Searching for Hereditary Hemochromatosis

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OBJECTIVE: To detect hereditary hemochromatosis (HH) in low-income residents of a medically underserved region through free screening and confirmatory laboratory testing and to raise awareness of HH in the general population.

DESIGN: Two-tiered reflexive laboratory testing was used to screen for HH. Participants evaluated the project by written survey upon its conclusion. Data were analyzed by descriptive techniques.

SETTING: Local public health departments in 18 counties in western North Carolina (WNC).

PARTICIPANTS/SUBJECTS: Phase 1: adult volunteers age ≥ 20 without previous diagnosis of HH; Phase 2: Phase 1 participants with elevated screening results and adult family members of Phase 2 participants found to have *HFE* mutations; Phase 3: randomly-selected Phase 1 participants (Survey A) and all Phase 2 participants with *HFE* mutations (Survey B).

INTERVENTIONS: Phase 1 (initial screening): non-fasting blood collection by venipuncture with testing for transferrin saturation (TS). Phase 2 (confirmatory testing): fasting blood collection by venipuncture for TS, serum ferritin (SF), and cheek swab for DNA analysis for two *HFE* mutations (C282Y and H63D). Phase 3: written Surveys A and B.

MAIN OUTCOME MEASURES: Total number participants screened for HH; prevalence of elevated TS in Phase 1 participants; prevalence of *HFE* genotypes consistent with HH (C282Y/C282Y and C282Y/H63D) in Phase 2 participants; prevalence of elevated SF in subjects with *HFE* mutations; number of family members tested; number of participants being treated for HH as a result of screening; increase in awareness of HH among Phase 1 participants.

RESULTS: 2,034 total subjects participated in screening events and/or family member testing. Of the 1,976 Phase 1 participants, 130 (6.6%) had elevated TS (≥ 45%). Twenty of 130 (15.4%) Phase 2 subjects were homozygotes for C282Y. The prevalence of the C282Y/C282Y genotype among the Phase 1 participants who were tested in Phase 2 was 20/1976 (1.0%). Fourteen of 20 (70%) C282Y homozygotes had elevated SF. Eleven of 130 (8.5%) Phase 2 subjects were compound heterozygotes for C282Y and H63D, and none had elevated SF. Of 58 family members tested, two (3.4%) were homozygotes for C282Y and eight (13.8%) were compound heterozygotes for C282Y and H63D. One of two (50%) family members homozygous for C282Y had an elevated SF. No compound heterozygotes had elevated SF. Sixty-four of 120 (54.2%) Phase 1 subjects responded to Survey A. 53.1% of respondents were unaware of HH prior to the screening event. 92.1% of respondents told their family and friends about HH after participating. 73.4% discussed their laboratory results with their healthcare provider. Twenty of 41 participants (48.8%) found to have *HFE* mutations associated with HH responded to Survey B. Eleven of 20 (55.0%) stated that they were being treated for HH.

CONCLUSION: The prevalence of the major genetic mutation, C282Y/C282Y, associated with HH among Phase 1 study participants in WNC was 1%, more than three times the national prevalence of approximately 0.33%. Results suggest that free screening using laboratory tests in a two-tiered reflexive approach may be an effective means of detecting HH, especially in high-risk populations. Early detection through free laboratory screening tests may reduce morbidity and, ultimately, healthcare costs for low-income individuals. Awareness of HH as a health concern may increase as a result of publicity generated by screening events.

ABBREVIATIONS: HESP = Hemochromatosis Education and Screening Project; HH = hereditary hemochromatosis; PHD = public health department; SF = serum ferritin; SI =

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serum iron; TIBC = total iron binding capacity; TS = transferrin saturation; WNC = western North Carolina.

INDEX TERMS: hemochromatosis; iron overload.

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Hemochromatosis is a progressive disease that results from iron overload. It can have genetic or non-genetic causes. Most cases of hemochromatosis in the United States are linked to mutations of the *HFE* gene and are referred to as hereditary hemochromatosis (HH). Genetic mutations associated with HH occur more frequently than those associated with other genetic disorders such as cystic fibrosis and sickle cell disease in which there is greater public familiarity. Very importantly, HH often goes unrecognized and undetected by healthcare providers during routine primary care. It is estimated that only ten percent of affected individuals are actually being diagnosed at the present time, suggesting that there is a need for educating healthcare providers about HH.[1]

HH is a disorder of iron regulation that may lead to an abnormal increase in dietary iron absorption. Iron in excess of normal storage capacity is toxic to cells. Progressive loading of iron can be seen in parenchymal cells in the liver, heart, pancreas, and other organs of some individuals affected by HH. Early detection and treatment of iron overload is important to prevent the serious morbidity that occurs in some patients.

In its early stages, clinical symptoms of HH are vague and nonspecific, posing a diagnostic challenge for clinicians. Early signs and symptoms may include fatigue, depression, irritability, joint pain, elevated liver enzymes (AST, ALT), amenorrhea, and impotence. Over time as iron is increasingly deposited in tissues, signs and symptoms associated with organ damage may appear. Late stage signs and symptoms include diabetes mellitus, gray or bronze skin tone, cirrhosis, hepatocellular carcinoma, joint disease, congestive heart failure, arrhythmias, hypopituitarism, increased incidence of bacterial infections, and chronic abdominal pain.[2] Results of biochemical tests for iron and DNA tests for *HFE* mutations coupled with clinical signs and symptoms provide the means for an accurate diagnosis of HH.

Several mutations of the *HFE* gene have been identified.[3] Two mutations, C282Y and H63D, have been studied extensively and are linked to HH. In studies of persons diagnosed with clinical HH, 90% or more of individuals are homozygous for C282Y. A small number of affected persons are compound heterozygotes for C282Y and H63D. A few affected individuals are homozygous for H63D, compound heterozygotes for C282Y and other mutations, or single heterozygotes for either C282Y or H63D.[4,5,6]

The C282Y/C282Y genotype is present in approximately 0.2% to 0.5% individuals in the United States. Ten percent to 12% of the US population may be carriers of a single C282Y mutation.[4,7] The highest prevalence is found in Caucasians, primarily those of northern European or Celtic descent, and HH is most prevalent in persons with Irish, Scottish, French, and Scandinavian ancestors.[8] The overall prevalence of the C282Y/C282Y genotype was found to be 0.33% in a recent study of almost 100,000 subjects in a diverse population. *HFE* mutations associated with HH were also found in other ethnic groups such as Hispanics and African Americans, although at much lower prevalence.[9]

Based on current data, at least 50% of males and 25% of females homozygous for the C282Y mutation will develop organ-damaging and life-threatening disease unless treated.[10] However, not all persons carrying *HFE* mutations develop symptoms of iron overload. Also, some individuals diagnosed with HH in screening studies are asymptomatic, in spite of laboratory evidence of iron overload.[2,11] One study found that persons diagnosed with HH through screening did not have a higher rate of symptoms than normal controls.[12] The penetrance of the C282Y/C282Y genotype, or proportion of persons with the genotype who develop clinical disease, is thought to be considerably less than 100%.[5,11] The penetrance of the other known *HFE* mutations is very low.[13] It may be that environmental or as yet unknown genetic factors interact with known *HFE* mutations to enhance or suppress phenotypic expression.

Therapeutic phlebotomy provides a low-cost, safe, and effective treatment for iron overload in HH. Through a series of periodic phlebotomies, excess iron is gradually removed from the tissues as it becomes incorporated into developing

erythrocytes. Therapy must be continued throughout the individual's lifetime to prevent excess iron from re-accumulating. Effectively treated individuals diagnosed early with HH have been found to experience normal lifespans.[14]

Primary iron overload due to HH must be differentiated from secondary or acquired iron overload caused by iron-loading anemias, liver disease, and other conditions. Clinical findings, patient history, and laboratory test results are used in the differential diagnosis of various forms of hemochromatosis.

The only reliable means of detecting and confirming a diagnosis of HH is through the use of appropriate laboratory tests. Biochemical tests for iron provide simple and inexpensive laboratory screening tests for iron overload associated with HH. An elevated fasting transferrin saturation (TS) > 45% provides the earliest evidence that iron overload is present and should be the initial screening test.[15] TS is based on measuring the serum iron (SI) and total iron binding capacity (TIBC) and calculating by the formula:

$$TS = (SI/TIBC) \times 100$$

A single, elevated TS should be followed by a repeat TS and serum ferritin (SF) performed on a fasting blood specimen. SF levels reflect iron stores and if elevated, provide evidence that iron is accumulating in the tissues. When coupled with an elevated TS, an SF >200 μg/L in pre-menopausal women or >300 μg/L in men or post-menopausal women is considered elevated and warrants confirmation of HH.[15]

SF levels are associated with the clinical signs and symptoms of HH, with higher SF levels found for persons with clinical manifestations.[16] It should be noted that ferritin is an acute-phase reactant and may be elevated in other disorders, notably inflammation, infection, and malignancies. These conditions should be ruled out in order to properly evaluate an elevated SF.

Confirmation of hemochromatosis in persons with elevated screening results (TS and SF) may be achieved by one of three methods: laboratory testing for *HFE* mutations, quantitative phlebotomy, or liver biopsy. Quantitative phlebotomy documents the number of units of blood, and thereby amount of iron, removed over time and is performed as part of iron overload therapy. Iron accumulation in tissue has traditionally been confirmed by liver biopsy, but biopsy is now recommended only if liver disease is suspected.[15]

The presence of *HFE* genotypes associated with HH such as homozygosity for C282Y or compound heterozygosity for C282Y and H63D, coupled with laboratory evidence of iron overload, typically confirms a diagnosis of HH. DNA analysis for *HFE* mutations is most useful in confirmatory testing of individuals with documented iron overload (increased TS and SF), in testing pre-symptomatic persons (increased TS, normal SF, and normal liver enzymes), and in screening family members of individuals diagnosed with HH. Genotyping of first degree relatives of affected family members is recommended, but testing of children can be postponed until age 20 because of typical lack of organ damage before this age.[17] DNA testing for *HFE* mutations alone can not predict severity of HH. At the present time the College of American Pathologists, Centers for Disease Control and Prevention, and other consensus groups do not recommend the use of genetic tests for routine screening of asymptomatic persons (population screening).[15,18,19]

Lack of access to healthcare may prevent some individuals from being tested for HH. Without regular health assessments, some persons with early HH may progress to develop significant iron overload, seeking healthcare only when serious and costly medical conditions arise. It has been estimated that at least 40 million Americans are without health insurance. Increasing access to laboratory screening tests may lead to earlier detection of HH, thus improving health and reducing healthcare costs in the long term.

The goal of the Hemochromatosis Education and Screening Project (HESP) was to provide free laboratory screening tests for HH to low-income residents of WNC. This area of the southern Appalachians is inhabited predominantly by persons of northern European descent, including Scots, Irish, and English.[20] The percentage of white residents in the 18 WNC counties included in this study was 93.3.[21] Because HH is found in the highest prevalence in persons of Celtic descent, it was thought that there might be many cases of HH among WNC residents.

WNC is a region with low per capita income and is considered a medically underserved area. The per capita income for the 18 counties participating in HESP is $23,254, which is well below the North Carolina state average of $27,785. Over 20% of residents are enrolled in Medicaid, and 12.9% live below the poverty level. There is, on average, one primary care physician per 1,513 residents, considerably below the state average of one per 1,193.[21] Due to lack of primary healthcare or medical insurance, many residents of WNC may have limited access to testing for HH.

Funding for HESP was obtained from a grant by a private foundation, the Kate B. Reynolds Charitable Trust (Winston-Salem, NC). Laboratory Corporation of America (Burlington, NC) and Kimball Genetics (Denver, CO) significantly discounted charges for the laboratory screening and confirmatory tests, respectively. Additional personnel support came from the NC Department of Health and Human Services Genetic Health Unit, 18 county health departments in WNC, and the Department of Allied Health Sciences at the University of North Carolina at Chapel Hill.

Members of an advisory board composed of clinical laboratory scientists, geneticists, public health directors, physicians, health educators, and patients reviewed all materials and evaluated methods prior to implementation. The Institutional Review Board of the University of North Carolina at Chapel Hill School of Medicine approved this project.

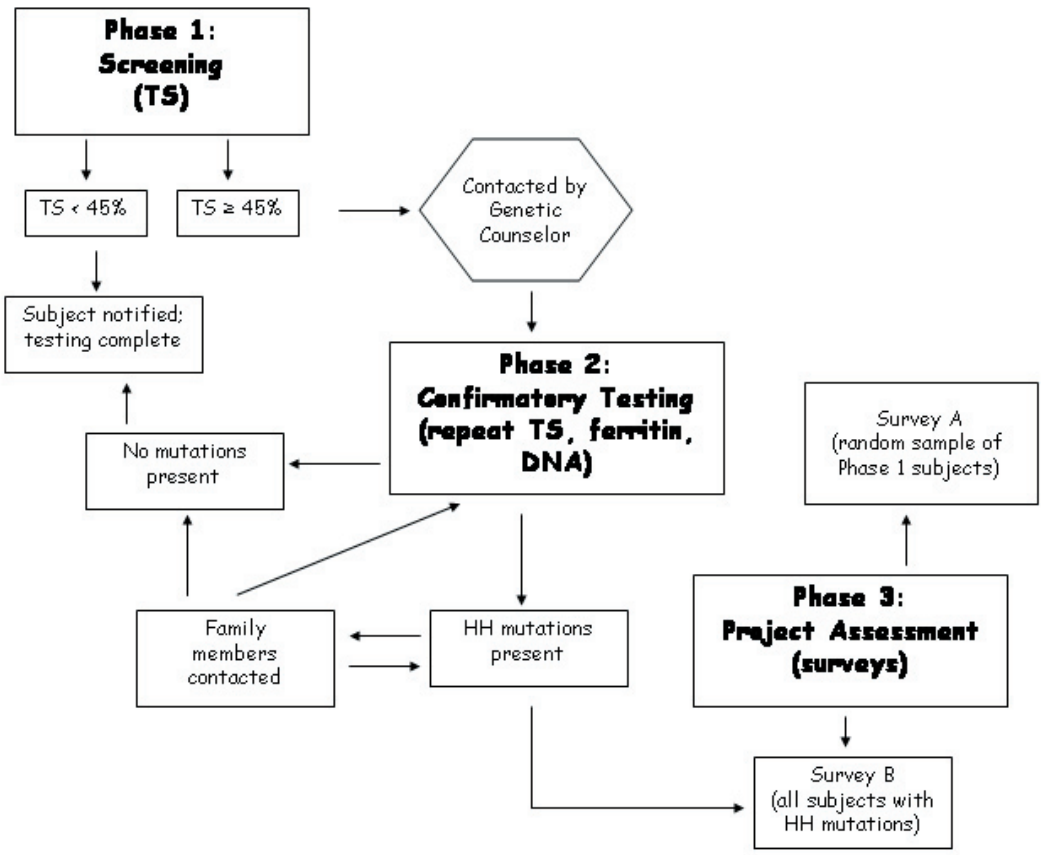
MATERIALS AND METHODS

Procedure

The Hemochromatosis Education and Screening Project was divided into three phases conducted over an approximate 15-month period (Figure 1).

Phase 1 (screening) consisted of 19 one-day screening events held at local public health department (PHD) facilities in 18 counties in WNC during 2001. In order to reach the widest audience, screening events were publicized several weeks in advance through the local PHDs. Methods of notification included flyers posted at PHDs, places of employment, churches, senior centers, and other locations. Public service announcements in local newspapers and on radio and television were also used. PHD staff advised HESP staff on suitable methods for promoting local screening events and assisted with distribution of promotional materials.

Figure 1. HESP phases over a period of approximately 15 months



Each participant spent approximately 45 minutes completing all HESP requirements. Typically two HESP staff members administered informed consent, completed laboratory test requisitions and other paperwork, and answered subjects' questions. One to three phlebotomists, hired by HESP, were scheduled for each event in order to perform venipunctures on the subjects. PHD staff assisted with directing participants and other functions such as specimen processing.

Venipunctures were performed on all subjects participating in Phase 1. Most subjects were non-fasting, as appointments were scheduled throughout the day of the screening event. Code numbers were used to identify subject samples. HESP staff later matched coded test results to subjects' identities for purposes of reporting. Blood specimens were sent by courier to a single reference laboratory in NC for testing.

Both subjects and their healthcare providers were notified in writing by HESP staff of the Phase 1 screening test results, including numerical results and a brief interpretation. Two copies of the letter were mailed to subjects who had not identified a healthcare provider. Primary healthcare was provided by local PHD staff for many subjects. Healthcare providers of participants with elevated TS results were sent additional materials on diagnosis and treatment of HH.

A regional genetic counselor telephoned each participant with elevated TS results to discuss HH and to determine the individual's desire to undergo further laboratory analyses including biochemical and genetic testing. Subjects could elect to withdraw from the study at this point.

Phase 2 consisted of conducting confirmatory laboratory tests on Phase 1 subjects who had elevated screening results. Participants in Phase 2 were asked to schedule an appointment for venipuncture and report to the local PHD after a 12 hour fast. PHD staff completed paperwork, collected blood, and sent specimens to the reference laboratory for the relative small numbers of subjects requiring Phase 2 testing. At this time, Phase 2 participants were also given home collection kits for DNA testing and instructions for collecting and mailing specimens to the reference laboratory.

Phase 2 subjects were mailed results of their confirmatory tests along with detailed interpretive information provided by the reference laboratory. Phase 2 participants were urged to share these results with their healthcare providers; however, providers were not given Phase 2 testing results by HESP.

Participants with *HFE* mutations associated with HH were advised by the regional genetic counselor to discuss these findings with their blood relatives. First-degree family members (mothers, fathers, siblings, and children) were invited through their relatives to participate in Phase 2 testing. HESP provided them with printed information for distribution. Testing was limited to only those relatives residing in the project's service area of WNC. PHD staff conducted Phase 2 activities on participating family members, including collecting blood and obtaining informed consent. The regional genetic counselor also contacted family members who consented to undergo Phase 2 testing in order to provide additional information about HH and genetic testing.

Phase 3 consisted of the administration of written surveys to study participants. Survey A (Table 1) was mailed in January 2002 to a random sample of 120 Phase 1 participants: 60 with normal TS and 60 with elevated TS (≥ 45%). Survey B (Table 2) was mailed in March 2002 to 41 subjects with mutations associated with HH.

HESP assumed the cost of laboratory testing of all subjects, but did not pay for transportation, medical care, or treatment of participants. HESP staff assisted participants with locating healthcare providers if needed. Genetic counseling was provided by the State of North Carolina regional genetic counselor. Participants received no financial incentives or inducements to join this study.

Laboratory analyses

Tests performed on Phase 1 participants were serum iron (SI), total iron binding capacity (TIBC), and the calculation of transferrin saturation (TS). Because screening events took place throughout the day, participants in Phase 1 had not been instructed to fast. Subjects with TS ≥45% were referred for Phase 2 confirmatory testing.

Tests performed on Phase 2 participants included SI, TIBC, TS, serum ferritin (SF), and DNA tests for two *HFE* mutations commonly associated with HH: C282Y and H63D. Participants were instructed to fast for 12 hours prior to Phase 2 blood collection. Subjects were given cheek cell home collection kits supplied by Kimball Genetics for DNA analyses.

Subjects who were found to be homozygous for C282Y or compound heterozygous for C282Y and H63D were considered to have *HFE* genotypes consistent with HH.

Table 1. HESP Phase 3 Survey A

Please circle the correct answer for each question.

1. I knew about the disease hemochromatosis **before** I took part in this project.
   YES NO

2. I **first** learned about hemochromatosis when I went for my blood test.
   YES NO

3. The videotape I watched was helpful in learning about hemochromatosis.
   YES NO

4. The printed information I got was helpful in learning about hemochromatosis.
   YES NO

5. Talking to the project staff was helpful in learning about hemochromatosis.
   YES NO

6. I told my friends and family about hemochromatosis because of this project.
   YES NO

7. My hemochromatosis test result (transferrin saturation) was
   NORMAL LOW HIGH

8. I talked to my health care provider (doctor or nurse) about my test results.
   YES NO

9. I talked to project staff on the phone about my test results.
   YES NO

10. Talking to project staff was helpful in understanding my test results.
    YES NO

11. I am now being treated for hemochromatosis.
    YES NO

12. I heard about the hemochromatosis testing event from. (Circle all that apply.)
    FRIEND RADIO TV CHURCH WORK
    DOCTOR HEALTH DEPARTMENT BULLETIN BOARD
    OTHER

Comments:

Subjects with these *HFE* genotypes and elevated SF were considered to have HH. SF levels > 200 μg/L in pre-menopausal women or >300 μg/L in men or post-menopausal women were considered elevated. Subjects were not assessed for clinical signs and symptoms of HH as part of the study.

Subjects

Subjects for Phase 1 were adult volunteers age ≥ 20 who were not known to have HH. Knowledge of health status with regard to HH was by self-report on the Participant Information Sheet. Two participants with previously diagnosed HH were tested, but were excluded from data analyses.

Subjects for Phase 2 consisted of two groups. One group was composed of Phase 1 participants with TS results ≥ 45%. A second group consisted of family members of the Phase 1 participants who had *HFE* mutations consistent with HH. All subjects in Phase 2 were adult (age ≥ 20) volunteers.

Subjects for Phase 3 were participants in Phases 1 and/or 2. Subjects were randomly selected to complete Survey A. All participants identified through testing as having HH mutations were mailed copies of Survey B.

Subjects gave written informed consent for participating in all phases of HESP.

Materials

A one page participant information sheet was used to collect subjects' demographic and contact information. Participants were also asked to list the name and address of their healthcare providers so that Phase 1 results could be directly mailed. An informed consent document was used to explain the project's methods, benefits, and

potential risks, and to give contact information for the study's sponsor and principal investigator. A copy was given to each participant for his/her personal records. A two-page brochure was used to provide printed information about HH for the participants to take home. All documents were written by HESP staff at appropriate literacy levels to reflect those of the target population.

A ten minute videotape was shown in order to give potential participants additional information on HH prior to giving informed consent. The Institutional Review Board of the University of North Carolina at Chapel Hill School of Medicine approved all materials.

RESULTS

Nineteen screening events were held in 18 counties in WNC over a 12-month period. The number of participants per one-day screening event ranged from 31 to 241, with an average of 92 subjects per event. Two events were held in one county to accommodate the large number of residents interested in being tested. A total of 1,976 subjects completed Phase 1 of the project by undergoing screening for HH.

The number of Phase 1 participants with elevated TS (≥ 45%) was 130 of 1,976 (6.6%). Participants with elevated TS were found in all but two counties. These were the two with the lowest number of participants: 31 and 39.

Table 2. HESP Phase 3 Survey B

Please circle YES or NO to the following questions

1. I saw my doctor (or nurse or other healthcare provider) and gave him/her the results of the laboratory tests for hemochromatosis.
   YES NO

2. I am being treated for hemochromatosis.
   YES NO

3. I am not being treated for hemochromatosis, but my doctor (or nurse or other health care provider) is aware of the laboratory test results.
   YES NO

4. I have told my family members about hemochromatosis.
   YES NO

5. This project provided useful information about my health.
   YES NO

Please feel free to add comments:

Of 129 Phase 1 subjects taking part in Phase 2, 31 (24.0%) had *HFE* mutations consistent with HH. Twenty of 129 (15.5%) subjects were homozygous for C282Y, and 11 (8.5%) were compound heterozygous for C282Y and H63D. The remaining 98 participants (76.0%) were homozygous for H63D, heterozygous for C282 or H63D, or had normal *HFE* genotypes. Of 1,976 total Phase 1 participants, 31 (1.6%) had *HFE* mutations commonly associated with HH. The prevalence of *HFE* mutations commonly associated with HH among all Phase 1 study participants was .016.

Of the 20 subjects who were homozygous for C282Y, 14 (70%) had elevated SF levels. The mean SF level for this group was 485.4 μg/L, and the range was 312 to 1,077 μg/L. None of the 11 compound heterozygotes demonstrated elevated SF. Fourteen participants in Phase 1 testing thereby met both criteria for a diagnosis of HH in this study: presence of an *HFE* mutation and elevated SF.

Fifty-eight family members of Phase 1 subjects with *HFE* mutations took part in Phase 2 testing. Ten of the 58 family members (17.2%) were found to have *HFE* genotypes associated with HH, including two who were homozygous for C282Y and eight who were compound heterozygous for C282Y and H63D. Twelve family members were unable to complete biochemical testing as they resided outside of the project area. Of the 46 family members undergoing biochemical testing for iron, 12 (26.1%) had either an elevated TS or SF or both. One family member, a C282Y homozygote with an elevated SF, met both criteria for a diagnosis of HH as defined by this study.

A total of 2,034 subjects were screened for HH, including 1,976 Phase 1 participants and 58 family members. The mean subject age was 53.0 years, and the range was 20 years to 96 years. 70% of study participants were female. Race was indicated as white by 98.2% of subjects.

Sixty-four of the 120 (54.2%) randomly selected Phase 1 subjects responded to Survey A. 53.1% of respondents were unaware of HH prior to the screening event. 92.1% of respondents told their family and friends about HH after participating. 73.4% discussed their laboratory results with their healthcare provider. Twenty-four of 41 Phase 2 participants (58.5%) found to have *HFE* mutations responded to survey B. Eleven of 24 (45.8%) were being treated for HH.

DISCUSSION

Screening volunteers using free laboratory tests was found to be an effective way to detect undiagnosed hereditary hemochromatosis (HH) in a population of adults in a medically underserved region of western North Carolina. Fourteen previously undiagnosed subjects met the criteria for a diagnosis of HH through participation in this study. Eleven participants stated on a follow-up survey that they were currently being treated for HH.

Through the promotion of free screening events by local PHDs, over 2,000 individuals were tested for HH during a one year period. HESP staff considered the average of 92 subjects recruited per event adequate to justify using this approach. In one county, a second screening event was needed to accommodate the number of residents requesting screening. HESP staff believed that planning and working with PHD staff was crucial to the project's success and attests to the key role played by these agencies in delivering primary care to medically underserved residents. In all counties, HESP was viewed as providing a vital service to PHD patients. PHD directors serving on the HESP advisory board indicated that screening for HH in this population could not have been undertaken without the services of HESP.

The prevalence of the major mutation associated with HH, homozygosity for C282Y, was found to be 0.10% of the participants screened in Phase 1. This is considerably higher than the prevalence reported in other population screening studies. There are two possible interpretations of the high prevalence determined by this study. It may be that the true prevalence in the population of Caucasians residing in WNC, many of whom are descended from early settlers of Celtic ancestry, is actually 0.10%. An alternate explanation is that publicizing the screening events was effective in recruiting volunteers at greater risk for HH, in which case the study's findings over-estimate the true prevalence. Approximately 47% of Phase 1 participants responding to Survey A indicated they were familiar with HH before enrolling in the study. Because data were collected on volunteers who attended HH screening events and were not collected on a random sample of the area's population, the prevalence cannot be generalized. Only additional studies on random samples will adequately address this issue.

During Phase 2, fourteen participants in Phase 1 screening were found to have *HFE* mutations associated with HH and elevated SF. These subjects, along with one family member, meet the criteria for diagnosis of HH as defined by this study. Furthermore, 11 Phase 2 participants indicated on a self-report follow-up survey that they were being treated for HH. It should be noted that case definition of HH may take into account the presence of clinical signs and symptoms and that clinical findings were not included in this study. Inclusion of clinical findings could alter the number of persons diagnosed with HH.

The two-tiered reflexive approach used in this study appears to have been successful in that 129 of the 130 Phase 1 participants with elevated TS returned for confirmatory testing. Using a two-tiered reflexive approach with relatively low-cost biochemical tests may have kept the costs of screening lower than if more expensive genetic tests were included in Phase 1 testing of 2,034 subjects. Theoretically, screening could be more cost-efficient by also ensuring that subjects were fasting for Phase 1 testing, thereby eliminating the need for repeating TS. Determining the actual cost-effectiveness of screening for HH was not included in this project and could be the subject of future studies.

HESP appears to have been moderately effective in increasing awareness of HH as a health concern among participants. A substantial number, 53.1%, of respondents were unaware of HH prior to the screening event. Very importantly, 92.1% of respondents told their family and friends about HH after participating, and 73.4% discussed their laboratory results with their healthcare providers. Efforts to publicize HESP screening events may also have increased public awareness of HH. Laboratory results and information about HH sent to participants' healthcare providers may have contributed to increased awareness of HH in the medical community. The true impact of the project on increasing public awareness is difficult to assess.

The overall benefits of this screening project to the medically underserved residents of western North Carolina are also hard to quantify. Given the current belief that only 10% of affected persons are likely to be diagnosed, it is possible that many of 11 HESP participants who are currently being treated for HH would not have sought medical care for HH without this project. One can also speculate that they benefited from an earlier diagnosis. For the 15 participants identified with laboratory results consistent with HH, early diagnosis may have prevented the development of serious medical conditions associated with the late stage iron overload of HH and thereby reduced morbidity and associated healthcare costs.

Of concern is the project's inability to pay for treatment or to follow-up with subjects found to have HH. It is encouraging that 11 subjects stated on the survey that they were being treated. This finding suggests that resources are available, even in a population considered to be medically underserved. Another concern is that because a biochemical marker for iron, TS, was used as an initial screening test, it may be that some younger HESP participants will develop iron overload later in their lives. This project did not provide for future re-testing of younger participants.

Anecdotal evidence gathered from the follow-up surveys is supportive of the benefits of HESP. One participant commented, "This HESP project probably helped save my life and I greatly appreciate the effort it took to see this project through." A 28-year-old participant stated, "Because of all this, my mother, aunt, and uncle have also been diagnosed with hemochromatosis and are being treated. If it were not for the screening, none of us would have ever been aware of the disease." Another remarked that the project "really helped my family". One participant commented, "I wish I had been diagnosed earlier in life, as this disease has damaged my body considerably."

HESP could serve as a model for future efforts to provide screening for genetic disorders to targeted populations through collaboration between clinical laboratory scientists, public health agencies, the private sector, and others. HESP demonstrates that there is an important role for clinical laboratory scientists in directing the appropriate use of laboratory tests in a public health setting. However, the problem of long-term funding for such projects is unresolved. It is unlikely that state legislatures will fund screening for adult-onset disorders as they have for newborn screening. In general, while other studies have shown that screening for HH can be cost effective, questions about the likelihood that persons with *HFE* mutations will develop iron overload will also have an impact on the advisability of population screening. Education of healthcare providers to enhance case finding in symptomatic persons through the use of appropriate laboratory tests may afford another approach to improving detection of HH.

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