MOLEKULARGENETISCHE DIAGNOSTIK HEREDITÄRE HÄMOCHROMATOSE

Soweit in diesem Kontext personenbezogene Bezeichnungen nur in weiblicher oder nur in männlicher Form angeführt sind, beziehen sie sich generell auf Frauen und Männer in gleicher Weise.

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Unter welchen Voraussetzungen sollte eine genetische Untersuchung auf hereditäre Hämochromatose in Erwägung gezogen werden?

Gibt es einen nachgewiesenen Nutzen für ein sog. Case finding?

3 Kurzbericht

Schätzungen der Prävalenz des Genotyps der hereditären Hämochromatose in der Allgemeinbevölkerung variieren sehr stark, die Penetranz der Hämochromatose assoziierten Mutationen ist sehr gering, viele C282Y homozygote Mutationsträger weisen eine normale Transferrinsättigung auf und zeigen niemals klinische Symptome einer Eisenüberladung.

Es gibt relativ gute Evidenz, dass die Erkrankung infolge der hereditären Hämochromatose in der Allgemeinbevölkerung selten ist. Lediglich ein sehr geringer Teil der homozygoten Mutationsträger entwickelt Symptome einer Hämochromatose, und noch ein geringerer Teil dieser Personen entwickelt ein fortgeschrittenes Stadium der Erkrankung. Studiendaten zeigen, dass 40% der unbehandelten homozygoten Mutationsträger keine oder keine progressive Eisenüberladung nach Jahren der Nachbeobachtung zeigen. Obwohl Patienten mit der C282Y homozygoten Mutation öfter eine Erhöhung des Serumferritins und der Transferrinsättigung aufweisen, gibt es derzeit keine Möglichkeit einer sicheren Vorhersage, welcher Patient eine Erkrankung entwickeln wird.

In der Allgemeinbevölkerung wird kein genetisches Screening der HFE Mutation empfohlen.

Für das *case-finding* der hereditären Hämochromatose sollten Serumferritin und Transferrinsättigung bestimmt werden, da eine Erhöhung des Eisenferritinspiegels und der Transferrin Sättigung sich als bester Vorhersageparameter der hereditären Hämochromatose erwies. Es gibt allerdings keine einheitlichen diagnostischen Kriterien für die molekulargenetische Untersuchung.

Die Untersuchung von Angehörigen eines Patienten mit hereditärer Hämochromatose identifizierte die höchste Prävalenz von unentdeckten C282Y homozygoten Mutationen mit 23%, insbesondere bei Geschwistern mit 33%.

Es bestehen ethische Bedenken hinsichtlich des genetischen Screenings der hereditären Hämochromatose, da die Vorhersagekraft über die Entwicklung einer Erkrankung im Falle eines positiven Ergebnisses unsicher oder sehr gering ist.

Im Falle eines *case-finding* auf hereditäre Hämochromatose ist aufgrund der dargelegten Problematik jedenfalls eine genetische Beratung, wie im Gentechnikgesetz vorgesehen, erforderlich.

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4 Internationale Empfehlungen

In der Allgemeinbevölkerung wird kein genetisches Screening der HFE Mutation empfohlen,[1] beziehungsweise gibt es keine Evidenz für eine Empfehlung für oder gegen ein Screening in der Allgemeinbevölkerung.[2]

Es gibt relativ gute Evidenz, dass die Erkrankung infolge der hereditären Hämochromatose in der Allgemeinbevölkerung selten ist,[3] und es gibt relativ gute Evidenz, dass ein geringer Teil der homozygoten Mutationsträger die Erkrankung entwickelt.

Es gibt mangelhafte Evidenz, dass eine frühe therapeutische Aderlaßtherapie die Morbidität und Mortalität bei Personen mit HFE Mutation, die mittels Screening entdeckt wurden gegenüber Personen, die durch klinische Symptome entdeckt wurden, senkt.

Screening von Angehörigen eines Patienten mit hereditärer Hämochromatose identifizierte die höchste Prävalenz von bisher unentdeckten C282Y homozygoten Mutationen mit 23%, insbesondere bei Geschwistern mit 33%. Die Familienangehörigen sollten hinsichtlich einer genetischen Testung nach einer Labortestung als Teil des *case-finding* beraten werden. Es bestehen allerdings erhebliche ethische Bedenken hinsichtlich des genetischen Screenings, da die Vorhersagekraft über die Entwicklung einer Erkrankung im Falle eines positiven Ergebnisses unsicher oder sehr gering ist.

Obwohl Patienten mit der C282Y homozygoten Mutation öfter eine Erhöhung des Serumferritins und der Transferrinsättigung aufweisen, gibt es derzeit keine Möglichkeit einer sicheren Vorhersage, welcher Patient eine Erkrankung entwickeln wird.

Für das *case-finding* der hereditären Hämochromatose sollten Serumferritin und Transferrinsättigung bestimmt werden. Die cut off Werte für Serumferritin von mehr als 200 bei Frauen, mehr als 300 bei Männern und einer Transferrinsättigung von mehr als 55% könnten als diagnostisches Kriterium[4] herangezogen werden, es gibt allerdings keine einheitlichen diagnostischen Kriterien für die molekulargenetische Untersuchung.

Die *British Society for Haematology*[5] empfiehlt *case-finding* bei Europäern mit ungeklärter chronischer Müdigkeit, pathologischen Leberfunktionswerten, Arthralgie oder Arthritis, Impotenz, Diabetes im höheren Alter, Leberzirrhose oder Bronzepigmentierung der Haut, wobei diese Symptome häufig und unspezifisch sind, und Messung des Serumferritins und Nüchtern Messung der Transferrinsättigung. Transferrinsättigung von größer als 55% bei Männern und postmenopausalen Frauen oder 50% bei premenopausalen Frauen wird die genetische Untersuchung empfohlen. (Evidence IIb–IV; Grade B, C).

5 Zusammenfassung

5.1 Prävalenz von Genotyp und Phänotyp der hereditären Hämochromatose

Seit der Entdeckung des Hämochromatose Gens (HFE) 1996[6] haben die meisten Studien gezeigt, dass mehr als 90% der typischen Hämochromatose Patienten die homozygote Mutation C282Y des HFE Gens aufweisen,[7] oder die Mutationen C282Y/ H63D (HIS) bzw. C282Y/S65C.

Schätzungen der Prävalenz des Genotyps der hereditären Hämochromatose in der Allgemeinbevölkerung variieren sehr stark,[8,9,10] mit Raten von 1: 357 bis zu 1:625[11] in verschiedenen Populationen, mit der höchsten Rate von 1: 135 bei norwegischen Männern.[12] Allerdings ist die Penetranz der Hämochromatose assoziierten Mutationen sehr gering, viele C282Y homozygote Mutationsträger weisen eine normale Transferrinsättigung auf und zeigen niemals klinische Symptome einer Eisenüberladung.[13,14,15,16,17] Studiendaten zeigen, dass 40%[18] der unbehandelten homozygoten Mutationsträger keine oder keine progressive Eisenüberladung nach Jahren der Nachbeobachtung zeigen.

Lediglich ein sehr geringer Teil der homozygoten Mutationsträger entwickelt Symptome einer Hämochromatose, und noch ein geringerer Teil dieser Personen entwickelt ein fortgeschrittenes Stadium der Erkrankung. Die vorhandenen Studiendaten sind aber derzeit zu limitiert, um genaue Schätzungen der Penetranz anzugeben.

Ein höherer Prozentsatz der homozygoten Mutationsträger als der Nicht-Mutationsträger in der Allgemeinbevölkerung zeigt eine Eisenüberladung, die klinische Wertigkeit dieses Befundes ist allerdings viel weniger klar als bei der klinisch manifesten Hämochromatose.[19] Die Assoziation zwischen den Laborparametern der Eisenüberladung, Erhöhung des Serumferritins und der Transferrin Sättigung, und der Entwicklung einer dadurch bedingten Erkrankung ist inkonsistent.[20]

5.2 Serumferritin und Transferrin Sättigung - Diagnostischer Nutzen in der Identifikation von hereditärer Hämochromatose

Eine anhaltende Erhöhung dieser Laborparameter erwies sich als beste Bestimmung zur Vorhersage der hereditären Hämochromatose. Die verwendeten cut off Werte für Serumferritin und Transferrinsättigung variierten in den Studien, der höchste cut off Wert für die Transferrin Sättigung größer 62% und dem Serumferritin größer als 500 µg/l identifizierte eine Patientengruppe, in welcher alle eine hereditäre Hämochromatose hatten, bei einer Transferrin Sättigung größer als 45% und einem

Serumferritinspiegel größer als 200 µg/l hatten nur mehr 11.5% eine hereditäre Hämochromatose.

5.3 Effektivität der Aderlaßtherapie bei hereditärer Hämochromatose

Es gibt keine Daten aus randomisierten Studien über die Effektivität der Aderlaßtherapie.[21] Einige Studien zeigen ein gewisses Ansprechen der Symptome und des Krankheitsprozesses auf die Aderlaßtherapie.[22]

5.4 Benefit und Risiko von Screening im niedergelassenen Bereich

Neuere Studiendaten haben den Nutzen der genetischen Untersuchung in Frage gestellt, da viele Personen mit der HFE Mutation keine Erkrankung entwickeln. Weiters gibt es keine prospektiven Daten zur Inzidenz der Leberzirrhose oder des Diabetes mellitus bei Patientinnen mit Erhöhung von Serumferritin und der Transferrinsättigung, aber ohne Erkrankung zum Zeitpunkt der Diagnose.[23]

5.5 Ist die Identifikation von Risikogruppen für eine hereditäre Hämochromatose vor einem genetischen Screening möglich?

Potentielle Hochrisikogruppen wurden in Hinblick auf die Prävalenz der C282Y homozygoten Mutation untersucht, 150 Familienmitglieder von Personen mit hereditärer Hämochromatose[24] und 42,636 Patienten mit chronischer Müdigkeit oder erhöhten Leberenzymen aus dem hausärztlichen Bereich oder hepatologisch, endokrinologisch oder rheumatologischen Fachabteilungen. Das Familienscreening identifizierte die höchste Prävalenz von bisher unentdeckten C282Y homozygoten Mutationen mit 23%, insbesondere bei Geschwistern mit 33%.

Unter symptomatischen Patienten aus dem hausärztlichen Bereich, endokrinologisch oder rheumatologischen Fachabteilungen lag die Prävalenz von C282Y homozygoten Mutationen bei 0% bis 5.8% im Vergleich zu 0,2% bei Gesunden einer *health appraisal clinic.*[25]

Männer, aber nicht Frauen, mit einem chronischen Müdigkeitssyndrom hatten eine gering höhere Prävalenz (0.85%) an C282Y homozygoten Mutationen gegenüber Personen ohne Symptome (0.14%).[26]

6 Prädiktive Genanalyse

Die prädiktive Gendiagnostik ermöglicht die Prognose von nicht manifesten Krankheiten und Krankheitsrisiken.

Genetische Untersuchungen an asymptomatischen Patienten werden als prädiktive Genanalysen bezeichnet. Sie dienen zur Beurteilung der Prädisposition eines Patienten für bestimmte Erkrankungen, die zum Zeitpunkt der Analyse klinisch nicht manifest sind. Die Berechtigung zur Durchführung prädiktiver Genanalysen erwirbt ein Labor im Rahmen eines Zulassungsverfahrens im Gesundheitsministerium. Eine Liste der zugelassenen Labors findet sich auf der Website des Bundesministeriums für Gesundheit, Familie und Jugend.[27] Die Zulassung betrifft die Testdurchführung, nicht aber die bei prädiktiven Genanalysen vorgeschriebene Beratung der zu untersuchenden Person.

6.1 Rechtliche Grundlage

Gesetzliche Anforderungen an eine prädiktive Genanalyse

Prädiktive Genanalysen, die der Feststellung einer Prädisposition für eine Krankheit, insbesondere der Veranlagung für eine möglicherweise zukünftig ausbrechende Erbkrankheit, oder der Feststellung eines Überträgerstatus dienen, dürfen nur auf Veranlassung eines in Humangenetik ausgebildeten Arztes oder eines für das betreffende Indikationsgebiet zuständigen Facharztes erfolgen (§ 65 Abs 1 Z 1 GTG).[28]

7 Hereditäre Hämochromatose (HHC)

Die primäre (genetisch bedingte) Hämochromatose weist die Mutation C282Y (CYS) homozygot oder die Mutationen C282Y/ H63D (HIS) bzw. C282Y/S65C kombiniert heterozygot auf. Die Hämochromatose wird autosomal rezessiv vererbt. Das HFE-1 Gen liegt auf Chromosom 6. Die homozygote Form der C282Y Mutation ist am häufigsten mit der Hämochromatose assoziiert. Ein gleichzeitiges Auftreten der heterozygoten Mutationen C282Y und H63D ist in bis zu 5% der Hämochromatosen zu finden.

Bei der Erkrankung Hämochromatose kommt es zu einer Fehlregulation der intestinalen Eisenabsorption, die zu einer inadäquaten Erhöhung der täglichen Eisenaufnahme führt und damit zu einer Eisenakkumulation in verschiedenen Organen, insbesondere der Leber. Als Folge einer klinisch manifestierten Hämochromatose treten Diabetes mellitus, Kardiomyopathien, Arthropathien, Infektanfälligkeit, Impotenz und Erschöpfungszustände auf. Aufgrund der starken Anreicherung von Eisen in der Leber besteht für Betroffene das Risiko, eine Leberzirrhose und als Folge ein hepatozelluläres Karzinom zu entwickeln.

7.1 Prävalenz des Genotyps

Seit der Entdeckung des Hämochromatose Gens (HFE) 1996[29] haben die meisten Studien gezeigt, dass mehr als 90% der typischen Hämochromatose Patienten die homozygote Mutation C282Y des HFE Gens aufweisen.[30]

Schätzungen der Prävalenz des Genotyps der hereditären Hämochromatose in der Allgemeinbevölkerung variieren sehr stark,[31,32,33] neuere Untersuchungen in verschiedenen Populationen unter Anwendung der Kriterien der HEIRS Studie,[34] haben eine Schätzung der Prävalenz der hereditären Hämochromatose von 1: 357 bis zu 1:625 ergeben, mit der höchsten Rate von 1: 135 bei norwegischen Männern.[35]

Von 99,711 Teilnehmern der HEIRS Studie,[36] hatten 299 eine homozygote C282Y Mutation. Die Prävalenz der C282Y Homozygoten war mit 0,44 Prozent bei Europäern nicht spanischer Abstammung (non-Hispanic whites) am höchsten, bei Ureinwohner Amerikas (Native Americans) 0,11 Prozent, Eurpäer spanischer Abstammung (Hispanics) 0,027 Prozent, Afroamerikaner (blacks) 0,014 Prozent, Hawaianer (Pacific Islanders) 0,012 Prozent und Asiaten 0,000039 Prozent. Unter den Teilnehmern, die eine homozygote C282Y Mutation hatten, bei denen noch keine Eisenüberladung diagnostiziert war, (277 Teilnehmer) hatten 88% der Männer Serumferritinspiegel, die größer als 300 µg/l und 57% der Frauen Serumferritinspiegel, die größer als 200 µg/l waren.

7.2 Prävalenz des Phänotyps

In der Genetik bedeutet der Begriff Penetranz, dass nur ein bestimmter Anteil der Genotypen den Phänotyp ausbildet.[37] Neuere Screening Studien zeigen, dass die Penetranz der Hämochromatose assoziierten Mutationen sehr gering ist, das bedeutet, dass viele C282Y homozygote Mutationsträger eine normale Transferrinsättigung aufweisen und niemals klinische Symptome einer Eisenüberladung zeigen.[38,39,40,41,42]

Heterozygote Mutationsträger bilden in der Regel lebenslang keine klinisch relevante Eisenüberladung aus, zeigen aber manchmal veränderte Eisenstoffwechsel-parameter.

7.3 Diagnostische Kriterien für Eisenüberladung

Test positiv für erhöhte Eisenwerte

	Männer	Frauen
Transferrinsättigung %[43,44,45]	>50	>45
Serum Ferritinspiegel µg/l[46,47]	>300	>200

Mögliche Eisenüberladung

	Männer	Frauen
Wiederholte Transferrinsättigung %	>50	>45
oder		
Wiederholte Serum Ferritinspiegel µg/l	>300	>200
oder		

Erhöhte Transferrinsättigung und Ferritinspiegel und klinische Untersuchungsergeb-nisse

Primäre Eisenüberladung - nicht bewiesen[48]
Wiederholte Transferrinsättigung und erhöhte Serum Ferritinspiegel, Ausschluß einer Lebererkrankung, Entzündung oder sekundärer Ursachen für Eisenüberladung

Primäre Eisenüberladung - bewiesen [49]
Die oben genannten Kriterien und zumindest eines der folgenden Kriterien treffen zu:
Hepatische Eisenkonzentration (Biopsie): ≥90 µm/g, ≥5000 µg/g Trockengewicht
Mobilisation von Eisen mittels Aderlaß: ≥4 g Eisen
Histologie: vereinbar mit Hämochromatose und
hepatischer Eisenindex: ≥1.9 oder
hepatische Eisenfärbung: 3+, 4+

8 Systematische Übersichtsarbeiten

8.1 Screening for hereditary hemochromatosis: a systematic review for the U.S.Preventive Services Task Force[50]

8.1.1 Key question 1: What is the risk for developing clinical hemochromatosis among those with a homozygous C282Y genotype?

We have data on the risk for developing signs or symptoms of iron overload and hemochromatosis in 33 C282Y homozygote adults monitored over 17 to 25 years and on the burden of disease at the time of identification for an additional 228 newly identified C282Y homozygote adults from the general population. Taken together, these data suggest that up to **38% to 50% of C282Y homozygotes develop iron overload according to our criteria and up to 10% to 33% develop definite disease (fibrosis, cirrhosis, or diabetes)**. Much lower estimates are also compatible with available data. Findings from a large case series on the disease expression of 271 patients with hereditary hemochromatosis identified through genetic testing of those with elevated serum iron levels detected at health appraisal screening complement our review.[51] Although these patients' disease expression would represent only C282Y homozygotes already exhibiting iron accumulation by definition, rates of cirrhosis (6.3%), fibrosis (10.7%), diabetes (3.6%), or any combination of these (20.6%) were similar to or marginally higher than limited results from general population screening found in our review. Available data remain too limited to clearly establish estimates of disease penetrance, since so few people have been studied in depth (only 10 C282Y homozygotes were evaluated per our criteria for iron overload or hemochromatosis in longitudinal studies), and in those studied over time, disease could still develop with longer follow-up. Indeed, 8 of 33 of those followed longitudinally were women age 50 years or younger at last follow-up, in whom disease may not have yet developed. Also, while a higher proportion clearly develop iron overload, its clinical significance is less clear than that of clinical hemochromatosis. Finally, data reported here (and elsewhere) clearly articulate that a subgroup of untreated homozygotes, perhaps even 40% [52] do not exhibit any or progressive iron accumulation over years of follow-up, thus complicating any message that would be given to asymptomatic screening-detected individuals.

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.

8.1.2 Key question 2: Does earlier therapeutic phlebotomy of individuals with primary iron overload due to hereditary hemochromatosis reduce morbidity and mortality compared with treatment after diagnosis in routine clinical care?

In the best available evidence on the effects of phlebotomy treatment, pretreatment and post-treatment liver biopsies in 260 patients who received a diagnosis through routine clinical practice suggest some reversibility of hepatic disease, with 7% to 23% showing improvement and 1% to 3% showing worsening.[53,54] Improvement in histologic characteristics was more common (32.6%) in patients with less severe, precirrhotic liver disease than in patients with cirrhosis (14.8% improved).[55] In a highly selected subgroup of family (and health check) screeningdetected patients (*n* = 25) who underwent a second biopsy after treatment for persistently elevated liver enzyme levels or uncertainty about cirrhosis on first biopsy, 19 of 20 showed improvement in hepatic fibrosis scores after treatment; the only case with baseline cirrhosis was unchanged[56]. These findings are not clearly generalizable because of the selected nature of the patient group and because biopsy results in 5 cases with high alcohol intake were not reported. Several studies suggest that some, but not all, other disease process and symptoms will respond to phlebotomy treatment.

8.1.3 Key question 3: Are there groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening?

Potential high-risk groups were examined for a higher prevalence of C282Y homozygosity, including 150 family members of probands and 42 636 patients with fatigue or increased liver enzyme levels from primary care or hepatology, endocrinology, and rheumatology specialty settings. Family screening identified the highest prevalence of undetected C282Y homozygotes (23% overall), particularly among siblings of probands (33% homozygosity). Among symptomatic patients selected from primary care, rheumatology, endocrinology, or referral medicine clinics, 0% to 5.8% were C282Y homozygotes, compared with 0.2% of a random sample of persons attending a health appraisal clinic.[57] Overall, the prevalence of C282Y homozygosity did not differ between patients in the health appraisal clinic and primary care patients with an index sign or symptom. Compared with controls, C282Y homozygosity was significantly more prevalent only in hospitalized diabetic patients from an endocrinology clinic (5.8%) and in patients from a referral medicine clinic with chronic fatigue and arthralgias (5.7%). Three other studies confirm or extend these results. Males, but not females, with chronic fatigue symptoms visiting a health appraisal clinic had a slightly higher (0.85%) prevalence of C282Y homozygosity than patients without symptoms (0.14%).[58] The prevalence of C282Y homozygosity in patients from a rheumatology clinic was similar to that in the general population.[59]. In patients with a history of coronary heart disease, prevalence of C282Y homozygosity was the same as, or lower than, that of patients without symptoms (0.17% to 0.28%).[60] Findings may not be conclusive in comparisons based on fewer than 300 patients, given the population prevalence of C282Y homozygotes (3 to 5 per 1000

white persons). Some studies restricted genotyping to symptomatic patients who also had some laboratory abnormality. The prevalence of C282Y homozygosity was somewhat increased in a range of patients with hemochromatosis-compatible signs and symptoms and elevated iron measures. Among 667 patients from a liver clinic who had elevated iron measures, 7.1% were homozygous for C282Y.[61] For hospitalized patients with diabetes and patients with chronic fatigue or arthralgias who were referred to specialists, C282Y homozygosity was higher in patients with transferrin saturation greater than 0.40 or serum ferritin level greater than 300 µg/L than in patients with disease but without elevated iron measures (6.6% to 17.3% compared with 5.7% to 5.8%)[62] . The sensitivity of transferrin saturation greater than 0.40 for detecting C282Y homozygosity in diabetic patients hospitalized for disease-related complications was 100%, but the specificity was 13%. In diabetic patients, the sensitivity of a serum ferritin level greater than 300 µg/l was 86% and the specificity was 56%. For patients referred for arthralgias and unexplained fatigue, transferrin saturation greater than 0.40 and a serum ferritin level greater than 300 µg/l were about equally sensitive and specific for C282Y homozygosity (100% sensitive and 65% to 67% specific). In patients from a health appraisal clinic who had elevated liver enzyme levels, the prevalence of C282Y homozygosity appeared the same (in women), or slightly higher (0.57% vs. 0.28%, in men), compared with those with normal enzyme levels.[63].

8.2 Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review[64]

8.2.1 Subquestion 1: What Is the Prevalence of Hereditary Hemochromatosis in the Primary Care Setting?

On the basis of the literature, hereditary hemochromatosis is a common genetic disease within the primary care setting, especially in white men older than 40 years of age. Given the relatively high estimated prevalence of hereditary hemochromatosis (1 in 127 patients to 1 in 270 patients) we must understand the magnitude of the burden that will likely occur.

8.2.2 Subquestion 2: In Asymptomatic Patients with Hereditary Hemochromatosis, What Is the Risk for Developing Morbid Complications or for Death?

The available data demonstrate low penetrance of *HFE* mutations and suggest that the magnitude of burden may be less than commonly believed. Specifically, 3 small longitudinal studies[65],[66],[67] of patients homozygous for the C282Y mutation did not demonstrate predictable progression to overt clinical hereditary hemochromatosis over long periods of follow-up.

8.2.3 Subquestion 3: How Diagnostically Useful Are Transferrin Saturation and Serum Ferritin Level in Identifying Primary Care Patients with Hereditary Hemochromatosis?

The association between phenotypic measures of iron overload (transferrin saturation and ferritin levels) and the development of iron-related complications is inconsistent. The identification of the *HFE* gene and development of a genetic test to detect the presence of C282Y mutation has made the case definition of hereditary hemochromatosis vary.[68] This has resulted in several different approaches for studying the diagnostic efficacy of available tests. Some investigators used genotyping as the gold standard and determined the sensitivity and specificity of phenotypic tests in predicting the presence or absence of homozygous C282Y genotypes. Without convincing data to demonstrate that patients with *HFE* mutations will progress to disease or early death, this definition may not have clinical utility. Other investigators have used persistently elevated transferrin saturation and serum ferritin levels, without biopsy or quantitative phlebotomy, to diagnose hereditary hemochromatosis. This results in a diagnostic incorporation bias.[69]

Consequently, we selected a gold standard for hereditary hemochromatosis for our review that required independent demonstration of iron overload (liver deposition or the amount of iron removed by phlebotomy). The use of this case definition limits the ability to determine the diagnostic efficacy of phenotypic tests in the primary care setting because patients with transferrin saturation or a second serum ferritin level interpreted as normal do not undergo liver biopsy, and no prospective follow-up data are available for those with negative test results to identify false-negative results. Further, only those with sustained elevations of transferrin saturation and serum ferritin levels are offered the gold standard test.

Determining the likelihood of disease in those with positive test results defined as sustained elevations of phenotypic measures (positive predictive value) was the best existing measure available. The diagnostic cutoff levels for transferrin saturation and serum ferritin have varied across studies as well. The higher cutoff levels (transferrin saturation ≥ 62% and serum ferritin levels ≥500 µg/l) identified a subgroup in which all patients had hereditary hemochromatosis. The least stringent criteria (transferrin saturation ≥ 45% and serum ferritin levels > 200 µg/l) identified a group in which only 11.5% had hereditary hemochromatosis.

8.2.4 Subquestion 4: Is Phlebotomy Efficacious in Reducing Morbid or Fatal Complications in Asymptomatic Patients with Hereditary Hemochromatosis?

No data based on randomized trials indicated the true efficacy of phlebotomy.

8.2.5 Subquestion 5: Do the Benefits Outweigh the Risks in Screening Primary Care Patients for Hereditary Hemochromatosis?

More recent data have raised additional questions about the usefulness of genetic testing because many people with *HFE* mutations do not progress to overt disease, and we have no prospective data on the incidence of cirrhosis or diabetes mellitus in patients with elevations of transferrin saturation and serum ferritin levels but without disease at the time of diagnosis.

9 Übersichtsarbeit

9.1 Screening in liver disease[70]

In conclusion genotypic screening is not the ideal screening tool for hereditary hemochromatosis. The key point is that genotypic testing identifies many patients that will not progress into overt disease, while phenotypic testing circumvents this problem, because the combined use of serum ferritin and transferrin saturation is directly related to iron overload. Serum ferritin is unreliable as a sole marker, but is beneficial in classifying patients with regard to the presence or absence of cirrhosis.[71] Serum ferritin has a high sensitivity but poor specificity for iron overload[72] and therefore needs to be supplemented by the use of transferrin saturation. The best thresholds for these tests have been defined in the HEIRS studies.[73] An elevated ferritin level was defined in this study[74] as greater than 300 µg per liter in men and greater than 200 µg per liter in women. An elevated transferrin saturation was higher than 45 percent in women and higher than 50 percent in men. A serum ferritin level greater than 1000 µg per liter has previously been reported to be associated with liver disease in C282Y homozygotes.[75,76]

Both the American Association for the Study of the Liver and the American College of Physicians deem that there is insufficient evidence for population screening, but recommend targeted screening of individuals at high risk. The target population should be:

(1) patients with unexplained liver disease or known liver disease with elevated serum iron markers,
(2) type 2 diabetics,
(3) first degree relatives of hemochromatosis patients,
(4) patients with early onset atypical arthropathy, cardiac disease or male sexual dysfunction,
(5) unexplained changes in skin pigmentation.

There is no data available to risk-stratify the patients according to these conditions and to recommend more intensive screening for a particular group.

10 Leitlinien

10.1 Screening for hemochromatosis: recommendation statement[77]

The U.S. Preventive Services Task Force (USPSTF) recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population.
(Grade D recommendation)[78]

There is fair evidence[79] that disease due to hereditary hemochromatosis is rare in the general population.

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.[80]

There is poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals.[81]

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). 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. 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.

10.2 Screening for hereditary hemochromatosis: a clinical practice guideline[82]

10.2.1 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[83]

10.2.2 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 µg/l in women or more than 300 µg/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.

10.2.3 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,[84] 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.

10.2.4 Recommendation 4:

Further research is needed to establish better diagnostic, therapeutic, and prognostic criteria for hereditary hemochromatosis.

The lack of information on the natural history of the disease makes it difficult to manage patients with hereditary hemochromatosis. There are no clearly defined criteria to risk-stratify patients into groups more or less likely to develop overt disease. Future developments in technology and genetic screening might help in the

diagnosis and management of hereditary hemochromatosis. In addition, there is a need for more uniform diagnostic criteria.

10.3 Guidelines on the diagnosis and therapy of Genetic Haemochromatosis[85]

10.3.1 Recommendation 1: Clinical features which justify investigation for HC

Subjects of European ancestry presenting with unexplained weakness or fatigue, abnormal liver function tests, arthralgia/arthritis, impotence, diabetes of late onset, cirrhosis, or bronze pigmentation should be investigated as in Recommendation 2. (Evidence IIb–IV; Grade B, C)[86]

Unfortunately, early diagnosis is not easy. The symptoms with which patients present are relatively common and non-specific. Raised ferritin concentrations are common in hospital patients, and serum iron concentrations are very labile, but most adults with HC have an elevated, fasting transferrin saturation[87]. A genetic test offers the best approach to early detection, but the lack of information on clinical penetrance is delaying its use for population screening.

10.3.2 Recommendation 2: Detecting iron accumulation

- Measure serum iron concentration and total iron-binding capacity and calculate transferrin saturation.
- If transferrin saturation is greater than 50% repeat the measurement on a fasting sample. A fasting transferrin saturation of greater than 55% (men and post-menopausal women) or 50% (pre-menopausal women) indicates iron accumulation.
- Measure serum ferritin concentration.

(Evidence IIb–IV: Grade B, C)

10.3.3 Recommendation 3: Confirming the diagnosis of HC in a patient with evidence of iron overload but no evidence of liver damage

No hepatomegaly, AST activity normal, serum ferritin concentration is > 300 mg/l (200 mg/l pre-menopausal women) and < 1000 mg/l:

- In most cases genotyping will confirm the diagnosis of genetic haemochromatosis. 90% of patients have the genotype C282Y +/+, 5% have C282Y +/-, H63D +/-.
- Commence quantitative phlebotomy. Removal of more than 4 g iron (about 20 phlebotomies of 450 ml) demonstrates that body iron stores are compatible with genetic haemochromatosis.

(Evidence IIb–IV; Grade B, C)

10.3.4 Recommendation 4: Confirming the diagnosis of HC in a patient with evidence of liver damage

Serum ferritin concentration is > 300 mg/l (200 mg/l in pre-menopausal women), AST activity is above normal or there is hepatomegaly:

- Genotyping (see Recommendation 3)
- Carry out liver biopsy to show hepatic architecture (normal/fibrosis/cirrhosis). The presence of cirrhosis has significant prognostic implications and will affect management (see Recommendation 8).
- Carry out histological grading of iron concentration (Perl's stain). Increased stainable iron in hepatic parenchymal cells confirms iron loading.

(Evidence IIb–IV; Grade B, C)

10.3.5 Recommendation 5: Confirming the diagnosis of HC in a patient with only a raised transferrin saturation

If the fasting transferrin saturation is raised (see Recommendation 2) but serum ferritin and AST levels are normal:

- In most cases genotyping will confirm genetic haemochromatosis (see Recommendation 3).
- If the genotype is that of homozygous haemochromatosis, transferrin saturation and serum ferritin should be monitored at yearly intervals. If serum ferritin becomes elevated, phlebotomy should be started (see Recommendation 6).
- If the genotype is normal the serum ferritin concentration should be monitored at yearly intervals.

11 Frequenz der C282Y Mutation in Europa[88]

Figure 1 Frequency (%) of the C282Y mutation in various countries or regions in Europe and Algeria. There are more than 90 subjects in each sample. Sources of data: Iceland, Norway, Italy and Greece[41], Norwich[42], Oxford[43], Belfast[44], S. Wales[45], France[29], Brittany[25], Finistère Sud[46], Brest[47], Austria[48], Germany[27], Hungary (Budapest)[49], Eastern Hungary/Romany[50], Denmark[51], Sweden and N. Finland[52], Spain[53], Algeria[54] and N.E. Scotland[121]. Note the surprising variations between adjacent regions, probably reflecting variation due to sample size as well as population differences. Allele frequencies for the H63D mutation are about 12%[41].

12 Suchstrategie

In folgenden Quellen wurde gesucht:
bibliographische Datenbanken: Medline, Pubmed
Guidelines International Network, British Society for Haematology,
Es wurden systematische Reviews, Reviews und Guidelines gesucht, Zeitraum von 2002 bis 2007 in englischer oder deutscher Sprache, im Volltext online zugänglich.

• Search	Most Recent Queries	Time	Result
#22	Search **"Hemochromatosis/diagnosis"[MeSH]** Limits: **English, German, published in the last 5 years, Meta-Analysis, Practice Guideline, Review**	08:19:17	80
#10	Search **"Hemochromatosis/diagnosis"[MeSH]**	08:18:42	1840

• Search	Most Recent Queries	Time	Result
#35	Search **"Hemochromatosis/diagnosis"[MeSH] AND "Mass Screening"[MeSH]** Limits: **English, German, published in the last 5 years, Meta-Analysis, Practice Guideline, Review**	08:48:43	29

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[78] Grade Recommendation*
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 [the 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.
* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to 1 of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

[79] **Grade Definition***

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
* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).

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[86] **Level of evidence** *

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
II a	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasiexperimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Grade of recommendation Grade Evidence level Recommendation

Grade	Evidence level	Recommendation
A	Ia, Ib	Required – at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation
B	IIa, IIb, III	Required – availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation
C	IV	Required – evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities Indicates absence of directly applicable clinical studies of good quality

*Derived from US Agency for Health Care Policy and Research

[87] Bradley LA, Haddow JE, Palomaki GE. Population screening for hemochromatosis: expectations based on a study of relatives of symptomatic patients. J Med Screening 1996; 3: 171–7

[88] British Committee for Standards in Haematology Guidelines on diagnosis and therapy. British Society for Haematology. Genetic Haemochromatosis http://www.bcshguidelines.com/pdf/chpt9B.pdf aufgesucht am 11.5.2007