Population-Based Screening for Hemochromatosis: Not Ready for Prime Time

David Atkins, MD, MPH

Although biochemical tests for hemochromatosis have been available for many years, interest in more widespread screening has been fueled by the recent isolation of the gene responsible for hemochromatosis. Routine screening of asymptomatic adults has been recommended by some experts and by the College of American Pathologists [1], but mass screening is not yet endorsed by any major primary care organization nor by any public health agency. A 1997 expert panel convened by the Centers for Disease Control and Prevention (CDC) and the National Human Genome Research Institute concluded that genetic testing was not recommended for population-based screening for hemochromatosis [2]. Independent reviews by experts at the CDC [3] concluded that the current evidence is not yet sufficient to recommend a policy of routine screening with genetic or biochemical tests, except among persons with possible symptoms and among relatives of affected persons. The U.S. Preventive Services Task Force (USPST) [4] did not address hemochromatosis screening in its 1996 evaluations of common screening tests but is likely to include it among the new assessments planned over the next several years. The Canadian counterpart of the USPST, the Canadian Task Force on the Periodic Health Examination (http://ctfphc.org) has completed a review of hemochromatosis screening and is expected to release a policy statement on screening later this year (Feighnter, personal communication, 1999).

On initial examination, screening for hemochromatosis appears to fulfill all of the criteria for a useful screening program: hereditary hemochromatosis is common and can have serious or fatal consequences; there is an acceptable screening test and a safe and effective intervention (phlebotomy); and the disease has a long latent period during which intervention can forestall progression to irreversible end-organ damage. Why then isn’t support for screening stronger? An excellent series of papers arising from the 1997 CDC conference and published as a supplement to the Annals of Internal Medicine in December 1998 [5] explores in detail the evidence underlying each of the above assertions. These papers reveal numerous uncertainties regarding the natural history of hemochromatosis and the feasibility, accuracy, and efficacy of screening. The uncertainties described below currently make it impossible to answer the fundamental question: Would routine screening of asymptomatic adults for hemochromatosis significantly reduce current morbidity and mortality from hemochromatosis, and would these benefits be large enough to justify the inconvenience, potential harms, and costs of screening?

How Important Is the Disease Burden?

Prevalence estimates from genetic studies stand in sharp contrast to the experience of most primary care clinicians. Whereas genetic surveys suggest that hemochromatosis is among the most common genetic disorders among whites (4 to 8 per 1000), national statistics indicate it accounts for only 3000 to 6000 hospitalizations and fewer than 200 deaths (1 to 2 per million persons) per year. One obvious source for this discrepancy is underdiagnosis: the clinical consequences of iron overload (eg, cirrhosis, diabetes, heart failure) are common and not specific to hemochromatosis. At the same time, it is also apparent that the risk of developing clinical disease is variable among persons with specific mutations in the HFE allele and among individuals with biochemical evidence of iron overload. Due to incomplete penetrance and environmental and individual modifiers of risk, the number of people who would actually benefit from early detection and treatment (ie, live a longer or healthier life) is considerably smaller than the number that would be identified by a screening program. Current knowledge, however, is not yet adequate to allow us to easily identify those subgroups most likely to benefit.

How Accurate and Acceptable Is the Screening Test?

Biochemical assays and genetic testing can be performed easily on routine blood specimens, but important questions...
remain about the accuracy and feasibility of screening in the
general population. One immediate problem is the lack of uni-
versal criteria to define abnormal biochemical results for
either screening or diagnostic purposes. The cut-off used for
initial screening using transferrin saturation has varied from
45% to 62% in different studies. The sensitivity and specificity
of screening vary substantially depending on the threshold
used. Similarly, the probability that an elevated transferrin sat-
uration indicates a true case (its positive predictive value) is
much lower when screening is applied to the general popula-
ton instead of high-risk groups. A study among blood donors
suggested as few as 4% of persons with abnormal screening
results have hereditary hemochromatosis. One problem is the
variability of the measure itself, which can vary as much as
50% within the same individual depending on meals and
medications. Up to 65% of those with an initial positive screen
will have normal transferrin saturation when repeated with a
fasting sample. Furthermore, because other medical condi-
tions can cause iron overload, fewer than a third of patients
with abnormal transferrin saturation on repeated samples have
hemochromatosis. In a screening study [6] of more than
16,000 primary care patients, 255 patients completed follow-
up after repeatedly positive screening; 18% had proven
hemochromatosis and another 9% had probable hemochro-
matosis.

Is Screening Feasible?
This study and others reveal another reality of primary care
screening programs that require a sequence of screening and
confirmatory tests. At each step in the protocol, 15% to 20% of
patients do not complete the recommended testing or follow-
up, with the result that only a little more than half of the possi-
able cases make it through to a presumptive diagnosis. Even
then, the substantial number of patients (40% to 50%) who
decline liver biopsy further limits the ability to obtain defini-
tive diagnostic and prognostic information that is helpful for
treatment decisions. Thus, although the sensitivity of avail-
able tests is high, problems with patient compliance, diag-
nostic criteria, and the assay itself will substantially reduce
the number of cases that would actually be detected by a
screening program while contributing to a high proportion of
false-positive screening results. Although genetic screening
requires only a single sample, the true sensitivity of screening
using the 2 known mutations is not known, but may be as
low as 69%. At the same time, the clinical significance of dif-
ferent mutations is not known. The high costs of genetic
screening, and lack of quality standards for genetic testing,
are further barriers to widespread genetic screening for hemo-
chromatosis at present.

How Effective and Acceptable Is the Treatment?
Although the efficacy of phlebotomy has not been proven
with prospective and controlled studies, evidence for its
benefits comes from a combination of case-series, retrospec-
tive data, and time-trend data suggesting improved sur-
vival among treated patients. Although phlebotomy is a
safe and simple procedure, asymptomatic patients detected
by screening are likely to be less willing to undergo the
inconvenience of repeated phlebotomy than symptomatic
patients or individuals detected by screening affected fami-
lies. In one primary care screening study, treatment was
accepted by only 50% of the patients who had clinically
proven hemochromatosis in the absence of a biopsy. Not
surprisingly, patients were much more likely to follow
through on treatment if they had consented to biopsy to
confirm the diagnosis.

How Safe and Cost-Effective Is Screening and
Treatment?
Although the medical risks of hemochromatosis screening
and treatment are confined to the risk of liver biopsy, screen-
ing asymptomatic persons for serious medical conditions
always carries the potential for harm. The most immediate
arises from false-positive results, which are inevitable and
which may lead to unnecessary follow-up testing, biopsies,
or treatments. Additional “correctly” diagnosed patients
might never have developed clinical disease, yet will be sub-
jected to a lifetime of treatment. Some previously well peo-
day may experience increased anxiety and reduced well-
being as a result of being diagnosed with a chronic disease,
a phenomenon known as labelling. The diagnosis of hemo-
chromatosis may also lead to discrimination in obtaining life
or health insurance, a problem exacerbated by our incom-
plete understanding of the clinical implications of newly
identified genetic defects. These issues arise in any screening
program and would be incidental concerns in the face of
clear data on the benefits of screening. They loom more sig-
ificant with regard to hemochromatosis screening because
the benefits of a population-based screening program are
currently speculative rather than based on actual experi-
ence. Finally, although some analyses have suggested that
screening could be cost-saving or cost-effective, these
analyses are highly sensitive to the prevalence of disease,
accuracy of screening, risk of progression to symptomatic
iron overload, and compliance with screening and treat-
ment. Few of the assumptions in these analyses are likely to
apply to primary-care based screening, and the true cost-
effectiveness of screening (relative to current practice of case
finding among symptomatic patients and family members)
remains unknown.

Future Directions and Current Recommendations
In the face of these many unanswered questions, the good
news is that important new studies have arisen from the
research agenda set out in the 1997 CDC conference. The National Institutes of Health are currently in the planning stages of a large, multicenter study of the prevalence, genetics, and clinical consequences of hemochromatosis in a multiethnic, primary-care based sample of 100,000 patients. Until results from this and other ongoing studies are available, the general recommendations from the conference seem reasonable: screen patients with symptoms compatible with hemochromatosis (eg, liver disease, diabetes, arthralgias) and first-degree relatives of affected cases with transferrin saturation, and consider DNA testing only as a confirmatory test in relatives of cases with 2 hemochromatosis mutations. Although future findings may eventually build a more compelling case for routine screening, current strategies should emphasize improving case-finding among high-risk groups rather than expanding screening to the asymptomatic general population.

The views contained in this paper are solely those of the author and do not reflect official policies of the Agency for Health Care Policy and Research or of the U.S. Public Health Service.

References

Copyright 1999 by Turner White Communications Inc., Wayne, PA. All rights reserved.