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

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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 (Feightner, 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

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remain about the accuracy and feasibility of screening in the general population. One immediate problem is the lack of universal 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 saturation indicates a true case (its positive predictive value) is much lower when screening is applied to the general population 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 conditions 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 hemochromatosis.

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 possible 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 definitive diagnostic and prognostic information that is helpful for treatment decisions. Thus, although the sensitivity of available tests is high, problems with patient compliance, diagnostic 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 different 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 hemochromatosis 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, retrospective data, and time-trend data suggesting improved survival 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 families. 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, screening 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 subjected to a lifetime of treatment. Some previously well people 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 hemochromatosis may also lead to discrimination in obtaining life or health insurance, a problem exacerbated by our incomplete 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 significant with regard to hemochromatosis screening because the benefits of a population-based screening program are currently speculative rather than based on actual experience. 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 treatment. 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