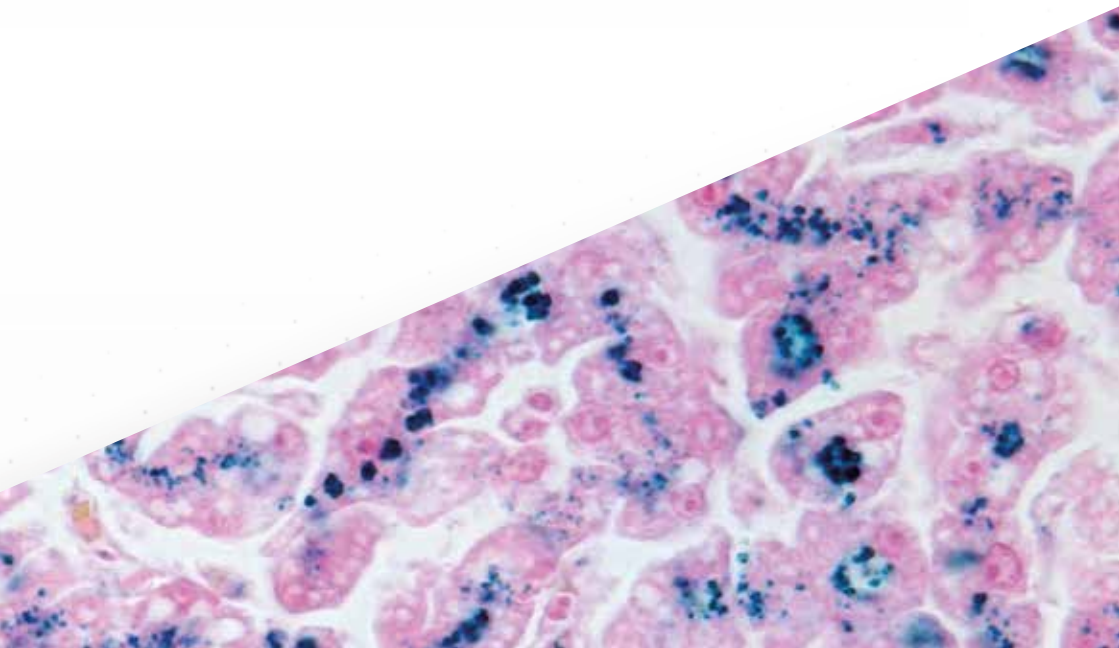
IT'S TIME FOR CHANGE – TOWARDS GENETIC SCREENING IN ADULTS ACROSS THE UK

Haemochromatosis • UK
Helping people live with iron overload
+Fe



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WE CALL UPON THE UK NATIONAL SCREENING COMMITTEE (UK NSC), NHS POLICY-MAKERS, THE DEVOLVED ADMINISTRATIONS AND OUR ELECTED REPRESENTATIVES TO **PROGRESS GENETIC SCREENING OF ADULTS** ACROSS THE UNITED KINGDOM **FOR GENETIC HAEMOCHROMATOSIS**.

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Executive **summary**

Genetic haemochromatosis (GH) is the UK's most common genetic condition, directly affecting over 380,000[i] people. Although it is commonplace, the condition is significantly under-diagnosed in the UK. The NHS is aware of just 14,000[ii] people with genetic haemochromatosis.

Untreated, the condition can lead to iron overload, where the body is unable to process excess iron. Excess iron is extremely toxic. Genetic haemochromatosis can cause liver disease, cancer, heart disease, chronic fatigue, diabetes, severe joint pain, sexual health issues and neurological issues.

Compared to people without haemochromatosis, people living with the most common form of the condition have significant health risks:

- quadruple the risks of liver disease
- double the risk of arthritis
- 50% more pneumonia
- 50% more diabetes
- ten times the risk of liver cancer, in men[iii]
- almost twice the risk of dementia, in men[iv]

Early diagnosis saves lives. Recent studies based on UK Biobank data suggest that each year in the UK, haemochromatosis is responsible for 564 new patients with liver disease and 125 new liver cancer patients[v]. According to Cancer Research UK, five-year survival rates for liver cancer can be as low as 2%, depending upon age at diagnosis and gender. The costs to the NHS of delivering care following the onset of disease are substantial – and largely avoidable.

Diagnosed early, haemochromatosis is manageable and not life-limiting. **Treatment is simple and cost effective**; primarily through regular blood donation. In many situations, following initial treatment, NHS Blood & Transplant can make use of the blood drawn during treatment. It's a win-win for patients and our hard-working NHS clinicians.

We are calling for your support to:

- develop a nationwide genetic screening programme, that will identify people affected early and save lives
- improve rates of diagnosis, which are currently poor
- encourage our NHS to develop and promote best practice in treatment

Our **key findings**

Our understanding of the prevalence and consequent excess ill-health attributable to genetic haemochromatosis has advanced significantly over recent years.

There is recent, reliable clinical evidence to show that:

- 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.
- there are serious health consequences to people who are undiagnosed or diagnosed late in life. Early diagnosis saves lives.
- existing ad-hoc mechanisms for identifying people at risk of GH and subsequent ill-health are not working effectively.

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

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[1].

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.

We advocate trialling population-based genetic screening within a nation or region of the UK for all adults male and female, per paragraph 5.4 above. This would enable collation of data on the effectiveness and costs/benefits of such a programme before it is rolled out more widely.

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.

We also advocate genetic screening of adults 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 (especially in the second or third metacarpal joints of the hands) and/or chronic fatigue.

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.

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.



1 THE **PREVALENCE OF GENETIC HAEMOCHROMATOSIS (GH)** IN THE UNITED KINGDOM

1. The **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%[2] 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[3], 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.

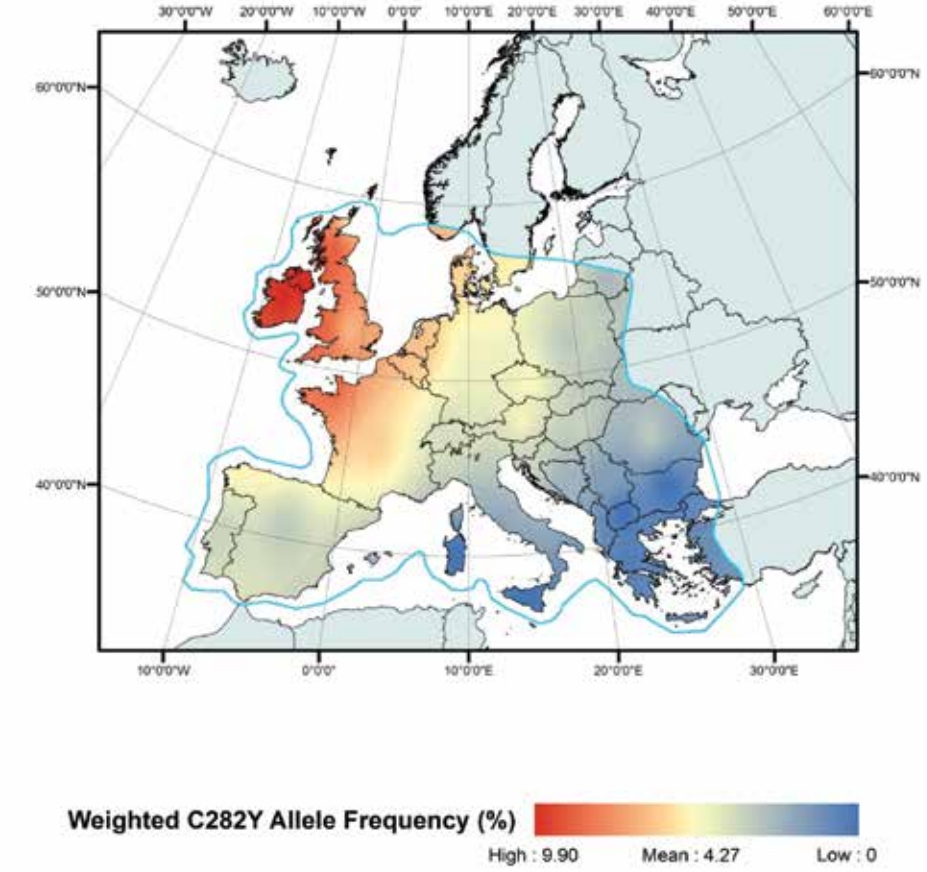
1.6 Earlier studies, including Heath et all (2016)[4] summarised prevalence data from a wide range of other studies across Europe. For example, Murphy et all (1998) assessed the prevalence of GH in Northern Ireland as being 9.9% of the population studied. The NISRA 2020 estimates the population of Northern Ireland to be 1.894 million people[5]. 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%[6]. Taking National Records of Scotland's most recent population estimates (October 2020[7]), this suggests that over 458,000 people in Scotland are affected.

1.8 Similarly, in Wales, Jackson et al (2001[8]) 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.

1.9 In summary, the chart in Figure 1 (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.

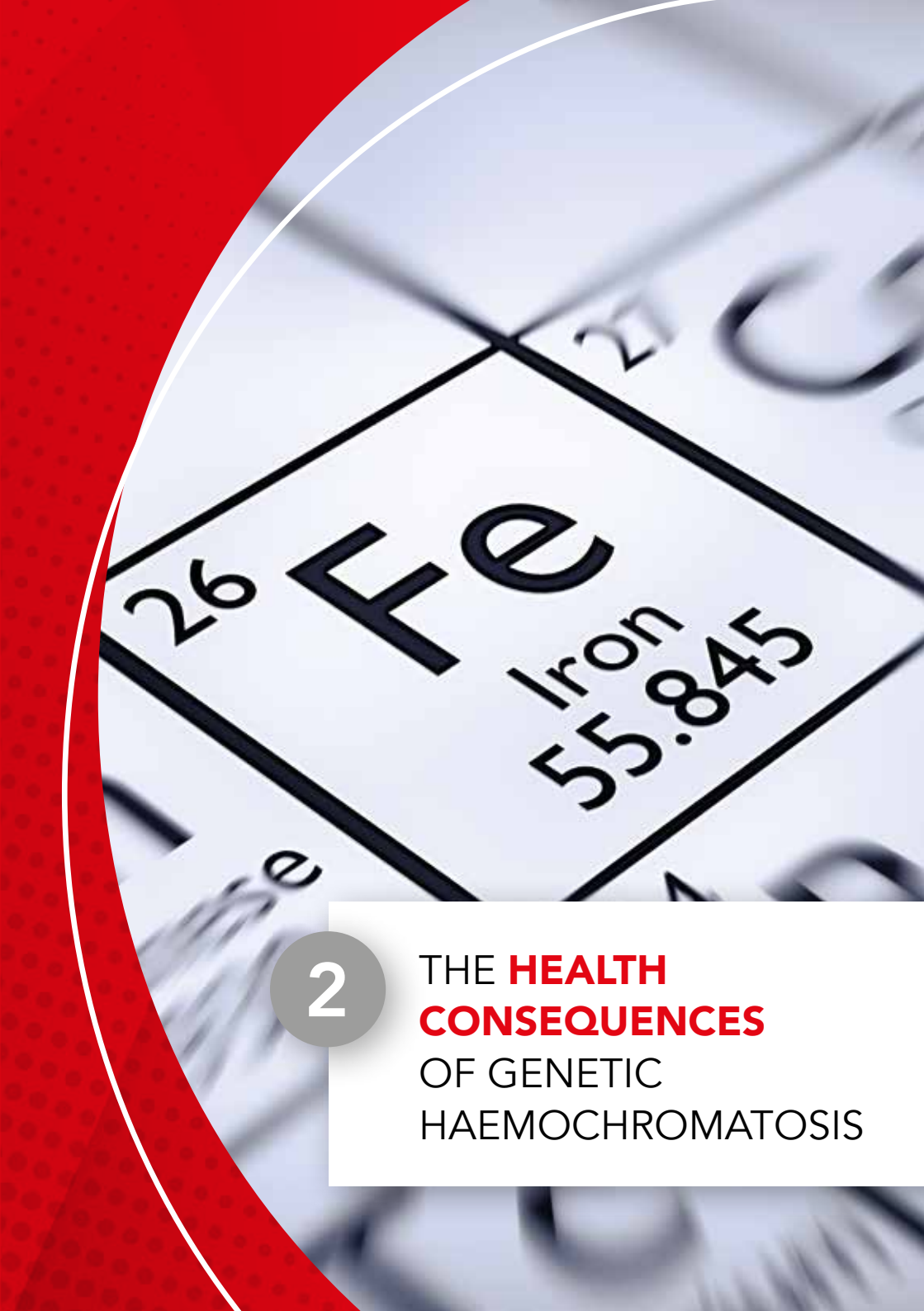
Figure 1:


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20°0'0"E
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50°0'0"E
60°0'0"E
60°0'0"N
50°0'0"N
40°0'0"N
10°0'0"W
0°0'0"
10°0'0"E
20°0'0"E
30°0'0"E
Weighted C282Y Allele Frequency (%)
High : 9.90
Mean : 4.27
Low : 0

1.10 A presentation by Melzer & Atkins to the All-Party Parliamentary Group on Genetic Haemochromatosis in Autumn 2019[10] 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. 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.

All Diagnoses	Men: Excess Number Diagnosed	Woman: Excess Number Diagnosed
Haemochromatosis	20,000	10,500
Any Liver Disease	3,350	470
Liver Cancer	989	No excess
Arthritis	6,500	3,063
Hip replacement	3,836	1,926
Diabetes	2,580	552

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.

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.

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[11] 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

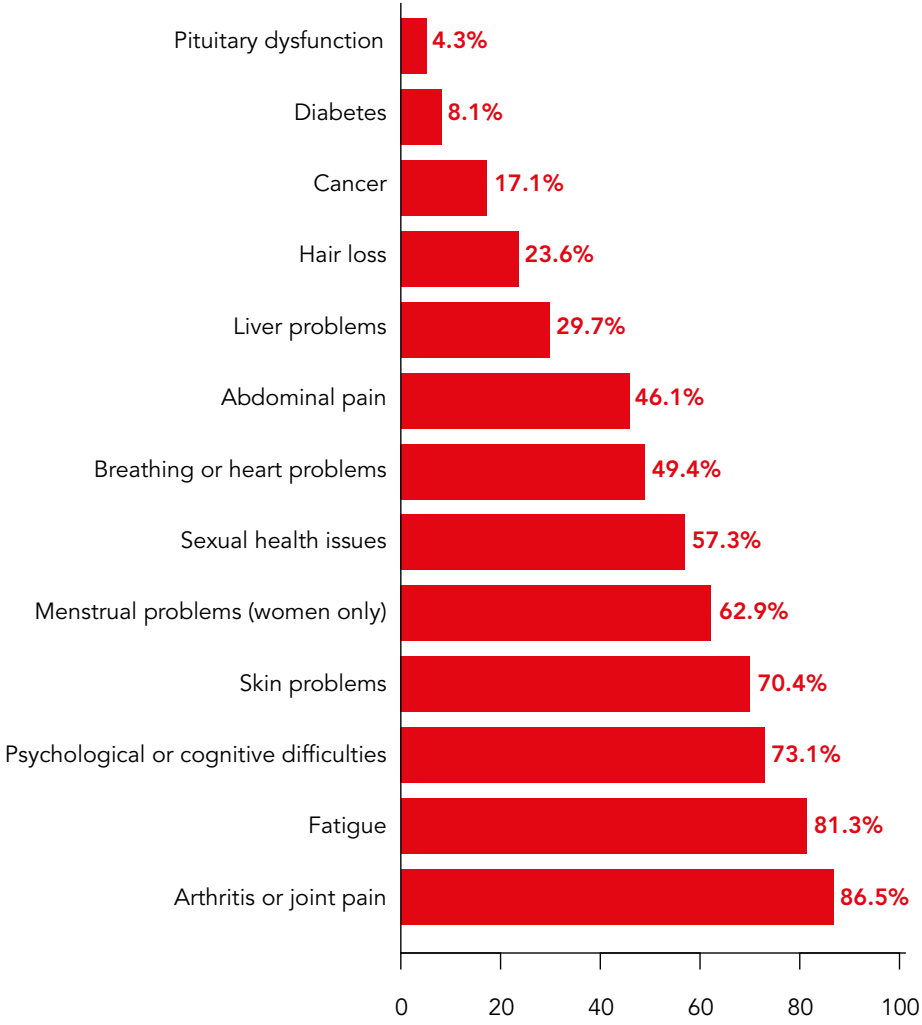
2.7 The study illustrates the wide range of ill-health experienced by people with GH, including heart problems, liver disease, cancers, diabetes and skin problems. Many of these conditions (e.g. fatigue) are non-specific and difficult to assess and triage in the initial stages. Screening would provide a definitive assessment of patients' genetic susceptibility to GH, as a cause of related ill-health. See figure 2.

2.8 Earlier studies including Niederau at al, 1996[12], Niederau et al, 1985[13], Adams et al, 1991[14] 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[15], Connell et al, 2011[16], McDonnell et al 1996[17] and Adams et al 1996[18] 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.

Figure 2:

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



2.10 A very recent study[19] 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:

- Liver disease
- Cancers, including liver cancer
- Diabetes
- Arthritis and severe joint pain
- Chronic fatigue
- Heart disease including cardiomyopathy
- Endocrine/pituitary failure
- Sexual health dysfunction
- Mental health and memory issues



3 THE BENEFITS OF **EARLY DIAGNOSIS THROUGH SCREENING** – CURRENT DIAGNOSTIC AND CARE PATHWAYS

3. The benefits of **early diagnosis through screening** – current diagnostic and care pathways

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[20]).

3.2 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 figure 3.

3.3 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. See figure 4.

3.4 Unfortunately, most patients presenting to primary care with raised serum ferritin[21] levels are not screened for GH (Ogilvie et al, 2010[22]).

3.5 Ogilvie et al (2015[23]) re-iterated the challenges experienced by primary care in diagnosing GH in patients through serum ferritin and transferrin saturation[24] 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[25]. 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[26]), while clinically significant GH predominates in males. Consequently, we advocate a genetic screening-led approach to ensure health equality between the genders.

Figure 3:

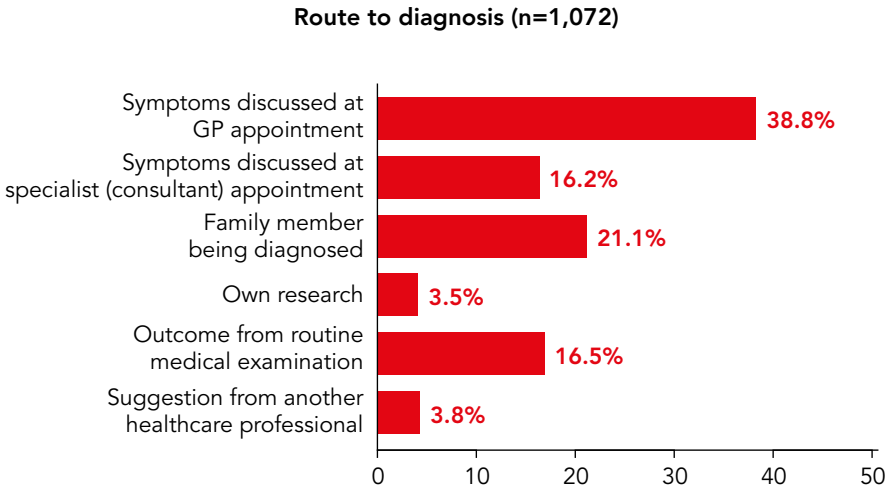
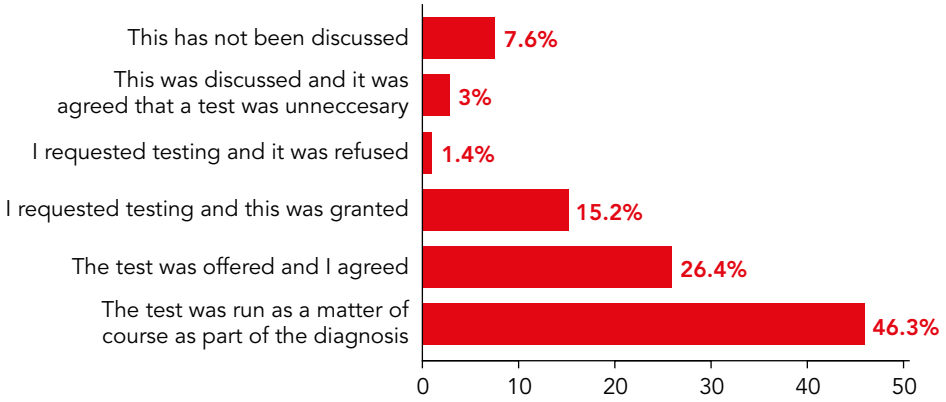
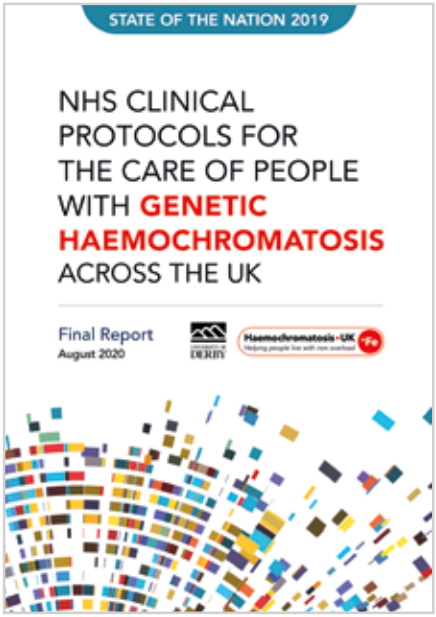


Figure 4:



3.6 Haemochromatosis UK published its State of the Nation report (Mortimer, McClements) in August 2020[27]. 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.





4 UK NSC **METHODOLOGY AND** SELECTION OF **EVIDENCE**

4. UK NSC **methodology and** selection of **evidence**

In Autumn 2020, the UK National Screening Committee (UK NSC) launched a public consultation process on their recommendation to **not** screen adults for genetic haemochromatosis.

They explained that screening is not recommended for three key reasons:

- although a faulty HFE gene is known to cause iron to build up, this does not happen to every person with a faulty gene
- screening would identify people who may never experience symptoms
- there was no evidence to suggest that a screening programme would be effective

The full consultation papers and further details may be found online:
https://legacyscreening.phe.org.uk/haemochromatosis

Our charity Haemochromatosis UK, supported by the Genetic Alliance, disagree with the UK NSC's recommendations to not screen adults for genetic haemochromatosis.

We provided a detailed a thoroughly evidenced response to the consultation paper, extracts of which are set out below.

4.1 The UK NSC consultation document sets out a summary of publications included and excluded as part of their 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.

4.1.1 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.

4.1.2 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.

4.1.3 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.

4.1.4 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.

4.1.5 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.

4.1.6 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."*

4.1.7 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.

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

4.3 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.

4.4 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: **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.



5 IN **CONCLUSION**

5. In conclusion

5.1 Our response to the UK NSC consultation demonstrates that there is recent, reliable evidence to show that:

5.1.1 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.

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

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

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

5.3 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[28].

5.4 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 (e.g. Scotland or Northern Ireland) to enable the effects of such a programme to be studied in depth.

5.5 We advocate trialling population-based genetic screening within a nation or region of the UK for all adults male and female, per paragraph 5.4 above. This would enable collation of data on the effectiveness and costs/benefits of such a programme before it is rolled out more widely.

5.6 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.

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

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

OR

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

OR

5.7.3 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.

5.8 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.

5.9 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.



6 REFERENCES

6. References

[i] *"Hereditary Haemochromatosis – Estimates of Excess Disease In The UK"* (July 2019) – Professor David Melzer & the Exeter Haemochromatosis research group, University of Exeter

[ii] HUK Freedom of Information Study (2016) – Neil McClements

[iii] *"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 available from **https://jamanetwork.com/journals/jama/article-abstract/2773273**

[iv] *"Hemochromatosis mutations, brain iron imaging and dementia in the UK Biobank cohort"*, by Janice L Atkins, Luke C Pilling, Christine J Heales, Sharon Savage, Chia-Ling Kuo, George A Kuchel, David C Steffens and David Melzer, and is published in the Journal of Alzheimer's Disease. Available from: **https://content.iospress.com/articles/journal-of-alzheimers-disease/jad201080**

[v] *"Hereditary Haemochromatosis – Estimates of Excess Disease In The UK"* (July 2019) – Professor David Melzer & the Exeter Haemochromatosis research group, University of Exeter

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

[2]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

[3]See **www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/adhocs/008781populationdenominatorsbybroadethnicgroupandforwhitebritishlocalauthoritiesinenglandandwales2011to2017**

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

[5]See **www.nisra.gov.uk/sites/nisra.gov.uk/files/publications/MYE19-Bulletin.pdf**

[6]See **https://onlinelibrary.wiley.com/doi/full/10.1002/ajpa.22937#ajpa22937-bib-0124**

[7]See **www.nrscotland.gov.uk/statistics-and-data/statistics/stats-at-a-glance/registrar-generals-annual-review/2019**

[8]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.

[9]See **https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/nationallevelpopulationestimates-by-year-age-ukcountry**

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

[11]See **www.haemochromatosis.org.uk/the-impact-of-iron-overload**

[12]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.

[13]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.

[14]See Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary haemochromatosis. Gastroenterology. 1991;101(2): 368-72.

[15]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.

[16]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.

[17]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.

[18]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.

[19]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

[20]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.

[21]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.

[22]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**

[23]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**

[24]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.

[25]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.

[26]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 **www.nejm.org/doi/full/10.1056/nejmoa041534**

[27]See **www.haemochromatosis.org.uk/state-of-the-nation-2020**

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

Notes

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Author : Neil McClements,
Chief Executive, Haemochromatosis UK
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We welcome comments and feedback
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We work to support anyone affected by genetic haemochromatosis.

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