Population screening for haemochromatosis:
A position paper by the HI/EFAPH Joint Scientific Committee

ABSTRACT

Haemochromatosis is an inherited iron overload disorder that affects millions of people globally, particularly those of northern European descent. More than 90% of cases are caused by homozygosity for the p.Cys282Tyr variant in the *HFE* gene (previously called C282Y). The p.Cys282Tyr variant can be detected through a simple genetic test, while body iron overload can be assessed indirectly by measuring the transferrin saturation level and serum ferritin concentration in the blood using routine biochemical tests, and directly by liver magnetic resonance imaging. Severe morbidity from haemochromatosis can be prevented by maintaining normal body iron levels through blood removal.

Given the high prevalence of *HFE* variants in many populations around the world, there is a groundswell of support among patient advocacy organizations for the implementation of population screening programs for haemochromatosis. However, as *HFE* variants show incomplete penetrance and variable expressivity (i.e. not all individual with homozygosity for p.Cys282Tyr develop iron overload and even fewer develop clinical disease), these calls have stirred debate amongst experts as to whether to screen for haemochromatosis in the general population and, if this is done, the most appropriate way to do so.

In an attempt to establish international consensus recommendations regarding population screening, we recruited 40 expert haemochromatosis stakeholders to participate in a modified Delphi study, using three rounds of online surveys to seek consensus (≥75%) on key aspects of haemochromatosis screening. The study revealed consensus for haemochromatosis screening in high-prevalence populations and consensus against screening in low-prevalence populations. While there was no consensus on the ideal age at which to screen, the vast majority of respondents indicated that screening should occur before the age of 40 (and ideally between 20-30). There was no consensus on an optimal approach to first-line screening (i.e., biochemical vs. genetic), suggesting that either approach (or a combination of the two) may be acceptable for screening in high-prevalence populations. In the case of an individual with normal iron levels being identified as p.Cys282Tyr homozygous by genetic screening, there was consensus that follow-up biochemical testing (measuring both transferrin saturation and serum ferritin) should be conducted within 5 years.

In summary, this study has consolidated the opinions of international experts on haemochromatosis to develop some consensus recommendations for screening, which can form the basis for policy development and advocacy strategies in different jurisdictions worldwide.

INTRODUCTION

Haemochromatosis is a genetic condition characterized by an excess of body iron, which can progressively deposit in the liver, joints, and other organs presenting with a variety of clinical signs and symptoms. It is one of the most common genetic disorders among people of northern European ancestry, with the vast majority of cases caused by homozygosity for the p.Cys282Tyr variant (present in 1:150 to 1:220 people of northern European descent) [1]. The prevailing paradigm is that the disease-associated *HFE* genotype, by impairing the expression of the HFE protein at the cell surface of hepatocytes, leads to insufficient signalling and diminished synthesis of the iron regulatory hormone hepcidin, precipitating iron overload [2, 3].

Although the *HFE* genotype that predisposes individuals to haemochromatosis is relatively common in certain populations, it exhibits incomplete penetrance. Among individuals with *HFE* p.Cys282Tyr homozygosity, men are at greater risk of developing iron overload and consequent morbidity than women. A recent analysis of data from the UK BioBank has revealed that *HFE* p.Cys282Tyr homozygosity in men is associated with a 1.2-fold increase in the cumulative death rate at 80 years of age, a 10-fold increased risk of liver cancer [4] and >2-fold increased risk of arthritis [5].

The p.Cys282Tyr variant in the *HFE* gene can be easily detected using existing PCR-based assays, or as part of next-generation DNA sequencing. Iron overload is typically assessed using routine biochemical assays. Serum iron parameters can serve as surrogate parameters for body iron status, where a high transferrin saturation is a typical finding in patients with penetrant haemochromatosis. While low ferritin excludes iron overload, high ferritin can indicate iron overload in the absence of inflammation or metabolic conditions. Iron overload can be directly detected by magnetic resonance imaging using R2* imaging.

If iron overload is detected in a person known to be p.Cys282Tyr homozygous at a young age, it can be easily corrected at an early stage through regular blood removal (i.e. venesection/blood donation), normal body iron can be maintained with a close follow-up, and therefore morbidity can be prevented [1, 2].

Although the knowledge and tools are readily available to detect, monitor, and treat haemochromatosis, many patients continue to suffer serious health consequences because of this condition due to late diagnosis [6]. Despite being a common condition, public awareness, clinical assessment, and care pathways for haemochromatosis vary markedly between different healthcare systems in different countries. This has led to patient advocacy groups and some experts in the field calling for the implementation of population screening programs to prevent the consequences of haemochromatosis.

The present study was initiated in response to a request by the Irish Haemochromatosis Association in July 2020 asking for expert opinion on the value of population screening for HFE haemochromatosis. The boards of Haemochromatosis International (HI) and the European Federation of the Associations of Patients with Haemochromatosis (EFAPH) agreed to undertake a study with the objective of developing a consensus position from the clinical and scientific experts in the field. Members of the HI/EFAPH Joint Scientific Committee and other experts in the field were invited to participate in a modified Delphi study seeking to reach consensus on the following three questions:

1. Should population screening for haemochromatosis be recommended?
2. At what age should population screening and follow-up occur?
3. Which type of test (i.e. biochemical or genetic) should be deployed for first-line screening?

METHODS

All study protocols were approved by the University of Tasmania Human Research Ethics Committee. The process followed aligns with Häder's Type 4 Delphi Technique, aimed at achieving 'the highest possible degree of consensus among participating experts,' including representatives from 'interest groups or the interested public. [7]. Letters of invitation outlining the purpose and objectives of the study were sent to 61 potential respondents from different stakeholder groups, comprising all the members of the HI/EFAPH Joint Scientific Committee (n=24) and other internationally recognized clinical or scientific experts in the field (n=37). Invitees included medical doctors of various specialties (hepatology=18; haematology=11; internal medicine=6; genetics=3; clinical pathology=3; rheumatology=3), biomedical researchers (n=10), experts in health economics and statistics (n=4) and patient representatives (n=3). Invitees spanned global regions where haemochromatosis is particularly prevalent, including Europe (n=29), Australia (n=19) and America (n=12), with one invitee from China.

Expert opinion was collected via anonymous online surveys, which contained a combination of multiple-choice questions and free text responses. For this study, 'consensus' was defined *a priori* as ≥75% agreement for a specific option. Surveys were conducted over three rounds, with responses to previous surveys informing iterative refinements to subsequent surveys for issues where consensus was not reached.

Of the 61 invitees, 40 participated in the first-round survey, corresponding to a response rate of 66%. Following a review of results from the first-round survey by the investigator team, a second-round survey was developed and sent to the 40 respondents of the first round. There were 33 responses to the second-round survey, corresponding to a response rate of 83%. The investigator team reviewed the results from the second-round survey to inform the third and final survey, which was again sent to all 40 respondents of the first round. There were 27 responses to the third-round survey, corresponding to a response rate of 68%.

The recommendations arising from the Delphi study were discussed and endorsed at a meeting of the HI/EFAPH Joint Scientific Committee and other experts on 1 September 2023.

RESULTS

Should population screening for haemochromatosis be recommended?

The first-round survey posed the questions of (1) whether population screening for haemochromatosis should be recommended in high prevalence populations (defined as >0.4% prevalence of p.Cys282Tyr homozygous in the general population), and (2) whether population screening for haemochromatosis should be recommended in low prevalence populations (defined as <0.1%). Of the 40 respondents, 33 (83%) indicated that population screening should be recommended in high-prevalence populations, and 31 (78%) indicated that population screening should not be recommended in low-prevalence populations (Figure 1A). Thus, **there was consensus in favour of screening for haemochromatosis in high-prevalence populations and a consensus against screening in low-prevalence populations**.

Which type of test (i.e. biochemical or genetic) should be deployed for first-line population screening?

The first-round survey posed the question of which tests should be used for screening in high-prevalence populations, with respondents choosing one of three options: genetic, biochemical, or a combination of both. This question was only presented to respondents favouring population screening in high-prevalence populations (see above). There was no consensus response to this question, with 24% (n=8) favouring genetic, 33% (n=11) favouring biochemical, and 42% (n=14) favouring a combination approach (Figure 1B).

The first-round survey was further stratified to determine the favoured genetic and biochemical screening approach. Of the 25 respondents who favoured the use of biochemical screening as a first-line approach, 80% (n=20) favoured the simultaneous measurement of transferrin saturation (TS) and serum ferritin (SF), as opposed to 20% (n=5) who favoured a staged approach in which TS is measured first and only followed by SF if TS is consistently high (Figure 1C). Thus, **for biochemical screening, there was consensus in favour of measuring both TS and SF**.

In the second-round survey, the question concerning the approach to screening was refined to provide just two options: (1) first-line biochemical screening (simultaneous TS and SF) followed by *HFE* genotyping in suspected cases and (2) first-line *HFE* genotyping followed by biochemical screening (simultaneous TS and SF) in suspected cases. Of the 32 respondents, 50% (n=16) favoured biochemical screening, while 50% (n=16) favoured genetic screening. The third-round survey posed the same question, with 41% of respondents (n=11) favouring biochemical screening and 59% of respondents (n=16) favouring genetic screening (Figure 1B). Thus, after three rounds of surveys, **no consensus was reached regarding an optimal approach to population screening, indicating that biochemical followed by genetic screening, or vice versa, might both be acceptable.**

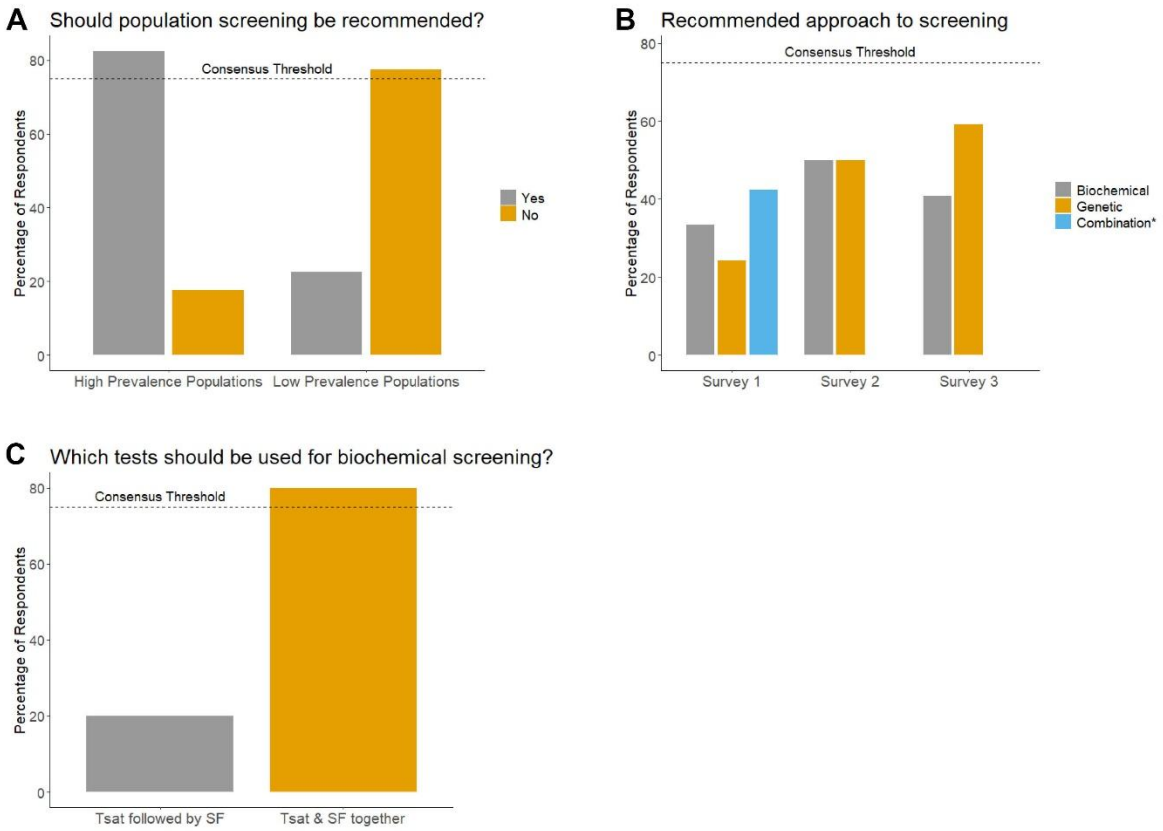

Figure 1. Survey outcomes related to the approach to population screening. (A) The consensus recommendation for population screening in high-prevalence populations and against screening in low-prevalence populations was achieved in the first-round survey. (B) No consensus regarding the optimal approach to screening across the three surveys (NB 'combination' was not offered as an option in the second- and third-round surveys). (C) Consensus recommendation for simultaneous measurement of both transferrin saturation (TS) and serum ferritin (SF) for biochemical testing.

At what age should screening occur?

In attempting to understand opinions concerning the ideal age for screening, the first-round survey posed the question separately for genetic and biochemical screening, males and females, and provided a large number of age brackets. While no consensus was achieved on a particular age range, the large majority of respondents were of the view that screening should occur in age ranges below 40 years, irrespective of approach or sex. As such, the second-round survey did not distinguish between screening approach or sex and provided three options: (1) 18-20 years of age, (2) 20-30 years of age, and (3) 30-40 years of age. Of the 33 respondents, 21% (n=7) favoured 18-20 years, 58% (n=19) favoured 20-30 years and 21% (n=7) favoured 30-40 years. In the third-round survey, a similar distribution was observed in response to the same question, with 19% of respondents (n=5) favouring 18-20 years, 63% (n=17) favouring 20-30 years and 19% (n=5) favouring 30-40 years (Figure 2A). Thus, **while the majority of respondents favoured the 20–30-year age bracket, no consensus was reached for an ideal age range for screening.**

Should follow up testing be conducted for people with normal iron parameters at screening?

Of the respondents who recommended first-line genetic screening in the second-round survey (n=16), 100% recommended follow-up of p.Cys282Tyr homozygous individuals with normal iron parameters at screening. Across the second-round and third-round surveys, these respondents were asked to recommend the period post-screening at which follow-up should occur. For both males (78% - third-round survey) and females (88% - third-round survey), a **consensus was achieved for follow-up testing 5 years post-screening, where the initial test of iron indices was normal** (Figure 2B).

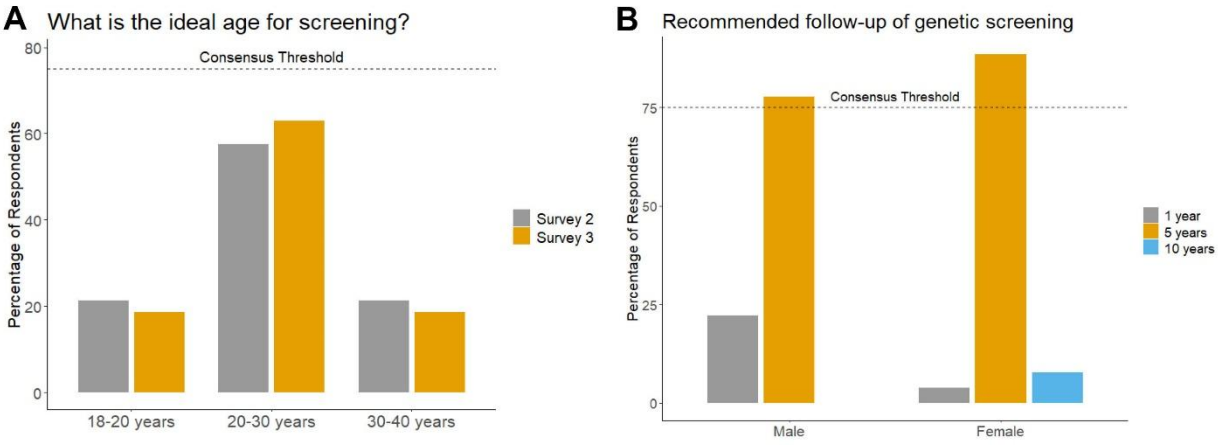

Figure 2. Survey outcomes related to the optimal age and follow-up for population screening. (A) No consensus regarding an optimal age range at which screening should be targeted, but majority support was for 20-30 years of age. (B) Consensus recommendation for a 5-year follow-up period for both men and women with a p.Cys282Tyr homozygous genotype but normal iron indices during genetic screening.

Analysis of qualitative data

The third-round survey also provided the opportunity for respondents to provide free-text responses to justify their recommendations. With respect to the approach to screening (genetic vs biochemical), a thematic analysis is provided in Table 1. Below we transcribe some of the text responses provided in the survey.

Responses in favour of first-line *HFE* genotyping were grouped into five themes, including the possibility of early intervention for those with p.Cys282Tyr homozygosity together with increasing acceptability of genetic screening and a lack of evidence of discrimination against people with a genetic predisposition to hemochromatosis. Responses also argued that first-line *HFE* genotyping is a straightforward, definitive approach (i.e. a once off strategy whereas biochemical screening needs to be repeated) compared to biochemical iron studies, which also lack precision. Some responses referred to findings from previous research, including the HEIRS study (2005), showing that only a small percentage of individuals with elevated serum ferritin have hemochromatosis, that mean transferrin saturation and serum ferritin levels differ across racial/ethnic groups, that the *HFE* p.Cys282Tyr variant rarely accounts for elevated iron indices in non-Caucasian individuals [8], and that participant acceptance of genotypic testing is comparable to that of phenotypic testing [9].

Responses noted potential benefits of first-line *HFE* genotyping, including the prevention of harm from iron overload, the reduction in cost to national health budgets from early diagnosis, the contribution to national blood supplies from therapeutic donors recruited as young adults, and the potential for further research into iron disorders. Genetic testing was seen as a positive step towards preventing harm in later life, especially if conducted between the ages of 20 and 30. '*Screening for HFE genotypes in high prevalence populations accompanied by appropriate information about the benefits of donating blood regularly was thought to potentially have a positive impact overall. Evidence for the prevention of harm and cost of illness associated with untreated haemochromatosis should be included when presenting governments with any screening proposal'.*

Responses in favour of first-line biochemical screening were grouped into six themes, including the lower cost and greater availability of biochemical versus genetic tests, the potential to identify non-*HFE* hemochromatosis and other iron disorders, and the low penetrance of p.Cys282Tyr homozygosity leading to unwarranted anxiety. *'The presence of* p.Cys282Tyr *is not a disease. The presence of a* p.Cys282Tyr *mutation may not necessarily have any medical implication. We are interested in iron overload, and a finding of raised iron parameters has to be followed up independently if it is due to haemochromatosis or other conditions. That means that by screening via iron parameters, we might prevent other conditions, not only haemochromatosis, and ultimately improve patient health'.*

The possibility of discrimination because of a genetic predisposition was also raised in support of biochemical testing. *'First-line genetic screening would, in case of* p.Cys282Tyr *homozygosity, open a double risk for the concerned individual: i) unjustified anxiety since the risk for developing the disease remains very low; ii) societal discrimination, the interpretation of homozygosity remaining very unsatisfactory in the vast majority of countries. Moreover, the feasibility of mass genetic screening would likely raise major ethical issues in most countries'*.

Table 1. Thematic analysis of free-text responses regarding screening approach

Arguments favouring genetic screening	**Arguments favouring biochemical screening**
Iron studies lack precision (n=5)	Cheaper than genotyping (n=4)
Straightforward, definitive approach (n=3)	Will identify other iron disorders (n=4)
Early intervention/prevention (n=2)	Genetic testing may unnecessarily increase anxiety (n=2)
Increasing acceptability of genetic testing (n=1)	Genetic discrimination and ethical issues (n=2)
No evidence for genetic discrimination (n=1)	Iron studies more accessible (n=2)
	Focus should be on iron overload, not risk (n=1)

The third-round survey also provided the opportunity for respondents to comment on their recommendations for follow-up. Common themes among these responses related to the importance of preventing iron overload and maintaining participant contact and compliance. While some respondents indicated that it was appropriate to implement consistent follow-up guidelines for males and females, others suggested that a 10-year period between screening and follow-up testing might be more appropriate for pre-menopausal women.

DISCUSSION

This modified Delphi study canvassed the expert opinions of a range of haemochromatosis stakeholders globally with the aim of identifying consensus positions on population screening for haemochromatosis. While there was a consensus recommendation for the implementation of screening programs in high-prevalence populations but not low-prevalence populations (fitting the Wilson and Junger's principles) [10,11], consensus support for utilising transferrin saturation and serum ferritin in combination for biochemical testing, and consensus support for integrating follow-up testing 5 years post-screening for people at genetic risk of haemochromatosis, there was no consensus as to which approach (biochemical vs genetic testing) should be used as a first-line screening tool. While there was no consensus on the ideal age for screening, the majority of respondents nominated the 20–30-year age bracket.

Of the issues explored in this study, the most contentious was whether biochemical or genetic testing should be deployed for first-line screening. A number of factors may contribute to this difference of opinion, including political, cultural, and experiential perspectives that reflect the diversity of our survey sample. For example, there may be differences across jurisdictions in the:

- Prevalence and prognosis of haemochromatosis, affecting the benefit derived from population screening
- Clinical guidelines for diagnosing and managing haemochromatosis, representing a barrier to change
- Degree of socialization of the healthcare systems, affecting the relative cost to the individual and the government
- Societal acceptance of screening (particularly genetic screening)
- "Clinical ideology" – prevention or treatment?
- Feasibility of rolling out a population screening program, depending on the scalability of existing testing and reporting services
- Cost of implementing a population screening program

It will be important to take these factors into consideration when designing the most appropriate screening program for a given jurisdiction.

One major argument in favour of biochemical screening relates to cost – historically, genetic testing has been considerably more expensive than biochemical testing. However, recent advances in SNP and NGS technologies have radically reduced the cost per gene variants of interest. As a result, population screening for haemochromatosis using single SNP assays may no longer be financially prohibitive. Moreover, it was recently shown that combining *HFE* variants with other actionable genetic variants through comprehensive genomic sequencing offers a potentially stronger economic argument, as it could provide more information in a single test, increasing the cost-effectiveness of screening programs. [12]. One major limitation of this argument is that the costs of biochemical vs genetic testing were not analysed in that study – if all things were equal, would this have changed the outcome? In any case, a recent systematic review of health economic evaluations of haemochromatosis screening strategies suggests that both biochemical and genetic screening are cost-effective compared to no screening [13].

Population-wide genetic testing also evokes concerns about the societal acceptability of collecting genetic information and possible implications for various forms of genetic discrimination (e.g. insurance, employment). A recent review by Schmidtke of studies exploring attitudes of individuals who participated in *HFE* genetic screening programs found that *HFE* genotyping was viewed

positively by the majority of participants, with few negative psychosocial outcomes [12]. These studies collectively covered the USA and Canada, Australia, and Germany; however, as community attitudes towards genetic testing and legislative safeguards against genetic discrimination are likely to vary markedly across different jurisdictions, extensive public consultation will be required before implementing any population screening program.

As explored in a recent review by Schmidtke [14], no national/international professional organizations have recommended population screening programs for haemochromatosis to date, although most do recommend cascade screening for first-degree relatives of a positive case. The American College of Medical Genetics and Genomics recently added *HFE* to their actionable genes list [15]. However, this will only be relevant to a relatively small number of individuals who have undergone exome or genome sequencing for other reasons.

The opposition to population screening for haemochromatosis is generally based on cost-benefit argument – that risk of disease due to *HFE* genotype or iron loading is low. However, recent data from the UK BioBank suggest that p.Cys282Tyr homozygosity might have more pernicious and widespread effects than previously realized, with p.Cys282Tyr homozygotes (particularly men) having a greater cumulative risk of a range of different co-morbidities and even death [4-6]. As the UK BioBank did not collect data on iron status, one limitation of this analysis is the inability to stratify the p.Cys282Tyr homozygous cohort into those with/without iron overload to correlate iron status with outcomes. Consequently, is it not possible to predict whether iron-lowering therapies will mitigate or correct these co-morbidities. Indeed, recent large cohort studies from Denmark revealed an increased risk of diabetes, liver disease and infection in p.Cys282Tyr homozygous subjects that was not associated with iron overload [16, 17], highlighting an unmet need to look for other still unidentified factors that may impact on morbidity and mortality in p.Cys282Tyr homozygous subjects.

RECOMMENDATIONS

Based on the findings of this study, we put forth the following recommendations:

1. Population screening programs should be considered in high-prevalence populations but not in low-prevalence populations.
2. Ideally, these programs should be targeted at individuals aged 18-40 to prevent the development of disease.
3. The most appropriate approach to first-line screening (i.e., biochemical vs genetic) should be determined by each healthcare system based on relevant local factors.
    a. In cases where first-line biochemical screening is implemented, testing should include both TSat and serum ferritin.
    b. In cases where first-line *HFE* genetic screening is implemented, proper counselling with informed consent should be warranted, and individuals with *HFE* p.Cys282Tyr homozygosity but normal iron parameters should receive follow-up biochemical testing no later than 5 years after initial screening.
4. Any population screening program that is implemented must be supported by easily accessible educational materials that provide appropriate and accurate patient-centred information.

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