UK National Screening Committee

UK National Screening Committee (UK NSC)

Screening for hereditary haemochromatosis in adults

Date: 05 March 2021

Contents

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for hereditary haemochromatosis in adults meets the UK NSC criteria for a systematic population screening programme.

Current Recommendation

2. The UK NSC currently does not recommend systematic population screening for hereditary haemochromatosis in adults. The Committee based this recommendation on the evidence provided by the 2015 review carried out by the Ottawa Hospital Research Institute.

Evidence Summary

3. The 2020 evidence summary was undertaken by the University of Warwick, in accordance with the triennial review process: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

4. The 2020 evidence summary covered relevant literature since 1996 and addressed 4 key questions:

a. What is the penetrance of type 1 hereditary haemochromatosis (HH) in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity? (NSC criterion 1)

    - Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?

b. What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)? (NSC criterion 1)

    - Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?

c. Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms? (NSC criterion 9)

d. What is the effectiveness of screening to reduce HH-related morbidity and mortality? (NSC criteria 11 and 13)

5. The conclusion of the 2020 evidence summary is that the current recommendation should be retained and therefore whole population screening for hereditary haemochromatosis in adults should not be introduced in the UK. This is for the following reasons:

    a. no eligible studies were identified which addressed the question on the benefits and harms of screening for hereditary haemochromatosis in adults. **Criteria 11 and 13 not met**

    b. there was insufficient evidence from a systematic review (published in 2006) and a cohort study (published in 2017) on whether intervention at an earlier/asymptomatic stage leads to better outcomes compared to intervention at a later/symptomatic stage in individuals with hereditary haemochromatosis. **Criterion 9 not met**

    c. 12 prioritised studies (and 45 deprioritised articles) were identified in relation to question 1 on penetrance, and 13 prioritised studies (and 46 deprioritised articles) were identified on the association between hereditary haemochromatosis-related biochemical and clinical features and relevant mutations in the HFE gene (question 2):

- the studies were typically at moderate-to-high (question 1) and high or unclear (question 2) risk of bias. For many of the outcomes (by genotype) the data were limited to individual studies, often with limited sample size and suboptimal study designs

- there is clear and consistent evidence for an association between the 3 hereditary haemochromatosis genotypes and iron overload, though some inconsistent results were reported in relation to the association between elevated serum ferritin and the homozygous H63D genotype

- the proportion of people with clinical outcomes was generally low (low penetrance), and the evidence regarding clinical conditions generally does not support associations with type 1 HH genotypes. The exceptions were liver cancer (only for the C282Y/H63D genotype), as well as hyperpigmentation, liver disease (any or liver cancer), and 'any' clinical outcome (only for the C282Y/C282Y genotype). Inconsistent results were reported in relation to the association of diabetes and fatigue with the homozygous C282Y genotype. However, these clinical outcomes are still 'not met' because of the volume, type of evidence, and risks of bias

- overall, **Criterion 1 is not met** because even though there is clear evidence for an association between the 3 hereditary haemochromatosis genotypes and iron overload, these are biochemical outcomes, which may or may not have clinical implications for individuals

d. in relation to whether, based on the quality and heterogeneity of the studies, a meta-analysis or a summary estimate is possible, the review noted that pooling together prioritised and deprioritised studies in a systematic review and/or meta-analysis may help to provide more refined estimates of penetrance and associations between genotypes and iron overload. For the homozygous H63D mutation, a meta-analysis would also provide clarity on the mixed results of the present review. Moreover, additional data on diabetes (and possibly fatigue) from deprioritised studies may help to provide some clarity on their potential association with the homozygous C282Y genotype.

Consultation

6. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 14 stakeholders. (Annex A)

7. The public consultation closed on 15 January 2021. The total number of consultation responses received was 5.

8. Comments were received from the following stakeholders:

    a. British Association for the Study of the Liver (BASL)

    b. Royal College of Nursing

    c. Genetic Alliance UK

    d. A member of the public volunteering for Haemochromatosis UK

    e. Haemochromatosis UK

9. The consultation comments received are presented below in Annex B.

10. BASL agrees with the latest UK NSC position and expressed its appreciation for the in-depth review performed. Despite the publication by Pilling et al 2019 showing significant morbidity in a sizeable cohort of HFE-related haemochromatosis based on UK biobank data, BASL noted that it is still premature to recommend a national screening programme. BASL added that emphasis remains on primary and secondary care clinician education to perform genetic testing and implementation of cascade screening after identification of index cases, as well as increased public awareness, for example via Haemochromatosis UK and the British Liver Trust.

11. The Royal College of Nursing agrees with the recommendation and noted that the evidence summary was “well evidenced”.

12. The member of the public noted that, though in many ways the evidence summary is “very diligent for a ‘rapid review’”, it is also complex and some “common sense gets lost in that complexity”. The consultee added that triennial screening of men and women “on suitable occasions, such as GP and/or hospital visits after the age of 35 would be a good first step until safety from iron overload is assured”.

13. Haemochromatosis UK and Genetic Alliance UK (which endorsed the response of Haemochromatosis UK) disagreed with the conclusion of the

evidence summary and advocate the implementation of systematic genetic screening for haemochromatosis in adults across the UK. They also made the following points:

a. genetic haemochromatosis is not rare – it is rarely diagnosed, and population-level screening is therefore a meaningful and relevant tool to improve both the rates and the timeliness of diagnosis

b. the burden of morbidity caused by unmanaged haemochromatosis is serious and, if cases can be identified early, morbidity can be mitigated well

c. current diagnostic pathways are ineffective

d. it would be unreasonable to expect or demand a randomised control trial to provide evidence that early diagnosis of genetic haemochromatosis through screening improves clinical outcomes

14. Haemochromatosis UK and Genetic Alliance UK also advocate that:

a. a screening programme should be established in a region/nation of the UK with high genetic haemochromatosis prevalence (for example, Scotland or Northern Ireland) to enable the effects of such a programme to be studied in depth and enable collection of data on the effectiveness and costs/benefits of such a programme before it is rolled out more widely

b. where wide-scale population-based screening is perceived as undesirable or poorly supported by the evidence, there should be a serum ferritin and transferrin saturation screening as part of the NHS Health Check for all people at or around age 40

c. genetic screening of adults should be carried out opportunistically in primary and secondary care, for men and women of Northern European ethnic heritage where either a patient presents with an excess serum ferritin and/or excess transferrin saturation or where the patient has a family history of genetic haemochromatosis (first degree relative) or where the patient has or is being assessed for liver disease, diabetes, cardiomyopathy, severe joint pain and/or chronic fatigue

d. though medical research into neonatal and juvenile forms of genetic haemochromatosis is limited at present, the UK NSC should initiate a separate review of the case for genetic screening in young people under 19 years old

e. the UK NSC should plan a regular 3-yearly review of screening evidence, effectiveness and opportunities for both adults and young people at risk of genetic haemochromatosis

Response: the UK NSC takes this opportunity to thank the member of the public and the other stakeholders for their contribution to the consultation process. The UK NSC acknowledges the importance of timely diagnosis. However, in keeping with the conclusions of the previous UK NSC review, the evidence from this evidence summary at present does not support screening for type 1 hereditary haemochromatosis (HH) in adults. This is driven by a lack of evidence for associations between the type 1 HH genotypes and clinical outcomes, incomplete penetrance, and gaps in the evidence base in relation to the lack of evidence on the benefits of screening for type 1 HH in adults, and limited evidence comparing treatment effects at pre-symptomatic (or earlier) versus symptomatic (or later) phases of type 1 HH.

Population screening is delivered in large populations of predominantly healthy people and one of the UK NSC's aim is to maintain oversight of the evidence relating to the balance of good and harm of existing screening programmes, as well as possible new ones. UK NSC evidence summaries are developed using rapid review methodologies. Rapid evidence assessments provide a proportionate approach as stated by the UK Government Social Research Service (https://webarchive.nationalarchives.gov.uk/20140402163101/http://www.civilservice.gov.uk/networks/gsr/resources-and-guidance/rapid-evidence-assessment/how-to-do-a-rea). They provide an evaluation of the volume and direction of the literature on a single question or set of questions on a given screening topic. They are produced in accordance to the UK NSC evidence review process published on the GOV.UK webpage and available to the public: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process

The aim of the process is to ensure that each topic is addressed in a proportionate manner and to provide reassurance to stakeholders that decisions are grounded in, and informed by, up to date evidence.

Hereditary haemochromatosis has been considered as a potential candidate for population screening since 1996 when the HFE mutation was first discovered. However, the 2015 UK NSC review found that it was not possible to draw conclusions on the penetrance and expressivity of the HFE genotypes in the general population and that an effective screening strategy (phenotypic or genotypic) for population screening could not be determined.

During the initial scoping stage for the 2020 evidence summary, the UK NSC was aware of recent research by Pilling et al (2019) based on a UK biobank cohort suggesting that penetrance is higher than previously estimated. Given this renewed interest in screening for hereditary haemochromatosis and the increasing use of genomics to predict and diagnose inherited and acquired disease at scale, it was decided that the 2020 evidence summary should focus on key issues for screening for hereditary haemochromatosis and that it should cover relevant literature since 1996 in order to have a comprehensive overview of the evidence base. However, at present the findings of this evidence summary do not support a change in the current recommendation.

The question on whether there is evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms is an important one, as well as to whether screening is effective at reducing morbidity and mortality. The evidence summary sought to address this. Though randomised controlled trials (RCTs) represent the gold standard in evidence-based medicine, they were not the sole type of study designs eligible for inclusion in this evidence summary. For example, for question 3 on the intervention, systematic reviews and cohort studies were also eligible. Indeed, the evidence summary found that there was insufficient evidence from a systematic review and a cohort study on whether intervention at an earlier/asymptomatic stage leads to better outcomes compared to intervention at a later/symptomatic stage in individuals with hereditary haemochromatosis. For question 4, systematic reviews, RCTs and non-randomised controlled trials were eligible for inclusion, but no studies met the eligibility criteria. This is turn highlights existing gaps in the evidence base, which would benefit from further research.

The stakeholders advocated trialling screening in some parts of the UK in order to collect data on the effectiveness and costs/benefits of such a programme before it is rolled out more widely. This activity should be pursued via means of primary research. However, the UK NSC is not a research commissioning or funding body, and primary research on screening topics should be undertaken to standards which are current in the UK. Uncertainties, limitations of the available evidence and evidence gaps are outlined and discussed in all UK NSC evidence summaries, including this one on hereditary haemochromatosis and they can form the basis upon which primary research is developed (please see ‘evidence uncertainties’ section in the executive summary, the ‘conclusions and implications for policy’ section and the discussion for each individual question).

The stakeholders also raised a point that diagnostic pathways are not working as well as they should and that this is another reason to adopt screening.

However, it is important that clinical management of the condition and patient outcomes is optimised in all health care providers before considering the implementation of a screening programme. In 2010 and 2011 the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have respectively published practice guidelines making recommendations for the screening, diagnosis, and management of hereditary haemochromatosis. Both guidelines do not recommend genetic screening for hereditary haemochromatosis in the general population due to incomplete disease penetrance and limited progression of C282Y homozygotes to iron overload. However, the guidelines recommend cascade screening for all first-degree relatives once a patient with hereditary haemochromatosis has been identified (EASL 2010, Bacon et al 2011). In the UK, guidelines for diagnostic and treatment pathways were updated in May 2018 by the British Society for Haematology: these do not advocate for unselected population screening for HFE gene mutations, though they recommend targeted screening of family members of an individual found to be C282Y homozygous (Fitzsimons et al 2018). As noted by another consultee (British Association for the Study of the Liver), emphasis should remain on raising awareness among clinicians in primary and secondary care settings to perform genetic testing and implementation of cascade screening after identification of index cases, as per existing guidelines, and on increasing public awareness.

In relation to screening for hereditary haemochromatosis in young people, this is not currently a topic on the UK NSC recommendations list, which gets regularly reviewed every 3 years. New topics which might be evaluated against the UK NSC criteria can be suggested via the Annual Call for Topics process. This is normally advertised in the first week of September, with 3 months to make a submission. However, as the stakeholder pointed out, the medical research into neonatal and juvenile forms of genetic haemochromatosis is limited at present, and this in turn might limit the chances to consider the topic in greater depth at this stage.

The UK NSC will review again the topic of screening for hereditary haemochromatosis in adults in 3-years' time when new evidence published since December 2019 can be considered for inclusion in the next update.

References

a. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver D. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American

Association for the Study of Liver Diseases. Hepatology. 2011;54(1):328-43.

b. European Association for the Study of the Liver. EASL clinical practice guidelines for HFE hemochromatosis. Journal of Hepatology. 2010;53(1):3-22.

c. Fitzsimons EJ, Cullis JO, Thomas DW, Tsochatzis E, Griffiths WJH, the British Society for Haematology. Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). British Journal of Haematology. 2018;181(3):293-303.

d. Pilling LC, Tamosauskaite J, Jones G, Wood AR, Jones L, Kuo C-L, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. BMJ. 2019;364:k5222.

15. Haemochromatosis UK questioned the exclusion of some papers and asked that they would be re-assessed for inclusion

Response: the reviewers re-assessed the papers flagged up in section 5 of Haemochromatosis UK's consultation response. The reviewers are satisfied that the studies were rightly excluded, and that the conclusions of the evidence summary are appropriate based on the available evidence. Detailed assessment by the reviewers for each individual paper is provided below:

a. 5.1.1 Niederau et al (1996, citation reference 471): the population of interest for the review was adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity. In the paper by Niederau et al (1996), the participants were included on the basis of "clinical, biochemical, and histological evidence of hereditary hemochromatosis". All of the study participants were identified before the haemochromatosis gene HFE was discovered, and the paper makes no mention of their genetic status. Therefore, it did not meet the review inclusion criteria

b. 5.1.2 Adams et al (1996, citation reference 16): this study was excluded on the basis of sample size, as outlined in the exclusion criteria in Table 2 of the NSC review (please see page 18). The review was conducted in accordance to the UK NSC Rapid Evidence Assessment (REA) process. Rapid Evidence Assessment provide an evaluation of the volume and direction of the evidence base, using rapid review methodologies. These methods are not intended to replicate systematic reviews, which might provide a comprehensive assessment of all the available data. The methods of rapid reviews

differ from those of systematic reviews in a number of ways, including that they are narrower in scope (as evidenced by the inclusion and exclusion criteria of the present review), include fewer steps or person resources, and focus on a descriptive approach to synthesis. The limitations of this approach are presented on page 79

c. 5.1.3 Roest et al (2001, citation reference 471): the reason for exclusion of this paper is incorrectly listed as “review study”. In fact, it was excluded because the study participants are hereditary haemochromatosis carriers. This is an ineligible population as in the present review the population of interest was adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity. The reason for exclusion will be amended accordingly in an updated version of the evidence summary

d. 5.1.4 Tamosauskaite et al (2019, citation reference 526): the outcomes of interest for the review are outlined in Table 2 of the NSC review (see page 18). The chosen outcomes are not intended to cover all possible outcomes (please see response to Adams et al. (1996) regarding the rapid evidence assessment process). The outcomes reported in the Tamosauskaite et al (2019) study (sarcopenia, pain, and frailty) were not included in this list, therefore the study was not eligible for the present review

e. 5.1.5 Sukiennicki et al (2019, citation reference 521): the outcomes of interest for the review are outlined in Table 2 of the NSC review (please see page 18). The outcome used in the Sukiennicki et al (2019) study (lung cancer) was not included in this list and is therefore ineligible for the present review. Please see response to Adams et al. (1996) regarding the rapid evidence assessment process

f. 5.1.6 Rozwadowska et al (2019, citation reference 479): this study was excluded on the basis of sample size, as outlined in the exclusion criteria in Table 2 of the NSC review (please see page 18). Please see response to Adams et al. (1996) regarding the rapid evidence assessment process

g. 5.1.7 McLaren et al (2019, citation reference 359): the objective of the review to which the study of McLaren et al. (2019) might apply was to examine “the proportion of people with type 1 hereditary haemochromatosis (HH) genetic mutations who develop biochemical/clinical outcomes”. McLaren et al. did not provide the data

that is required to calculate these proportions; therefore, this study was excluded from the review

Recommendation

16. The Committee is asked to approve the following recommendation:

A systematic population screening programme for hereditary haemochromatosis in adults is not recommended in the UK

17. The UK NSC discussed this recommendation. The Committee agreed that it was unlikely that a screening programme could be recommended on the basis of the current and previous reviews. However, the Committee agreed that a stakeholder workshop focusing on potential research questions may help to move the discussion forward for future reviews of screening for haemochromatosis.

Table 1: Criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Criteria (only include criteria included in the review)	**Met/Not Met**
The Condition	
The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease. (NSC criterion 1)	**Not met**
The Intervention	
There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered. (NSC criterion 9)	**Not met**
The Screening Programme	
There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. (NSC criterion 11)	**Not met**
The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications. (NSC criterion 13)	**Not met**

Annex A: List of organisations contacted

1. British Association for the Study of the Liver
2. British Liver Nurses' Forum
3. The British Liver Trust
4. The British Society for Haematology
5. British Society of Gastroenterology
6. Faculty of Public Health
7. Haemochromatosis UK
8. PHE adult screening programmes
9. Royal College of General Practitioners
10. Royal College of Nursing
11. Royal College of Pathologists
12. Royal College of Physicians
13. Royal College of Physicians and Surgeons of Glasgow
14. Royal College of Physicians of Edinburgh

Annex B: Consultation comments

1. British Association for the Study of the Liver

"UK NSC has externally reviewed the position on population screening for hereditary haemochromatosis (HH) via a position paper dated September 2020. Previous reviews in 2009 and 2015 have found insufficient evidence to support population screening in HH. In particular, there is a lack of studies examining the benefit of any specific screening strategy. Since the last review there has been an important publication showing significant morbidity in a sizeable cohort of HFE-related haemochromatosis based on UK biobank data (Pilling LC et al BMJ 2019). Nonetheless, we have not moved sufficiently forward as yet to justify a national screening programme. Further interrogation of the UK biobank data may provide some insight into screening strategies which may be effective, and lead to relevant pilot studies. Until then it would be premature to recommend national screening for HH. The emphasis remains on primary and secondary care clinician education with low index of clinical suspicion to perform HFE gene testing and implementation of cascade screening after identification of index cases, as well as increased public awareness e.g. via Haemochromatosis UK and the British Liver Trust. In summary, BASL supports the latest UK NSC position and is appreciative of the in-depth re-review performed here".

2. Royal College of Nursing

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Nursing		
Role:	xxxx xxxx		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes **No**

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General	General	In support of key recommendations at this current time as outlined by the UK NSC
General	General	Well evidenced document

UK National Screening Committee

3. Genetic Alliance UK

Name:	Jayne Spink PhD	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Genetic Alliance UK		
Role:	Chief Executive		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ~~**No**~~

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
General		Genetic Alliance UK has reviewed the response to this consultation from Haemochromatosis UK, a member of Genetic Alliance UK. We support and endorse this response.

		The response from Haemochromatosis UK describes new evidence (since the previous UK NSC review of this topic) indicating that genetic haemochromatosis is a common condition in the UK population, with very low identification / diagnosis rates. The fact that the pivotal study here is from the UK Biobank is important. Haemochromatosis UK's response goes on to establish that the burden of morbidity caused by unmanaged haemochromatosis is serious, and that if cases can be identified early, morbidity can be mitigated well. Further, the route by which individuals might currently be expected to be identified is shown to be ineffective. Genetic Alliance UK supports the conclusion reached by Haemochromatosis UK, including but not limited to: - the implementation of systematic genetic screening for haemochromatosis in adults across the United Kingdom, - the establishment of a screening programme for all adults, in a region/nation of the UK with high GH prevalence (eg Scotland or Northern Ireland) to enable the effects of such a programme to be studied in depth.

4. Member of the public

Name:	Martin Johnson	**Email address:**	xxxx xxxx
Organisation (if appropriate):	HUK Volunteer		
Role:	Helpline volunteer and member, clinical advisory board		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
79	In keeping with the conclusions of the previous UK NSC review, the evidence from this review does not support screening for type 1 HH in adults. This is driven by a lack of evidence for associations between the type 1 HH genotypes and clinical outcomes, incomplete penetrance, and important gaps in the evidence	The report is complex, but it seems to me that some common sense is lost in that complexity. First, it is clear that about 250,000 people in the UK have two copies of the HFE mutated gene and that, even at a relatively low penetrance many of these go on to develop liver cancer, heart disease, diabetes, etc. because our health system does not discover them until it's too late. Most are discovered by chance on routine screening for other

		conditions, or because they finally complain of distressing symptoms. An iron panel is cheap and a very strong indicator that the gene test should be done. Triennial 'screening' of both sexes on suitable occasions, such as GP and/or hospital visits after the age of 35 would be a good first step until safety from iron overload is assured.
P79	This review has a number of limitations	Yes. In many ways it is very diligent for a 'rapid review' but to demand best quality RCT evidence to make such a policy change here is like saying that because John Snow's 1854 study did not meet modern canons of an RCT the management of cholera by closing water pumps like the one on Broad Street should not have been actioned or that smoking should be encouraged because the anti-smoking campaign was not based on human RCT evidence either. The review admits the HFE gene was only identified in 1996 and we all know that this condition has had low priority in terms of research. Fortunately we can draw on research done with a wider purpose such as the very high quality large UK Biobank studies. From these thanks to Atkins et al (2020) we DO know that HFE C282Y homozygous men die of liver cancer at 10 times the rate of so called 'normals'. That concerns me, I'm one of them and know many more. Clearly even medical opinions vary, but the arguments

		against checking of serum ferritin routinely on every appropriate occasion with follow up with a genetic test where necessary seem to me weak. Reference: Atkins, J., Pilling, L.C., Masoli, J.A. et. al. (2020) Association of haemochromatosis HFE p.C282Y homozygosity with hepatic malignancy. JAMA 324, 20, 2048-2057. doi:10.1001/jama.2020.21566

5. Haemochromatosis UK

On 15 February 2021, the stakeholder emailed the UK NSC noting that they had spotted an error in their original submission and that paragraph 1.8 should read:

Similarly, in Wales, Jackson et al (2001) studied 10,500 Welsh blood donors and discovered that “1 in 42 were compound heterozygotes...Homozygosity for H63D occurred in 1 in 42 donors and 1 in 147 (72) were homozygous for C282Y”. The ONS’ latest population figures (2019) show a population of 3.152 million. This suggests that many tens of thousands of people in Wales are affected

Source :
https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/wapop/pop

The stakeholder’s original submission is available in full below.

Haemochromatosis • UK
Helping people live with iron overload
+Fe

Henrith Business Centre,3 Enterprise Way
Spalding, Lincolnshire, PE11 3YR
www.ironoverload.org.uk

The Secretariat
UK National Screening Committee

By email to screening.evidence@nhs.net

14th January 2021

Dear Sir or Madam,

Submission in response to consultation on screening for haemochromatosis in adults

Thank you for your invitation to submit a response to your consultation on screening for haemochromatosis in adults.

I am pleased to attach our submission on behalf of Haemochromatosis UK. We consent to our name and submission being published on the UK NSC website.

For convenience, we have supplied various papers we ourselves have published via a cloud folder. These are referenced in our submission and publicly available on our website, however it may be more expedient to download them from this link : *https://www.haemochromatosis.org.uk/uk-nsc-papers*

We believe that genetic screening can play an effective contribution in early diagnosis and preventing avoidable ill-health. **Early diagnosis really does save lives**.

Stay safe and take care.

Yours faithfully,

Neil McClements
Chief Executive
Haemochromatosis UK

Response to UK NSC Consultation on Screening in Adults for Haemochromatosis

1. Prevalence of Genetic Haemochromatosis (GH) in the United Kingdom

1.1 This section collates the pertinent academic publications and describes their findings before concluding with the latest estimates of GH population level.

1.2 Our scientific knowledge and understanding of the prevalence of GH has improved greatly since the last UK NSC review in 2015. We encourage the UK NSC to weight its consideration of medical research to those more recent and up-to-date studies, published post 2015.

1.3 Research published in the British Medical Journal in 2019 – *"Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank"* (https://doi.org/10.1136/bmj.k5222 ; BMJ 2019;364:k5222) - conducted by Pilling, Melzer et al considered over 451,000 sequenced genomes of people aged 40-70 years in the UK Biobank. This study focussed on a single variant of GH, p.C282y Other variants are known and so this study is indicative of the scale of GH prevalence, perhaps accounting for 80-85%[1] of cases of the condition.

1.4 This study found that homozygous haemochromatosis was diagnosed in 21.7% (95% confidence interval 19.5% to 24.1%, 281/1294) of men and 9.8% (8.4% to 11.2%, 156/1596) of women by end of follow-up period.

1.5 If we scale-up the findings of the BMJ 2019 study and apply them to the White British and White Irish populations of the United Kingdom[2], there are over 380,000 people potentially affected and at risk of GH. This means that GH is a more common condition and therefore, screening may be effective in identifying people potentially at risk of ill-health *before* serious illness becomes manifest. Typical symptoms of GH are common in the general population; it is difficult to diagnose effectively in primary care without testing or screening for the condition genetically.

1.6 Earlier studies, including Heath et all (2016)[3] summarised prevalence data from a wide range of other studies across Europe. For example, Murphy et all (1998) assessed the prevalence of GH in Northern Ireland as being 9.9% of the population studied. The NISRA 2020 estimates the population of Northern Ireland

[1] See Gallego et al Penetrance of Hemochromatosis in HFE Genotypes Resulting in p.Cys282Tyr and p.[Cys282Tyr];[His63Asp] in the eMERGE Network; Am J Hum Genet. 2015 Oct 1; 97(4): 512–520. Published online 2015 Sep 10. doi: 10.1016/j.ajhg.2015.08.008

[2] See https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/adhocs/008781populationdenominatorsbybroadethnicgroupandforwhitebritishlocalauthoritiesinenglandandwales2011to2017

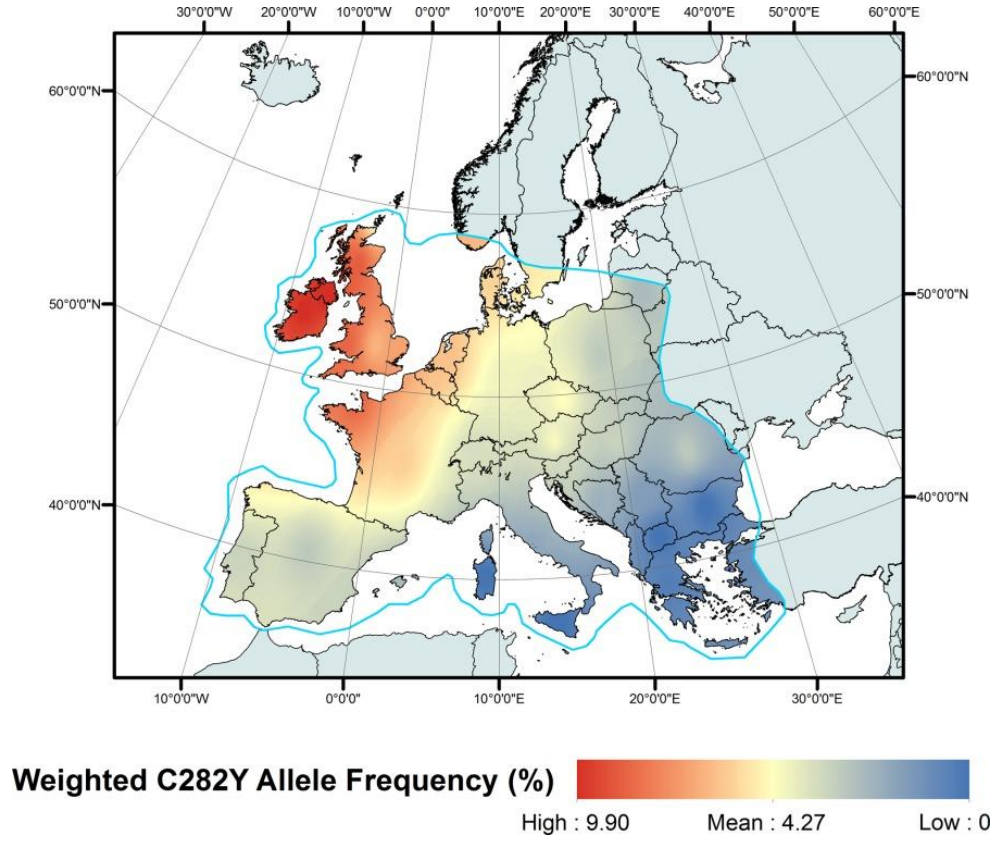
[3] The evolutionary adaptation of the C282Y mutation to culture and climate during the European Neolithic Kathleen M. Heath Jacob H. Axton John M. McCullough Nathan Harris. First published: 22 January 2016 https://doi.org/10.1002/ajpa.22937

to be 1.894 million people[4]. This suggests that almost 190,000 people are affected by GH in Northern Ireland.

1.7 Similarly, in Scotland, Miedzybrodska et al (1999) estimated prevalence at 8.4%[5]. Taking National Records of Scotland's most recent population estimates (October 2020[6]), this suggests that over 458,000 people in Scotland are affected.

1.8 Similarly, in Wales, Jackson et al (2001[7]) studied 10,500 Welsh blood donors and discovered that 1 in 7.9 donors were homozygous for C282y, 1 in 4.2 donors were homozygous for H63d and 1 in 42 donors were compound heterozygotes. StatsWales' latest population figures (May 2020[8]) show a population of 5.463 million. This suggests that many tens of thousands of people in Wales are affected.

1.9 In summary, the chart below (after Heath et al, 2016) illustrates visually the high levels of prevalence of GH across the United Kingdom. Genetic haemochromatosis is not rare – it is rarely diagnosed. Population-level screening is therefore a meaningful and relevant tool to improving both the rates and the timeliness of diagnosis.



[4] See https://www.nisra.gov.uk/sites/nisra.gov.uk/files/publications/MYE19-Bulletin.pdf
[5] See https://onlinelibrary.wiley.com/doi/full/10.1002/ajpa.22937#ajpa22937-bib-0124
[6] See https://www.nrscotland.gov.uk/statistics-and-data/statistics/stats-at-a-glance/registrar-generals-annual-review/2019
[7] See Jackson, H.A., Carter, K., Darke, C., Guttridge, M.G., Ravine, D., Hutton, R.D., Napier, J.A. & Worwood, M. (2001) HFE mutations, iron deficiency and overload in 10 500 blood donors. British Journal of Haematology, 114, 474–484.
[8] See https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/nationallevelpopulationestimates-by-year-age-ukcountry

1.10 A presentation by Melzer & Atkins to the All-Party Parliamentary Group on Genetic Haemochromatosis in Autumn 2019[9] surmised from various sources that overall, C282y homozygous GH accounted for 1 in 115 people in Scotland, 1 in 164 people in Wales and 1 in 163 people in England.

1.11 Over the past two years, studies into the UK Biobank have shown that GH is much more prevalent than previously thought. The condition is not "rare" *per se* but it is certainly rarely diagnosed. We believe that screening can play an effective role in dramatically increasing the rates of early diagnosis and preventing avoidable ill-health.

1.12 Given the widespread prevalence of GH in the UK population, we believe that screening is the most effective method of identifying people at risk, before ill-health develops. As we set out in section 2, we believe this would support the NHS to prevent expensive, avoidable demands on finite public healthcare resources, by eradicating longer-term ill-health at minimal cost.

2. The health consequences of Genetic Haemochromatosis

2.1 The BMJ 2019 study in 1.3 concluded that p.C282Y homozygous men aged 40 to 70 had a higher prevalence of diagnosed haemochromatosis (odds ratio 411.1, 95% confidence interval 299.0 to 565.3, P<0.001), liver disease (4.30, 2.97 to 6.18, P<0.001), rheumatoid arthritis (2.23, 1.51 to 3.31, P<0.001), osteoarthritis (2.01, 1.71 to 2.36, P<0.001), and diabetes mellitus (1.53, 1.16 to 1.98, P=0.002), versus no p.C282Y mutations (n=175 539). This study demonstrates that ill-health resulting from genetic haemochromatosis *is* common.

2.2 A subsequent study *"Association of hemochromatosis HFE p.C282Y homozygosity with hepatic malignancy"*, by. Janice L Atkins, Luke C Pilling, Jane AH Masoli, Chia-Ling Kuo, Jeremy D Shearman, Paul C Adams, David Melzer, (JAMA. 2020;324(20):2048-2057. doi:10.1001/jama.2020.21566 published in November 2020 looked specifically at *just one form of ill-health* – hepatic carcinoma – in people over a nine-year period. The source of data was again the UK Biobank.

2.3 The Jama 2020 study concluded that among men with HFE p.C282Y homozygosity, there was a significantly increased risk of incident primary hepatic malignancy and death compared with men without p.C282Y or p.H63D variants; there was not a significant association for women. Put simply, genetic haemochromatosis makes men ten times more likely to experience liver cancer than men without the condition; a ten-fold increase in excess disease.

[9] Presentation may be downloaded from : https://www.haemochromatosis.org.uk/minutes-of-the-third-meeting-of-the-appg-for-genetic-haemochromatosis-october-2019

2.4 A presentation by Melzer & Atkins to the All-Party Parliamentary Group on Genetic Haemochromatosis in November 2019, based upon their studies of the UK Biobank revealed significant, observable levels of excess disease attributable to Genetic Haemochromatosis :

All Diagnoses	Men: excess number diagnosed	Women: excess number diagnosed
Haemochromatosis	20,000	10,500
Any Liver disease	3,350	470
Liver cancer	989	-*
Arthritis	6,500	3,063
Hip replacement	3,836	1,926
Diabetes	2,580	552

2.5 Melzer & Atkins estimated that C282y homozygotes need approximately 12,486 more days of NHS in-patient treatment very year, than people without the mutation. This represents a significant cost to the NHS, a cost which could be reduced through earlier diagnosis resulting from a national screening programme.

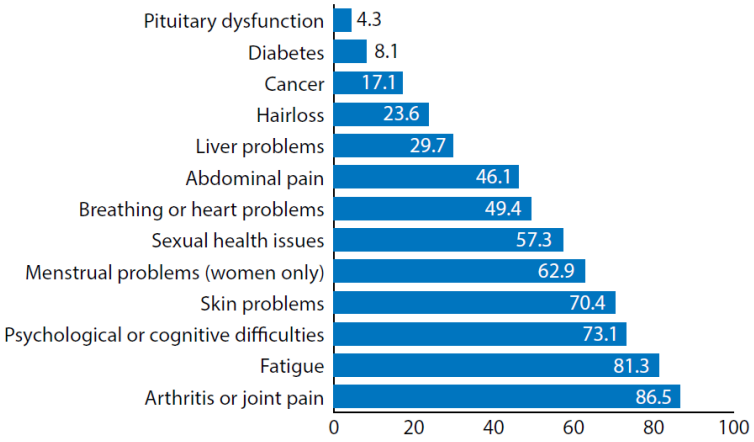
2.6 The Impact of Iron Overload Report (Smith, Fife-Shaw, Dibb, Griffiths) published by Haemochromatosis UK in 2018[10] was the world's first and largest study on the lived experience of people affected by Genetic Haemochromatosis. This study showed that the majority of people diagnosed with GH experienced symptoms and ill-health :

2.6.1 48.7% of respondents reported persistent fatigue and joint pain

2.6.2 14.7% of respondents reported other persistent and painful symptoms

2.7 The study illustrates the wide range of ill-health experienced by people with GH, including heart problems, liver disease, cancers, diabetes and skin problems. Many of these conditions (eg fatigue) are non-specific and difficult to assess and

Figure 8: Percentage of respondents that had *ever* experienced symptoms (n=1,689)



[10] See https://www.haemochromatosis.org.uk/the-impact-of-iron-overload

triage in the initial stages. Screening would provide a definitive assessment of patients' genetic susceptibility to GH, as a cause of related ill-health.

2.8 Earlier studies including Niederau at al, 1996[11], Niederau et al, 1985[12], Adams et al, 1991[13] evidence that the serious complications of GH can reduce life expectancy. Screening would help to identify people at risk, earlier. There is significant evidence that early diagnosis improves outcomes.

2.9 Other studies including Pearce et al, 2018[14], Connell et al, 2011[15], McDonnell et al 1996[16] and Adams et al 1996[17] demonstrate that GH symptoms impact on the quality of life and wellbeing for people with the condition. Screening would enable people at risk to be assessed and treated in a timely manner, to reduce the unnecessary suffering associated with the non-fatal but quality-of-life affecting symptoms of GH.

2.10 A very recent study[18] in January 2021 by Atkins, Pilling et al based upon UK Biobank datasets has identified that incident dementia was more common in p.C282Y homozygous men (Hazard Ratio HR = 1.83; 95% CI 1.23 to 2.72, p = 0.003), as was delirium, although there were no associations in homozygote women or in heterozygotes. Dementia is particularly difficult to identify before the onset of irreversible symptoms. A genetic screening programme would help to identify people at risk of dementia through iron overload, long before the onset of disease.

2.11 The studies referenced in this section indicate that GH can cause significant and predictable incidence of the following symptoms:

2.11.1 Liver disease

2.11.2 Cancers, including liver cancer

2.11.3 Diabetes

2.11.4 Arthritis and severe joint pain

[11] See Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary haemochromatosis. Gastroenterology. 1996;110(4): 1107-19.
[12] See Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary haemochromatosis. New England Journal of Medicine. 1985;313(20):1256-62.
[13] See Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary haemochromatosis. Gastroenterology. 1991;101(2): 368-72.
[14] See Pearce J, Ray RA, McKenzie S. The voice of haemochromatosis journeys in regional Australia: A qualitative study exploring self-management. Australian Journal of General Practice. 2018;47(1/2): 64.
[15] See Connell EO, Sheahan O. Learning to live with hereditary haemochromatosis: a qualitative descriptive study. Journal of Nursing and Healthcare of Chronic Illness. 2011;3(3): 257-64.
[16] See McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC, et al. A survey of 2,851 patients with haemochromatosis : Symptoms and response to treatment. The American Journal of Medicine. 1999;106(6): 619-24.
[17] See Adams P, Speechley M. The effect of arthritis on the quality of life in hereditary haemochromatosis. The Journal of Rheumatology. 1996;23(4): 707-10.
[18] See Atkins, Pilling et al Hemochromatosis Mutations, Brain Iron Imaging, and Dementia in the UK Biobank Cohort : J Alzheimers Dis. 2021 Jan 3. doi: 10.3233/JAD-201080

2.11.5 Chronic fatigue

2.11.6 Heart disease including cardiomyopathy

2.11.7 Endocrine/pituitary failure

2.11.8 Sexual health dysfunction

2.11.9 Mental health and memory issues

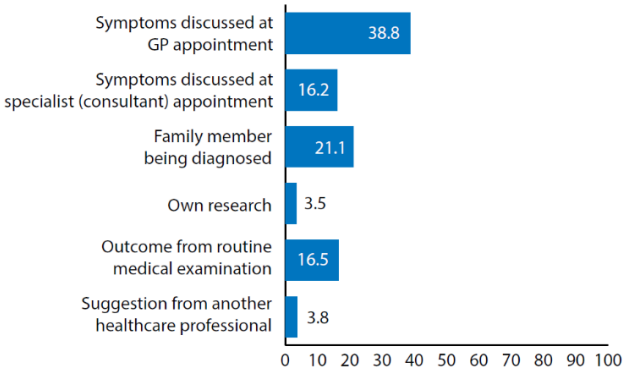
3. The benefits of early diagnosis through screening

3.1 If people with GH are diagnosed in the pre-cirrhotic, pre-diabetic stage and treated by venesection to remove excess iron, then life expectancy is normal (Niederau et al, 1996[19]).

4. Current diagnostic and care pathways

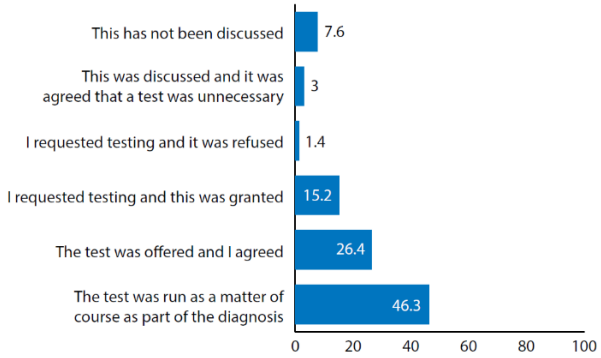
4.1 Current diagnostic pathways are not working well. The Impact of Iron Overload report (2018) revealed that diagnosis most commonly followed symptoms, there was little pre-emptive screening of families as shown in this figure :

Figure 13: Route to diagnosis (n=1,072)



4.2 Similarly, people with GH experienced significant difficulty in obtaining a definitive genetic test for their condition. Fewer than half of people surveyed had been offered genetic testing as a matter of course. Consequently, many people at risk of disease go un-diagnosed until ill-health occurs, typically later in life.

Figure 17: Experience of obtaining genetic test for self (n=1,072)



[19] See See Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary haemochromatosis. Gastroenterology. 1996;110(4): 1107-19.

4.3 Unfortunately, most patients presenting to primary care with raised serum ferritin [20] levels are not screened for GH (Ogilvie et al, 2010[21]).

4.4 Ogilvie et al (2015[22]) re-iterated the challenges experienced by primary care in diagnosing GH in patients through serum ferritin and transferrin saturation[23] testing. This study outlines an algorithm for detecting GH without genetic screening, yet five years after publication, many primary care practitioners remain unaware of the role of both transferrin saturation and serum ferritin in diagnosis[24]. A limitation of this approach to improve early diagnosis is that females predominate in both volunteer studies and primary care requests for serum ferritin (Adams et al, 2005[25]), while clinically significant GH predominates in males. Consequently, we advocate a genetic screening-led approach to ensure health equality between the genders.

4.5 Haemochromatosis UK published its State of the Nation report (Mortimer, McClements) in August 2020[26]. This study examined the current NHS care pathways for people affected by GH, based upon Freedom of Information searches conducted in the latter half of 2019. The study, which was reviewed by the All-Party Parliamentary Group on Genetic Haemochromatosis, showed that GH is rarely diagnosed, not rare. It also showed that there is inconsistent adoption of recognised care protocols and guidelines for GH.

5. UK NSC methodology and selection of evidence

5.1 Appendix 2, figure 4 sets out the summary of publications included and excluded as part of the UK NSC review. We do not believe that many of the excluded studies should have been excluded. We advocate that the UK NSC should re-assess all studies excluded for relevance to the issues of GH penetrance, clinical outcomes from early versus delayed diagnosis and quality of life aspects of un-diagnosed GH.

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[20] Serum ferritin can be assessed using a simple, inexpensive (<£1.80) blood test. It indicates whether a person has too much or too little iron in their body. A figure of 200 ug/l (females) or 300 ug/l (males) is strongly indicative of genetic haemochromatosis.

[21] See Ogilvie, C., Fitzsimons, K. & Fitzsimons, E.J. (2010) Serum ferritin values in primary care: are high values overlooked. Journal of Clinical Pathology, 63, 1124–1126. See https://jcp.bmj.com/content/63/12/1124

[22] See Ogilvie, C., Gaffney, D., Murray, H., Kerry, A., Haig, C., Spooner, R. & Fitzsimons, E.J. (2015) Improved detection of hereditary haemochromatosis. Journal of Clinical Pathology, 68, 218–221. See https://jcp.bmj.com/content/68/3/218.short

[23] transferrin saturation is assessed using a simple blood test, often in combination with serum ferritin. It represents how much serum iron is safely bound within the body. A figure of >45% (females) or >50% (males) is strongly indicative of genetic haemochromatosis.

[24] Haemochromatosis UK operate an eLearning module with the Royal College of GPs to assess primary care clinician knowledge of diagnosis and provide training. In September 2020, GPs undertaking the training scored an average of 48.4% pre-training, versus an average of 84.6% post-training. Over the period June 2019-August 2020 387 GPs completed the training course and assessments.

[25] See Adams, P.C., Reboussin, D.M., Barton, J.C., McLaren, C.E., Eckfeldt, J.H., McLaren, G.D., Dawkins, F.W., Acton, R.T., Harris, E.L., Gordeuk, V.R., Leiendecker-Foster, C., Speechley, M., Snively, B.M., Holup, J.L., Thomson, E. & Sholinsky, P. (2005b) Hemochromatosis and iron-overload screening in a racially diverse population. The New England Journal of Medicine, 352, 1769–1778. See https://www.nejm.org/doi/full/10.1056/nejmoa041534

[26] See https://www.haemochromatosis.org.uk/state-of-the-nation-2020

5.1.1 For example, Niederau et al (1996, citation reference 403) has been excluded on the grounds that it studied an "ineligible population". Although this study focussed on people in the then West Germany, it has broad applicability to the UK. It demonstrates that iron deficiency is more prevalent in women and that iron overload is more prevalent in men. The UK population contains both men and women; this study should not have been excluded on the grounds cited and should be included as it also demonstrates evidence of the effects of excess iron on liver health in both men and women. Conversely, the inclusion on Hendricksen 2016 based on a Danish general population study seems inconsistent on the basis of geography.

5.1.2 For example, Adams et al (1996, citation reference 16) was excluded on grounds that it studied "fewer than 100 participants". The UK NSC's determination that 100 is a meaningful or clinically valid number of participants for a study to be included is perverse. This appears to be an arbitrary and unjustified means of ignoring otherwise valid research data. In practice, this study has been widely cited in the literature as it provides a statistically rigorous insight into how arthritis is a prominent clinical factor affecting quality of life in people with haemochromatosis.

5.1.3 For example, Roast et al (2001, citation reference 471) was excluded on the basis that it was a "review study". Such studies are useful for setting out the research context and key aspects of the clinical outcomes associated with haemochromatosis. In this study, it was demonstrated that GH is a risk factor for cardiovascular disease and should therefore have been included, not excluded. It's findings have been confirmed by later studies, included those conducted by Haemochromatosis UK cited above.

5.1.4 For example, Tamosauskaite et al (2019, citation reference 526) has been excluded on grounds that there are "no eligible outcomes". This seems odd given that the study examined over 200,000 older patients ("more than 100 participants") and demonstrated that people with genetic haemochromatosis had increased likelihood of reporting pain and were more likely to experience sarcopenia and frailty than others without the condition. This would seem to be an eligible outcome, which points to the impacts of haemochromatosis on quality of life of people aged 60 – 70 years old.

5.1.5 For example, Sukiennicki et al (2019, citation reference 521) has been excluded on the grounds that lung cancer is an "ineligible starting condition". It is commonly accepted that genetic haemochromatosis can increase the risks of certain cancers. To exclude a study which demonstrates a relationship between higher iron/ferritin and lung cancer on the basis of the cancer type is puzzling. This study considered 200 people with lung cancer and 200 people without against their ferritin levels. As such, it is relevant, recent and should have been included.

5.1.6 For example, Rozwadowska et al (2019, citation reference 479) was rejected on the grounds of the cohort size. Yet the study makes powerful

observations on the impact of delayed diagnosis on people with cardiomyopathy attributable to GH : *"Hereditary haemochromatosis, not only long-lasting, but also early-diagnosed, could lead to exacerbation of LV wall thickness and cardiac hypertrophy. This effect is not simply connected with hypertension and diabetes that are frequent additional diseases in these patients, but with the time from HH diagnosis."*

5.1.7 For example, McLaren et al (2019, citation reference 359) was excluded on the basis of there being "no numerical outcome data", yet this is a 12-year longitudinal Australian study which demonstrates a "model [which] is transferable from one white population to another" through bivariate mixture modelling, an approach which might be relevant to informing the UK NSC in its approach to assessing the prevalence of GH in the UK.

5.2 We believe that additional studies should be included in the UK NSC review of evidence, specifically those cited in our response above.

5.3 As a charity supporting people affected by genetic haemochromatosis to live well with the condition, we welcome being invited to provide a response to the UK NSC's consultation. As a patient-led and focussed organisation, we encourage the UK NSC to consider qualitative data as well as quantitative data when considering screening for the condition.

5.4 Every year, we support over 14,000 families via our Facebook Support Group, email helpline, telephone helplines and local support groups. We are regularly told by families of their frustrations from delayed or late diagnosis, difficulty in accessing genetic testing/counselling services and the associated ill-health that arises, unnecessarily. We have collated some accounts from our community on our website here : https://www.haemochromatosis.org.uk/Blogs/blog . There are real people behind the figures; so we also commend these actual patient stories to you, when considering the case for screening.

6. In conclusion

6.1 Our response demonstrates that there is recent, reliable evidence to show that :

6.1.1 there is a relatively high prevalence of GH in the UK, compared to diagnosis rates. Fewer than 1 in 20 people at risk are diagnosed, presently.

6.1.2 there are serious health consequences to people who are undiagnosed or diagnosed late in life. Early diagnosis saves lives.

6.1.3 existing ad-hoc mechanisms for identifying people at risk of GH and subsequent ill-health are not working effectively.

6.2 Our charity advocates the implementation of systematic genetic screening for haemochromatosis in adults across the United Kingdom.

6.3 Given the volume of evidence that un-treated iron overload caused by GH causes ill-health, it would be unreasonable to expect or demand a randomised control trial to provide evidence that early diagnosis of GH through screening improves clinical outcomes. To do so would imply withholding treatment from a cohort of patients, against the background of their higher likelihood of organ damage. As such, this would be in contravention of the Helsinki Declaration[27].

6.4 There are obvious challenges in running extended, long-term longitudinal studies to ascertain the effectiveness of screening to reduce GH-related morbidity and mortality, without running a screening programme. We therefore advocate that a screening programme be established in a region/nation of the UK with high GH prevalence (eg Scotland or Northern Ireland) to enable the effects of such a programme to be studied in depth.

6.5 We advocate trialling population-based genetic screening within a nation or region of the UK for all adults male and female, per paragraph 6.4 above. This would enable collation of data on the effectiveness and costs/benefits of such a programme before it is rolled out more widely.

6.6 Where wide-scale population-based screening is perceived as undesirable or poorly supported by the evidence, we advocate serum ferritin and transferrin saturation screening as part of the NHS Health Check for people at or around age 40. Both men and women should be screened. This approach would enable the majority of people at risk to be identified, typically at an age before irreversible organ damage had occurred.

6.7 We also advocate genetic screening of adults opportunistically in primary and secondary care, for men and women of Northern European ethnic heritage where either :

6.7.1 a patient presents with an excess serum ferritin and/or excess transferrin saturation

or

6.7.2 where the patient has a family history of genetic haemochromatosis (first degree relative)

or

6.7.3 where the patient has or is being assessed for liver disease, diabetes, cardiomyopathy, severe joint pain (especially in the second or third metacarpal joints of the hands) and/or chronic fatigue.

[27] See https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

6.8 We advocate that the UK NSC initiate a separate review of the case for genetic screening in young people under 19 years old. Whilst there is presently limited medical research into neonatal and juvenile forms of genetic haemochromatosis, a screening review may prompt an increase in research activity in this area, which would be of benefit to families at risk.

6.9 In view of the rapidly emerging data from UK Biobank and other medical research, we advocate that the UK NSC plans a regular 3-yearly review of screening evidence, effectiveness and opportunities for both adults and young people at risk of genetic haemochromatosis.

Neil McClements
Chief Executive
Haemochromatosis UK
14th January 2021

// ENDS