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Health-related quality of life in a racially diverse population screened for hemochromatosis: results from the Hemochromatosis and Iron Overload Screening (HEIRS) study

Lari B. Wenzel, PhD[1], Roger Anderson, PhD[2], Diane C. Tucker, PhD[3], Shana Palla, MS[2], Elizabeth Thomson, DNSc[4], Mark Speechley, PhD[5], Helen Harrison, MSc[6], Ometha Lewis-Jack, PhD[7], Margaret Fadojutimi-Akinsiku[7], John H. Eckfeldt, MD, PhD[8], Jacob A. Reiss, MD[9], Charles A. Rivers, PhD, MSPH[10], Ebony Bookman, PhD[11], Beverly M. Snively, PhD[2], Christine E. McLaren, PhD[12], for the Hemochromatosis and Iron Overload Study Research Investigators

Purpose: The HEIRS Study screened 101,168 primary care participants for iron overload with serum transferrin saturation (TS), serum ferritin (SF), and C282Y and H63D mutations of the *HFE* gene. The objective of this study was to evaluate the impact of screening on participants' well-being. **Methods:** All C282Y homozygotes, participants with an elevated TS and SF concentration, and a control group of phenotype-genotype negative persons, with neither C282Y nor H63D mutations in the *HFE* gene were recalled for a clinical evaluation. Health-related quality of life was assessed before screening and approximately 1 week after receipt of the results. Health worries were assessed only at follow-up. **Results:** Participants (N = 1478) completed both initial and follow-up surveys. After adjusting for model covariates, phenotype and genotype combinations were statistically significant predictors of changes in psychological well-being ($P = 0.0001$) and general health ($P = 0.0014$). C282Y homozygotes with transient elevations in TS or SF were significantly more likely to worry about their health compared to study controls. Race, ethnicity, and preferred language subgroups differed on psychological well-being, general health, and health worry. **Conclusion:** Iron phenotype and *HFE* genotype are associated with health-related quality of life. Health worry was greatest among those considered genetically "at risk. " This may have important implications for multi-ethnic population-based screening studies in which genotype and phenotype are communicated. ***Genet Med* 2007:9(10):705–712.**

Key Words: *quality of life, hemochromatosis, screening, iron overload, multi-ethnic population*

Hereditary hemochromatosis (HH) is an inherited tendency to absorb excessive amounts of dietary iron that can progress to iron overload (IO) and cause organ damage. Most patients with HH are homozygous for a common missense mutation (C282Y/C282Y) in the hemochromatosis gene (*HFE*), whereas some are compound heterozygotes (C282Y/H63D). Others are homozygous for an H63D mutation (H63D/H63D), simple heterozygotes (C282Y/+ or H63D/+), and wildtype with respect to these two loci (+/+). Hemochromatosis is a relatively common genetic disorder in North America. However, few are aware of this disorder or the associated health risks. Therefore, it is often not diagnosed until irreversible organ damage has occurred.[1] If untreated, the long-term risks include life-threatening hepatic and cardiac conditions.[2] Although population-based *HFE* screening may be a justifiable way to identify individuals at risk, it is important to evaluate screening risks and benefits, including the impact of an *HFE* screening program on psychosocial status or quality of life.[3,4]

Previous studies examining acceptability of genetic testing for hemochromatosis note *HFE* genotyping is acceptable to many[5] or even most[6] individuals offered testing, and studies

From the [1]Center for Health Policy Research, Department of Medicine, University of California, Irvine, California; [2]Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; [3]Department of Psychology, University of Alabama at Birmingham, Birmingham, Alabama; [4]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; [5]Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada; [6]London Health Sciences Centre London, Ontario, Canada; [7]Department of Psychology, Howard University, Washington, DC; [8]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota; [9]Kaiser Permanente, Northwest, Portland, Oregon; [10]Microbiology/Immunogenetics Program, University of Alabama at Birmingham, Birmingham, Alabama; [11]Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, NIH, DHHS, Bethesda, Maryland; and [12]Epidemiology Division, Department of Medicine, University of California, Irvine, California.

Lari B. Wenzel, PhD, Center for Health Policy Research, Department of Medicine, University of California, Irvine, CA 92697-7550. E-mail: lwenzel@uci.edu.

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have not shown deleterious psychosocial outcomes.[7–9] This has led to a preliminary conclusion that population-based screening should not be discouraged on the basis of potential adverse psychosocial effects. However, many of these studies on the impact of testing, though scientifically sound, have either been based on a relatively small sample of cases,[9] or have not included samples diverse in race or ethnicity. A recent *HFE*-associated hemochromatosis workplace screening study has shown that anxiety did not increase in those notified that they were homozygous for the Cys282Tyr mutation, or those non-homozygous. Similarly, general health perceptions also did not change after receipt of results. Moreover, the majority of study participants were pleased to have had the test, and most identified to be at risk took steps to prevent disease.[10] Further examination noting the type of genotype risk together with the type and magnitude of phenotype risk communicated to patients may also be important when considering the impact of screening on well-being, but has rarely been examined.

In the Hemochromatosis and Iron Overload Screening (HEIRS) study, a large multisite project that screened 101,168 persons for genotypic and phenotypic risk for HH and IO, an important study objective was to describe the impact of screening on participant's well-being across levels of risk.[11] The present study reports the main results of HEIRS in this regard, testing the hypothesis that levels of perceived psychological well-being, general health, and health worry would vary depending on the level of risk characterized through genotypic and phenotypic results communicated subsequent to the clinical examination. As an exploratory aim, it was also hypothesized that racial/ethnic differences in health perception would emerge in our multi-ethnic sample.

PARTICIPANTS

The study was approved by the Field Centers and the Institutional Review Boards. Participants in the HEIRS Study were recruited from five Field Centers in the United States and Canada.[12] Study recruiters approached patients who appeared to be older than 25 in waiting areas of participating HEIRS clinical sites. After briefly describing the HEIRS study, signed informed consent was obtained from those who met the age requirement and who expressed interest in participating. Information about the study was available in English, Spanish, Vietnamese, and Mandarin from recruiters fluent in these languages.

Participants were given an Initial Screening Questionnaire, in the preferred language, which included questions related to demographic status and current health perceptions. Questionnaires were translated by University-regulated translation services and then approved by the institutional IRB. Race/ethnicity was determined by self-report with two questions: one about Hispanic background and one about racial groups. Seven mutually exclusive groups representing preference according to both race/ethnicity and language included English-speaking and non-English-speaking Asians, English-speaking African Americans, Caucasians, and Hispanics, non-English-speaking Hispanics, and English-speakers with other or unknown race/ethnicity. Self-reported history of hemochromatosis or IO was noted on the questionnaire. Participants were instructed about procedures for questionnaire completion and blood draw.

Laboratory measures and clinical examination

Case subjects had specific genetic mutations and/or elevated iron parameters identified at the initial screen. Blood measurements from HH screening included transferrin saturation (TS), serum ferritin (SF) concentration, and *HFE* C282Y and H63D alleles, with elevated serum measurements of iron status defined as TS $>50\%$ for men and $>45\%$ for women, and SF >300 μg/L for men and >200 μg/L for women. Eligible participants received letters and telephone calls from Field Center staff, describing their HEIRS screening results and inviting them to participate in the clinical examination. Participants eligible for the clinical examination included 333 who were homozygous for the *HFE* C282Y allele and 1923 non-C282Y homozygotes with elevations in TS and SF. Additionally, a sample of 1231 controls with normal iron values and without known or suspected *HFE* genes was randomly selected by frequency-matching to cases with respect to Field Center, age, and time period of initial screening visit. Information on educational attainment was collected at the clinical examination and subsequently categorized as "less than high school," "high school degree," "some university, college, or vocational training," "bachelor's degree," or "postgraduate training."

Results letters

After results from the clinical examination blood work were available, a clinician at each Field Center wrote the participant a letter summarizing the evaluation. These letters were not standardized. Almost all results letters included a laboratory report with TS and SF values, their reference ranges, and the *HFE* genotype. The terms "heterozygote" and "homozygote" were explained as appropriate when one or more C282Y or H63D mutation(s) were reported. Additionally, letters included information on current presence or absence of IO, familial implications, and recommendations for clinical follow-up.

General health and psychological well-being

Perceived health was assessed at the initial screen and through a postresult questionnaire, which was mailed approximately one week after the results letter was sent. Perceived general health and psychological well-being was assessed at screening and follow-up with the two corresponding subscales of the SF-36 version 2.[13] These subscales were selected because of their sound psychometric properties, prior validation in multiple languages, and responsiveness to change among diverse medical and ethnic populations. Scale scores were calculated by converting the sum of the items to a 0–100 point range. Change scores from baseline to follow-up were used as dependent variables.

Health worry

Nine items assessing health worry (e.g., feeling upset, sad, or anxious about your test results) were adapted from the Core Items of the Cancer Genetics Studies Consortium[14] and were assessed only on the postresults survey. This measure has demonstrated capacity to discriminate HEIRS study participants' perceptions of concern for having hemachromatosis.[15] A factor analysis of this scale indicated that all nine "worry " items loaded on this single scale, with high internal consistency (alpha of >.90). The nine health worry items included (1) worry about risk of developing IO or hemochromatosis, (2) thoughts about test results caused problems in work or home life, (3) feeling frustrated that no known mutations have been found to explain IO, (4) worry about confidentiality of test results, (5) feeling that people don't think you're as good as they are, (6) worry about risk to family members, (7) having problems enjoying life because of test results, (8) feeling loss of control because of test results, (9) feeling upset, sad or anxious about test results. Answers range from 1 to 4 where 1 = Never, 2 = Rarely, 3 = Sometimes, and 4 = Often. A dichotomous variable was created because the data were skewed toward the lower end of the scale (e.g., few health worries). Therefore, participants who answered "Sometimes " or "Often " to at least one of the nine items were categorized as "worried. " Those who never answered "Sometimes " or "Often " were categorized as "not worried. " Participants must have answered at least eight of the nine items in order for them to be categorized.

Phenotype and genotype characterization

Among case subjects, three groups were formed according to genotype: (1) No *HFE* mutation detected; (2) *HFE* C282Y homozygote; (3) All other genotypes (i.e., C282Y/H63D, H63D/H63D, C282Y/+, H63D/+). Controls comprised a fourth category. Phenotype was characterized by three groups: (1) nonelevated, indicating that TS and SF were not elevated at screening, and either TS or SF or both were not elevated at the clinical examination; (2) transient elevation, indicating that TS and SF were elevated at screening, but at least one of them returned to the normal range at the clinical examination; or (3) sustained elevation, indicating that both TS and SF were elevated at both the screening and the clinical examination. The remaining potential combinations of TS and SF were not represented in the data.

A single variable with eight mutually exclusive categories represented potential interaction between genotype and phenotype: (1) nonelevated phenotype and wt/wt *HFE* genotype (controls); (2) nonelevated phenotype and C282Y/C282Y genotype; (3) transient elevation in phenotype and wt/wt genotype; (4) transient elevation in phenotype and C282Y/C282Y genotype; (5) transient elevation in phenotype and H63D/wt, H63D/H63D, C282Y/wt, or C282Y/H63D genotype; (6) sustained elevation in phenotype with wt/wt genotype; (7) sustained elevation in phenotype and C282Y/C282Y genotype; and (8) sustained elevation in phenotype and H63D/wt, H63D/H63D, C282Y/wt, or C282Y/H63D genotype.

Data analysis

Differences between study participants who responded to the second survey mailed after the clinical exam results were compared to those who did not respond. Logistic regression was used to model the binary outcome, response to survey, with adjustment for age, gender, race/ethnicity, genotype, TS, natural log of SF, general health, and psychological well-being, measured at initial screen. Multiple linear regression analysis was used to model the outcome variables, general health, and psychological well-being change scores. Predictors included continuous variables representing age and baseline scale values for general health or psychological well-being, and categorical variables representing gender, race/ethnicity/language preference, education, and the eight-level genotype-phenotype characterization. Using a similar strategy, logistic regression was applied to analyze the dichotomous outcome variable representing health worry.

RESULTS

Participant characteristics

Of 2256 participants invited as cases for clinical examinations based on the criteria noted above, 1678 (74%) participated. Of 1231 eligible participants invited into the control group, 640 (52%) individuals who carried neither the C282Y nor the H63D *HFE* alleles (wt/wt) and had SF and TS levels between the 25th and 75th percentiles of gender-specific distributions also had clinical examinations. Controls were frequency-matched to cases with respect to Field Center, age, and time period of initial screening visit. A total of 2318 eligible individuals participated in a clinical exam as either "cases" or "controls." Additional study details are described elsewhere.[11,12]

Of clinical examination participants, 720 had insufficient responses on the Initial Screen or Postresult forms to determine the change in general health and psychological well-being, and 12 did not have measurements of TS and SF at the clinical examination. Data were excluded from 108 participants who reported that they had previously been told by a doctor that they had hemochromatosis, IO, or increased iron in the body due to the possible lowering of TS or SF as a consequence of treatment. The primary analytic sample consisted of 1478 cases and controls.

Response versus nonresponse participant characteristics were compared for the 1478 cases and controls (responders) versus 674 clinical examination participants who never returned the postresults survey (nonresponders). The logistic regression model showed that younger age, race/ethnicity, lower psychological well-being, and higher SF were significant predictors of nonresponse, with no significant effect for genotype. After adjustment for covariates, non-English-speaking Asians were two times more likely to respond than Caucasians (95% CI, 1.3–2.9). African Americans, however, were 39% (29–53%) less likely to respond than Caucasians. English-speaking Hispanics were 41% (24–70%) less likely and non-English-

speaking Hispanics were 28% (18–43%) less likely to respond than Caucasians. Table 1 displays the demographic characteristics, genotype and phenotype, and health status of participants at Initial Screening. Of the 1478 participants, 68% were characterized as "no mutation detected," with sustained TS and SF elevations in 20% of this group. Further, 12% of the participants were C282Y homozygotes. In that group, 54% had sustained TS and SF elevations. The remainder of participants (20%) included all other genotypes, with 42% having sustained TS and SF elevations.

General health and psychological well-being

The variable representing phenotype-genotype combination was a statistically significant predictor of changes in psychological well-being ($P = 0.0001$), adjusting for age, race/ethnicity/language preference, education, gender, and initial screening baseline scores on psychological well-being. A mean increase in psychological well-being of 3.7 was found in controls (Table 2). Relative to the controls, we found significant decreases in psychological well-being among individuals with no *HFE* mutation detected and a transient elevation or sustained elevation in TS or SF (−0.4, −1.3, respectively), as well as non-C282Y homozygotes with a sustained elevation in both TS and SF (−1.7).

Similarly, phenotype-genotype combination was predictive of changes in general health ($P = 0.0014$), adjusted for covariates. A decrease in mean general health of −3.2 points was found in controls (Table 2). Non-C282Y homozygotes with transient elevations in TS or SF, as well as those individuals with no *HFE* mutation detected and a sustained elevation in TS and SF, had significantly decreased mean changes in general health, varying from −7.1 to −9.8.

Health worry

Phenotype-genotype combination was a statistically significant predictor of health worry ($P < 0.0001$), adjusting for age, race/ethnicity/language preference, education, and gender. For the model, Table 3 presents adjusted odds ratios and corresponding 95% confidence intervals (CIs) comparing the probability of having one or more health worry for a given genotype-phenotype combination versus that of controls. For C282Y homozygous participants with transient or sustained elevations in TS and SF, the estimated odds of reporting one or more (out of nine) health worries was 22.8 (95% CI, 8.6–60.5), and 18.1 (10.4–31.5) times greater than that of genotype-phenotype controls. Phenotype-negative C282Y homozygotes were 11.7 (6.1–22.5) times more likely than controls to report health worries, after adjusting for other covariates in the model.

Differences by race and language preference

Race/ethnicity/language preference was significantly related to change in psychological well-being, adjusted for covariates ($P < 0.0001$). Non-English-speakers reported declines in psychological well-being. Non-English-speaking Hispanics had an adjusted mean change of −5.1 on the psychological well-being scale, and non-English-speaking Asians had a mean change of −1.3 (Table 4). These declines stand in contrast to English-speakers who improved, with adjusted mean changes of 4.9 for Caucasians, 4.4 for Hispanics, 4.4 for Asians, and 2.1 for African Americans.

A significant effect of race/ethnicity/language preference also emerged with respect to mean change in general health ($P = 0.012$), with African Americans reporting a significantly greater decline (−9.2) over time than Caucasians ($P < 0.002$). Health worry was also significantly different and varied among race/ethnicity/language groups ($P < 0.0009$), with non-English-speaking Hispanics reporting 3.9 (1.75–8.83) times greater odds of health worry than that of Caucasians.

DISCUSSION

An important component of the HEIRS study was the longitudinal evaluation of the quality of life and perceptions of health associated with being screened and examined for hemochromatosis and IO, particularly given the complexities of conveying genotypic and phenotypic information in a multiethnic sample. We hypothesized that perceived general health, psychological well-being, and health worries would vary in intensity depending on the level of risk characterized through both genotypic and phenotypic results, and would differ from the control population. Indeed, in contrast to the controls, psychological well-being declined over time among participant groups considered "at risk" (e.g., those with transient or sustained elevations in TS and SF). Similarly, greater general health declines were observed in these "at risk participants" when compared to controls. Taken together these results suggest that the genotype-phenotype case groups differed from controls in health-related quality of life, although these differences were small. However, it is interesting to note that with respect to the +/+ group, for example, having a known IO phenotype but no genetic explanation may lead to some distress regarding perception of health, as demonstrated by the decline in psychological well-being and general health. Such a decline was not demonstrated within the C282Y homozygote participants. Possible explanations for this contrasting result could include the fact that the C282Y homozygote participants received more detailed genetic counseling specific to their condition within this study, which may have mitigated untoward effects on psychological well-being and general health. This is particularly plausible if they were not symptomatic from IO and if they believed and were reassured that proactive health measures could be undertaken to prevent illness or correct their health state, as indicated. In contrast, the non-C282Y participant population, including the +/+ IO group, did not receive detailed counseling and were much more likely to have ambiguity associated with interpreting their IO status in the absence of an at-risk genotype. In addition, it is possible that the uncertainty of this physical manifestation of a potential health problem, in the absence of a genetic explanation (therefore, behavioral or environmental) may lead to some distress regarding perception of health.

Table 1
Characteristics of sample

Variable	Total cases and controls	Phenotype		
		Nonelevated TS and SF	Transient elevation TS and SF	Sustained elevation TS and SF
Total, N	1478	504	549	425
Age, Mean ± SD	55.8 ± 13.5	55.3 ± 13.8	56.0 ± 13.0	56.1 ± 13.8
Gender, N (%)				
Female	749 (51%)	326 (65%)	247 (45%)	176 (41%)
Genotype, N (%)				
+/+	1003 (68%)	449 (89%)	350 (64%)	204 (48%)
H63D/+	141 (10%)	0	93 (17%)	48 (11%)
C282Y/+	64 (4%)	0	37 (7%)	27 (6%)
H63D/H63D	33 (2%)	0	19 (3%)	14 (3%)
C282Y/H63D	61 (4%)	0	24 (4%)	37 (9%)
C282Y/C282Y	176 (12%)	55 (11%)	26 (5%)	95 (22%)
Phenotype				
TS at CE, Mean ± SD, %	45.0 ± 20.6	31.5 ± 15.1	39.2 ± 10.6	68.4 ± 15.9
SF at CE, (μg/L)[a]	296 (125, 514)	90 (53, 137.5)	362 (247, 529)	534 (378, 799)
Race N (%)				
Non-Hispanic white	765 (52%)	334 (66%)	222 (40%)	209 (49%)
Black	181 (12%)	54 (11%)	79 (14%)	48 (11%)
Hispanic—English	33 (2%)	15 (3%)	12 (2%)	6 (1%)
Hispanic—Non-English	43 (3%)	11 (2%)	21 (4%)	11 (3%)
Asian/Pacific Is.—English	225 (15%)	55 (11%)	99 (18%)	71 (17%)
Asian/Pacific Is.—Non-English	198 (13%)	24 (5%)	107 (19%)	67 (16%)
Other/unknown	33 (2%)	11 (2%)	9 (2%)	13 (3%)
Education N (%)				
<High School	194 (13%)	40 (8%)	92 (17%)	62 (15%)
High School graduate	341 (23%)	109 (22%)	141 (26%)	91 (21%)
Some college	484 (33%)	177 (35%)	177 (32%)	130 (31%)
Bachelor's degree	198 (13%)	66 (13%)	68 (12%)	64 (15%)
Postgraduate training	244 (17%)	106 (21%)	69 (13%)	69 (16%)
Missing/blank	17 (1%)	6 (1%)	2 (0.4%)	9 (2%)
Health status				
General health, Mean ± SD	68.0 ± 20.7	70.5 ± 20.1	66.4 ± 20.4	67.0 ± 21.6
Psychological well-being, Mean ± SD	75.9 ± 17.8	77.1 ± 16.3	75.0 ± 18.4	75.6 ± 18.7
Change in GENERAL HEALTH	−4.8 ± 17.5	−2.4 ± 14.7	−5.9 ± 19.0	−6.3 ± 18.0
Change in psychological well-being	3.2 ± 18.1	5.8 ± 15.6	2.7 ± 19.4	0.7 ± 18.7
Worries, N (%)	635 (43%)	108 (21%)	258 (47%)	269 (63%)
Glad participated often, N (%)	710 (48%)	221 (44%)	267 (49%)	222 (52%)

TS, transferrin saturation; SF, serum ferritin; CE, clinical examination.
[a]Data are reported as median (25th percentile, 75th percentile).

Table 2
Multiple linear regression models considering the effect of genotype-phenotype on change in perceived psychological well-being (N = 1425) and general health (N = 1424)

Categorical variable level	Phenotype elevation	Genotype	Adjusted mean change in psychological well-being[a]	P^b	Adjusted mean change in general health[c]	P^d
1	Nonelevated	+/+control	3.7	N/A	−3.2	N/A
2	Nonelevated	C282Y/C282Y	4.7	0.62	−4.9	0.47
3	Transient	+/+	−0.4	0.001	−7.1	0.002
4	Transient	Other Genotypes	4.1	0.78	−7.3	0.005
5	Transient	C282Y/C282Y	3.2	0.87	−3.2	0.99
6	Sustained	+/+	−1.3	0.0003	−9.8	<0.001
7	Sustained	Other Genotypes	−1.7	0.001	−4.8	0.35
8	Sustained	C282Y/C282Y	1.0	0.12	−5.7	0.18

[a]Adjusted for gender, age, race/ethnicity/language preference, education and baseline psychological well being.
[b]*P* value for the test of the null hypothesis that the estimated mean change in psychological well-being for that of a specified phenotype-genotype group is not significantly different from that of the control group with nonelevated phenotype.
[c]Adjusted for gender, age, race/ethnicity/language preference, education, and baseline general health.
[d]*P* value for the test of the null hypothesis that the estimated mean change in general health of the phenotype-genotype group is not significantly different from that of the control group with nonelevated phenotype.

Table 3
Multiple logistic regression model to consider the effect of genotype-phenotype on probability of having one or more health worry (N = 1393)

Phenotype elevation	Genotype	Adjusted odds ratio[a]	95% confidence interval	
Nonelevated	+/+control	Ref	Ref	Ref
Nonelevated	C282Y/C282Y	11.7	6.1	22.5
Transient	+/+	4.2	2.9	6.1
Transient	Other Genotypes	4.4	2.9	6.8
Transient	C282Y/C282Y	22.8	8.6	60.5
Sustained	+/+	8.0	5.2	12.3
Sustained	Other Genotypes	11.4	7.1	18.5
Sustained	C282Y/C282Y	18.1	10.4	31.5

[a]Adjusted for gender, age, race/ethnicity/language preference and education.

It was important to determine whether these differences were clinically meaningful, and if so what implications this might have. For the model of changes in psychological well-being reported in Table 2, the estimated standard deviation (SD) in change score was 14.6 points. Using a change in excess of one-third SD in absolute value (4.85 points) to indicate a clinically meaningful change,[16] none of the phenotype/genotype differences reported in Table 2 exceed this limit. In contrast, non-English-speaking Hispanics did exhibit a clinically meaningful decrease in psychological well-being after screening (Table 4). For change in general health the model-based estimate of 1 SD was 15.8 points. On the basis of a decrease in excess of 5.26 points, only individuals with no mutation detected and sustained elevations in TS and SF exhibited a clinically meaningful decrease in general health below that of controls (Table 2). Clinically meaningful decreases in general health were detected in non-English-speaking Asians, African Americans, and English-speaking Hispanics (Table 4), but no race/ethnic groups had a clinically-meaningful decrease relative to that of English-speaking Caucasians. The fact that those with sustained TS and SF had lower general health and psychological well-being scores at baseline compared to those with nonelevated iron suggests that they may have already known that they had health problems, or were experiencing symptoms associated with a given health problem. Recruitment occurred within multiple medical settings; therefore, these are plausible explanations.

With respect to general health and psychological well-being changes, our results can be contrasted to those of Delatycki et al., in which genotypic but not phenotypic risk information was communicated to workplace participants.[10] The information communicated in the HEIRS study added a level of complexity through inclusion of phenotypic risk information, in a population recruited from health care settings. Importantly, our results suggest that phenotype-genotype information could predict changes in both psychological well-being as well as general health. However, many have noted that measuring general mood or other psychological states may lack sensitivity to the important and unique issues that surround genetic testing,[17,18] or screening.

The concept of health worry was predicted to be a more sensitive measure of potential health concerns raised from this study. Indeed, health worry was differentially affected by screening, with the potentially most vulnerable populations, defined by genotype, reporting the most health worry. However, this should be considered within the context of the overall data, in which relatively few study participants endorsed significant health worries as a result of receiving information through this study. This may corroborate the work of Delatycki et al., who found that most participants were not made

Table 4
Regression model results considering the effect of race/ethnicity/language preference on change in perceived psychological well-being (N = 1425), change in general health (N = 1424), and health worry (N = 1393)

						Health worry	
Race/ethnicity	Language	Adjusted mean change in psychological well-being[a]	P^d	Adjusted mean change in general health[b]	P^d	Adjusted odds ratio[c]	95% confidence interval[c]
Asian	English	4.4	0.67	−2.9	0.23	1.7	(1.15–2.51)
	Non-English	−1.3	<0.001	−6.6	0.18	1.6	(1.03–2.41)
African American	English	2.1	0.04	−9.2	0.002	2.1	(1.38–3.14)
Hispanic	English	4.4	0.84	−7.2	0.36	1.8	(0.78–4.00)
	Non-English	−5.1	0.0001	−4.4	0.96	3.9	(1.75–8.83)
Other/ Unknown	English	2.4	0.34	−5.6	0.71	2.0	(0.89–4.61)
Caucasian	English	4.9	NA	−4.5	NA	Ref	Ref

[a]Adjusted for gender, age, education, baseline value for pyschological well-being, and genotype/phenotype group.
[b]Adjusted for gender, age, education, and baseline value for General Health, and genotype/phenotype group.
[c]Adjusted for gender, age, education, and baseline value for Health Worry, and genotype/phenotype group.
[d]*P* value for the null hypothesis of no difference in mean change in perceived psychological well-being, mean change in general health, or mean health worry for race/ethnicity/language group relative to English-speaking Caucasians, after adjustment for covariates.

anxious by study participation. Similarly our results suggest that most did not develop worries over their health status as a result of participation. These results therefore have important implications for population-based screening studies in which genotype is characterized and communicated. In general, large scale HH and IO screening does not seem to have deleterious affects on health-related quality of life. Indeed, information provided through this study could be helpful to those ultimately in need of treatment for this potentially life-threatening condition.

When considering these data, the overall result of communicating complicated genotypic and phenotypic information requires careful evaluation. A unique contribution of this study was the evaluation of the health-related quality of life changes among minority populations when considering the potential impact of this information. To that end, results from this study underscore the importance of a multiethnic representation in population-based screening studies, because these data suggest that perceptions of health and responsiveness to health information conveyed in this type of setting and manner are culturally variable. Indeed this may have been evident through the differential response rates, in which minorities in general were less likely to return the follow-up questionnaire. Future attention and study regarding recruitment and retention in population-based screening studies is essential.

Even after controlling for many explanatory variables, including genotype and phenotype, non-English-speakers seemed to report worse psychological well-being and more health worry. It is important to note, however, that issues associated with both translation and cultural competency of our instrumentation and data collection procedures may be an inherent study weakness. This may actually have additional implications for a more generic negative effect of screening on non-English-speaking or lower socioeconomic status populations, and an indication to do more with respect to educating during trial participation, regardless of phenotype or genotype and perhaps tailoring genetic counseling to address culturally relevant concerns. In addition, African Americans reported the most general health deterioration. Anecdotal impressions from staff recruiting African Americans implied that the health information conveyed through HEIRS was often considered yet another piece of "bad news" to be dealt with in an already difficult time. Vulnerable study participants are likely to have difficulty accessing regular, coordinated care. Therefore, it is also likely that additional effort is required on the part of the study team to truly provide benefit from a phenotypic-genotypic population-based screening program.

Future research should further investigate the reasons for health worries in the vulnerable and non-English-speaking participants.[19] Focus could be placed on those told that HH and IO were not a threat, yet their perception of health worry exceeded that of others who potentially had the disorder(s). For example, non-English-speaking or other potentially underserved study participants may have serious concerns about their health if without insurance coverage. Indeed, the implications of potentially negative news about their health may have much more far reaching implications for participants without a health care safety network. Future research should examine the potential value of educational support for those who have health concerns as a result of participating in a study in which information regarding possible health risks is given to participants as a built-in component of the study.

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Field Centers: University of Alabama at Birmingham, Birmingham, AL—Dr. Ronald T. Acton (Principal Investigator), Dr. James C. Barton (Co-Principal Investigator), Ms. Deborah Dixon, Dr. Charles A. Rivers, Dr. Diane Tucker and Ms. Janice C. Ware; University of California, Irvine, CA—Dr. Christine E. McLaren (Principal Investigator), Dr. Gordon D. McLaren (Co-Principal Investigator), Dr. Hoda Anton-Culver, Ms. Jo Ann A. Baca, Dr. Thomas C. Bent, Dr. Lance C. Brunner, Dr. Michael M. Dao, Dr. Korey S. Jorgensen, Dr. Julie Kuniyoshi, Dr. Huan D. Le, Dr. Miles K. Masatsugu, Dr. Frank L. Meyskens, Dr. David Morohashi, Dr. Huan P. Nguyen, Dr. Sophocles N. Panagon, Dr. Chi Phung, Dr. Virgil Raymundo, Dr. Thomas Ton, Professor Ann P. Walker, Dr. Lari B. Wenzel and Dr. Argyrios Ziogas; London Health Sciences Center, London, Ontario, Canada—Dr. Paul C. Adams (Principal Investigator), Ms. Erin Bloch, Dr. Subrata Chakrabarti, Ms. Arlene Fleischhauer, Ms. Helen Harrison, Ms. Kelly Jia, Ms. Sheila Larson, Dr. Edward Lin, Ms. Melissa Lopez, Ms. Lien Nguyen, Ms. Corry Pepper, Dr. Tara Power, Dr. Mark Speechley, Dr. Donald Sun and Ms. Diane Woelfle; Kaiser Permanente Center for Health Research, Northwest and Hawaii, Honolulu, HI, Oregon Health and Science University, Portland, OR—Dr. Emily L. Harris (Principal Investigator), Dr. Mikel Aickin, Dr. Elaine Baker, Ms. Marjorie Erwin, Ms. Joan Holup, Ms. Carol Lloyd, Dr. Nancy Press, Dr. Richard D. Press, Dr. Jacob Reiss, Dr. Cheryl Ritenbaugh, Ms. Aileen Uchida, Dr. Thomas Vogt and Dr. Dwight Yim; Howard University, Washington, DC—Dr. Victor R. Gordeuk (Principal Investigator), Dr. Fitzroy W. Dawkins (Co-Principal Investigator), Ms. Margaret Fadojutimi-Akinsiku, Dr. Oswaldo Castro, Dr. Debra White-Coleman, Dr. Melvin Gerald, Ms. Barbara W. Harrison, Dr. Ometha Lewis-Jack, Dr. Robert F. Murray, Dr. Shelley McDonald-Pinkett, Dr. Juan Romagoza and Dr. Robert Williams. *Central Laboratory*: University of Minnesota and Fairview-University Medical Center, Minneapolis, MN—Dr. John H. Eckfeldt (Principal Investigator and Steering Committee Chair), Ms. Catherine Leiendecker-Foster, Dr. Ronald C. McGlennen, Mr. Greg Rynders and Dr. Michael Y. Tsai. *Coordinating Center:* Wake Forest University, Winston-Salem, NC—Dr. David M. Reboussin (Principal Investigator), Dr. Beverly M. Snively (Co-Principal Investigator), Dr. Roger Anderson, Ms. Elease Bostic, Ms. Brenda L. Craven, Ms. Shellie Ellis, Dr. Curt Furberg, Mr. Jason Griffin, Dr. Mark Hall, Mr. Darrin Harris, Ms. Leora Henkin, Dr. Sharon Jackson, Dr. Tamison Jewett, Mr. Mark D. King, Mr. Kurt Lohman, Ms. Laura Lovato, Dr. Joe Michaleckyj, Ms. Shana Palla, Ms. Tina Parks, Ms. Leah Passmore, Dr. Pradyumna D. Phatak, Dr. Stephen Rich, Ms. Andrea Ruggiero, Dr. Mara Vitolins, Mr. Gary Wolgast and Mr. Daniel Zaccaro. *NHLBI Project Office:* Bethesda, MD—Ms. Phyliss Sholinsky (Project Officer), Dr. Ebony Bookman, Dr. Henry Chang, Dr. Richard Fabsitz, Dr. Cashell Jaquish, Dr. Teri Manolio and Ms. Lisa O'Neill. *NHGRI Project Office:* Bethesda, MD—Ms. Elizabeth Thomson. Dr. Jean MacCluer, Southwest Foundation for Biomedical Research, also contributed to the design of this study.

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