.98–1.38
Disease penetrance								
The probability of manifestation should be 50% or more	42.6	45.5	0.89	0.73–1.08	39.3	50.4	0.64	0.53–0.76^b
Confidence								
I trust that a laboratory experienced in predictive genetic testing will produce a correct test result	59.9	66.2	0.76	0.63–0.93^a	64.2	64.5	0.99	0.83–1.18
Prevention								
Predictive genetic tests on preventable diseases allow one's health to be positively influenced by prophylactic measures	78.6	79.1	0.97	0.77–1.22	79.4	78.3	1.07	0.86–1.32
Public insurance								
Should public insurance regularly offer predictive genetic tests if there is a proven medical benefit?	87.5	88.8	0.88	0.66–1.18	87.9	88.9	0.91	0.70–1.20
Legislation								
Would it enhance your willingness to participate, if employers and insurers were legally forbidden to ask for genetic test results?	74.6	71.6	1.17	0.94–1.45	72.5	72.3	1.01	0.83–1.23
Innovation								
Is it important for you that your sickness fund actively participates in the implementation of innovative genetic tests?	68.6	79.5	0.56	0.45–0.70^b	71.5	81.5	0.57	0.46–0.70^b

Statistically significant differences are given in bold, significance levels were calculated using χ^2 test.

^a $p < 0.01$; ^b $p < 0.001$.

KKH, Kaufmännische Krankenkasse.

TABLE 5. SOCIODEMOGRAPHIC PARAMETERS OF THE INDIVIDUALS WHO RETURNED THE QUESTIONNAIRES

		Individuals who had been tested (MHH survey)				KKH members Number (%)
		Wild-type	Heterozygote	Homozygote	All	
Responders ^{a,b}		272 (60.7)	305 (62.9)	54 (80.6)	631 (63.1)	2141 (26.8)
HH in family ^{a,b}	Unknown	46 (17.0)	43 (14.2)	1 (1.9)	90 (14.4)	n.d.
	Yes	9 (3.3)	69 (22.8)	9 (16.7)	87 (13.9)	15 (0.7)
Diagnosis of HH ^{a,b}	No	215 (79.6)	191 (63.0)	44 (81.5)	450 (71.8)	2083 (99.3)
	Unknown	9 (3.3)	10 (3.3)	1 (1.9)	20 (3.2)	n.d.
Gender	Yes	2 (0.7)	9 (3.0)	26 (48.1)	37 (5.9)	14 (0.7)
	No	261 (96.0)	284 (93.7)	27 (50.0)	572 (90.9)	2087 (99.3)
Age groups, years ^a	Male	54 (30.3)	81 (32.7)	21 (41.2)	156 (32.7)	728 (34.1)
	Female	124 (69.7)	167 (67.3)	30 (58.8)	321 (67.3)	1408 (65.9)
Marital status ^a	18–44	62 (35.6)	84 (34.1)	16 (31.4)	162 (34.4)	1109 (52.0)
	> 64	112 (64.4)	162 (65.9)	35 (68.6)	309 (65.6)	1022 (48.0)
Educational level ^a	Single/divorced/widowed	73 (27.1)	85 (28.3)	12 (22.2)	170 (27.3)	760 (35.6)
	Married/partnership	196 (72.9)	215 (71.7)	42 (77.8)	453 (72.7)	1375 (64.4)
Professional status ^a	9 yrs of school	56 (21.0)	64 (21.6)	15 (28.3)	135 (21.9)	570 (26.9)
	10 yrs of school	104 (39.0)	119 (40.2)	22 (41.5)	245 (39.8)	752 (35.5)
Children	13 yrs of school	35 (13.1)	37 (12.5)	8 (15.1)	80 (13.0)	344 (16.2)
	University	72 (27.0)	76 (25.7)	8 (15.1)	156 (25.3)	454 (21.4)
Professional status ^a	Trainee	4 (1.5)	9 (3.2)	2 (3.8)	15 (2.5)	146 (6.9)
	Manual worker	4 (1.5)	5 (1.8)	0 (0.0)	9 (1.5)	128 (6.0)
Professional status ^a	Employee/civil servant	145 (54.5)	146 (51.6)	24 (45.3)	315 (52.3)	974 (45.9)
	Self-employed	19 (7.1)	12 (4.2)	6 (11.3)	37 (6.1)	140 (6.6)
Professional status ^a	Unemployed	24 (9.0)	25 (8.8)	2 (3.8)	51 (8.5)	240 (11.3)
	Retired	70 (26.3)	86 (30.4)	19 (35.8)	175 (29.1)	495 (23.3)
Children	Yes	207 (76.1)	214 (71.3)	36 (66.7)	457 (73.0)	1516 (71.0)
	No	65 (23.9)	86 (28.7)	18 (33.3)	169 (27.0)	619 (29.0)

Parameters with statistically significant differences among both surveys were marked with ^a. Differences among individuals with different genotypes (MHH survey) are marked with ^b. Significance levels were calculated using χ^2 test or Fisher's exact test, when appropriate.

^a $p < 0.001$; ^b $p < 0.001$.

n.d.: not determined; MHH, Institute of Human Genetics at Hannover Medical School; KKH, Kaufmännische Krankenkasse.

ing representative for all KKH members. Although only 5882 of the 1.4 million KKH members (0.4%) participated in the pilot study, we do not consider this relatively low rate of participation as a consequence of low acceptability for the following reasons. First, only 13% of the survey responders stated that they knew about the pilot study. Second, only 5% of those who knew about the study decided to participate, but the acceptance rate was higher among the nonparticipants who knew about the study than among those KKH members who did not know about it. Third, the number of KKH members who participated in the study (5,882) was not significantly different from the calculated number of potential participants from the KKH survey (9100; $1.4 \text{ million} \times 0.13 \times 0.05$) (95% confidence interval). The relatively low number of participants (members who requested information) is more likely a consequence of the unobtrusive mode of advertisement. Information on the possibility of participating in the study was given in the magazine *KKH Journal* in all four issues in the year 2001. In addition, flyers were displayed in the KKH office, a few short reports on the pilot study appeared in mass media (television, radio, newspaper), and in a few cases KKH members were informed about the pilot study by their doctors. From both surveys it is evident that information through the *KKH Journal* was the most important

primary source of knowledge about the pilot study. In addition, the number of requests for information and test material did not decline over the time period that testing was offered.

The rate of 5% of members who requested more information on the test is comparable to the rate of those persons (5.8%) seeking test information in a similarly structured, albeit workplace-based genetic screening programme for HH in Australia (Nisselle *et al.*, 2004).

Although the proportion of KKH members who objected to predictive genetic testing in principle is very low, it is noticeable that the highest rate of objection in principle occurred in the youngest age group, which corresponds to the results of an examination of attitudes about testing for HH in 118 young adults and 50 older adults in the USA, where young adults (19.7 ± 1.9 years) were significantly more likely to report disadvantages of genetic testing and were more concerned about potential negative psychological effects than older adults (58.5 ± 13.7 years) (Hicken *et al.*, 2003).

Finally, capillary blood samples were obtained from 3961 of the 5,882 KKH members who requested information and test material, corresponding to an uptake rate of 67.3%. The uptake rate was 97.7% among Australians, who attended the workplace information and screening sessions (Nisselle *et al.*, 2004).

Again, we assume that the lower uptake rate in our study was the result of a more unobtrusive approach (written information versus oral or video presentation in a group setting), requiring a more active role of the potential participants.

After comparing the sociodemographic data of the responders of both surveys (KKH survey and MHH survey), it is tempting to assume that the motivation to participate in a genetic screening program is higher among those KKH members with known or suspected cases of HH in their families or themselves, and among those individuals with higher age, higher education, and higher professional status, as well as among those who are married or living in a partnership. The notion that individuals with a known or suspected familial or personal history of HH will be more highly motivated to participate in HH screening is further substantiated by the genotypic results of our pilot study, because we detected significantly more C282Y homozygous and heterozygous individuals among the study participants than in the general German population (Stuhrmann *et al.*, 2005). Therefore, we postulate that any general population screening for HH will always partially be like a cascade screening, thereby raising the detection rate of individuals at elevated prior risk.

An important issue in any genetic screening programme is the availability of pretest and posttest counseling. In our study, although 57.1% of the KKH members stated that predictive genetic testing of a disease that can be prevented specifically should be carried out only after comprehensive genetic counseling by a specialist in clinical genetics, only one of the MHH survey responders (0.2%) attended individual pretest counseling, and only two homozygotes (3.8%) and nine heterozygotes (3.1%) answered that the test result was explained to them by a genetic counselor, despite the fact that the offer of genetic counseling was made in each report of homozygous or heterozygous results. The low uptake rate for personal genetic counseling can only partially be explained by the proportions of homozygotes (17.0%) and heterozygotes (17.7%), who instead received counseling by telephone with the MHH. Presumably, genetic counseling was not actively encouraged by the doctors communicating the test results. It is noteworthy that 12.2% of the test participants stated that they had not received the test result right up to the time of the survey and that 26.9% stated that the result was not explained to them. These figures were significantly influenced by the participants' genotypes, demonstrating that the participants' doctors were more motivated to disclose and to explain the result to the study participant in the case of a positive test result. This notion is further supported by the observation that individuals with positive test results received them significantly earlier than the others.

Inappropriate explanation of test results seems to be most problematic in heterozygote cases. For example, almost one fifth of the heterozygotes believed that a clinical diagnosis of hemochromatosis had been made by them in the context of the pilot study, and five of the six individuals who considered their participation as being probably harmful, and both individuals who considered their decision of having participated as most likely wrong, were heterozygotes. Although we assume that the problems that arose in heterozygotes could be circumvented if the results and their significance were to be explained in the setting of genetic counselling, it may also be an option in fur-

ther screening programs to follow the way of reporting results taken by the Australian pilot study (Nisselle *et al.*, 2004). There, heterozygotes were not primarily informed on their genotype but received a result indicating that they were at low risk for developing HH, with a phone number to ring if they wished to know their heterozygous status (Nisselle *et al.*, 2004). However, with this strategy, cascade screening would not be possible, making the screening program less effective.

Another argument for the need for better information comes from the assessment of understanding of clinical and genetic aspects of HH. The frequencies of correct answers to four different questions were between 24.8% and 67.9%, where homozygotes and heterozygotes gave significantly more often correct answers than individuals with wild-type. This relatively low level of knowledge contrasts with the much higher level of knowledge among the participants of the Australian Haem-Screen programme, where the frequencies of correct answers to similar questions ranged between 50.3% and 89.9% (Nisselle *et al.*, 2004). The efficiency of an oral or video presentation in a group setting seems to be higher with respect to imparting knowledge than the distribution of written material in combination with the offer to obtain further information from GPs and specialists. While only 25.6% of the participants in our study asked for more information from their GPs, even fewer individuals used other information sources, although the pilot study was designed in such a way that information from professionals was available for all interested persons.

The vast majority thought that participation was probably beneficial for them. However, one percent thought that it was probably harmful. We believe that inappropriate explanation of the test results was the cause for giving this answer, especially if we take into account the reasons given by these individuals.

The importance of appropriate posttest counseling becomes further evident if we consider the reported emotional reactions of the test participants, because significantly more individuals with positive test results (homozygotes and heterozygotes) reported on negative feelings at the time of disclosure of the test results than individuals with wild-type. No significant differences between individuals with positive and negative test results remained at the time of the survey with regard to feeling tense, upset, and afraid, but it is remarkable that still significantly more homozygotes and heterozygotes reported to feel very much or moderate worried, compared to individuals with wild-type. It is understandable that homozygotes were still worried about their results, even if they knew about the possibility to prevent disease manifestation. However, heterozygotes would presumably not have to worry, if appropriate information had been given to them. For T1 as well as for T2, significantly less homozygotes and heterozygotes reported to feel calm, relaxed, content, and relieved (positive feelings) than individuals with wild-type, although it was evident that the differences in the intensity of the respective feelings (as rated from 1 = very much to 4 = not at all) changed significantly in the groups of individuals with positive test results, while no significant changes were noted in the group of individuals with wild-type.

Accordingly, only 0.3% (two heterozygotes) considered their participation as probably wrong, while 94.6% of the participants answered that their decision to participate was right.

CONCLUSIONS

We conclude from this pilot study that many of the controversial issues surrounding population-based testing for HH could be resolved. With regard to the discussion on the reduced penetrance (Asberg *et al.*, 2001; Beutler *et al.*, 2002; Byrnes *et al.*, 2002; Ioannou and Kwodley, 2002; Poullis *et al.*, 2002; Ajioka and Kushner, 2003; Beutler 2003; Dubois and Kwodley, 2003), we feel that the benefit for those who can prevent disease by early detection of the genetic risk and possibly start preventive phlebotomies outweighs the possible fears and negative psychosocial consequences of those who carry the genetic predisposition but who will not develop clinical symptoms because of reduced penetrance. It is currently unknown which homozygotes definitely need prophylactic phlebotomy. Until this question is solved, population screening will remain controversial. Our impression that the penetrance does not necessarily have to be high is supported by the KKH members, of which only 12.8% would accept a predictive test only if the penetrance was 100%, while 40% would accept such a test if the penetrance was 10%. That the acceptance of genetic HH testing is potentially high is further substantiated by the very high frequency of members (88.4%) who opted for the general introduction of predictive genetic testing in the public health care system if a medical benefit is proven. The data from our study do not establish that screening is beneficial. The final proof that it is beneficial or not would require much more information about comprehension and psychological reaction plus long-term follow-up to determine if morbidity is in fact reduced. Nevertheless, we assume that DNA-based population screening for HH could be highly beneficial and potential psychosocial harm could be avoided if appropriate pretest and posttest information is provided by educated health professionals and adequate facilities to support screening, diagnosis, treatment, and follow-up are available. In our study, written information of the nature of the test and the benefits, risks and limitations, as well as the offer for pretest genetic counselling, monthly information meetings, and consultation with the GP did not provide sufficient pretest information. The study participants obviously did not recognize the need for appropriate pretest counseling, which could have been utilized throughout the country (monthly information meetings were in Hannover only). Additionally, it turned out that the primary care physician apparently cannot be relied upon to provide the necessary posttest education, including the referral for genetic counselling. The insufficient utilization of pretest and posttest genetic counselling lead to widespread misunderstanding of the meaning and the implications of the test results. The design of actual population screening therefore has to take these findings into account and has to differ from the design of our pilot study. Potential long-term negative psychosocial consequences such as persisting worries, less contentment, and relief should be taken into consideration when planning testing programmes and can presumably be prevented by appropriate settings including genetic counselling and follow-up-services. It has previously been assessed by others—albeit in a somewhat different setting—that individuals who have not undergone genetic testing for HH may overestimate the impact of a positive test result, and that few HH patients report that HFE genotyp-

ing was accompanied by negative psychosocial outcomes (Hicken *et al.*, 2004).

The risk of genetic discrimination should not be ignored, given the observation that insurance denial and increased premium rates are reported among individuals with HH (Shaheen *et al.*, 2003). In a country such as Germany, where public health insurance is obligatory and private health insurance presents an option of choice only under defined circumstances, the risk of discrimination with regard to obtaining health insurance may be less pronounced, but the potential risk of discrimination with regard to life insurance or employment may exist. Therefore, it is not astonishing that the majority of KKH members stated that their willingness to participate in predictive testing would be enhanced if employers and insurers were legally forbidden to ask for genetic test results.

Our study suggests that the implementation of a specific genetic testing program into a national health care system requires careful preparations not only in regard to the availability of epidemiological data such as prevalence and penetrance of a given mutation, the availability of suitable tests with known performance, the management of logistical issues such as integrating testing, diagnosis, treatment, and follow-up services at reasonable costs, in particular the physician and health system effort required for long-term follow-up, but also requires the careful evaluation whether the considered approaches are acceptable for consumers and how potential psychosocial harm resulting from a diagnosis of HH can be avoided.

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