NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

SCREENING FOR HEMOCHROMATOSIS

Guidelines

1. **American College of Physicians (ACP)**. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2005 Oct 4;143(7):517-21. [21 references]
2. **U.S. Preventive Services Task Force (USPSTF)**. Screening for hemochromatosis: recommendation statement. Ann Intern Med 2006 Aug 1;145(3):204-8. [12 references]

INTRODUCTION:

A direct comparison of the American College of Physicians (ACP) and the U.S. Preventive Services Task Force (USPSTF) recommendations for screening for hemochromatosis is provided in the tables below. In formulating its recommendations, USPSTF reviewed the conclusions of the ACP guideline. In addition to addressing to screening for hemochromatosis, both guidelines also address areas of future research needed.

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly that which is used in Tables 4, 5 and 6, is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of both guidelines.
- Table 3 provides a comparison of the methodology employed and documented by both groups in developing their guidelines.
- Table 4 provides a more detailed comparison of recommendations offered by each group for the topics under consideration in this synthesis, including:
  - Whom to Screen
  - Screening Methods and Tools
  - Patient and Family Member Education/Counseling
- Table 5 lists the potential benefits associated with the implementation of each guideline as stated in the original guidelines
- Table 6 presents the rating schemes used by USPSTF to rate the level of evidence and the strength of the recommendations.

A summary discussion of the areas of agreement and differences among the guidelines is presented following the content comparison tables.

Abbreviations

- ACP, American College of Physicians
- CINAHL, Cumulative Index to Nursing and Allied Health Literature®
- EPC, Evidence-based Practice Center
- HFE, the hemochromatosis gene
- USPSTF, U.S. Preventive Services Task Force

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	ACP (2005)	USPSTF (2006)
Routine genetic screening in asymptomatic persons	✓	✓
Case-finding approach for hereditary hemochromatosis	✓	✓
Serum ferritin and transferrin saturation tests as part of case-finding	✓	✓
Counseling of family members of probands regarding genetic testing, with further diagnostic testing as warranted as part of case-finding	✓	✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT

Objective and Scope	

ACP (2005)	• To increase physician awareness of hereditary hemochromatosis, particularly the variable penetrance of genetic mutations; aid in case finding; and explain the role of genetic testing
	• To answer the following questions:
	  • What is the prevalence of hereditary hemochromatosis in the primary care setting?
	  • In asymptomatic patients with hereditary hemochromatosis, what is the risk for end-organ damage or death?
	  • How diagnostically useful are transferrin saturation and serum ferritin in identifying patients with hereditary hemochromatosis in the primary care setting?
	  • Is phlebotomy efficacious in reducing morbidity or fatal complications in asymptomatic patients with hereditary hemochromatosis?

	• Do the benefits of screening primary care patients for hereditary hemochromatosis outweigh the risks?
USPSTF (2006)	• To summarize the U.S. Preventive Services Task Force recommendations on screening for hemochromatosis, and the supporting focused evidence review
Target Population	
ACP (2005)	All persons who have a probability of or susceptibility for developing hereditary hemochromatosis, including the relatives of individuals who already have the disease
USPSTF (2006)	Asymptomatic general population
Intended Users	
ACP (2005)	Physicians
USPSTF (2006)	Advanced Practice Nurses Allied Health Personnel Health Care Providers Nurses Physician Assistants Physicians

TABLE 3: COMPARISON OF METHODOLOGY

	ACP (2005)	USPSTF (2006)
Methods Used to Collect/Select the Evidence	• *Hand-searches of Published Literature (Primary Sources)* • *Searches of Electronic Databases* **Note from the National Guideline Clearinghouse (NGC)**: This guideline is based on the systematic review of the evidence in the	• *Hand-searches of Published Literature (Primary Sources)* • *Hand-searches of Published Literature (Secondary Sources)* • *Searches of Electronic Databases* **Note from the National Guideline Clearinghouse (NGC)**: A focused

	background paper. Evidence Review: Schmitt, B, Golub, RM, Green, R. Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians. Ann Intern Med. 2005 Oct 4;143(7):522-36. Electronic copies: Available from the Annals of Internal Medicine Web site. *Described Process*: The authors of the background paper conducted a systematic review for each question in MEDLINE for papers published from 1966 through April 2004 by using PubMed Clinical Queries filters for a sensitive search of prognosis, diagnosis, etiology, or treatment depending on the question. They included only English-language studies. Two reviewers independently reviewed all abstracts. A third reviewer resolved conflicts about inclusion of an article. The authors also manually searched references from included studies. The appendix of the background paper includes details for conducting the search	systematic review of the literature was prepared by the Oregon EPC and Oregon Health & Science University for the Agency for Healthcare Research and Quality (AHRQ) for use by the USPSTF. Evidence Review: Whitlock EP, Garlitz BA, Harris EL, Bell TL, Smith PR. Screening for hereditary hemochromatosis: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med; 2006;145:209-223. Electronic copies: Available from the U.S. Preventive Services Task Force (USPSTF) Web site. Also available from the Annals of Internal Medicine Online. *Described Process*: **Data Sources** EPC staff developed literature search strategies and terms for each key question and conducted four separate literature searches (for Key Questions 1, 2, 3, and background) in Medline, CINAHL, and the Cochrane Library databases from 1966 through February 2005. Literature searches were supplemented with source material from experts in the field and by examining the bibliographies of included studies. A single

	for each subquestion. *Number of Source Documents*: **Question 1**: 3 studies in primary care settings and 12 studies in general population setting **Question 2**: 11 studies on the relationship between transferrin saturation--serum ferritin level and hereditary hemochromatosis-related disease; 13 studies on the relationship between primary iron tissue deposition and hereditary hemochromatosis-related disease **Question 3**: 3 studies **Question 4**: 2 studies **Question 5**: 4 studies *Number of References*: 21	investigator reviewed abstracts, and a second reviewer abstracted all excluded abstracts. Interreviewer discrepancies were resolved by consensus. **Study Selection** Using inclusion criteria developed for each key question, EPC staff reviewed 1,886 abstracts for inclusion in all key questions. Literature searches were focused for each key question, but were reviewed with all key questions in mind. Two investigators quality rated all included articles for quality, as well as those excluded for quality-related reasons, using the USPSTF criteria. *Number of Source Documents*: Using inclusion criteria developed for each key question, the Oregon Evidence-based Practice Center (EPC) staff reviewed 1,886 abstracts for inclusion in all key questions. Literature searches were focused for each key question, but were reviewed with all key questions in mind. They reviewed 134 full-text articles for Key Question 1, 69 articles for Key Question 2, and 55 articles for Key Question 3. *Number of References: 12*

Methods Used to Assess the Quality and Strength of the Evidence	*Expert consensus* *Described Process*: Methodologic quality of studies was assessed for a specific question by using accepted epidemiologic criteria. No formal method of quality assessment or scoring was used.	*Weighted according to a rating scheme (refer to Table 6)* **Note**: See the following background document for a more detailed description of the methods used to assess the quality and strength of the evidence for the three strata at which the evidence was reviewed: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):21-35. Electronic copies: Available from U.S. Preventive Services Task Force (USPSTF) Web site
Methods Used to Analyze the Evidence	• *Systematic review with evidence tables* *Described Process*: For some key questions, data from more than one study were aggregated and/or examined after applying different definitions or criteria. For other key questions, data from individual studies were summarized and reviewed.	• *Systematic review with evidence tables* *Described Process*: **Data Extraction and Quality Assessment** To overcome inconsistent uses of terminology in the literature, EPC staff adopted a set of terms for use in extracting data from studies into tables in a consistent format. They also established *A priori* screening and diagnostic criteria for elevated iron measures and iron overload due to hereditary

		hemochromatosis to guide the review and to establish comparability between studies. Data were abstracted into evidence tables by a single reviewer and checked by a second reviewer. EPC staff critically appraised studies according to USPSTF methods using quality criteria specific to their design. To augment criteria provided for nonrandomized studies of treatment effectiveness, they added criteria from the Cochrane Non-Randomized Studies Methods Group. Any case series or nonrandomized comparative treatment study that used a nonsystematic method of case accrual was eliminated. EPC staff critically evaluated reported results, including the comparability of constructed comparison groups, concerning whether confounding factors (age, sex, alcohol intake, population prevalence of C282Y homozygosity, and comorbid liver disease) and secular trends in disease diagnosis and medical care were adequately considered. Studies with possible serious biases were eliminated. **Data Synthesis** Studies were extremely heterogeneous and could

		not be easily synthesized quantitatively. To evaluate whether the review identified adequate data to create one or more outcomes tables for illustrating the expected yield from screening, EPC staff used an approach adapted from a previous report. They considered whether there were adequate data for genetic screening of two different screening populations (general population and family-based). Insufficient data were available to create a reliable outcomes table for either screening approach since very few studies reported results for all required measures (genotype, iron measures, iron overload, and disease) among screening study participants, resulting in extremely small numbers for within-study morbidity estimates. Therefore, they summarized screening data in tables. Data was selected from studies that met minimum *a priori* criteria for three variables: 1) screening positive for elevated iron parameters, 2) documented iron overload, and 3) morbidity due to clinical hemochromatosis. For iron overload and morbidity, EPC staff calculated two proportions (selected and all). Among patients selected for further evaluation, they reported the proportion of positives among those who were actually tested for

		iron overload or morbidity (maximum penetrance) and, for all, the proportion who screened positive among all those evaluated at the first screening step (minimum penetrance). They then evaluated whether results were similar enough to combine across studies, and, when they were, they quantitatively combined study results for each variable to generate a single point estimate for that variable. A range of results for any variable for which individual study results were too different to be meaningfully combined were reported. EPC staff did not include individual study results with 10 or fewer subjects in the denominator to define a range, but they did include these results if they could be combined with other results in a single parameter estimate. Study results were reported as raw numbers for denominators of 10 or fewer.
Outcomes	• Prevalence of hereditary hemochromatosis in the primary care setting • Risk for complications (cirrhosis, diabetes, idiopathic dilated cardiomyopathy) and death in asymptomatic persons with hereditary hemochromatosis	• Risk for developing clinical hemochromatosis among persons with a homozygous C282Y genotype • Reductions in morbidity (e.g., cirrhosis and other liver diseases, diabetes, weakness, lethargy, abdominal pain, arthralgia, impotence, joint pain), and mortality in

	• Sensitivity and specificity of serum ferritin and transferrin saturation for identifying hereditary hemochromatosis in the primary care setting • Efficacy of phlebotomy for reducing morbidity (liver histology) and improving survival in patients with hemochromatosis without cirrhosis • Risks and benefits of screening	individuals with primary iron overload due to hemochromatosis receiving earlier therapeutic phlebotomy versus treatment after diagnosis in routine clinical care • Identification of groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening
Methods Used to Formulate the Recommendations	• *Expert consensus* *(Process not described)*	• *Balance Sheets* • *Expert Consensus* <u>*Described Process*</u>: When the overall quality of the evidence is judged to be good or fair, the U.S. Preventive Services Task Force (USPSTF) proceeds to consider the magnitude of net benefit to be expected from implementation of the preventive service. Determining net benefit requires assessing both the magnitude of benefits and the magnitude of harms and weighing the two. The USPSTF classifies benefits, harms, and net benefits on a 4-point scale: "substantial," "moderate," "small," and "zero/negative."

		"Outcomes tables" (similar to "balance sheets") are the USPSTF's standard resource for estimating the magnitude of benefit. These tables, prepared by the topic teams for use at USPSTF meetings, compare the condition specific outcomes expected for a hypothetical primary care population with and without use of the preventive service. These comparisons may be extended to consider only people of specified age or risk groups or other aspects of implementation. Thus, outcomes tables allow the USPSTF to examine directly how the preventive service affects benefits for various groups. When evidence on harms is available, the topic teams assess its quality in a manner like that for benefits and include adverse events in the outcomes tables. When few harms data are available, the USPSTF does not assume that harms are small or nonexistent. It recognizes a responsibility to consider which harms are likely and judge their potential frequency and the severity that might ensue from implementing the service. It uses whatever evidence exists to construct a general confidence interval on the 4-point scale (e.g., substantial, moderate, small, and zero/negative).

		Value judgments are involved in using the information in an outcomes table to rate either benefits or harms on the USPSTF's 4-point scale. Value judgments are also needed to weigh benefits against harms to arrive at a rating of net benefit. In making its determinations of net benefit, the USPSTF strives to consider what it believes are the general values of most people. It does this with greater confidence for certain outcomes (e.g., death) about which there is little disagreement about undesirability, but it recognizes that the degree of risk people are willing to accept to avert other outcomes (e.g., cataracts) can vary considerably. When the USPSTF perceives that preferences among individuals vary greatly, and that these variations are sufficient to make the trade-off of benefits and harms a "close-call," then it will often assign a C recommendation (see the "Recommendation Rating Scheme" field). This recommendation indicates the decision is likely to be sensitive to individual patient preferences. The USPSTF uses its assessment of the evidence and magnitude of net benefit to make recommendations. The

		general principles the USPSTF follows in making recommendations are outlined in Table 5 of the companion document cited below. The USPSTF liaisons on the topic team compose the first drafts of the recommendations and rationale statements, which the full panel then reviews and edits. Recommendations are based on formal voting procedures that include explicit rules for determining the views of the majority. From: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):21-35.
Financial Disclosures	Potential financial conflicts of interest: None disclosed.	Potential financial conflicts of interest: None disclosed.

TABLE 4: COMPARISON OF RECOMMENDATIONS FOR THE SCREENING OF HEMOCHROMATOSIS	
Whom to Screen	
ACP (2005)	**Recommendation 1**: There is insufficient evidence to recommend for or against screening for hereditary hemochromatosis in the general population.

	There is currently insufficient evidence to determine whether the benefits of screening the general population outweigh the risks. The C282Y mutation is prevalent in certain populations, particularly white men, and treatment is not costly nor is it associated with any significant harm. Although patients homozygous for C282Y are more likely to have elevated serum ferritin level and transferrin saturation percentage, there currently is no way of predicting which patients will progress to overt disease. For clinicians who choose to screen, 1-time phenotypic screening of asymptomatic non-Hispanic white men with serum ferritin level and transferrin saturation would have the highest yield (Adams et al., 2005).
USPSTF (2006)	• The USPSTF recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population. This is a **grade D** recommendation. <u>*Rationale*</u> **Importance**: There is fair evidence that disease due to hereditary hemochromatosis is rare in the general population **Detection**: The USPSTF found fair evidence that a low proportion of individuals with a high-risk genotype (C282Y homozygote at the HFE locus, a mutation common among white populations presenting with clinical symptoms) manifest the disease. **USPSTF assessment**: The USPSTF concludes that the potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits. <u>*Clinical Considerations*</u>

	This recommendation applies to asymptomatic persons. This recommendation does not include individuals with signs or symptoms that would include hereditary hemochromatosis in the differential diagnosis. Furthermore, it does not include individuals with family history of clinically detected or screening-detected probands for hereditary hemochromatosis. *Clinically important disease due to hereditary hemochromatosis appears to be rare. Even among individuals with mutations on the hemochromatosis (HFE) gene, it appears that only a small subset will develop symptoms of hemochromatosis. An even smaller proportion of these individuals will develop advanced stages of clinical disease.* *Screening of family members of probands identifies the highest prevalence of undetected C282Y homozygotes (23% of all family members tested), particularly among siblings (33% homozygosity).* *<u>Other Considerations</u>* *System issues: Genetic screening for hereditary hemochromatosis is not widespread in the United States.* *Value: Systematic screening is potentially costly and may lead to additional diagnostic tests, regular followup, and treatment.* *Policy issues: There are important ethical concerns about screening for genetic conditions when the ability to predict the development of disease in those who screen positive is uncertain or very low. Identification of homozygosity could lead to diminished insurability.* *Community issues: While clinical disease associated with hereditary*

	hemochromatosis is uncommon, there is significant variation in the prevalence of C282Y homozygotes according to race and ethnicity.
Screening Methods and Tools	
ACP (2005)	**Recommendation 2**: In case-finding for hereditary hemochromatosis, serum ferritin and transferrin saturation tests should be performed. *There is no information available on risk-stratifying in patients with an associated condition or conditions such as type 2 diabetes, cardiac arrhythmias and cardiomyopathies, liver failure, hepatomegaly, cirrhosis, elevated liver enzyme levels, hepatocellular carcinoma, arthritis, hypogonadism, or changes in skin pigmentation. The initial symptoms associated with iron overload might be nonspecific, and the decision to perform tests should be based on clinical judgment regarding what may cause such protean manifestations. If testing is performed for these patients, the cutoff values for serum ferritin level of more than 200 micrograms/L in women or more than 300 micrograms/L in men and transferrin saturation greater than 55% may be used as criteria for case-finding; however, there is no general agreement about diagnostic criteria. Case-finding may also be considered if there is a family history of hereditary hemochromatosis for an individual, as the risk for developing the disease may be higher than that of the general population.*
USPSTF (2006)	No recommendation offered. <u>*Accuracy of Screening Tests*</u> *Because of the targeted nature of this review, the USPSTF did not focus on the accuracy of genetic screening tests. Nor did the USPSTF assess the validity of various combinations of phenotypic and genotypic approaches to screening.*

	Rather, the USPSTF focused on genetic screening for hereditary hemochromatosis, specifically C282Y homozygosity. The USPSTF did not assess the role of increased serum iron measures such as transferrin saturation and serum ferritin in screening. While elevated serum iron measures may provide more "clinically" relevant information about early disease, the predictive value for progression of disease is limited (Andersen et al., 2004). *<u>Clinical Considerations</u>* *In addition to genotyping, more common laboratory testing can sometimes identify iron overload. Clinical screening with these laboratory tests, or phenotypic screening, was not included in the evidence synthesis on which this recommendation [see Recommendation 1 above] is based. Genotyping primarily focuses on the identification of the C282Y mutation on HFE. While other mutations exist, C282Y homozygosity is most commonly associated with clinical manifestations. Identifying an individual with the genotypic predisposition does not accurately predict the future risk for disease manifestation.*
Patient and Family Member Education/Counseling	
ACP (2005)	**Recommendation 3**: Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation. *Before genetic testing, individuals should be made aware of the benefits and risks of genetic testing. This should include discussing available treatment and its efficacy; costs involved (Beutler et al., 2002); and social issues, such as impact of disease labeling, insurability and psychological well-being, and the*

	possibility of as-yet-unknown genotypes associated with hereditary hemochromatosis.
USPSTF (2006)	No recommendation offered. *Clinical Considerations* *Individuals with a family member, especially a sibling, who is known to have hereditary hemochromatosis may be more likely to develop symptoms. These individuals should be counseled regarding genotyping, with further diagnostic testing as warranted as part of case-finding.*
Supporting References	
ACP (2005)	**USPSTF (2006)**
Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, et al. Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med. 2005;352:1769-78. [PubMed] [Abstract/Free Full Text] Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G—>A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet. 2002;359:211-8. [PubMed]	Andersen RV, Tybjaerg-Hansen A, Appleyard M, Birgens H, Nordestgaard BG. Hemochromatosis mutations in the general population: iron overload progression rate. *Blood* 2004;103:2914-9. [PubMed]

TABLE 5: BENEFITS AND HARMS	
Benefits	
ACP (2005)	• Appropriate screening for hereditary hemochromatosis in light of efficacy of available treatment and value of detecting individuals who are homozygous for the mutation but may not develop iron overload. • Serum ferritin level and transferrin saturation have been useful in

	identifying patients who are prone to or already have hereditary hemochromatosis.
USPSTF (2006)	• Appropriate screening for hereditary hemochromatosis in primary care settings
Harms	
ACP (2005)	• The value of detecting individuals who are homozygous for the mutation but do not develop iron overload is controversial. The psychological and social implications of identifying such individuals must be considered. Issues such as the impact on insurability and the anxiety of being labeled with a hereditary illness need to be considered when comparing the benefits and risks of screening. • False reassurance in the setting of a negative genetic test result is not unreasonable.
USPSTF (2006)	• Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments. • Harms associated with screening are not well studied. Potential harms include the psychological burden of being labeled as having a chronic disease, the potential consequence of this labeling on a person's ability to obtain health or life insurance, and concern associated with genetic testing in the absence of qualified genetic counseling. Phlebotomy, a somewhat invasive procedure, is associated with some harms.

TABLE 6: EVIDENCE RATING SCHEMES AND REFERENCES	
ACP (2005)	The recommendations are supported by data from cohort, cross-sectional, and case-control studies.
USPSTF (2006)	The U.S. Preventive Services Task Force grades the **quality of the overall evidence** for a service on a 3-point scale (good, fair, poor): **Good** Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess

effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Strength of Recommendations

The USPSTF grades its **recommendations** according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A

The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.

B

The USPSTF recommends that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.

C

The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.

D

The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that

	[the service] is ineffective or that harms outweigh benefits. **I** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

GUIDELINE CONTENT COMPARISON

The American College of Physicians (ACP) and the U.S. Preventive Services Task Force (USPSTF) present recommendations for screening for hemochromatosis and provide explicit reasoning behind their judgments. Both organizations performed a systematic review of the literature that included applying quality criteria to published studies to select those suitable for evidence review and guideline formulation. The USPSTF systematic review document (see "Availability of Companion Documents" in the NGC summary of this guideline) provides quality rankings for included studies and provides reasons for rejection of excluded studies. In addition, its recommendation statement grades the strength of the evidence that supports its recommendation. The ACP systematic review document (see "Availability of Companion Documents" in the NGC summary of this guideline) lists in table format the methodologic or quality issues of the studies that were considered by ACP in answering each of five key questions concerning screening for hemochromatosis. Although ACP does not explicitly rank the quality of studies reviewed or the strength of the evidence behind each recommendation, it discusses the strength of the evidence in narrative format.

Screening for Hemochromatosis: Comparison of Recommendations Between the ACP and USPSTF Guidelines	
ACP (2005)	**USPSTF (2006)**
• States there is insufficient evidence to recommend for or against routine screening for hemochromatosis in the asymptomatic general population	• Recommends against routine genetic screening for hemochromatosis in the asymptomatic general population
• Recommends serum ferritin and transferrin saturation tests as part of case-finding approach to	• Did not specifically address the role of serum ferritin and transferrin saturation testing in screening.

screening	Recommends, however, further diagnostic testing as warranted as part of case-finding approach to screening.
• Recommends genetic testing counseling for individuals with a family history of hereditary hemochromatosis or with elevated serum ferritin level or transferrin saturation	• Recommends genetic testing counseling for individuals with a family member with hereditary hemochromatosis

Areas of Agreement

Routine Genetic Screening

Both ACP and USPSTF found that there is insufficient evidence to support a recommendation for routine genetic screening of the general population for hereditary hemochromatosis. The ACP concludes that the evidence of benefit versus harm is insufficient to support a recommendation either for or against screening. The USPSTF goes a step further and recommends against screening, concluding that the potential harms of genetic screening do, in fact, outweigh the potential benefits.

Potential harms cited by USPSTF include identification of a large number of persons with the high-risk genotype but who may never manifest clinical disease, and related unnecessary surveillance, labeling, anxiety, diagnostic work-ups, and treatments. The ACP guideline notes that potential harms from screening include an adverse impact on insurability and the anxiety of being labeled with a hereditary illness. In addition, because the C282Y mutation does not explain high transferrin saturation and serum ferritin level in nonwhite persons and current research is identifying other genes involved in iron homeostasis, screening for the C282Y mutation could lead to false reassurance in the setting of a negative genetic test result.

In terms of benefits, the USPSTF finds there is only poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically-detected individuals. Similarly, ACP states that available data cannot definitively determine whether phlebotomy will delay or deter the development of cirrhosis (an important morbidity associated with iron overload) over the lifetime of an asymptomatic patient.

Both guidelines agree that prevalence of hereditary hemochromatosis in the general population is low, varies widely between subpopulations, and is highest in white populations. The guidelines further agree that information on the natural history of hemochromatosis is lacking, and this makes it difficult to assess the

potential value of early treatment for iron overload. For example, USPSTF points out that even among individuals with mutations on the hemochromatosis gene (HFE), only a small subset will develop symptoms of hemochromatosis and an even smaller proportion of these individuals will develop advanced stages of clinical disease.

Case-Finding

According to ACP, there are no clearly defined criteria to risk-stratify patients into groups that are more or less likely to develop overt disease. However, ACP and USPSTF agree that family members of persons with hereditary hemochromatosis may be more likely to develop symptoms of hemochromatosis; they should be counseled regarding genotyping, and diagnostic testing should be completed as warranted. While USPSTF does not address the nature of further diagnostic testing, ACP recommends that serum ferritin and transferrin saturation tests be performed for case-finding purposes.

Areas of Differences

The USPSTF concludes that the potential harms of genetic screening outweigh the potential benefits and therefore recommends against screening in the general population. The ACP states there is insufficient evidence to determine whether the benefits of screening outweigh the risks; it therefore recommends neither for nor against screening.

Conclusion

Neither ACP nor USPSTF recommend routine genetic screening for hemochromatosis in the general population. Both groups, however, are in favor of a case-finding approach to screening. ACP recommends serum ferritin and transferrin saturation tests as part of this approach, while the USPSTF more generally recommends "further diagnostic testing". Both groups recommend the genetic testing counseling for individuals with a family history of hemochromatosis.

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