

EDITORIAL

Screening in liver disease

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Abstract

A disease is suitable for screening if it is common, if the target population can be identified and reached and if both a good screening test and an effective therapy are available. Of the most common liver diseases only viral hepatitis and genetic hemochromatosis partially satisfy these conditions. Hepatitis C is common, the screening test is good and the therapy eliminates the virus in half of the cases, but problems arise in the definition of the target population. In fact generalized population screening is not endorsed by international guidelines, although some recommend screening immigrants from high prevalence countries. Opportunistic screening (case finding) of individuals with classic risk factors, such as transfusion before 1992 and drug addiction, is the most frequently used strategy, but there is disagreement whether prison inmates, individuals with a history of promiscuous or traumatic sex and health care workers should be screened. In a real practice setting the performance of opportunistic screening by general practitioners is low but can be ameliorated by training programs. Screening targeted to segments of the population or mass campaigns are expensive and therefore interventions should be aimed to improve opportunistic screening and the detection skills of general practitioners. Regarding genetic hemochromatosis there is insufficient evidence for population screening, but individual physicians can decide to screen racial groups with a high prevalence of the disease, such as people in early middle age and of northern European origin. In the other cases opportunistic screening of high risk individuals should be performed, with a high level of suspicion in case of unexplained liver disease, diabetes, juvenile arthropathy, sexual dysfunction and skin pigmentation.

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SCREENING STRATEGIES

Screening is defined as the application of a diagnostic test to an asymptomatic population in order to detect a disease at a stage when intervention may improve its outcome and natural history^[1]. For many years screening has attracted physicians and policy makers as a way of reducing the mortality of chronic illness with a cost effective model of medical care. It was perceived that generalized screening for the most common diseases, could reach the poorest population at higher health risk and in greatest need of medical care. With the advent of evidence based medicine, skepticism about the benefits of screening arose however in the medical community, particularly regarding the adverse consequences of false-positive and false-negative results of the tests utilized in the screening programs^[2]. It was evident that false positive results could produce anxiety, unnecessary examinations and incorrect labeling of part of the population, while false negative results could impair the cost efficacy of the screening. Criteria were therefore established to appraise the effectiveness and appropriateness of these programs^[3] and for their acceptability proof was required of evidence for the reduction of disease specific mortality from randomized controlled trials.

Together with the demand for more evidence based policies came also a better understanding of the different screening strategies. Screening can be performed in different ways and with different target populations.

(1) Population screening is the application of a test to the entire population, generally with age or sex, restrictions, e.g. mammography applied to women of more than 50 years of age.

(2) Targeted screening is the approach of screening only patients at higher risk for a specific disease, e.g. searching for atrial fibrillation in patients with a history of myocardial infarction, angina, diabetes mellitus, hypertension *etc*^[3,4]. Targeted screening utilizes existent disease registers in general practice and local health districts or prescribing information from computerized records.

(3) Opportunistic screening, also termed opportunistic case finding or simply case finding, looks for additional illnesses in a population already complaining of medical problems. In this strategy health professionals, most commonly general practitioners, apply a screening test

Table 1 Characteristics of the most common liver diseases and feasibility of screening

	Hepatitis C	Hepatitis B	Fatty liver	Hemochromatosis
Disease common and causing morbidity/mortality	Yes	Yes	Common, but increased mortality only if advanced NASH	Common, but only 1% of screened population with complications ^[13]
Target population identifiable	High risk groups	High risk groups	Obese, diabetics	Northern European ancestry
Screening test	HCV Antibody test	HBsAg test	Ultrasound	Transferrin saturation or genetic testing (unsettled)
Performance of test	Good	Good	Low PPV and NPV for fibrosis	Under investigation
Effective therapy	50% cure ^[14]	4%-24% HBsAg loss, 70% no progression ^[15,16]	Only lifestyle modification	Yes, but may be unnecessary

to individuals with specific risk factors for the disease and attending their offices with other medical problems. Opportunistic screening is the simplest and less expensive form of screening because there is no need of additional staff and of complicated reach out or recall procedures. The screening test is requested during the patient's consultation and the next appointment is scheduled immediately at the time of the first visit. This strategy however may miss a significant proportion of people who do not present for consultation, but who would otherwise benefit from treatment. Another drawback is that it can be conducted only in those countries with a well established primary care network.

(4) Surveillance is the application of targeted screening over time to a particular category at risk and already harboring a disease. Well known examples of this strategy are the use of periodic ultrasonography and upper gastrointestinal endoscopy in cirrhotic patients in order to detect early stage hepatocellular carcinoma or varices at higher bleeding risk. Another type of surveillance that has been proposed in the field of hepatology is the use of periodic liver chemistry for the detection of drug induced liver toxicity. The terms screening, case finding and surveillance are not uniformly used in the literature and are often inappropriately used interchangeably^[5]. In fact surveillance, strictly speaking is different from screening, being applied not to healthy and asymptomatic people, but to individuals who have already been recognized to suffer from a specific disease.

FEASIBILITY OF SCREENING IN LIVER DISEASE

The implementation of a screening program is requested to meet some basic criteria^[6]: (1) the disease must be common and produce significant morbidity and mortality. (2) The target population must be easily identifiable. (3) The screening test must have good sensitivity and specificity. (4) There must be well defined recall procedures (5) The test should be accepted by the population to be screened. (6) There must be an effective therapy for the disease.

Liver disease seems to meet at best only the first and third of the 6 established criterions. The three main causes of liver disease are viral hepatitis, alcoholic and non-alcoholic fatty liver, which are all quite common. Hepatitis C virus affects 200 million people in the world with an

expected increased mortality for end stage liver disease and hepatocarcinoma in the next 10-20 years^[7,8]. The global disease burden of Hepatitis B is also substantial: it is estimated that there are in the world 350 million chronic hepatitis B carriers^[9] and that 500 000 to 1.2 million people will die annually from the complications of HBV infection^[10]. The other most common causes of liver disease are fatty liver and alcoholic liver disease, which are widespread in the western world and a rising problem also in the developing world^[11]. However the natural history of fatty liver is less well defined compared to viral hepatitis and is characterized by concomitant cardiovascular risk factors such as the metabolic syndrome, diabetes and obesity. It is therefore difficult to predict its liver related mortality in the next 20 years. Alcoholic liver disease is, on the contrary, a multifaceted problem which is beyond the goals of population screening, even if physicians are using a wide array of diagnostic tools to detect alcohol problems on an individual basis. In addition to viral hepatitis, genetic hemochromatosis has also been proposed for population screening, being a common and treatable disease, but it is doubtful which is the optimal test to be used and if only people with northern European ancestry should be subjected to screening^[12]. The specific liver diseases potentially amenable to population screening are listed in Table 1.

In conclusion among the most common liver diseases only fatty liver lacks the characteristics that would render it feasible for a screening program. Both viral hepatitis and hemochromatosis can be considered for some form of screening and will be discussed in detail.

HEPATITIS C

Hepatitis C has many characteristics that render it potentially suitable for screening. In fact, it causes significant morbidity, high risk groups are identifiable as a target population and the screening test is good. The testing strategy utilizes the antibody test which has excellent specificity and sensitivity, if we exclude some false negative cases in acute infections and in the immunocompromised state^[17]. In these situations the diagnosis can be made with HCV-RNA by using amplification techniques. For the majority of patients the usual approach is to test them initially for the antibody and then to use HCV RNA to detect viremia and decide whom to treat^[17]. Current treatment of Hepatitis C is not entirely

Table 2 Indications for screening with anti-HCV antibody

Risk factors for which testing is indicated by all the guidelines	Risk factors for which testing is indicated by some of the guidelines	Additional risk factors for which testing is not formally recommended
Intravenous drug use (past and present)	Populations with high HCV prevalence ^[12,30]	Injections with reusable glass syringes ^[32]
Blood transfusion or transplantation before 1992 (or by known HCV positive donor)	Incarceration ^[12,33]	Heavy marijuana use ^[34]
Administration of clotting factors before 1997	Hepatitis B virus infection ^[12,33]	Promiscuous sex ^[34]
Clinical or biochemical evidence for chronic liver disease	Sharing intranasal cocaine equipment ^[12,33]	Poverty ^[34,35]
Percutaneous exposures to HCV	History of sexually transmitted disease ^[12,33] with genital erosions ^[28]	History of invasive procedures ^[36]
Haemophilia	Traumatic sex or vaginal sex during menstruation ^[14,33]	History of surgery ^[36]
Children born to HCV + ve mothers	Health Care Workers performing procedures at risk of transmission to the patient ^[37]	Beauty treatments ^[38]
HIV positivity		
Stable sexual partners of HCV + patients		

satisfactory because it can eradicate the virus in only half of the cases^[18,19], but in the future new treatments will be available with far greater efficacy^[14]. The low yield of treatment has prompted the US Preventive Services Task Force to dismiss Hepatitis C as a potential candidate for screening^[20]. Sufficient evidence from the literature has not found that screening and treatment of hepatitis C could prevent chronic liver disease and decrease mortality. This opinion has been challenged by other experts^[21] who pointed out that the lack of studies showing a favorable impact of antiviral therapy on mortality is due to the long history of the disease. According to these experts eradication of the virus with normalization of liver enzymes could be considered a surrogate marker for increased life expectancy, as indicated by studies with a long follow up of sustained responders to antiviral therapy^[22-24].

For this reason several international societies have now endorsed screening strategies for hepatitis C^[25-30]. Their official guidelines recommend selective screening targeted for high risk groups, but none of them endorse generalized population screening, mainly for the relatively low prevalence of hepatitis C outside the categories at risk. Other arguments against population screening are that nearly half of the detected patients will have normal ALT and a slow progressing disease^[31], that many patients will harbor conditions contraindicating antiviral treatment and last but not least, that many persons with mild disease will have deterioration in their quality of life after knowing the result of the test^[28]. These drawbacks limit the effectiveness of a mass screening program and render it not cost effective. The optimal method to detect HCV infection, according to all international guidelines is therefore to screen individuals with identifiable risk factors (Table 2).

There is general agreement among all the guidelines that there are major risk factors for hepatitis C and that all individuals with one or more of these factors should be screened with the antibody test. These factors are listed in the first column of Table 2 and basically include intravenous drug use and blood transfusions before 1992, the year when HCV testing of blood units was introduced. Other categories at increased risk that should be tested are

the hemophiliacs, HIV positive patients and children born to HIV positive mothers. Although many studies have shown that HCV transmission is rare^[39-41] or virtually non-existent^[42] in stable monogamous couples, all the guidelines recommend testing of the spouse or partner, mainly for reassurance.

Though there is consensus on the most important risk factors some disagreement exists for other conditions at risk, which are mentioned only by some of the guidelines and not by others. For example the Canadian College of Family Physicians emphasizes the problem of sexual exposure and recommends testing in case of promiscuous, traumatic or vaginal sex during menstruations^[33]. The Italian guidelines suggest testing individuals with high risk sexual behavior only if they have a history of genital erosions^[28]. Promiscuous sex is not considered an indication for testing by the other guidelines, being discussed in detail only by the US Preventive Services Task Force who examining 4 large population studies^[43-46] could not rule out a concealed association between promiscuous sex and unacknowledged drug use^[20]. For this reason systematic testing of individuals with multiple sex partners or homosexuals was not recommended. Another debated issue is whether health care workers performing exposure prone procedures should be screened for hepatitis C. For exposure prone procedures it is indicated that the performance of invasive procedures are putting the patient at risk to contract a blood borne virus. From 1994 to 2002 fifteen British patients have been infected by health care workers (HCWs) carrying the hepatitis C virus. Following these incidents the British Department of Health recommended screening all HCW performing or intending to perform exposure prone procedures first with an anti HCV antibody test and if they test positive, with an HCV RNA assay. Anti-HCV positive HCWs carrying the virus are restricted from performing such procedures until they receive treatment and get rid of the virus^[37]. This opinion is not shared by the other guidelines that do not recommend HCW screening, regardless of their type of duty.

Another source of disagreement is population screening. In spite of an apparent unanimity among the

guidelines against generalized population screening, two of them^[12,30] suggest to screen individuals coming from high prevalence countries, which is an indirect form of population screening. The two guidelines do not set a threshold to define a high prevalence country, but many experts think of Egypt and Pakistan, which have an anti HCV prevalence of more than 10% in the general population^[47-49]. Another particular form of screening a segment of the population is the testing of prison inmates, recommended by the Canadian Guidelines^[14,33].

Many other risk factors have been found to be associated with an increased risk of HCV infection in epidemiological studies, but none has proven useful in clinical practice. For example in the Mediterranean area many infections have been transmitted in the past through the use of reusable glass syringes. However, due to their widespread use, a positive history for this risk factor has a very low positive predictive value and is practically useless in the clinical setting^[32]. The same applies for the history of surgery and invasive procedures after a French study demonstrating that screening for these additional risk factors is not cost effective in general practice^[50].

In conclusion, there is only partial consensus among the international guidelines on the appropriate risk factors to be used in the clinical setting, but there are other problems to be considered. First, none of the guidelines indicate how the screening strategy should be actuated-e.g. if the screening should be targeted or opportunistic. In other words it is not clear if an active search for individuals belonging to categories at risk should be implemented or if the less demanding opportunistic screening will suffice. It is true that hemophiliacs, hemodialysis patients, HIV positive individuals and drug addicts on detoxification programs are usually registered on files and record charts that could be accessed for screening. In this case, individuals at risk easily recalled, but what about people transfused earlier than 1992? Many of them are women who received few blood units after delivery, a bad habit of the past, but are not aware of being at risk. Should we actively search for them in the blood bank files of our hospitals or simply wait until they come to their general practitioner and rely solely on his history skills? In addition the patient's privacy could be at issue when browsing into these records. There are also doubts that an organized, widespread targeted screening would be cost effective, as shown in a study conducted in a pilot French area highlighting the difficulty and cost of mobilizing a considerable number of health professionals in the screening campaign^[47]. In the only cost effectiveness study published in the literature, Josset^[36] calculated a cost of 2247-3318 € per identified case for the reference strategy, consisting of the opportunistic screening of individuals at risk. This cost skyrocketed to 10994 € for targeted organized screening with mobilization of health professionals^[47], which is surely a waste of money considering that only half of the detected cases can be cured.

If we admit that the most rational approach is opportunistic screening and not population or targeted screening, we are faced with the problem of assessing the performance of general practitioners in detecting the patients at risk. Many studies have addressed this issue,

chiefly using questionnaires, mail surveys and phone interviews, but the overall results are confusing. Some of them found a good knowledge of risk factors by family physicians^[51-54], but others have not^[55-60] irrespective of the geographical areas. The actual behavior of family physicians in real practice was investigated in one study, by scrutinizing the medical records of 229 hepatitis C patients from 26 primary care clinics in Michigan^[61]. It was found that testing was initiated based on physician-identified risk factors only in 20% of the patients, while the majority of them were tested because of liver enzyme elevations, history of hepatitis B or by direct patient request. It is noteworthy also that a minority of the patients already knew their HCV status and that only 10% of them were asked about risk factors during their first visit at the clinic. This means that, in a real practice setting, family physicians are less aware of the risk factors of hepatitis C, than when questioned in formal interviews. In another real practice study comparing different screening strategies, HCV infection was found in only 5% of the tested patients^[62] showing that, irrespective of the adopted strategy, the yield of this screening is rather low. These real practice studies depict a bleaker scenario than what was apparent from questionnaire and interview studies. Hopefully the performance of family physicians can be improved by training interventions and by the participation of these physicians to hepatitis C networks, as shown by the French experience^[63]. Both the screening efficacy and the appropriateness of referrals can be ameliorated by long term training and by the adoption of specific guidelines for family practice. These guidelines consist of easy to use flow charts for the identification and referral of the patients and can be utilized by general practitioners in their offices^[64]. The same goals can be achieved in far to reach rural areas by the use of CD based software, mailed to physicians practicing in the same areas. This comprehensive software contains the various aspects of the care of hepatitis C, including diagnosis, counseling, treatment and follow up^[65].

In summary, we can conclude that opportunistic screening of categories at risk is the best form of screening recommended in the literature, but that no consensus exists on some of the risk factors. Population screening is recommended only for some particular ethnic groups and only by some of the guidelines. In a real practice setting the performance of this type of screening by general practitioners is low but could be ameliorated by training interventions. The cost of other forms of screening is too high to merit consideration and therefore interventions should be aimed to improve the detection skills of general practitioners.

HEPATITIS B

The case of hepatitis B is completely different from hepatitis C. In fact, the treatment can eradicate the virus in only a small minority of the patients^[15,16,66], but an effective vaccine is available to prevent transmission of the infection. Screening therefore has been implemented in the categories at risk to optimize the vaccination strategies and not to detect infected individuals to be cured, as

in the case of hepatitis C^[67-69]. In some high prevalence populations such as Asian and Pacific island immigrants in the United States, some screening for treatment programs have been conducted. In the New York City program^[70] 1836 people were tested for HBV infection: 24% of them were found HBsAg positive and 90% returned for further evaluation and possible treatment. A total of 505 (27.5%) were negative for hepatitis B markers and were vaccinated with a discrete coverage rate (70% after the third dose). The results of the New York City program show that screening a high prevalence segment of the population is feasible and can identify in a cost effective way both susceptible people to be vaccinated and infected individuals to be treated. Control of hepatitis B is however achieved worldwide by means of vaccination and in fact the World Health Organization recommends the addition of HBV vaccine to all national immunization programs^[71]. The vaccination strategy depends on the prevalence of HBsAg carriers in the general population: in countries with intermediate and high prevalence (more than 2% and 8% of the general population), universal neonatal or infant vaccination is recommended. Even in countries at low risk (1%-2% prevalence) universal infant or adolescent vaccination is cost effective if the vaccine can be delivered efficiently^[67]. Only in countries at very low risk (around 0.05%) such as the United Kingdom, Scandinavia and the Netherlands a selective risk group vaccination could be more cost effective than universal vaccination^[67,72]. Regarding the categories at risk that should be screened and vaccinated, there is full consensus in the literature on their definition^[69,73]. These categories are listed in Table 3. Individuals with these risk factors should be screened with a case finding strategy in the context of vaccination delivery programs^[72] and those found to be HBsAg carriers evaluated by the specialist for possible treatment.

HEMOCHROMATOSIS

Hereditary Hemochromatosis is a genetic disorder of iron metabolism in which iron is excessively absorbed by the intestinal tract and accumulates in the liver, heart, joints, pancreas and other endocrine glands. There are 4 different forms of hereditary hemochromatosis: (1) HFE gene mutations which result in upregulation of iron absorption by intestinal cells (2) Juvenile hereditary hemochromatosis with mutations in the hemojuvelin gene HJV (type 2A) or in the HAMP gene (type 2B), (3) TFR-2 related hemochromatosis in which mutations in the transferrin receptor may lead to an increased uptake of iron by hepatocytes and (4) Ferroportin related iron overload in which mutations of the ferroportin gene cause the absence of ferroportin activity and the inappropriate iron sequestration within the reticuloendothelial cells^[74].

The most common form of hereditary hemochromatosis is related to the substitution of tyrosine for cysteine at position 282 of the HFE protein (C282Y): homozygosity for the C282Y mutation predisposes to iron accumulation and is found in 50%-95% of classic hemochromatosis, depending on the geographic areas. The highest frequency of this mutation is observed in people of northern European descent (0.3%-0.5% of the general population) while lower

Table 3 Categories at risk for hepatitis B that should be screened and vaccinated

Immigrants from high prevalence areas (> 8% population) Asia, Pacific Islands, Alaska, Greenland, Africa, Middle East, former USSR, Eastern Europe (except Hungary), Malta, Amazonian areas of Peru, Brazil, Bolivia and Venezuela
Refugees, adopted children, residents for more than 6 mo in the same areas
Blood transfusion before 1973
Drug addicts
Individuals with clinical or biochemical evidence for chronic liver disease
Percutaneous exposures to HBV
Haemophilia
Pregnant women
Haemodialysis
Household, sexual and needle sharing contacts of HBsAg patients
Sexual partners of HBsAg patients
Health Care Workers

frequencies (less than 0.1%) are found in Asians, Blacks and Hispanics^[75]. The second most common mutation of the HFE gene, linked to hemochromatosis, is the H63D mutation. One to 2 percent of people with compound heterozygosity for C282Y and H63D will eventually express the disease, while homozygosity for H63D does not seem to be associated with significant iron accumulation^[74]. A third mutation of the HFE gene, S65C has been described, but it is debated whether this mutation is associated with hemochromatosis in the compound heterozygous form with C282Y^[76]. Mutations in other genes different from HFE have been reported in Italian families with iron overload comparable to the classic HFE form^[77-79].

Hemochromatosis is a common disease and also amenable to treatment because venesection is safe and can change the natural history of the disease^[80,81]. It would therefore be advantageous to submit individuals to a screening test for hemochromatosis in order to detect the disease at an early stage, before the occurrence of damage to vital organs. Genetic testing of large samples of the general population in the USA (HEIRS Study: Hemochromatosis and Iron Overload Screening in a racially diverse population) and Norway^[75,82] showed that hemochromatosis is a common disease in non-Hispanic whites (0.44%) and Norwegian males (0.66%) while individuals of other racial origin show a much lower prevalence. For example only 0.027 of Hispanics and 0.014 of American Blacks were homozygous for the C282Y mutation. Asians have the lowest prevalence (0.00039%) of HFE mutations, but surprisingly have more iron overload than the other racial groups. Iron overload was defined as a serum ferritin greater than 300 mg/L in man and 200 mg/L in women plus serum transferrin saturation greater than 50% in men and 45% in women. These data clearly show that genetic testing is not sensitive enough to detect all cases of iron overload and neither is highly specific, since as reported in the HEIRS study 88% of men and only 57% of women homozygous for the C282Y mutation had elevated serum ferritin. In addition, it is by no means certain if these patients will develop significant life threatening complications over time. In fact in a large population based study

the prevalence of these complications in C282Y homozygosity was found as low as 1%^[13]. Other studies searching for a genotype-phenotype correlation in C282Y homozygosity have yielded varying results: increased ferritin levels were found in 19%-75% of these subjects with a median of 65%^[83,84]. Regarding liver damage approximately 50% of the C282Y homozygous with abnormal iron indexes in the Norwegian study underwent liver biopsy, and only a small minority was found to have cirrhosis^[82] indicating that finding a high ferritin and transferrin saturation does not necessarily indicate the presence of severe liver disease. The other genotypes linked with the development of familiar hemochromatosis, such as the C282Y/H63D compound heterozygous, have a lower risk of iron accumulation^[85] and are not worth screening. Similarly the non-HFE related hemochromatosis, such as ferroportin disease and mutations in the HJV and TFRF-genes are much less frequent than the homozygous C282Y form and their diagnostic tests have not yet been validated for population screening^[86]. In conclusion genotypic screening is not the ideal screening tool for hereditary hemochromatosis because it is uncertain whether the detected individuals will progress into overt disease.

Many guidelines have addressed the issue of population screening in genetic hemochromatosis^[87,88], the most recent of which was published in 2005 on behalf of the American College of Physicians^[89]. In none of these guidelines is widespread population screening recommended, but the American College of Physicians leave the specialist and general practitioner free to perform a once in a life phenotypic screening of asymptomatic non-Hispanic white men with ferritin and transferrin saturation (phenotypic test). The central issue is the sensitivity and specificity of these tests to detect true hemochromatosis and which is the best cut off to be used. Schmitt and colleagues^[90] require that the gold standard be an independent demonstration of iron overload through iron deposition by liver biopsy or the amount of iron removed by phlebotomy. Among the main studies of the literature^[80,82,85], however, a small minority of the identified patients was further investigated with liver biopsy or the amount of depleted iron precisely calculated. Hemochromatosis was diagnosed in all of these cases and therefore phenotype testing seems to give a higher yield compared to HFE genotyping in detecting both iron overload and liver disease^[89]. 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^[88]. Serum ferritin has a high sensitivity but poor specificity for iron overload^[87] 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 and have already been discussed^[75]. Transferrin saturation has the advantage that it is independent of body mass index^[91] but care should be taken to draw the blood sample in the morning to avoid interference by the post absorptive state

and circadian rhythm^[88]. Another advantage of phenotypic compared to genotypic testing could be the negative psychosocial consequences derived by stigmatization of the patients by a positive genotypic test, albeit two studies addressing this problem did not provide evidence of negative psychosocial consequences to the patients^[92,93]. What can be said in summary regarding screening of this disease?

(a) 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. (b) Individual physicians can decide to screen persons belonging to racial groups with high prevalence of genetic hemochromatosis, such as people of northern European origin. This disease could be a candidate for opportunistic screening as part of routine health maintenance when Caucasian patients in early middle age are seen by general practitioners in their offices. This strategy however has not yet been validated by a cost efficacy study. (c) Screening should be performed once in life with serum ferritin and transferrin saturation using the thresholds defined by the HEIRS study.

OTHER GENETIC LIVER DISEASES

Alpha-1-antitrypsin deficiency and Wilson's disease are the other most important metabolic diseases that could potentially be considered for population screening. Alpha-1-antitrypsin deficiency is a common autosomal recessive condition which may cause liver cirrhosis in children and young adults. The classic homozygous form of alpha-1-antitrypsin deficiency affects 1:1800 newborns and predisposes to the early development of pulmonary emphysema, cirrhosis and hepatocellular carcinoma^[94]. Population studies conducted in Sweden have shown a wide variation in the expression of liver disease among the homozygous carriers of the z allele, which is associated with alpha-1-antitrypsin deficiency^[95,96]. In one of these studies only 10% out of 127 homozygotes followed for over 20 years were found to develop significant liver disease. In another more recent study conducted in Austria 16410 asymptomatic individuals were tested for the alpha-1-antitrypsin phenotype. Eighty six percent of them were found to be carriers of the normal Pi-MM phenotype, 7% were heterozygous for the Pi-Z phenotype, 5% heterozygous for the less common Pi-S phenotype and 0.7% were found homozygous for the Pi-ZZ phenotype. There was no difference both in liver related mortality and cumulative survival in the four groups of individuals, even after a very long period of follow up, that is after a median of 53 years^[97]. All these data show that other

genetic and environmental factors may modify the expression of this abnormal genotype and render alpha-1-antitrypsin deficiency unfeasible for population screening in newborns, children and young adults. It should also be stressed that alpha-1-antitrypsin replacement therapy is not effective in preventing liver disease and therefore the identification of affected individuals could only be used for the prevention of pulmonary emphysema^[98].

Wilson disease, caused by copper accumulation within the liver parenchyma, is another important genetic disease that could benefit from effective chelation therapy^[99]. In the early nineties a putative gene causing Wilson disease was discovered (ATP 7B) and it was named the WND gene. This offered promise for its use as a genetic marker of the disease and also for population screening^[100,101]. However, the mutations of the ATP 7B gene are quite complex and a recent study failed to show significant correlations between symptoms, ceruloplasmin levels, hepatic copper content and any specific pattern of mutations^[102]. The prevalence of Wilson's disease in the general population is also relatively low, being on average 30 affected individuals per million people^[103] and therefore screening for this disease on a widespread scale is not justified.

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