

Should we genetically test everyone for haemochromatosis?

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Abstract

The increasing availability of DNA-based diagnostic tests has raised issues about whether these should be applied to the population at large in order to identify, treat or prevent a range of diseases. DNA tests raise concerns in the community for several reasons. There is the possibility of stigmatisation and discrimination between those who test positive and those who don't. High-risk individuals may be identified for whom no proven effective intervention is possible, or conversely may test "positive" for a disease that does not eventuate. Controversy concerning prenatal diagnosis and termination of affected pregnancies may arise. Haemochromatosis, however, is a disease that is not only treatable but also preventable if those at high risk are identified presymptomatically. This paper will identify and discuss key issues regarding DNA-based population screening for haemochromatosis, and argue that population-based genetic screening for haemochromatosis should be supported when a number of contentious issues are addressed. In the context of a health system with limited resources haemochromatosis is the paradigm of a disorder where there is an ethical and clinical imperative to encourage presymptomatic DNA testing for all in ethnically relevant communities.

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Introduction

Traditionally, disease diagnosis and management are initiated by the presentation of a patient with symptoms. A number of technologies now allow medical practitioners to identify an individual's propensity to a wide range of diseases and act to prevent their onset. Examples of such preventive management range from the identification of hypothyroidism and phenylketonuria through newborn screening to prevent mental deficiency, cervical screening to identify those with early-stage cervical cancer amenable to therapy, to the cessation of smoking to prevent lung cancer. This paradigm shift from treatment to prevention has resulted from the exponential increase in the range of diagnostic tests available to the physician,

including biochemical and haematological blood tests, microbiology, histology and radiology. New advances using DNA data from molecular genetics extend this by allowing medical practitioners not only to diagnose a disease at an early stage, but also to predict the likelihood of a disease developing in the future.

The increasing availability of DNA-based tests throws into relief questions of when genetic screening of the general population for common and treatable diseases is ethically sound, medically appropriate and financially cost-effective.¹⁻³ There have been many contributions discussing the appropriate times and contexts in which to offer carrier and presymptomatic testing.⁴⁻⁶ Presymptomatic identification of Huntington's disease is available to high-risk families, but this disease is severe and untreatable. Carrier testing for cystic fibrosis is offered to help couples make a decision about whether to continue a pregnancy. In contrast, haemochromatosis is both preventable and treatable, and it is unlikely that couples will wish to make decisions regarding the continuation of a pregnancy based on fetal genetic status. Thus haemochromatosis is an excellent example of a genetic test that offers presymptomatic genetic identification of a preventable adult-onset disease.

Since the discovery of the gene for haemochromatosis and the ability to identify homozygotes presymptomatically, many countries are considering whether haemochromatosis is an appropriate disease for which to employ population genetic screening. Critical issues of "how", "when", and, more importantly "who" should be screened remain to be resolved.

Hereditary haemochromatosis

Hereditary haemochromatosis (HH) is a recessively inherited metabolic disorder caused by a defect in the cells lining the intestine which leads to excessive and unregulated absorption of iron from the diet. HH (referred to as haemochromatosis in this paper) describes an iron overload syndrome without any external cause such as seen following repeated blood transfusions, prolonged inappropriate administration of iron, or in associ-

ation with alcoholic liver disease. If haemochromatosis is left undiagnosed and untreated, the excess iron stored in the parenchymal cells of major organs, primarily the liver, pancreas, heart, pituitary and joints, eventually leads to severe tissue damage and premature death from liver and cardiac failure. A few grams of iron are normally stored in the liver but accumulation of more than 16 grams is associated with serious symptoms of iron overload.

Haemochromatosis has protean manifestations and a patient may present to any number of clinical specialties with signs of liver disease, heart failure, diabetes, hypogonadism, arthritis or even chronic fatigue. Because symptoms of haemochromatosis are often non-specific, have a gradual onset and can mimic other common disorders, diagnosis is frequently delayed. Liver disease may present as an abnormal elevation in liver enzymes, clinical signs of cirrhosis or hepatocellular carcinoma.⁷ Patients usually present with symptoms in the 5th or 6th decade of life though there have been reports of individuals presenting with cirrhosis as early as the 3rd decade of life.⁷

With the possible exception of arthritis, the clinical manifestations of HH can be prevented by prophylactic phlebotomy.⁷ Regular phlebotomy can also prevent progression of disease in patients presenting with symptomatic iron overload.⁸ When phlebotomy is started prior to the development of cirrhosis or diabetes, affected people have a normal life expectancy.⁹ Preventive phlebotomy (giving one 500ml unit of blood - approximately 1 gram of iron - every few months) is not usually recommended until the individual is in his/her 3rd decade, although this may change with definitive presymptomatic diagnosis. Avoidance of alcohol is also often advised for patients with HH since a heavy alcohol intake may be a synergistic cofactor in the development of liver fibrosis.¹⁰

The gene mutated to cause haemochromatosis, HFE, has recently been identified.¹¹ A missense mutation (C282Y) is the most common gene defect and affects more than 85% of HH patients of Northern European descent,¹²⁻¹⁴ while a second mutation (H63D) is possibly associated with a less severe form of the disease.¹²

The prevalence of HH in certain populations is very high. Recent research estimates that 10% of people of Northern European ancestry are heterozygous for HH, and one person in 300 from this ethnic group expresses the disease,¹⁵ making it a significant public health problem in communities of Northern European extraction.

Environmental factors impact on whether and/or when homozygous individuals develop clinical haemochromatosis. It is well established

that women with haemochromatosis usually present later in life than men, probably because blood loss through menstruation retards the accumulation of pathological iron stores. Supplemental iron and vitamin C (which increases iron absorption) are likely to precipitate earlier phenotypic expression, whereas blood donation and physiological or pathological blood loss will lower the amount of iron stored in the liver and delay phenotypic expression.¹⁶ Associations between several diseases (porphyria cutanea tarda, alcoholic liver disease, non-alcoholic steatohepatitis and hepatitis B)¹⁷ and haemochromatosis have been noted. Investigations as to whether these diseases are associated with haemochromatosis expression in homozygotes are necessary.

Despite the identification of several factors that can influence the time of expression of the disease, there still appears to be a subgroup of people who are homozygous for HH mutations but who do not develop symptoms.¹⁸ While the clinical expression of symptomatic disease is variable, Powell *et al* state that approximately 90% of male and 50-70% of female homozygotes will develop organ dysfunction and potentially life-threatening complications of haemochromatosis.

Regardless of the variability of disease manifestation in HH, the earlier the disease is identified the better the prognosis.⁹ Many investigators have shown the benefit of phlebotomy for disease prevention as well as retardation of disease progression. In contrast, the prognosis for those with cirrhosis for many years is bleak. Up to 30% of male haemochromatotics with cirrhosis will develop hepatocellular carcinoma.¹⁶ Since regular phlebotomy to prevent haemochromatosis is relatively benign and the potential consequences of developing disease are so serious, it is likely that most homozygotes would embark on a preventive management strategy to minimise the risk of developing disease even if each has a small chance of not developing symptoms.

Haemochromatosis and heterozygosity

It is still not clear whether there is any phenotype associated with HH heterozygosity. A study of proband relatives performed before the gene was identified found that a small proportion of presumed heterozygotes (from family studies) presented with elevated serum iron measures. Very few of these individuals had documented iron overload or clinical symptoms. Among those who did, other contributing factors such as alcohol abuse were present.¹⁹⁻²⁰ These data suggest that clinical HH occurs rarely in heterozygotes, and possibly only in the presence of other environmental risk factors.

Compound heterozygote individuals, on the other hand, can express haemochromatosis without a precipitating cofactor. Compound heterozygotes are those individuals who carry both known HH mutations, C282Y and H63D. Several large series of haemochromatosis patients have identified a small number of compound heterozygotes who express disease. These individuals probably have a lower risk of disease expression than C282Y/C282Y homozygote patients since the proportion of C282Y/H63D genotypes among HH cases is low despite an equal frequency of carrier rate for the H63D and C282Y mutation.¹⁷

Why screen for haemochromatosis?

Because the presymptomatic phase of haemochromatosis is prolonged, there is a large window of opportunity in which to diagnose risk of disease well before disease onset. For those who are presymptomatic, disease prevention is possible. For those who present with early symptoms, treatment to retard disease progression is available. In contrast, untreated haemochromatosis can result in serious morbidity and early death.

Population-based screening has the potential to prevent the development of disease, but will only be effective if appropriate education and treatment strategies are implemented alongside a screening programme. Such a programme would represent a cost-effective use of the ever-diminishing health care dollar. Bassett *et al* estimate the cost of screening in Australia to be AU\$4,943-AU\$11,016 per case detected depending on the screening strategy and method of confirmation of diagnosis.²¹ This compares favourably with other public health screening initiatives already in use such as cervical cancer screening (AU\$30,782 adjusted cost per life year) and breast cancer screening (AU\$6,600-11,000).²²

How should we screen for haemochromatosis?

The starting point for identifying individuals who would participate in a screening programme could be based on phenotype or genotype. Phenotype is assessed by investigating liver function or haematological iron values. Genotype is determined by identifying a gene mutation in HFE, either by cascade screening of relatives of index cases, or in the community without preselection.

In the past, phenotypic screening of first degree relatives has occurred on an ad hoc basis following the identification of a symptomatic proband. Suspicion of disease is based on abnormal iron studies (ie elevated serum ferritin and transferrin saturation) and confirmed by an elevated hepatic iron index on liver biopsy. Liver biopsy is also

undertaken to identify the presence or absence of cirrhosis, a hallmark of irreversible and advanced disease.²³ Phenotypic identification of presymptomatic homozygotes using serum iron markers is less reliable, particularly in women, and heterozygotes can only be identified using genetic analysis rather than phenotype.

Current genotype assessment in Australia is based on cascade screening of first degree relatives of affected homozygote probands. Although this is an effective way to identify further cases of haemochromatosis, siblings of affected patients may already have severe iron loading and early or even advanced symptoms of disease. In addition, ethical issues arise around the possibility of coercive interaction within a family when genetic testing in an affected relative is necessary before screening can be provided to other family members.

There are two important reasons why we believe population-based genotype screening for HH should not be delayed. Firstly, the prospective diagnosis of many homozygous HH individuals will be missed if widespread screening is not implemented before complete information is known about penetrance. Secondly, incomplete data regarding disease penetrance and prevalence is not an a priori reason not to screen since people are likely to cope well with a degree of uncertainty when counselled about risk of disease expression if the disease is preventable and/or treatable.

The ability to identify homozygous HH before disease onset is the greatest advantage of DNA-based testing. With the identification of the mutations responsible for haemochromatosis, DNA testing has become the method of choice to identify those with HH. DNA samples from individuals can be obtained easily, cheaply and reliably either from blood or mouthwash samples.²⁴

Who is affected by a decision to screen the general population?

The arguments for and against genetic screening can be viewed from the individual perspective, or from the point of view of public health policy. Both need to be considered.

A) THE PUBLIC PERSPECTIVE

From the public perspective, screening to prevent a common disease is usually a cost-effective use of the health dollar. The cost of identifying more homozygotes through DNA screening than by current phenotypic measures would be offset by the fact that it should be cheaper to prevent disease through a health maintenance programme than to treat and manage HH patients as they present to a specialist unit. If all persons were screened and agreed to enrol in a prevention pro-

gramme, it is probable that symptomatic haemochromatosis would become a very rare disease. In addition, blood donated regularly to transfusion services by homozygous but healthy presymptomatic individuals as part of a health maintenance programme would be a valuable public resource.

Another important public issue is the possibility that a group is created within the population that could be discriminated against because of their genotype, even in the absence of clinical symptoms. There are data indicating that women with familial breast cancer are reluctant to accept genetic screening because of fears of discrimination in insurance.²⁵ In the case of haemochromatosis, we suggest that discrimination would be irrational and based on a misunderstanding of disease progression, as the individual would be healthier and have a longer lifespan if tested, provided a prevention programme was accepted. Many countries are implementing legislation or agreements which prevent discrimination in insurance or employment due to genetic testing.²⁶⁻²⁷

It must be emphasised that a major educational programme of both the lay and medical communities would need to be implemented to raise awareness of issues surrounding diagnosis and management of haemochromatosis. Educational programmes would assist implementation of a successful screening programme as well as help minimise any misinformation and resultant inappropriate discrimination. Such programmes would not be simple or cheap, but any advances in understanding of genetics in one area, such as haemochromatosis, would also provide benefits in other areas of gene testing.

B) THE HOMOZYGOTE'S PERSPECTIVE

The homozygous individual clearly benefits from the implementation of screening, as development of disease can be prevented. Since compound heterozygote individuals also appear to be susceptible to disease expression, we believe these individuals also stand to benefit from having their HH genetic status identified.

It is possible that a small proportion of individuals with symptomatic haemochromatosis may have alternate genetic mutations to those already identified and thus would be missed by screening programmes that identify only the two common mutations. This proportion is likely to be very small in Anglo-Celtic populations, but may be greater in Southern Europeans.²⁸ Identification of any further disease-causing mutations will increase our ability to screen for presymptomatic homozygotes.

A further issue is that unless catch-up screening is administered to the whole population, a cohort

of people will be unaware of their HH status and may remain unidentified until presentation with advanced disease. The increased level of education in the community following the implementation of a population-based screening programme would, however, serve to benefit these individuals by increasing the vigilance for HH disease identification.

C) THE HETEROZYGOTE'S PERSPECTIVE

From the perspective of the heterozygote, information regarding predisposition to iron loading or other diseases is central to whether identification of the heterozygote status is beneficial to the individual, though it must be remembered that heterozygosity may equally be associated with a selective advantage. For instance, it has been suggested that heterozygote women may have a reproductive advantage, as they are less likely to have iron deficiency.¹⁹

Data on the incidence of iron loading in heterozygotes is currently inconclusive. The likelihood of a heterozygote developing haemochromatosis in the absence of a second aggravating disease appears to be very low. Bulaj *et al* studied over one thousand heterozygotes. Although 4% of females and 8% of males had abnormal haematological iron profiles, only one patient had evidence of mild liver damage on biopsy in the absence of any further identifiable precipitating factor.¹⁹ This would suggest that heterozygotes are unlikely to develop primary iron loading, but that they may have an increased risk of developing iron loading in the presence of a second disease. It has been suggested that phlebotomy may prevent iron accumulation in heterozygote patients with a precipitating environmental factor.²⁰ Until there is definitive research about the propensity for disease expression in heterozygotes and whether phlebotomy in such situations is beneficial to the individual then it is difficult to inform heterozygotes appropriately. As new research is carried out this situation may change.

The question of whether to inform heterozygotes of their genetic status remains a difficult ethical dilemma that warrants further study and consideration. Such consideration applies to many commonly inherited diseases, since we all carry a number of recessive genes that are not clinically important unless two persons with the same recessive mutation have children.

With regard to reproductive issues, since haemochromatosis is a preventable disease, it is unlikely that a heterozygote couple at risk of having a child who is homozygous for the mutation would choose prenatal diagnosis and terminate an affected pregnancy. It is unlikely that either the

medical or lay community would support termination of an affected fetus since the disease is adult-onset and can be compatible with normal health if preventive strategies are appropriately implemented.

We believe the current cost of informing heterozygotes in both financial and psychological terms is too high. Not only would the number of people needing counselling increase greatly but the complexity of counselling would increase dramatically because not enough is known about the risk of disease expression. In the future the community may desire such information and be better equipped to deal with such complex genetic data, but the initial introduction of population-based heterozygote screening alongside homozygous screening would only serve to confuse such a programme.

Offering information on carrier status would massively increase the cost of education and counselling, and risk creating a group of "worried well". When more is known about the medical implications of heterozygosity, decisions about whether to inform individuals of their status should become clearer. Cascade screening of relatives of probands currently identifies heterozygotes, but whether individuals are informed of their carrier status appears to be individualised by the caring physician. At this point we would not advocate informing heterozygotes identified by population screening of their status unless requested by the individual or dictated by the clinical setting.

Who and when should we screen?

It is not clear whether it is discriminatory to offer screening only to those who are in a high-risk ethnic group, omitting to screen those in other groups. Even if it appears costly to offer screening to those in low-risk populations (which, in the Australian context, would include those of Aboriginal, South East Asian and African origin) this may have significant implications in a city with much ethnic mixing, such as Melbourne. Although the cost of needless screening is an issue, so too is perceived and real discrimination against those who are not screened, with all the problems in defining ethnicity in a multicultural environment.

Implementation of population-based genetic screening will be most beneficial if administered to a receptive population and at a time when the cost-benefit ratio is most favourable. Screening to detect presymptomatic homozygotes can be directed at three main groups: neonates, adolescents and young adults.

Neonates are an easy group to target because efficient and acceptable screening is already in place for phenylketonuria and other serious

diseases affecting neonates. It would be logistically simple to add a further test to those currently performed. Screening in the neonatal period ensures that homozygotes identified will definitely be presymptomatic. However, neonatal screening means there is a long lead time before the information is relevant and preventive measures can be implemented, as regular phlebotomy would be unlikely to be organised before the infant was at least 20 years of age. Parents of presymptomatic homozygous individuals may perceive their child as unwell. Parents may also implement inappropriate care such as eliminating iron from a growing child's diet. Many years of individual follow-up will be required to ensure that appropriate preventive strategies are implemented at the appropriate age.

If we compare haemochromatosis with cystic fibrosis (CF), a disease for which neonatal screening for all is already in place in Australia, we can say:

- HH is more common than CF (1 in 300 v 1 in 2,500);
- HH is a preventable disease while CF is not;
- prenatal testing for HH is not likely to be implemented because (unlike CF) it is both preventable and treatable;
- a single mutation accounts for more than 80-90% unlike CF where there are many mutations, the most common of which accounts for about 70% of mutations.

All parents of homozygote HH infants would be obligate heterozygotes and a small percentage would be homozygous for HH by chance. An added benefit of neonatal screening would be the identification through reverse cascade screening of further presymptomatic homozygous individuals since parents, as well as aunts and uncles, of newborns are likely to be young adults. Neonatal testing may be an option in the future when more is known about disease prevalence and penetrance and if and when there is increased awareness of HH in the community.

The advantage of screening adolescents is their potential to take responsibility for their own health and any preventive strategies that need implementation. Unfortunately adolescents can be susceptible to stigmatisation through peer pressure. Knowledge of HH homozygosity may initiate inappropriate reactionary high-risk behaviour in the individual. In addition, this group is difficult to access since school-based screening may not be acceptable to parents or school authorities.

Screening of young adults (20-30 year olds) has many ethical advantages. Young adults are autonomous and capable of giving consent, and if they have counselling will be aware of the useful-

ness of the test and the possible implications for relatives and with regard to insurance. They also are likely to be motivated to enter into a prevention programme. However, a small minority of cases may already have liver damage below the age of 30.

We favour screening of young adults with the proviso that health maintenance programmes be implemented for individuals identified as homozygous for HH. Ongoing support, education and counselling would help ensure that homozygous individuals remain informed of the latest research developments and have ready access to information regarding health maintenance. However, public education programmes and resolution of issues of stigmatisation need to be addressed before implementation of population-based screening. Participation in a screening programme would need to be completely voluntary.

Conclusions

Haemochromatosis is an ideal disease in which to implement population-based genetic screening because it is both common and preventable. On balance, the public and the individual stand to gain from the implementation of genetic screening. At this point in time, screening of young adults would be the most readily accepted by the community and the most efficient to implement. Education of the medical and lay communities would be vital to the success of such a programme and pilot studies of population-based screening would help address many of these issues. Before a widely applied programme could be implemented, issues regarding funding and implementation of health maintenance programmes for all homozygous individuals identified would need to be fully explored. In addition, issues around the health status of heterozygotes need further consideration. Finally legislation against genetic-based discrimination and misuse of genetic information should be given priority before embarking on a programme of population-based screening.

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