LIVING WITH THE IMPACT OF IRON OVERLOAD

Report from a large survey of people with haemochromatosis

Authors: Dr. Kimberley J Smith[a], Professor Chris Fife-Schaw[a], Dr. Bridget Dibb[a] and Dr. William Griffiths[b]

University of Surrey[a], School of Psychology, Guildford, UK
Addenbrooke's Hospital[b], Cambridge Liver Unit, Cambridge, UK

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INTRODUCTION

The large response to our 2017 patient survey, 2,000 in all, speaks to the need for people living with haemochromatosis to have a voice. Whilst our knowledge of the biological mechanisms at work in haemochromatosis continues to develop, little research is published on the impact of the condition on people's lives.

This report is the result of an independent expert analysis of the 2017 survey responses. It highlights the wide array of symptoms experienced by people with haemochromatosis. You will read that most of the people who responded reported debilitating symptoms including fatigue and pain, particularly those for whom diagnosis was delayed. Yet, treatment is relatively simple. The report provides support for its effectiveness in reducing some of the symptoms although for some patients, treatment is a difficult and unpleasant experience.

In the report you will read about haemochromatosis patients' experiences of healthcare. Whilst most patients are satisfied with the information and support provided by medical specialists, this is not the case with regard to their GPs. Greater awareness of recent guidelines for screening for haemochromatosis is recommended by the report authors, and we strongly support implementation of these guidelines in order to avoid delays in treatment and prevent irreversible tissue damage.

At HUK, our aims are to support those with haemochromatosis and those at risk, to educate patients, families, the wider public and healthcare community about the condition in order to raise awareness of haemochromatosis, and to stimulate research into the condition and its impact on people's lives. We hope that this report will contribute to all of these aims and, in particular, that it will encourage earlier diagnosis and stimulate much needed new research.



Corrina Towers
Chair of Trustees
Haemochromatosis UK



David Head
Chief Executive
Haemochromatosis UK



FOREWORD

Iron: the most common element found on our Earth, consumed by the ancient Greek warriors in readiness for battle, and widely promoted today as a remarkable remedy, able to deliver strength and wellbeing.

Much is known about the effects of iron deficiency. By contrast, however, there is little awareness of the significant risks posed by iron overload (too much iron) to some 250,000 UK residents. How can this be? Haemochromatosis is the answer.

Haemochromatosis is one of the most frequent genetic disorders found in North European populations. Yet it is a condition that only too easily escapes diagnosis. It has a most insidious onset and lacks any easily identifiable symptoms. In the UK approximately 10% of our European and particularly Celtic populations (i.e. about 5,000,000) are genetic carriers with one mutated copy of the haemochromatosis gene (*HFE*). Approximately 0.5% (i.e. about 250,000) have 2 mutated copies of the *HFE* gene and are at risk of iron overload and iron related diseases. Yet for every one patient diagnosed and at risk, there are some 8 to 10 who are undiagnosed and unaware of their risk. A risk that is far greater for men than for women.

Haemochromatosis UK gives voice to those patients who have been diagnosed, and campaigns vigorously on behalf of the vast but silent majority of undiagnosed patients. We come to the House of Commons today to seek help in promoting awareness (amongst the population and within primary care services), diagnosis, support and treatment for haemochromatosis. It is without doubt 'the most common condition you have never heard of.'



Dr Edward (Ted) Fitzsimons
Consultant Haematologist and Honorary Associate Clinical Professor,
University of Glasgow



We are stardust: iron scattered by supernovae explosion. Crab Nebula image courtesy of NASA.



Highlighted findings and recommendations

- Nearly 2,000 people with haemochromatosis from around the world took part in a survey on their perception of symptoms, research priorities, information about treatment and their perception of support
- The research shows that many people with haemochromatosis report experiencing issues with arthritis or joint pain and fatigue
- When we grouped people according to their experience of symptoms, we found three distinct groups:
  Group 1 (48.7%): Who report persistent fatigue and joint pain
  Group 2 (36.6%): Who report no or low symptoms
  Group 3 (14.7%): Who report many persistent and painful symptoms
- Respondents rated their top five research priorities as:
  1st: Arthritis or joint pain
  2nd: Liver problems
  3rd: Fatigue
  4th: Breathing or heart problems
  5th: Psychological or cognitive difficulties
- Most people who have undergone or are undergoing treatment report that de-ironing helps improve their experience of many haemochromatosis-related symptoms
- Many people with haemochromatosis in the UK receive tests that are in line with the clinical recommendations of Fitzsimons et al.[1] However, our analysis indicates that there are still a relatively high percentage of people who report not getting the tests that they need (e.g. 40% do not receive routine transferrin saturation testing)
- Within the UK, most people rated the support and information they receive from their consultant and venesection staff as excellent or very good. However, people rated the knowledge of their GP as only adequate
- Within the UK, people indicated that their main sources of support for their haemochromatosis were Haemochromatosis UK, the internet and their consultant
- As a result of carrying out this report, we have been able to develop a series of recommendations:

  Recommendation 1: We need to improve awareness of haemochromatosis and current clinical recommendations
  Recommendation 2: Research is needed to better characterise the symptoms associated with haemochromatosis
  Recommendation 3: More research is needed to better understand the impact of haemochromatosis-related symptoms on people living with this condition
  Recommendation 4: We need to better understand why differences in treatment and monitoring exist



Report background

In 2017, Haemochromatosis UK (HUK) developed and promoted an online survey for people with haemochromatosis. Nearly 2,000 people from around the world, with haemochromatosis or the genetic markers for the condition, answered questions on a wide range of topics including demographics, perception of symptoms, experience at diagnosis, information about treatment and perception of support.

HUK had undertaken a similar but less extensive survey in 2005,[2] and considered that an update of the previous survey was important for a number of reasons:

- Haemochromatosis is now perceived as a chronic rather than a terminal condition,[1] and the symptoms that people with haemochromatosis experience may have changed
- The diagnosis and treatment of haemochromatosis has changed over the last 10 years,[1] so it is important to re-examine people's experiences of treatment and diagnosis within the UK
- The results from the survey could be used to raise awareness of the problems that people living with haemochromatosis experience
- The results from the survey could help highlight areas where future research can be developed to help improve the lives of people living with this condition

We begin by describing haemochromatosis; what the condition is, what the commonly associated symptoms are and how people are diagnosed and treated. In the section that follows, we describe how the 2017 survey was undertaken, detailing its strengths and limitations. We then describe the results from the survey, again focusing on symptoms, diagnosis and treatment. Following that, we place the results of the report into a wider research and clinical context. We end the report with a summary of our research and clinical recommendations.



Haemochromatosis

Haemochromatosis is a long-term condition where the body absorbs too much iron.[1, 3, 4] This iron is then deposited in different parts of the body such as the joints, skin, heart, liver, pancreas and other endocrine organs.[3] This can lead to different symptoms including fatigue, joint pain, sexual dysfunction, diabetes, heart disease, liver disease and associated cancer amongst others.[2, 4-10]

Haemochromatosis is the most commonly inherited genetic condition in White European populations,[3, 6] particularly people of Celtic and Northern European descent.[11] Because it is a genetic condition, it is often called 'genetic haemochromatosis' (GH). The main gene linked with the development of GH is the *High Iron FE (HFE)* gene, and there are particular mutations of this gene that can lead to GH (see Table 1). GH is regarded as a recessive genetic condition, meaning that we need to inherit a gene abnormality from both parents to have the potential of developing the condition. However, some patients who inherit only one abnormal *HFE* gene may go on to load iron,[12] so there are likely to be other factors at play.

HFE is involved with iron absorption, so when there is a problem with this gene, the body can be fooled into thinking it is short of iron.[4] This means that the

Table 1: Mutations in *HFE* gene most commonly associated with iron overload

HFE abnormality	Description
C282Y HOMOZYGOUS	Two copies of the major mutation associated with the *HFE* gene (C282Y/C282Y). Both parents are carriers of the C282Y mutation. Siblings will have a 1 in 4 chance of also being affected by this mutation. The abnormality most commonly observed in people diagnosed with GH. C282Y homozygotes is by far the most common cause of *HFE* Haemochromatosis and iron overload.
H63D HOMOZYGOUS	Two copies of the minor mutation associated with the *HFE* gene (H63D/H63D). Both parents were carriers of the H63D mutation.
C282Y/H63D HETEROZYGOUS	One copy of the *HFE* major mutation (C282Y) and one copy of the minor mutation (H63D). One parent was a carrier of the C282Y mutation and one parent was a carrier of the H63D mutation. Some studies refer to this genotype as 'compound heterozygous'. C282Y/H63D compound heterozygotes are found more commonly than C282Y homozygotes, but are much less likely to develop iron overload.

Table 2: Rare causes of iron overload

These abnormalities cause iron overload through different mechanisms to those linked with the *HFE* gene. They can be broadly grouped as:
Type 2 (A and B) haemochromatosis is linked to mutations in the hemojuvelin and hepcidin genes.
Type 3 haemochromatosis is related to the transferrin receptor 2 mutation.
Type 4 haemochromatosis is linked to ferroportin disease.

Tables based on Bardou-Jacquet et al. Non-HFE haemochromatosis: Pathophysiological and diagnostic aspects. 2014 and Harrison and Adams. Haemochromatosis: Common Genes; uncommon illness? 2002. (13, 14.)

body continues to absorb iron when it is not needed. When this occurs, the body can store potentially toxic levels of iron, leading to a state that is commonly called 'iron overload'.

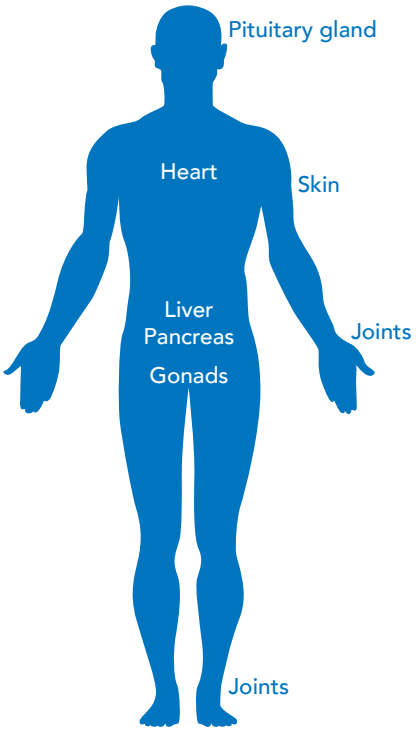
SYMPTOMS

Iron overload can occur in diverse parts of the body. It is linked with the development of a range of unpleasant and, at their most extreme, life threatening symptoms.[15, 16] These symptoms range from fatigue and joint pain, to diabetes, heart disease, liver disease and associated cancer[5, 6, 17] (see Figure 1). Alongside the physical symptoms that can be linked to iron overload, there is also some evidence that people with GH can also experience psychological problems such as depression.[8]

A number of studies have examined symptoms associated with this condition (see Appendix I). Generally, these studies have found that the most commonly occurring symptoms associated with haemochromatosis are joint pain, fatigue, sexual dysfunction, impaired mood and skin discolouration.[2, 5-8, 17-20] Joint pain often occurs in the hands and is known as 'iron fist', which can cause the fingers to close and limit function. Pain associated with iron fist occurs in the knuckle and first joint of the first two fingers.[21]

Those studies where participants have been compared to the general population found that people with GH were more likely to experience joint pain, arthritis, osteoporosis and knee or hip replacements than people who did not have GH.[20] Additional

Figure 1: Symptoms linked with GH



Associated symptoms

- Arthritis or joint pain: particularly in the hands and feet
- Fatigue
- Heart problems
- Mental health issues: particularly mood and memory
- Sexual problems
- Abdominal pain
- Hair loss
- Liver disorders: particularly enlargement, cirrhosis and liver cancer
- Diabetes
- Pituitary dysfunction

In women

- Menstrual problems: particularly irregular or missing periods
- Early menopause

In men

- Impotence

Information taken from Haemochromatosis UK. Genetic Haemochromatosis: An Iron Overload Disorder. 2016. (80.)

research also found that GH-related symptoms occurred at younger ages in people with GH. [8]

While work that examines GH-related symptoms is plentiful, there is less examining the impact of these symptoms on people with GH. When asked about their experience of symptoms, people living with GH sometimes talk about the negative impact that symptoms can have on their psychological wellbeing and quality of life. [22, 23] For instance, researchers have found that fatigue and arthritis significantly impact the quality of life for people with GH. [22, 24] Furthermore, when asked about the impact of GH-related symptoms on their life, those with severe symptoms were more likely to experience marital difficulties, job loss and difficulty doing day-to-day tasks, than people who had less severe symptoms. [8]

DIAGNOSIS

We know that if GH is diagnosed early, and treatment to reduce the amount of iron in the blood is implemented before serious complications develop, people living with haemochromatosis can expect to have a normal life expectancy. [25] However, delayed diagnosis without treatment for iron overload can result in organ damage, leading to a reduced life expectancy. [3]

Despite this, many people with GH are initially misdiagnosed, with some people reporting a delay in correct diagnosis of up to 10 years. [8, 20] Delayed diagnosis is common as the symptoms associated with haemochromatosis are varied (see Figure 1) and shared with many other conditions. This may make it more difficult to identify GH. [3]

For example, in their survey McDonnell et al. [8] found that prior to their diagnosis with GH, many people received a range of differential diagnoses including arthritis, liver disease, gastric disorders, hormonal issues or psychiatric illness.

Given these issues it may be difficult for clinicians to know when people should be screened for GH. Sood et al. [26] have suggested that when patients present with fatigue, joint pain and abdominal complaints (especially if erectile dysfunction and heart failure are issues), it is important to screen for GH.

If GH is suspected, it is important that clinical tests are undertaken to confirm if there is excess iron in the body. These tests are relatively simple and the recent 2018 guidelines from the British Society of Haematology provide clear information about how to test for and recognise GH. [1] To test for iron overload, clinicians use two important biomarkers: transferrin saturation (TS) and serum ferritin (SF).

The liver makes a protein called transferrin. This protein in the blood binds to the iron absorbed from food and moves it around the body. Transferrin saturation (TS) represents the percentage of this protein that is saturated with iron. Normally about one-third of the transferrin is saturated with iron, leaving two-thirds as a reserve for binding extra iron should it be required. In cases of GH, a high level of saturation means that additional iron circulates without being bound to transferrin which can result in toxic levels of iron in the body.

Ferritin is the major iron storage protein in the body. Raised levels of this protein in blood serum often means that more iron is being stored in the body than is needed.

Table 3 shows the clinical thresholds from the British Society for Haematology, [1] which can be used to identify people with possible GH.

Table 3: Clinical thresholds for TS and SF

Transferrin saturation thresholds: Indicates how much iron is bound by the transferrin protein	
Clinical threshold for possible haemochromatosis in men	> 50%
Clinical threshold for possible haemochromatosis in women	> 40%
Serum ferritin thresholds: Indicates how much iron is stored in body tissue	
Clinical threshold for possible haemochromatosis in men	> 300µg/l
Clinical threshold for possible haemochromatosis in women	> 200µg/l

Thresholds taken from Fitzsimons et al. Diagnosis and therapy of genetic haemochromatosis. British Journal of Haematology. 2018. (1)

Once iron overload has been established, and particularly if people are of Northern European ancestry, they should go through genetic testing for hereditary haemochromatosis. If a patient is diagnosed with GH, their immediate family should also undergo screening (i.e. full blood count, liver function tests, SF levels and TS testing), unless they are identified as a C282Y/H63D compound heterozygote. [1]

TREATMENT

The usual first line treatment for the iron overload associated with GH is venesection, which involves periodically removing 200-500ml of blood from the body. [1, 3, 27] This decreases the amount of iron in the body

as, after the blood has been removed, the remaining iron will be used to make new red blood cells. [1, 3, 27] This process is referred to as 'de-ironing'.

Typically, in the first active phase of treatment, it is recommended that venesection be performed weekly until the amount of iron stored in the body is decreased (see Figure 2). Patients are then moved into the maintenance phase of treatment, where the goal is to maintain the levels of SF and TS reached through the initial de-ironing. Once in maintenance, if the treating clinician thinks it is appropriate, patients can donate blood at a blood donation centre for the purposes of maintenance venesection. [1]

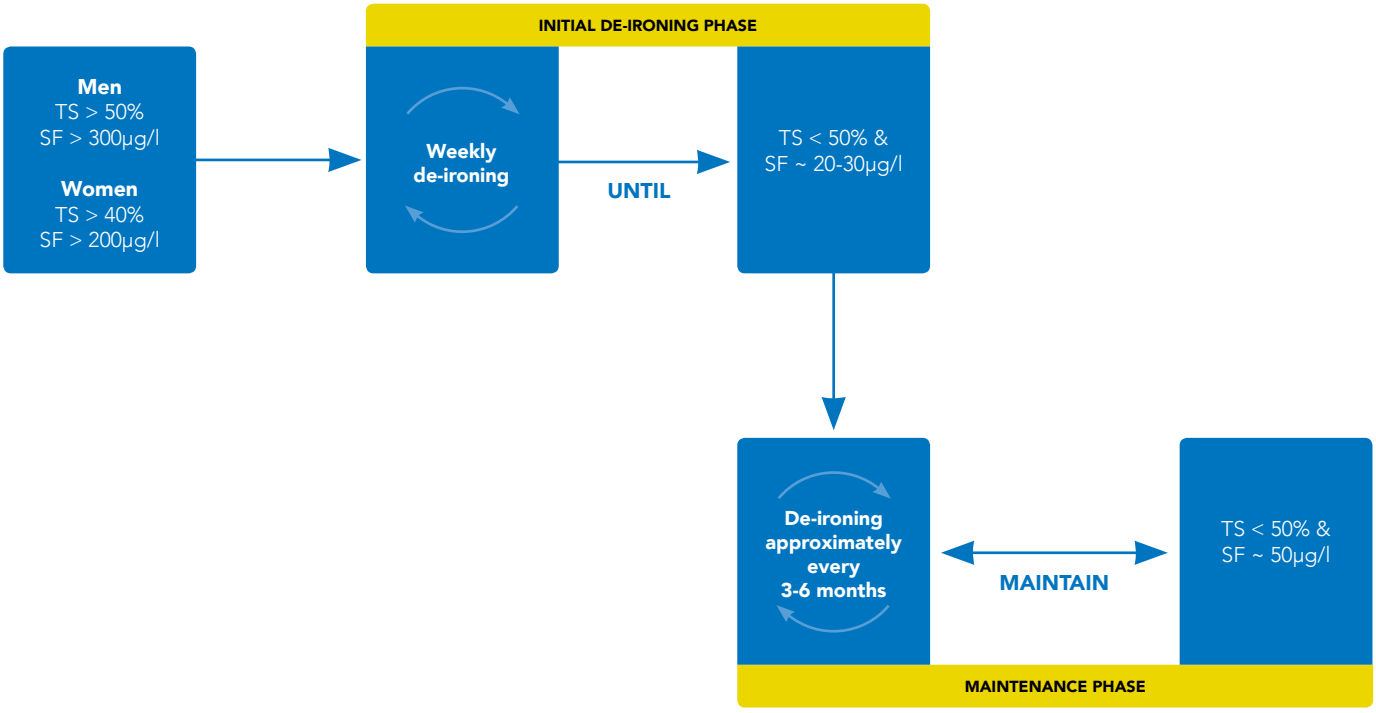
People are treated in a variety of locations including day centres and hospitals. [8] Blood donation clinics do not provide a service as therapy for GH and they use the blood taken as usual. It is likely that there is also variation in how patients experience treatment for GH. In 2017, Haemochromatosis UK requested venesection protocols from 89 NHS trusts through the Freedom of Information initiative. Only 35 of the 66 trusts who treated GH patients had clear protocols for conducting venesection. †

Alongside venesection, there are recommendations that if levels of SF exceed 1000µg/l and/or liver function tests are abnormal, patients should be referred to a liver specialist. [1] Additional testing may then include liver imaging and fibrosis assessment, typically via a Fibroscan® and/or biopsy. Imaging may include an ultrasound or MRI, the latter enabling iron quantification if the correct software is available (Ferriscan® uses this method). The Fibroscan® test uses shear wave elastography to assess liver stiffness. Stiffness correlates with fibrosis (scarring) which, at severe levels, equates to cirrhosis.

For patients who find it hard to give blood, for example because of difficulties in finding suitable veins or circulatory problems, a drug therapy called chelation may be an option. This involves drugs such as parenteral desferrioxamine, which binds to the iron in the body and excretes it in the urine. While this can be successful, it has side effects including muscle cramps, dizziness, visual and auditory impairments and racing heart beats among others. [3] Research continues into alternative forms of chelation, such as the oral iron chelator, deferasirox, but de-ironing through venesection remains the preferred and most commonly used treatment for most people with GH. [3]

A systematic review published in 2017 summarised the results of three studies that looked at treatment in GH. It found no evidence that de-ironing improved

Figure 2: Recommended treatment for iron overload associated with haemochromatosis based on Fitzsimons et al. (1)



†The information regarding NHS trusts reporting venesection protocols is available on request from haemochromatosis.org.uk/venesection-protocols-2018



symptoms or the wellbeing of participants over the short-term.[28] However, work from large scale patient surveys indicates that people with GH perceive improvement in some symptoms as a result of treatment.[2, 8] For instance, in the McDonnell survey,[8] 86% of respondents felt that venesection improved their experience of symptoms, although this often took a long time to be realised (an average of 39 weeks).

Despite improvements in symptoms, venesection can be an unpleasant experience.[22, 29] Repeated venesection can be both anxiety provoking and uncomfortable,[8, 22] and the lack of experience and skill of some staff who perform venesection can sometimes make the experience more difficult.[29] A patient survey in 2011 asked 164 people with GH about their experience of treatment. The majority reported that they had experienced issues with needle insertion. They had also experienced post-venesection side-effects such as tiredness or fainting.[7] However, while the process of venesection can be unpleasant, there is agreement from both patient-led interviews and surveys, that the benefits of symptom reduction outweigh the side-effects of this sometimes unpleasant treatment.[7, 8, 22, 29]



The 2017 Survey

Participants were recruited using convenience sampling. The survey was hosted online through the Haemochromatosis UK website. Responses were collected between June and October 2017. The survey was promoted through social media, the Haemochromatosis UK magazine, at Haemochromatosis UK events, support groups and venesection clinics.[†]

METHOD

In order to complete the survey, participants had to respond positively to a screening question about either (a) having a diagnosis of haemochromatosis or (b) having the genetic mutation for haemochromatosis. The survey included questions about people's characteristics, symptoms and their impact, experiences of diagnosis, treatment and support.

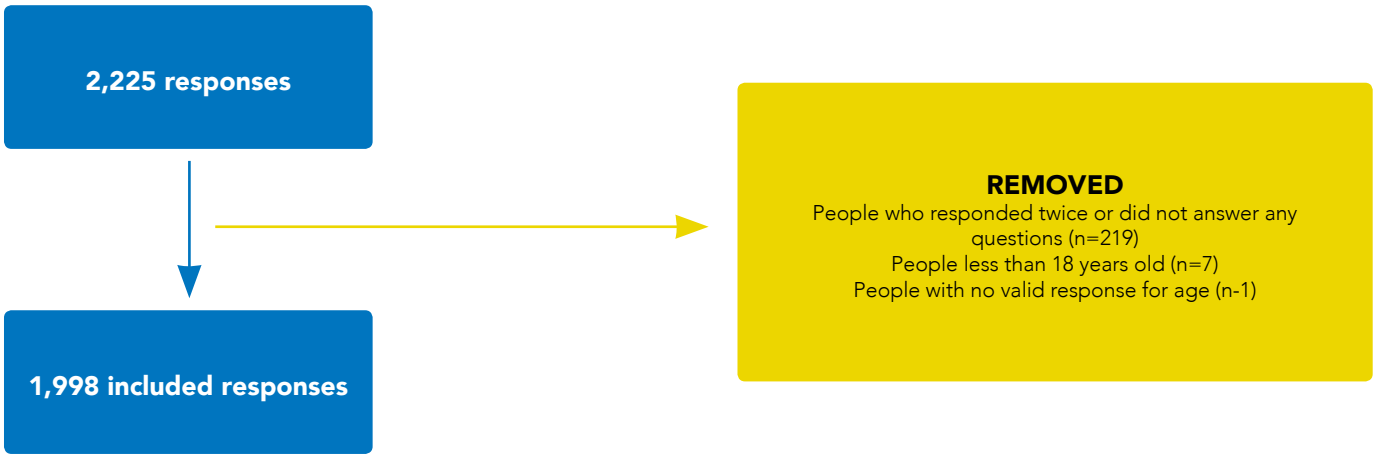
The survey was in English and comprised 136 questions developed by HUK[†]. We provide more information about the analysis in Appendix II. There were 2,225 initial responses to the survey. After the removal of some participants (for reasons outlined in Figure 3), 1,998 survey respondents were included in the analysis.

RESULTS

We begin the results section by reporting on the characteristics of the people who responded to the survey (the 'respondents').

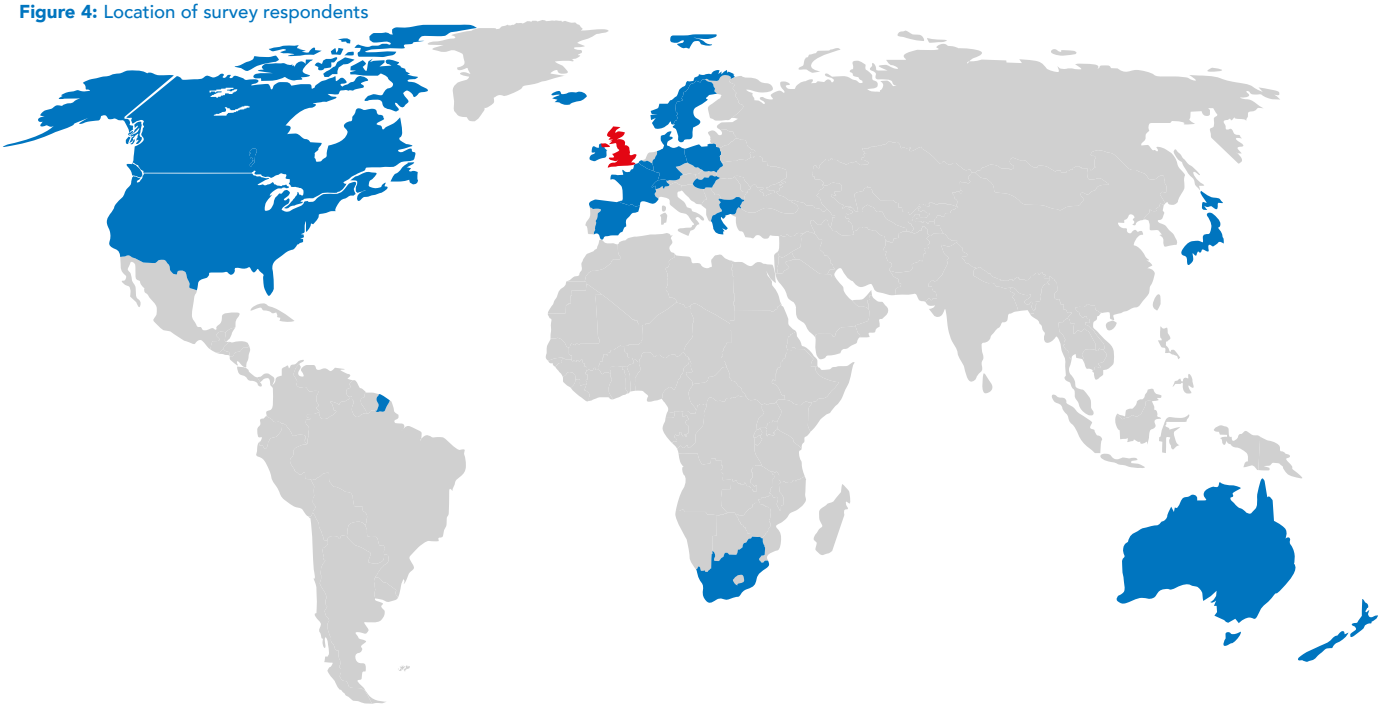
We continue by examining the respondents' experience of symptoms, followed by their experience of diagnosis and ending with their experience of treatment.

Figure 3: Study flowchart



[†]The questionnaire is available on request from haemochromatosis.org.uk/2017-survey

Figure 4: Location of survey respondents



Red indicates where the majority of survey respondents were living at the time of the survey. Blue indicates the other countries in which people responded.

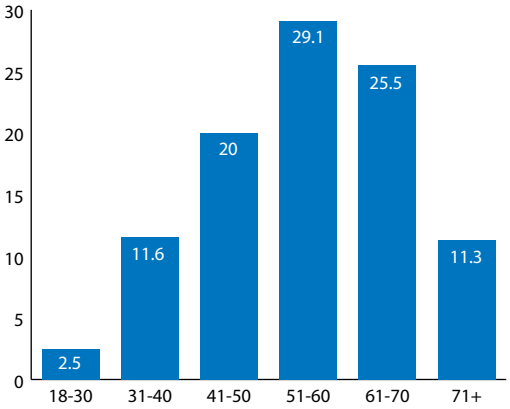
CHARACTERISTICS OF SURVEY RESPONDENTS

Firstly, we looked at the characteristics of people who responded to the survey in terms of their location, ethnicity, age range and genetic mutation.

Those who completed the survey were based mainly in the UK (70.7%), North America (11.1%) and Ireland (7.7%). The remainder were from Australasia (4.8%), mainland Europe (2.1%), Africa (0.6%), Asia (0.2%) or Central/South America (0.1%). A further 2.7% specified only that they were 'non-UK' (see Figure 4).

The average age of respondents was 55.4, ranging from a minimum age of 18 to a maximum age of 91 (see Figure 5).

Figure 5: Range of survey respondent ages (n=1,998)

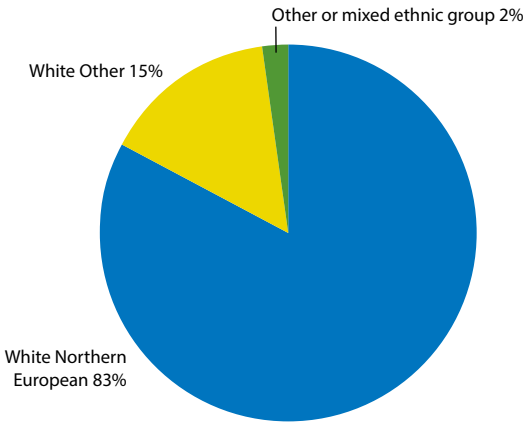


Numbers represent percentages and ranges refer to the age range of respondents.

In total 57.7% (n=1,148) of the sample were female.

Of those who answered the question on ethnicity, the vast majority reported being White Northern European or White Other (see Figure 6).

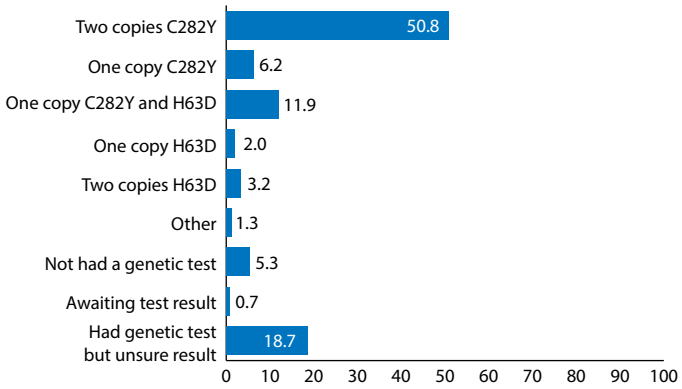
Figure 6: Ethnicity of survey respondents (n=1,896)



Numbers represent percentages.

Of those who answered the question about which genetic mutation was associated with their GH diagnosis, nearly a quarter (24.7%) reported either not knowing the results of their tests or having never received a test (see Figure 7). Of those who did know their mutation, the most frequently reported was two copies of C282Y (i.e. being C282Y homozygous), with the second most frequently reported mutation being the C282Y/H63D compound heterozygote.

Figure 7: Genetic mutation information (n=1,881)



Numbers refer to percentages.

Finally, of the 1,421 respondents who gave their date of diagnosis:

- 12.1% had been diagnosed for less than a year
- 53.8% had been diagnosed for 1-5 years
- 34.1% had been diagnosed for more than 5 years

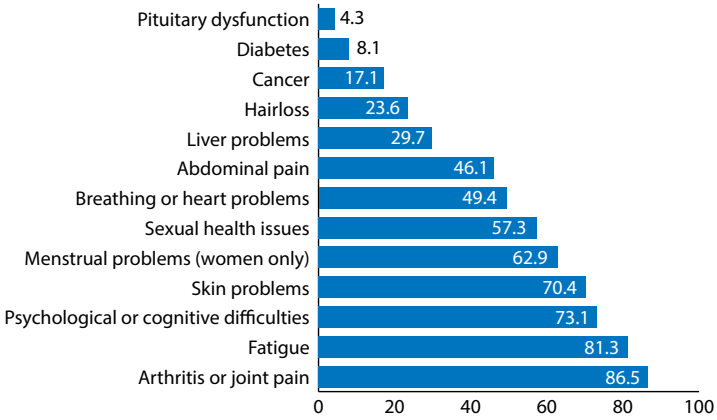
SYMPTOMS

In this section we investigate the respondents' experience of symptoms commonly associated with GH. We firstly examine whether people reported *ever* experiencing symptoms. We then present data on their *current* experience of symptoms, which includes a symptom grouping analysis.

Symptoms *ever* experienced

The most common symptoms that survey respondents reported having *ever* experienced were arthritis or joint pain, fatigue, psychological or cognitive difficulties, skin problems, menstrual problems and sexual health issues (see Figure 8).

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



Percentage of respondents that had ever experienced each symptom (the remaining percentage had reported not experiencing that symptom). For sexual health problems we did an additional analysis stratifying for gender and found that a similar proportion of men (57.6%) and women (57%) reported sexual health issues. We only included data for those survey respondents who had answered a minimum of 6 questions on symptoms (n=-1,689, 85% of total sample).

We then looked at the more detailed information collected for the most commonly experienced symptoms; arthritis or joint pain, psychological or cognitive difficulties, skin issues and sexual health issues. (Analysis of all symptoms is available in Appendix III.) The key findings from these additional analyses are summarised below:

- In those survey respondents who reported that they had *ever* experienced arthritis and/or joint pain, the most common locations were knuckles (69.3%), hip (56.8%) or hand/wrist (46.9%)
- The most commonly reported cognitive or psychological difficulties that survey respondents *ever* experienced were forgetfulness or 'brain fog' (60.44%) and depression (37.93%)



- The most commonly reported types of skin issues that survey respondents *ever* experienced were itchiness (45.31%), tanning or bronzing of the skin (27.93%) or blotchiness or rashes (24.33%)
- When asked about specific sexual health issues they had *ever* experienced, 58.4% of women reported that they had experienced a loss of libido, and 39.41% of men had experienced issues with impotence

Symptoms *currently* experienced

The survey also asked respondents about their *current experience of specific symptoms* which they rated on a 10-point scale according to painfulness and persistence. We categorised these symptoms as no/low (scored 0-2), persistent (scored 3-6) or painful and persistent (scored 7-10).

The most commonly reported symptoms that had a persistent or painful impact on people were arthritis or joint pain, fatigue, psychological and cognitive difficulties, sexual health issues or skin problems (see Figure 9, below). For example, almost a quarter reported having painful arthritis or joint pain, with a further 39% reporting persistent symptoms.

As a next step, we investigated patient characteristics that could impact on the experience of current symptoms. We re-examined the experience of symptoms, firstly by accounting for age, and secondly by accounting for current treatment (see Appendix IV). The findings from these analyses are summarised below:

Current symptoms: Experience in different age groups (Appendix IV: Table A)

We looked at the difference in current symptoms between the following age groups; 18-39, 40-59 and 60 or older. We found age groups differed in their current experience of arthritis or joint pain, fatigue, abdominal pain, psychological or cognitive difficulties, sexual health issues, menstrual problems, breathing or heart problems, liver problems and pituitary dysfunction.

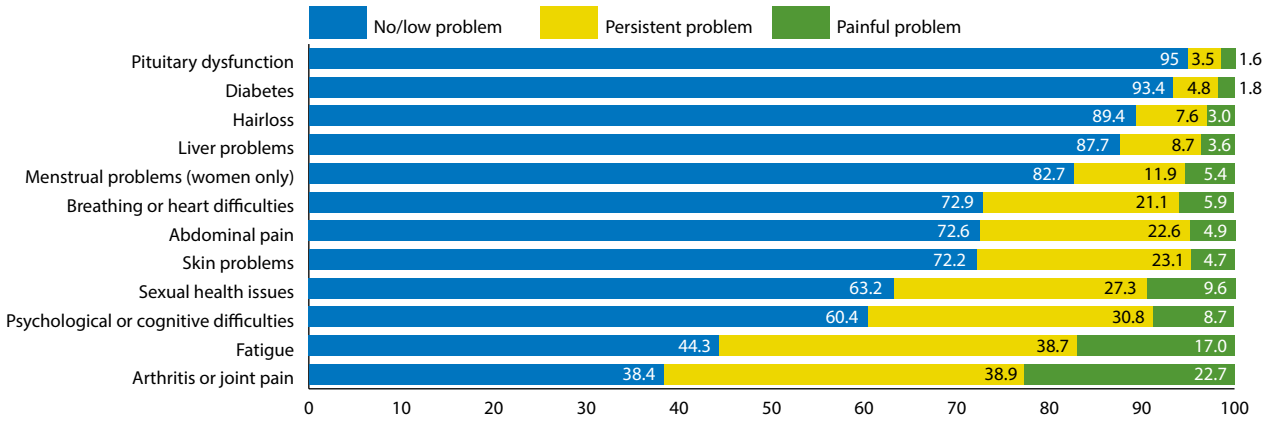
- People aged 40-59 and 60 or older were *more likely* than the youngest age group to report current issues with arthritis or joint pain
- People aged 60 or older were *less likely* than the younger age groups to report current issues with fatigue, abdominal pain, psychological or cognitive difficulties, breathing or heart difficulties or liver problems
- People aged 18-39 were *more likely* than older age groups to report current issues with sexual health problems, menstrual problems and pituitary dysfunction
- People aged 40-59 were *more likely* than other age groups to report current issues with breathing or heart difficulties

Current symptoms: Experience in different treatment groups (Appendix IV: Table B)

We also examined the difference in current symptoms between the following treatment groups; diagnosed but treatment not started, undergoing de-ironing, in maintenance, diagnosed with no treatment intended and ceased treatment. We found a difference between the treatment groups for the current experience of arthritis or joint pain, fatigue and psychological or cognitive difficulties.

- People who had been diagnosed but had no treatment intended were *less likely* than other groups to report current issues with arthritis or joint pain

Figure 9: Current experience of symptoms



Numbers refer to percentages. As for the 'ever experienced' analysis, we only included those survey respondents who answered a minimum of half of all questions. The number of included respondents for each question varied from 1,627 (for fatigue) to 1,014 (for pituitary dysfunction). As only women were included in the menstrual problems assessment, there were 724 respondents who answered that question.

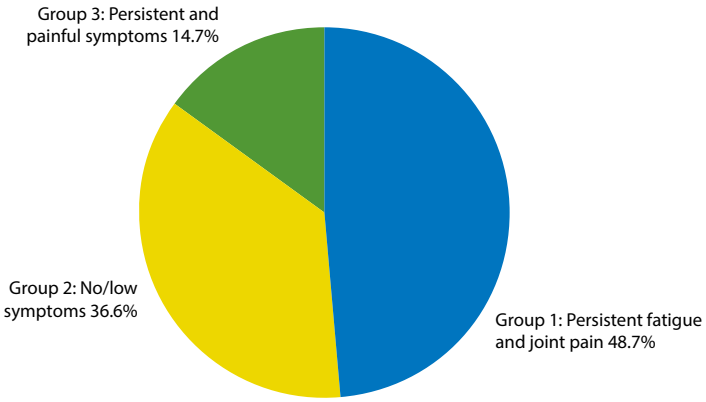
- People who were in maintenance were *less likely* than other treatment groups to report current problems with fatigue or psychological and cognitive difficulties
- People who were in the initial de-ironing phase were *more likely* to rate arthritis or joint pain as a current issue than other treatment groups
- People who had been diagnosed but were not yet treated were *more likely* than other groups to report current psychological and cognitive difficulties
- People who had stopped treatment were *more likely* to report current problems with arthritis or joint pain and fatigue than other groups

Grouping of symptoms

In order to see if we could group survey respondents according to their *current* experience of symptoms, we used a clustering analysis (Appendix V: Tables A and B). We were able to identify three different groups distinguished by the types and perceived severity of the symptoms respondents reported currently experiencing (see Figure 10).

When we then examined the three groups by their presentation of symptoms (Appendix V: Table B) we were able to identify three distinct groups (see Figure 10).

Figure 10: Overview of symptom groups and their associated characteristics (n=924)



Group 1 was the largest group we observed (48.7% of respondents). This group had a high probability of responding that they currently experienced persistent problems with fatigue and arthritis or joint pain, but they tended to respond that they had no/low current issues with the other symptoms asked about in the survey (see Appendix V: Table B). Because of this, we named this group 'Persistent fatigue and joint pain'.

Group 2 was the second largest group we observed (36.6% of respondents). This group had the highest probability of responding that they had no/low current issues with any of the symptoms that were asked about (see Appendix V: Table B). Therefore, this group was named 'No/low symptoms'.

Group 3 was the smallest group (14.7% of respondents). However, this group had the most severe symptom profile. They had a high probability of having currently persistent skin problems, heart or breathing problems, abdominal pain, psychological or cognitive difficulties and sexual health issues (see Appendix V: Table B). They also had a high probability of responding that their current experience of both fatigue and joint pain was painful (see Appendix V: Table B). Given the high probability of experiencing all of these symptoms, we named this group 'Persistent and painful symptoms'.

We then examined how the groups might differ in terms of characteristics including socio-demographic background, treatment and health (see Appendix V: Table C). The results of this comparative analysis are summarised in Figure 11. The main results from this analysis are summarised below:

- People in Groups 1 and 3 were *more likely* to be aged 40-59 and female and more likely to report that it took 5 years or more to be diagnosed after noticing symptoms.
- People in Group 2 were *more likely* to be in maintenance than the other two groups.
- People in Group 3 were *less likely* to be currently receiving treatment and more likely to have experienced cancer at some point in their lives.
- Groups 1 and 3 were *more likely* to have experienced pituitary dysfunction at some point.

Figure 11: Summary overview of differences between symptom groups (n=924)

Group 1: Persistent fatigue and joint pain	• 47.9% aged 40-59 • 60% female • 14% reported 5 or more years between noticing symptoms to being diagnosed • 60.8% undergoing active de-ironing • 24.2% in maintenance
Group 2: No/low symptoms	• 40.6% aged 40-59 • 45.5% female • 5.9% reported 5 or more years between noticing symptoms to being diagnosed • 46.8% undergoing active de-ironing • 41.8% in maintenance
Group 3: Persistent and painful symptoms	• 63.6% aged 40-59 • 55.3% female • 25.7% reported 5 or more years between noticing symptoms to being diagnosed • 49.5% undergoing active de-ironing • 27.5% in maintenance

Is de-ironing effective?

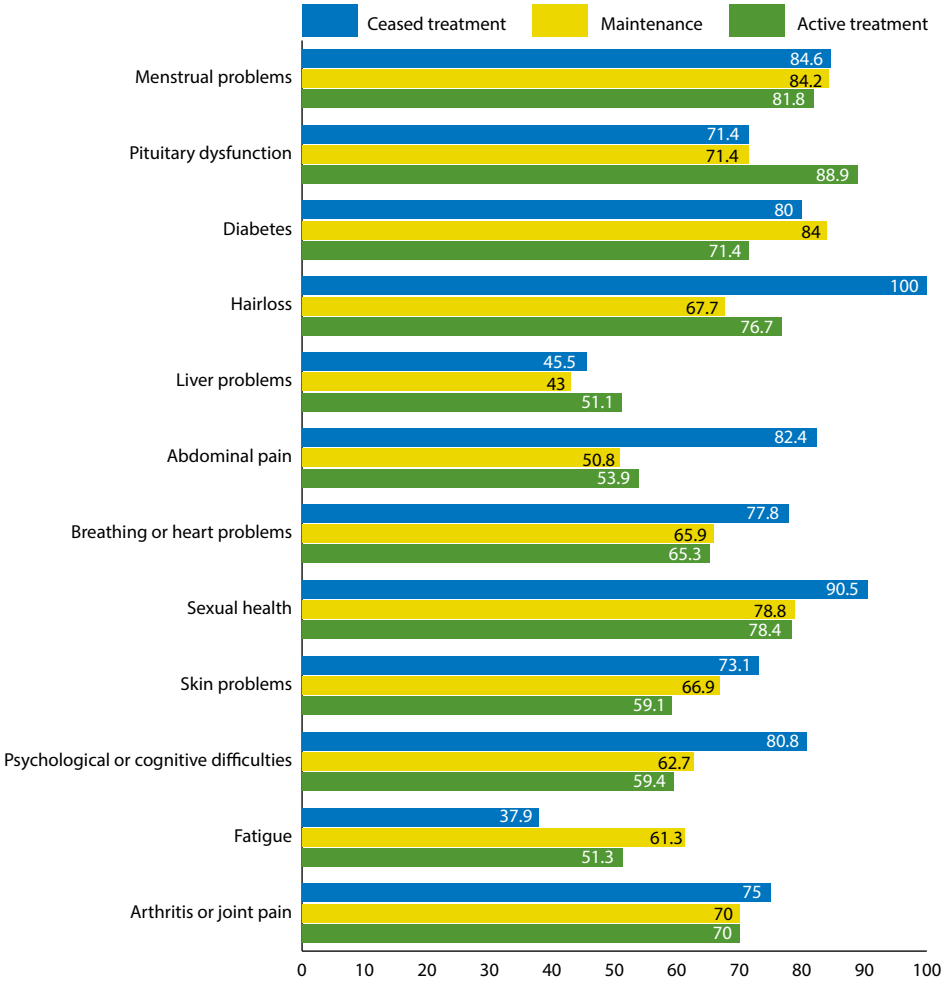
In the survey, respondents who reported experiencing a particular symptom (e.g. fatigue) were then asked whether they felt that de-ironing had improved their experience of that symptom, had no effect on it or worsened it.

This enabled us to look at whether people felt that treatment had improved their experience of each symptom, while accounting for whether they were in active treatment, in maintenance or had ceased treatment (see Figure 12).

The results show that for most symptoms, survey respondents felt that de-ironing improved their experience of that symptom, regardless of current treatment status. For ease of interpretation we have summarised the main points from Figure 12 below:

- More than 70% of those treated perceived that de-ironing had improved their experience of; menstrual problems, pituitary dysfunction, diabetes, sexual health issues and arthritis or joint pain
- Fatigue and breathing or heart problems were the two symptoms where treatment groups differed significantly on their perception of symptom improvement (p=.003 and p=.04 respectively)
- People in maintenance were *more likely* than the other groups to perceive that de-ironing had improved their experience of fatigue. People who had ceased treatment were *less likely* to perceive that de-ironing had improved their experience of fatigue
- People who had ceased treatment were *more*

Figure 12: *Whether de-ironing improved symptoms in people who have undergone treatment*



Numbers refer to percentages. This graph shows the proportion of survey respondents who reported that de-ironing improved or ceased their experience of each symptom, compared with reporting that de-ironing had either made no difference or had worsened their symptoms. Results are stratified by whether survey respondents were in maintenance, active treatment or had ceased treatment. Only those survey respondents who were currently or had ever been de-ironed were included in this analysis (n=-1,295). For sexual health issues we did an additional analysis, stratifying people by gender, and found that 80.0% of women undergoing initial de-ironing and 80.6% in maintenance reported that de-ironing had improved their sexual health issues. Furthermore, 75.6% of men undergoing initial de-ironing and 76.9% in maintenance reported that de-ironing improved their sexual health issues.

It is important to note that due to the fact that participants needed to have experienced the symptom and de-ironing to respond to these questions, the numbers for some of these analyses are low. The number of participants within these analyses ranged from 1,061 for fatigue to 44 for pituitary dysfunction.

likely to report that treatment had improved their experience of breathing or heart difficulty than people who were in active treatment or maintenance



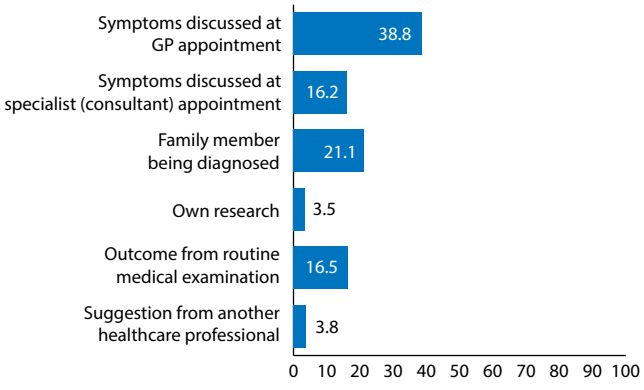
DIAGNOSIS (UK ONLY)

In this section we present data that was collected on the experience of diagnosis. We have limited this analysis to people in the UK (n=1,413) due to the variation in healthcare systems across different countries. The data we present in this section examines the experience of diagnosis, additional information or support that was offered at diagnosis and the experience of genetic testing for the survey respondents and their families.

Experience of diagnosis

First, we looked at the route to diagnosis (see Figure 13). The majority (55%) reported that their route to diagnosis commenced after discussing symptoms with a healthcare professional. Of the remaining respondents, the next most common routes to diagnosis were as a result of a family member being diagnosed or as an outcome from a medical examination.

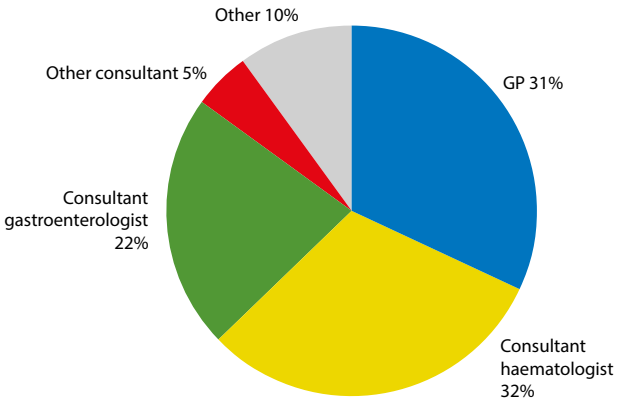
Figure 13: Route to diagnosis (n=1,072)



Numbers refer to percentages.

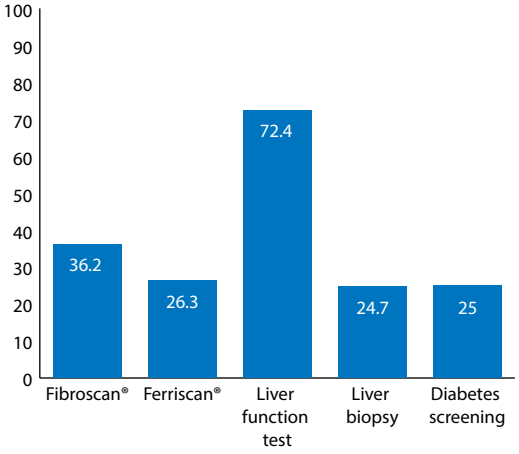
We then examined who made the formal diagnosis of GH (see Figure 14). The majority indicated that their diagnosis had been made by a consultant haematologist, their GP or a consultant gastroenterologist.

Figure 14: Who made the formal diagnosis of GH (n=1,072)



Clinical guidelines specify that people should have their liver function checked if GH is suspected, with additional tests being undertaken if indicated[1]. As such, we examined the sorts of tests people reported being offered at diagnosis (see Figure 15). Specifically, we looked at the percentage of people who were offered a Fibroscan®, Ferriscan®, liver function test, liver biopsy and/or diabetes screening. Two thirds indicated that they had been offered liver function tests when they were diagnosed.

Figure 15: Tests offered at time of GH diagnosis (n=1,072)



Numbers refer to percentages. This graph shows the number of people who responded positively to having been offered each test at their time of diagnosis (therefore each line represents the number of people who responded positively to that particular test; survey respondents would have responded to each test individually). The total number of survey respondents who answered these questions ranged from 628 to 716.

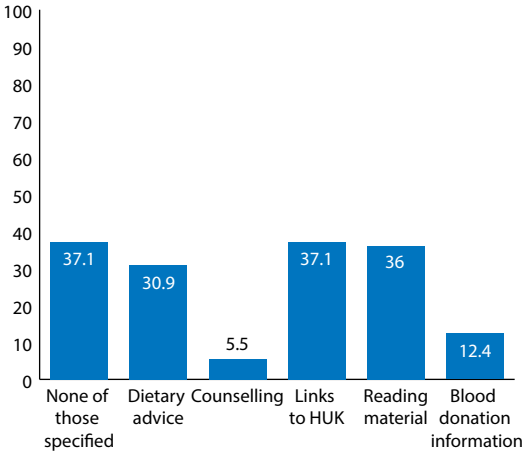
We also wanted to see whether the types of tests that people were offered at diagnosis might differ based on the type of healthcare professional who diagnosed GH (see Appendix VI: Figures 1 and 2). The results are summarised below:

- There was no difference in the likelihood of being offered a liver function test or diabetes screening at diagnosis based on the healthcare professional who made the diagnosis
- Those people who were diagnosed by a consultant gastroenterologist or consultant haematologist were *more likely* to be offered a Ferriscan® or Fibroscan®, than people diagnosed by other healthcare professionals
- Those people who were diagnosed by a consultant gastroenterologist were *more likely* to be offered a liver biopsy at the time of diagnosis

Information or support offered at diagnosis

People were also asked about any additional sources of information or support that they might have been offered at diagnosis (see Figure 16). In total, 62.9% said they had been offered at least one source of information or support that they could choose from. The most common types of support or information offered at diagnosis were dietary advice, reading materials or links to HUK. The least common sources of support or information offered to survey respondents at diagnosis were counselling and information about blood donation.

Figure 16: Sources of information and support offered to people with GH at diagnosis (n=1,028)



Numbers refer to percentages.

To determine whether the support and advice offered at diagnosis might differ by the healthcare professional who made the diagnosis, we ran an additional analysis which is summarised below (see Appendix VI: Table A):

- The only difference that we observed was that those people who were diagnosed by a consultant haematologist were *more likely* to have been offered blood donation information (18.2%) than people diagnosed by other healthcare professionals such as a consultant gastroenterologist (9.3%), GP (11.0%) or other consultant (5.6%)

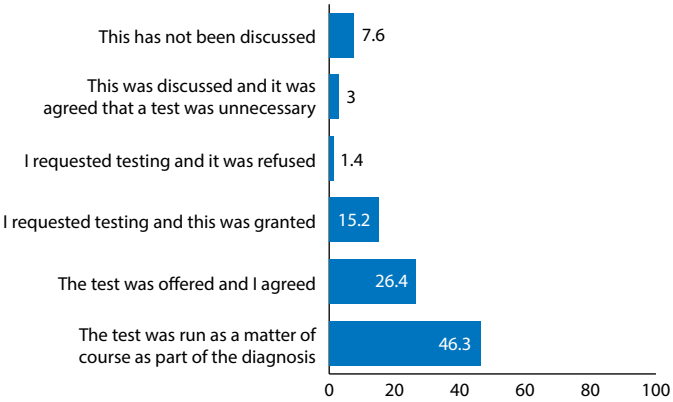


Experience of genetic testing for self and family

GH is a genetic disorder that we know is linked with particular gene mutations. It is possible to use this knowledge to help in the diagnostic process, by looking for those mutations using genetic screening. As part of this survey, respondents were asked about their own and their families experience of receiving this testing.

When asked about their own experience of obtaining genetic tests, the majority (87.9%) reported that they had received genetic testing for GH (see Figure 17).

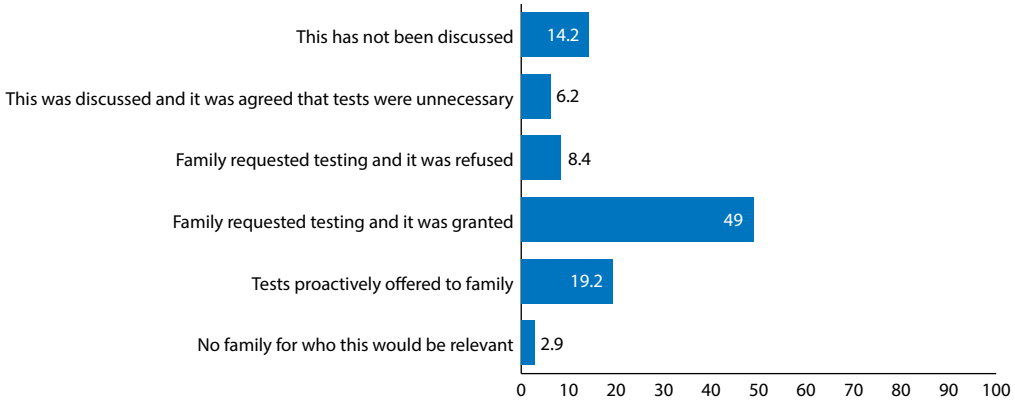
Figure 17: Experience of obtaining genetic test for self (n=1,072)



Numbers refer to percentages.

We then examined survey respondent's experience of obtaining genetic tests for their family. Most people (68.2%) reported that tests had been granted to their family. 8.4% reported that genetic screening for family members had been refused (see Figure 18).

Figure 18: Experience of obtaining genetic test for family (n=1,072)

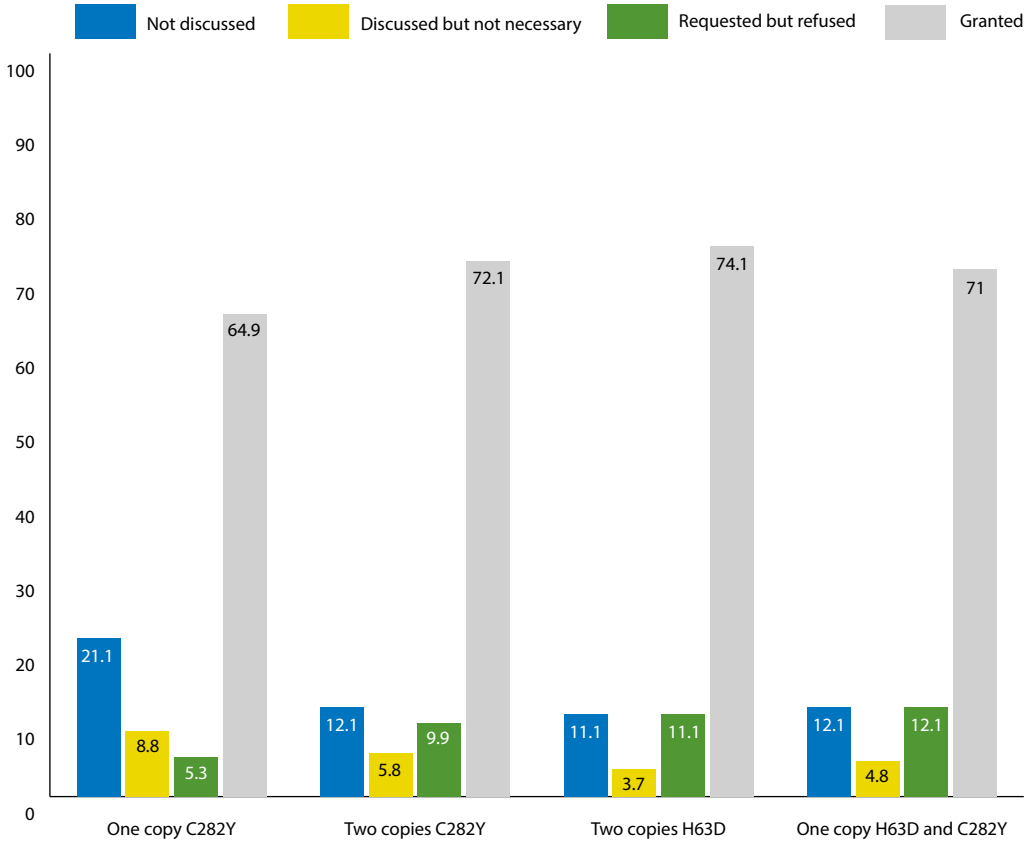


Numbers refer to percentages.

Recent clinical recommendations from the British Society of Haematology, state that people who are C282Y homozygous should have their family referred for genetic screening.[1] Additional recommendations state that those people who are C282Y/H63D heterozygous, do not need to have their family referred for screening.[1]

We wanted to see whether these recommendations are reflected in current clinical practice. We therefore looked at the relationship between whether family members were granted genetic testing and the genetic mutation that the respondent had (see Figure 19). We found that most people who were C282Y homozygous had been granted genetic tests for their families. Interestingly, a high proportion of people

Figure 19: Percentage of family members granted genetic screening based on genetic abnormality presented by person with haemochromatosis (n=743).



Numbers refer to percentages. As there were only 14 people with H63D and survey respondents with this abnormality did not endorse all responses, we did not include them in this graph. In total 57 people reported having one copy of C282Y, 535 had two copies of C282Y, 27 reported having two copies of H63D and 124 had one copy of H63D and one copy of C282Y.

who were C282Y/H63D heterozygous also had a relatively high proportion of their family referred for genetic screening (see Figure 19, on previous page).

TREATMENT (UK ONLY)

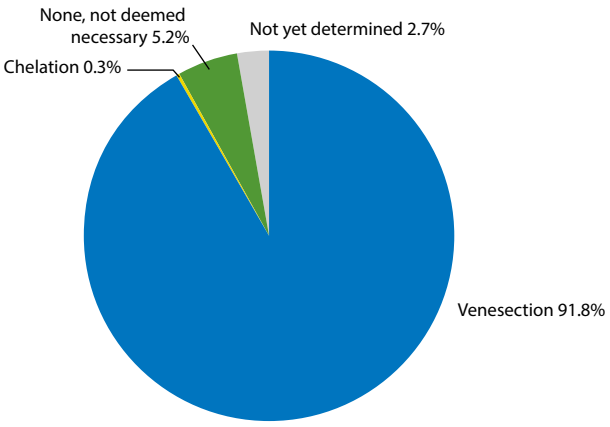
In this section of the results we present data collected on the experience of treatment and support provided to people resident in the UK (n=1,413). We looked specifically at the type of treatment people received, the location of treatment, additional tests and awareness of blood donation, the knowledge and support they received from their GH healthcare providers and from whom they felt they got the most support with GH.



Experience of treatment: UK only

With regard to treatment for their GH the majority of participants were undergoing venesection (see Figure 20). The only other treatment that people reported receiving was chelation (0.3%).

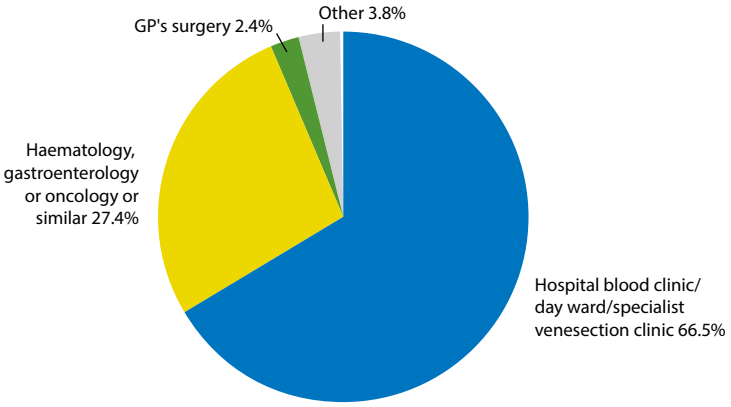
Figure 20: Currently recommended treatment (n=1,064)



Numbers refer to percentages.

When we assessed where people with GH were receiving their treatment, we found that most people indicated that they were receiving their treatment in a hospital day ward, blood clinic or specialist venesection clinic (see Figure 21).

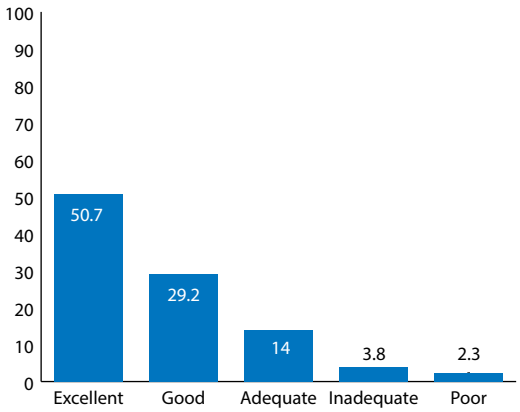
Figure 21: Location of treatment (n=1,012)



Numbers refer to percentages.

People were also asked to rate the skill and experience of the healthcare professional who carried out their venesection. Most rated the skill and understanding of their venesection nurse or doctor as excellent or good (see Figure 22).

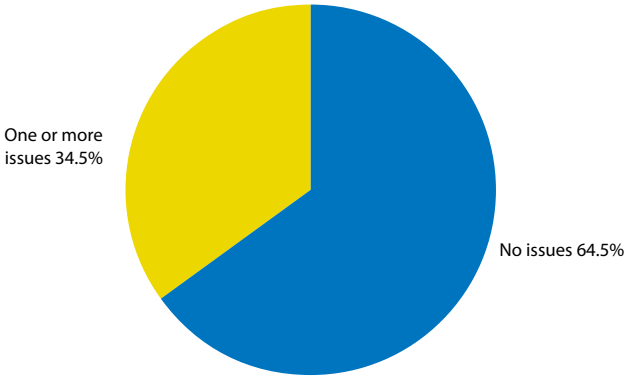
Figure 22: Rating the skill and understanding of the doctor/nurse performing venesection



As previous research has indicated that venesection may be difficult for some people, we then looked at whether respondents experienced issues with this treatment (see Figure 23, over the page). In total, 34.5% indicated that they had issues with venesection, and 65.5% did not. The issues people have with venesection are highlighted below:

- Skill level of venesection staff (n=138, 15.4%)
- Travel required or location of service (n=109, 12.2%)
- Appointment availability (n=103, 11.5%)
- Difficulty finding suitable veins (n=95, 10.6%)
- Need for additional support during the process (n=54, 6.0%)
- Accessibility issues (n=14, 1.6%)
- Medical reasons to use chelation instead (n=2, 0.2%)

Figure 23: The percentage of people who report issues with venesection (n=896)



We then wanted to determine whether the rating of the skill and understanding of the healthcare professional was linked to the issues that people reported experiencing with venesection (see Appendix VI, Table B). The results from this analysis are summarised below:

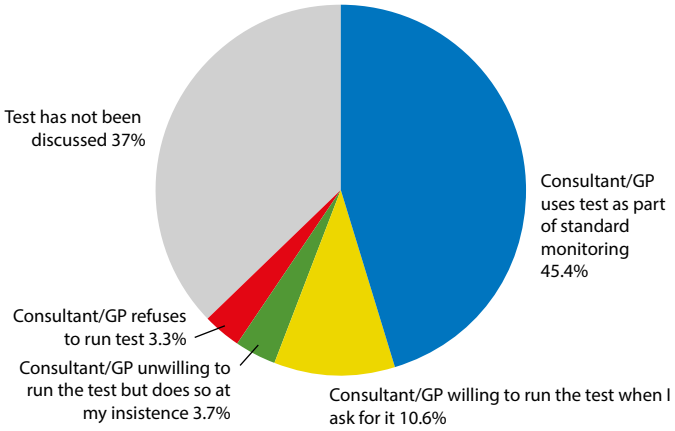
- When people rated the skill and understanding of their venesection nurse or doctor as good (responded excellent/very good/good), they were *more likely* to say they experienced no issues with venesection
- The specific issues that people who rated the skill and understanding of their venesection nurse or doctor as poor were *more likely* to experience were; difficulties finding suitable veins, problems with appointment availability and accessibility issues



Additional tests offered

Recent clinical recommendations from the British Society of Haematology, state that transferrin saturation (TS) testing should be used for monitoring people with GH. Transferrin saturation is one of the main biomarkers that tells us whether a person has iron overload. However, we do not know the extent to which these recommendations are reflected in current clinical practice.

Figure 24: Percentage of people who receive TS testing as part of monitoring their GH (n=973)

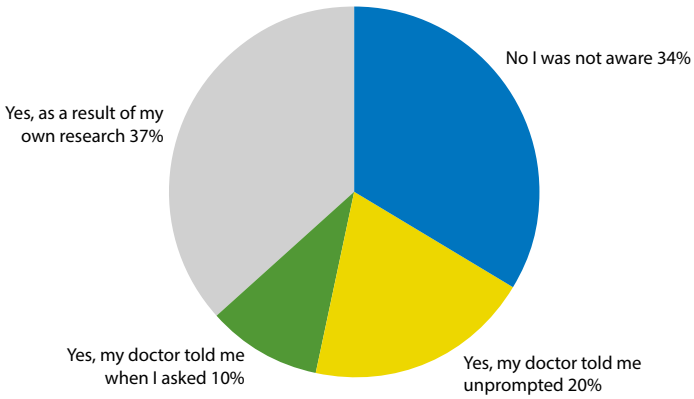


Respondents were asked about their experience of TS testing (see Figure 24). The data showed that the majority (59.7%) did receive TS testing as part of monitoring their GH. However, a large proportion (40.3%) of respondents indicated they did not receive TS monitoring as part of monitoring their GH. In most of these cases, TS testing had not been discussed, but 7% of respondents reported either that the consultant/GP had refused or had agreed only after the patient insisted.

Awareness of Blood Donation

Clinical recommendations state that once target SF and TS levels are reached, maintenance can take place at a blood donation centre.[1] During the course of the survey, respondents were asked to rate their own awareness of blood donation. Results indicated that 67% of respondents were aware that they could donate blood at a blood donation centre (Figure 25).

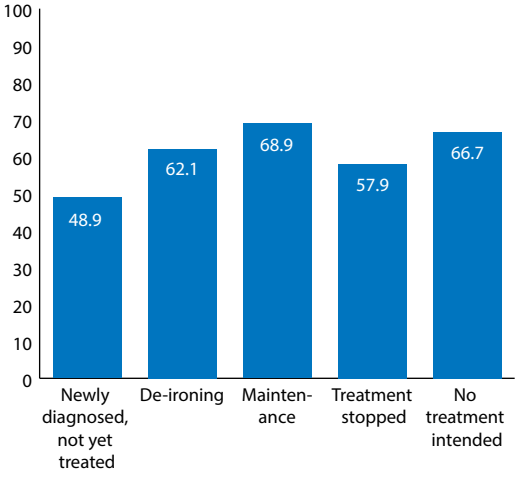
Figure 25: Percentage of people aware they can donate blood at a blood donation centre for maintenance (n=1,066)



Because awareness of blood donation may vary at different stages of treatment, we examined the awareness of blood donation while taking account of current treatment (see Figure 26). Generally, around

58-68% of survey respondents had an awareness of blood donation across different stages of treatment. However, a much lower percentage of people who were newly diagnosed and not yet treated (49%) reported that they were aware of blood donation during maintenance.

Figure 26: Percentage of people within each treatment group who are aware of blood donation during maintenance (n=1,024)

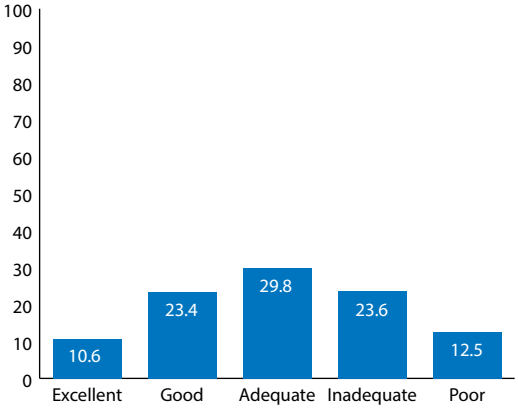


Numbers refer to percentages. For this analysis anyone who responded Yes (either told by doctor or as a result of their own research) was categorised as 'yes'. For each group, the remaining respondents not shown in the graph would have said they were not aware.

Support and knowledge

During the course of the survey, people were asked to rate the knowledge of their GP and the information and support that they received from their main consultant. Only 36.1% of people reported that their GP had good or excellent knowledge of GH. However most (30%) rated the knowledge of their GP as adequate (see Figure 27).

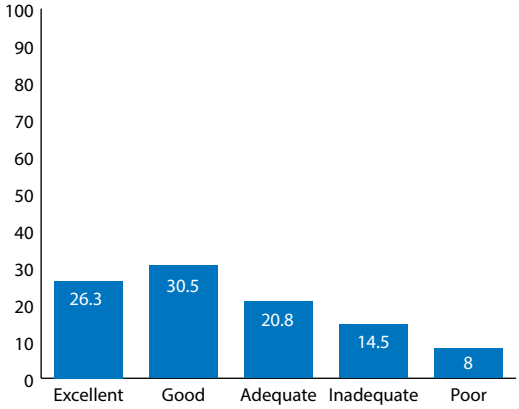
Figure 27: Rating the knowledge of haemochromatosis of GP (n=1,053)



Numbers refer to percentages.

Over half (57%) felt that they received good or excellent information and support from their main consultant (see Figure 28).

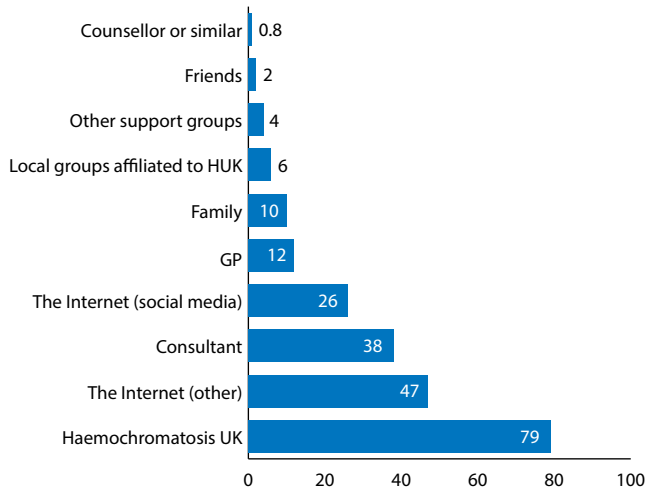
Figure 28: Rating the information and support provided by the main consultant (n=1,024)



Numbers refer to percentages.

Finally, people were asked to pick up to three sources of support from a list to indicate who they felt provides them with the most support with their GH. The most commonly endorsed responses were Haemochromatosis UK, the internet or their consultant (see Figure 29).

Figure 29: Main sources of support (n=1,069)



Numbers refer to percentages.

Research priorities

Respondents were also asked to prioritise symptoms as subjects for medical research. A separate analysis of these patient priorities is presented online at haemochromatosis.org.uk/2017-research-priorities.



Interpretation of findings

Results in this report have provided us with an interesting overview of the experience of GH-related symptoms in a worldwide sample of adults with GH. The results have also given us an overview of the experience of GH diagnosis, treatment and support within the UK.

In the following section, we interpret the results in the context of existing research and develop recommendations for future research. We start by discussing symptoms, move into diagnosis and then discuss treatment.

SYMPTOMS

Some of the most important issues facing people with GH are the associated symptoms and complications.[3, 4, 11, 27, 30, 31] This is for a number of reasons:

- The serious complications of GH can reduce life expectancy[15, 16, 32]
- For people who live with GH, symptoms impact on their quality of life and wellbeing[8, 22, 24, 29]
- Knowing which symptoms are linked with GH could help healthcare professionals make informed decisions about who should be screened

For these important reasons, one of the primary focuses for our research was to examine the experience of symptoms in people living with GH.

Our results and existing research suggest that joint pain, arthritis and fatigue are the symptoms most commonly reported in people with GH.[2, 6-8, 17, 18] In the past, the clinical presentation of GH was considered to be 'bronzed diabetes', but this is no longer common in GH.[33] Instead, fatigue, joint pain, arthritis, abdominal pain, skin discolouration and sexual dysfunction are more common in people with GH (see Appendix I). Our research adds to this, as we found that psychological and cognitive difficulties were also experienced frequently by people with GH. We will discuss the three most common symptoms after our summary below.

For this report we carried out a grouping analysis to see if we could identify groups of people with GH who experienced similar symptoms. To the best of our knowledge, this is the first study that has ever examined the symptoms experienced by people with GH using this analysis. We identified three main symptom groups:

- Group 1 (48.7%): Who report persistent fatigue and joint pain
- Group 2 (36.6%): Who report no or low symptoms
- Group 3 (14.7%): Who report persistent and painful symptoms

These findings again emphasised the prevalence of fatigue and joint pain in people with GH.[2, 6-8, 17, 18] However, the findings also add important new knowledge. They show us that we can distinguish groups of people based on their current pattern of symptoms and the severity of those symptoms. For instance, both Group 1 and Group 3 experienced fatigue and joint pain, but these symptoms were more severe in Group 3. Group 3, who had the most severe symptoms, were more likely to report having ever experienced serious conditions, were less likely to have commenced

treatment and more likely to report that it took them a long time to be diagnosed.

We will now discuss the three most commonly reported symptoms in more detail. We will then discuss the impact of de-ironing on symptoms.

Joint pain or arthritis

The symptoms most commonly reported in this survey were arthritis or joint pain. We found that 87% of respondents said they had ever experienced arthritis or joint pain and that, among those currently experiencing symptoms, 61.6% reported that the arthritis or joint pain was persistent or painful.

Due to the way the question was asked in this survey, it is difficult to make direct comparisons between the rate of arthritis or joint pain observed in this study with other studies. However, it still might be important to note how many people have arthritis or joint pain in the general population, so that the reader can make a general comparison. Statistics from the USA and UK find that arthritis and associated issues occur in approximately 21-28% of the general population. [34, 35]



A study by Richette et al. [20] directly compared people with GH to people who were the same age and sex but who did not have GH. They found that people with GH were 17.2 times more likely to experience pain in the hands, 12.2 times more likely to experience pain in the wrist and 11.3 times more likely to experience pain in the ankle, than people who did not have GH. [20] We also found within our survey that the knuckles and hands/wrist were the two most common areas where people with GH experienced joint pain.

There is also evidence that when compared with the general population, people with GH experience joint pain or arthritis at much younger ages. [8] When we looked at how many people experienced current joint pain or arthritis while accounting for age, we found that this symptom was more frequently observed in older age groups. However, half of people who were aged 18-39 reported that they experienced either persistent or persistent and painful problems with arthritis or joint pain. While we cannot compare this finding directly with the general population, looking at the age of onset of joint issues in people with GH and comparing to the general population, could be interesting to investigate in future research.

Previous research suggests that joint pain could be one of the key presenting symptoms of GH. Specifically, a need to screen for GH could be indicated if:

- Joint pain or arthritis occurs at younger ages than might be otherwise expected
- Joint pain occurs in specific joints (i.e., iron first) [21]
- Joint pain or arthritis occurs in combination with other symptoms such as fatigue, abdominal complaints, impotence, heart disease and/or skin discolouration [26]

However, it is important to note that these suggestions are mostly based on small self-report studies. We need more objective, longitudinal work to help us provide clinicians with better recommendations for GH screening.

When considering the importance of joint pain and arthritis in people with GH, it is important to consider the impact that these have on the person with GH. In the general population, there is evidence that arthritis is associated with poorer mental wellbeing [36] and poorer quality of life. [37] Furthermore, living with a painful condition has consistently been shown to be linked with poorer mental health, [38, 39] such as higher depressive symptoms. [40] Despite this, there is a lack of research looking at the impact of arthritis or joint pain on the wellbeing of people with GH.

It is especially important that we look at the impact that arthritis and joint pain has on the wellbeing and quality of life of people with GH, when we consider that existing evidence indicates that treatment does not always improve their experience of this symptom. [2] Work from our study suggests that around 30% of people with GH reported that de-ironing had no impact on their experience of joint pain. Therefore, it could be useful to know about alternative ways of coping with or treating pain, for example by using pain medications, talking therapies and exercise therapies. [41-43]

To summarise, due to the consistent finding that a high proportion of people with GH are affected by joint pain or arthritis, and the fact that this symptom was one of the top-rated research priorities, there is a

need for more research on this symptom. We suggest that some of the following could be useful:

- Formally characterising the types and locations of joint pain that present in people with GH. This would help clinicians screen people for GH more effectively (especially when this symptom occurs with other common symptoms)
- Conducting more research comparing the incidence (i.e., new cases of) arthritis or joint pain in people who have GH with the general population. This would help determine the likely efficacy of routinely screening younger people for GH if they present with joint pain or arthritis (especially when this occurs with other common symptoms)
- Conducting research that looks at the psychological impact of arthritis and joint pain in people with GH, as this is currently missing from the literature
- Research on potential alternative treatments or ways of coping with joint pain and arthritis to advise people on the various ways they can better cope with this symptom

Fatigue

Another commonly endorsed symptom in this survey was fatigue. The results showed that when asked if they had *ever* experienced fatigue, 81% of survey respondents said they had been affected, and 55.7% of respondents indicated this was currently a persistent or painful problem for them.

While the way our population was sampled, and the wording of questions, makes it hard to directly compare results from this survey with other surveys, we know that in the general population approximately 18-25% of people report experiencing a level of fatigue that impacts on their day-to-day life. [44, 45]

We know that fatigue is a common symptom linked to a range of long-term conditions that can affect people psychologically, physically and socially. [46, 47] Furthermore, fatigue is one of the main unexplained symptoms that leads to people visiting their GP. [48] Studies from primary care show us that approximately 6% of people who visit their doctor will state that it was extreme fatigue that prompted their visit. [49] In interviews, people who have GH, have stated that the experience of extreme and limiting fatigue prompted them to visit their GP. [22, 29] In the general population, fatigue has a substantial impact on quality of life and psychological wellbeing. [50-52] Interviews conducted with people with GH reveal that many people feel that their fatigue is difficult to live with and that it impacts on day-to-day living. [22, 29] Surveys in people with GH show that quality of life in this population is strongly linked to how tired they feel. [8]

Alongside the impact on quality of life, fatigue can impact on people's ability to think, leading to issues such as 'brain fog'. [53, 54] Interestingly, when we asked survey respondents which specific psychological or cognitive difficulties they experienced, the most commonly reported was forgetfulness or 'brain fog'. It would be helpful for future research to look at the cognitive issues people experience in GH and how these might be related to fatigue.



When we examined the perceived impact of treatment on the symptom of fatigue, we found that around half of those in active treatment and 60% of those in maintenance reported that treatment improved fatigue. However, ironically one of the most commonly reported side-effects of de-ironing treatment can be fatigue. [7] De-ironing can make fatigue worse in the short-term, but it may improve fatigue in the longer term. Previous work indicates that it can take 1.5 years before people will see an improvement in their symptoms as a result of venesection. [8] This suggests that additional therapies for fatigue to accompany de-ironing may be useful for people with GH. Therapies that the NHS advocates for chronic fatigue include talking therapies, exercise or activity therapies, medication, lifestyle changes or sleep changes. [55]

In summary, fatigue is also a commonly experienced symptom in people with GH and our fatigue-specific recommendations are:

- We need research that examines the causes of fatigue in people with GH. Specifically, whether fatigue is a direct effect of iron overload, or caused by other GH symptoms. By understanding this better, we could develop a clearer picture of the presenting symptoms in GH
- We need to know more about the consequences of fatigue in people with GH, particularly around wellbeing, cognition and quality of life
- Finally, we need more work to understand which therapies might help with fatigue in people with GH

Psychological and cognitive difficulties

The third symptom most commonly reported in this survey was psychological and cognitive difficulties. Almost three-quarters (73%) of respondents said they had *ever* been affected. The most common symptoms were 'brain fog' and depression.

When looking at our results more closely, we found that 38% of respondents reported *ever* experiencing depression and 32% reported *ever* experiencing anxiety. These rates are slightly higher than we might expect to find in the general population, where the lifetime prevalence of anxiety and depression is around 30%.[56, 57] However, it is important to note that people with any long-term condition are around 2-3 times more likely to report experiencing depression or anxiety than people who don't have long-term conditions.[58, 59] Therefore, it is possible that the rates of psychological issues that we observed could be in large part due to living with a long-term condition.

Some work has looked at how living with GH can affect people psychologically. Interview studies show that the feelings that people can have about their GH can be very different. Although some studies find that people with GH are largely accepting of their condition,[22] other studies have found that people with GH can feel misunderstood, isolated and even stigmatised.[23] Therefore, it could be that psychological issues stem in part from living with a poorly understood condition such as GH.

It is also possible that psychological issues stem from GH-related symptoms, rather than directly from iron overload. For example, research shows us that symptoms associated with GH such as arthritis,[60-62] pain,[39, 63] liver disease,[64, 65] diabetes[66, 67] and heart disease[68] are all associated with a high rate of depression and anxiety. Therefore, it will be interesting for future research to determine how living with GH and the associated symptoms affect people psychologically.

To the best of our knowledge this is one of the first studies that has looked at cognitive difficulties in a large sample of people with GH. Previous published case studies have examined dementia[69] or cognitive difficulties[70] in people with GH. However, as these are case studies, they are not representative of all people with GH. Our study found that over 60% of respondents felt that they experienced 'brain fog' or forgetfulness. We speculated above that this may be in part due to fatigue, which has also been shown to be associated with very similar cognitive issues.[54] However, there is a need for studies to properly examine the cognitive difficulties experienced in GH and what may cause them.

In summary, we have found that a high proportion of people in our sample report experiencing psychological and cognitive difficulties. We suggest that:

- There is a need for research that examines and better characterises the psychological issues that might be experienced in GH using clinical interviews for depression and anxiety. This would give a more accurate picture of the experience of mental illness in this population
- It is currently unclear whether GH has a direct impact on psychological and cognitive difficulties, or whether these difficulties arise because of other GH-related symptoms. Work that explicitly looks at the relationship of psychological and cognitive difficulties with the level of iron overload and other symptoms would help us to determine this
- There is a lack of research in to cognitive issues in people with GH. The results from our study indicate that a high proportion of people experience cognitive issues. It would be interesting for future work to examine cognitive difficulties in people with GH using formal cognitive tests, so that we can better characterise these issues

Other symptoms

Alongside the three most commonly reported symptoms, our work has indicated that other commonly occurring symptoms in people with GH include sexual health issues, skin problems (particularly skin discolouration and itchiness), abdominal pain, breathing or heart difficulties and menstrual problems.

When we looked at the more serious symptoms that can be associated with GH, we found that pituitary dysfunction, diabetes, liver issues and cancer had a lower prevalence than other symptoms. The rates of most symptoms that we found in this study were higher than other studies that have also looked at symptoms in people with GH (see Appendix I). However, this could be due to our self-selected sample and the broad nature of the questions.

While a detailed consideration of each of these additional symptoms is beyond the scope of this report, we do acknowledge that these symptoms will also be important for the wellbeing and quality of life of people living with GH.

In summary, we suggest that:

- When raising awareness of GH, the focus should be on the more common symptoms

Effect of de-ironing on symptoms

Although most people reported that treatment had improved their experience of various GH-related

symptoms, this was not a consistent finding. Depending on the symptom, we found that between 20-50% reported that de-ironing had *not* improved their experience of symptoms. The finding fits with other similar work, where most, but not all people say that de-ironing improves their symptoms.[2, 8] Interestingly, work from previous surveys and interviews shows that in the short term, de-ironing can even increase some symptoms (e.g. fatigue).[7, 29]

In summary, we suggest that:

- We need more high quality work that examines the effectiveness of de-ironing treatments for improving symptoms in people with GH
- There is scope for us to develop other treatments that could be used alongside de-ironing, to help alleviate some of the symptoms associated with GH

DIAGNOSIS

Within this survey, we asked people to let us know about their experience of being diagnosed with GH. We limited this analysis to the UK. Our main findings are summarised below:

- Most people were diagnosed with GH after they discussed symptoms with a healthcare professional
- Most people were diagnosed by their GP, a consultant haematologist or a consultant gastroenterologist
- 70% of the sample reported that they were offered a liver function test at diagnosis, in line with current clinical recommendations[1]
- When asked about any additional support they were given at diagnosis, 37% of respondents specified they were given no additional support. When people were given additional support, this was mostly reading or links to the HUK website
- Most people were able to access genetic testing for both themselves and family members
- Many people who reported that their family members had received screening had a genetic abnormality that did not necessitate family screening[1]

We will now discuss the findings in more detail under the following headings; pathways to diagnosis, tests and support received at time of diagnosis and availability of genetic testing.

Pathways to diagnosis

Our results showed that half our UK-based sample were diagnosed with GH after discussing symptoms with a healthcare professional. This differs from other studies where around one third of people are diagnosed in those circumstances.[7, 8] The higher rates of diagnoses due to symptoms may be because we looked only at the UK. Studies from other countries show a relatively high number of people are diagnosed with GH after routine check-ups,[7, 8] something we did not find in the UK sample.

Most people (not just people with GH) attend their doctor to discuss unexplained symptoms.[71] One of the most common symptoms that prompts people in the general population to go and see their doctor is fatigue[52, 72] which, as we know, is one of the main symptoms associated with GH (see Appendix I). It is not surprising, therefore, to find that when people with GH are interviewed, many of them state that it was extreme tiredness that led to them attending their doctor prior to being diagnosed.[22, 29]

As GH is a genetic condition, both clinical recommendations and HUK emphasise the importance of screening within families.[1, 2] In our study we found that one quarter of our respondents were diagnosed because of a family member's diagnosis. This is similar to previous studies where it is reported that 20-30% of people receive their diagnosis following a family member's diagnosis.[7, 8] However, this raises questions about why this proportion is not higher. This will be discussed in more depth in the section on genetic screening.

Our results showed that most people in our sample were diagnosed by their GP, a consultant haematologist or a consultant gastroenterologist.

To summarise the most common pathway to being diagnosed with GH in our UK sample was discussing symptoms with a healthcare professional, followed by diagnosis following a family member's diagnosis. These results suggest that:

- There is a need to better characterise the types of symptoms that lead to people being diagnosed with GH
- There is a need to determine whether the experience of GH treatment is in line with current clinical recommendations

Tests and support received at time of diagnosis

Our results indicate that around 70% of people were offered liver function tests at the time of diagnosis. This is in line with current clinical recommendations.[1] It is of concern that 30% of people report not being offered liver function tests. When we examined the types of tests that were offered at diagnosis across different healthcare professionals, we found that those people who were diagnosed by a gastroenterologist were more likely to be offered a liver biopsy or a Fibroscan®. Those people who were diagnosed by either a haematologist or gastroenterologist were

more likely to be offered a Ferriscan®. However, in the absence of data on iron overload, it is difficult to speculate on why different people attending different specialists may have been offered different tests, as clinical recommendations depend on the level of iron overload. Furthermore, it is possible that people may not have been aware of the tests they were offered at diagnosis. This could represent an interesting avenue for future research.

It is important to note that we were unable to examine the additional tests that were offered at diagnosis according to TS and SF levels. The clinical recommendations of Fitzsimons et al. [1] suggest that additional testing for liver problems is important if people have evidence of significant iron overload (i.e. SF >1000 mcg/l). We suggest that future work could examine whether the tests that people receive at diagnosis are consistent with current clinical recommendations.



In the survey, people were asked about the type of information and support offered at diagnosis including dietary advice, counselling, links to support groups and information about blood donation. More than a third reported receiving none of these. When people did receive information and support, it was mostly in terms of internet resources or reading materials. Only 12.4% were given information about potential blood donation, even though this is recommended in the most recently published clinical guidelines. [1]

It may be that information and support needed by patients diagnosed with GH is not well understood. Certainly, there is little literature about the impact of a diagnosis of GH on patients.

There are challenges associated with receiving a diagnosis of GH. In a qualitative study by O'Connell and Sheahan, [22] when recalling their experience of diagnosis of GH, people spoke about being fearful of developing potential complications of GH and of the need for more information, for example, about diet. Although this information is available through patient organisations, it was not routinely provided by healthcare professionals, with less than one third of survey respondents reporting that they received dietary advice.

For the most part, the offer of information and support did not differ based on the type of healthcare professional who made the diagnosis. However, haematologists were more likely than other doctors to advise patients of the possibility of blood donation during maintenance.

In the UK, blood donation for people with GH is now being encouraged among GH patients in maintenance, provided they have no GH-related tissue damage and are not taking medication for their condition.

To summarise, our research found a lot of variety in the support and tests that people were offered at diagnosis. Our results suggest that:

- More research is needed to determine the tests that people are offered at diagnosis across different specialities, and whether the tests people receive are in line with clinical recommendations [1]
- More research is needed about the support needs of people diagnosed with GH to inform good practice in terms of patient care

Availability of genetic testing

Although GH is a relatively common genetic disorder, [2, 4, 11] widespread population screening is not recommended. [1] Instead, screening is recommended for family members of those who are diagnosed with homozygous C282Y GH. On the other hand, family screening is not recommended for those with other genetic mutations, for example, compound heterozygous C282Y/H63D GH. Our results indicate that this distinction was not made for our sample of patients.

Firstly, almost 10% of respondents with homozygous C282Y GH reported being refused family screening, a further 12% reported that it had not been discussed and almost 6% reported that it was deemed unnecessary. Given the high risk of GH in families of people in this category this finding is a concern. On the other hand, over 70% of those with compound heterozygous C282Y/H63D GH, where risk of iron overload is lower, were offered family screening. Based on the most recently published guidelines, [1] family screening in this group is unnecessary.

These results need to be treated with caution however, as there was a lot of missing data for this question. Further research into practices with regard to offering family screening is needed to clarify the situation.

In summary, our results suggest that:

- We need more work to determine why there may be differences in the likelihood of people being offered genetic tests for themselves and their family at diagnosis
- We need to ensure that clinicians are aware of current clinical recommendations for genetic testing

TREATMENT

In the survey, people were asked about their experiences of GH treatment and support provided by health professionals in the UK. We found that:

- Over 90% of our sample reported their main GH treatment was venesection
- Most people (66.5%) received their GH treatment in a hospital blood clinic, day ward or specialist venesection clinic
- The majority of respondents (79.9%) rated the skill and understanding of their venesection nurse or doctor as excellent or good
- Most respondents (65%) indicated that they experienced no issues with venesection
- A relatively high proportion of people (40%) reported that they did not receive TS testing as part of their monitoring
- People generally rated the knowledge and support of their consultant as excellent or good
- There was less consistency in how people rated the knowledge of their GP, with most people (76.8%) responding good, adequate or inadequate
- The three main sources of support that people endorsed were HUK, the internet and their consultant

We will now discuss in more detail the experience of treatment and additional tests. We will finish by discussing sources of support and knowledge of healthcare professionals.

Experience of treatment and additional tests

When we looked at the type of treatment that people received, we found that over 90% were being treated through venesection; a process where blood is drained to help remove iron from the body. [1, 3, 27]

While generally perceived by healthcare professionals as a relatively easy procedure to implement, for some people undergoing the treatment, venesection can be invasive and unpleasant. [22] Encouragingly, results from our survey suggest that most people in our UK sample, feel the skill level and understanding they receive from the doctor or nurse who performs their venesection is good or excellent.

However, our results also indicate that 40% of people felt that they experienced issues with venesection, which were often related to the inadequate or poor skill and understanding of their venesection nurse or doctor. This suggests that it is important to ensure that health professionals are well trained in performing venesection. This could be helped through the development of best practice guidelines for venesection, something that HUK is currently supporting.



Even when patients find venesection unpleasant, they tend to accept that it is of benefit because it will help to avoid serious complications. [22, 29] For instance, over 60% of people with GH state that the benefits of venesection outweigh the costs. [7, 8] Raising awareness of the benefits of venesection could help people to cope well with this sometimes unpleasant procedure.

We also examined how many people received regular TS testing as part of their monitoring. We found that a relatively high proportion (40%) of participants reported that TS was not used to monitor the iron in their body. This is of particular concern because TS is one of the main biomarkers to measure iron overload. [3, 27] Therefore, there is an urgent need to understand why every person with GH does not have this monitored within the UK and ensure that those doctors who monitor people with GH, are aware of the most recent clinical recommendations. [1]

In summary, our findings and previous research suggest that:

- We need to ensure that there are clear guidelines for best-practice for venesection
- There is scope to improve clinical awareness of the tests and treatments that can and should be used for GH

Sources of support and knowledge of healthcare professionals

When people were asked to rate their GP's knowledge of GH, just over a third rated it as good or excellent. Awareness and knowledge of GH among non-specialist doctors has been found to be low. [73]

Our findings indicate that there is scope to improve awareness of GH amongst GPs.

The picture is more positive with regard to specialist consultants. Encouragingly, when asked to rate the support and understanding that they received from their main consultant, the majority of survey respondents rated it as excellent or good and consultants were identified as one of the top three sources of support for GH. Interview studies have shown that people with GH can feel isolated and alone due to having a condition that they feel is not very well understood.[23] Improving the understanding of healthcare professionals could be a key way to provide support to people with GH.

When asked to rate their most important sources of support, the two most common responses were HUK (79%) and the internet (47%). However, as this was an online survey and people were recruited mostly through the HUK website, these responses may be biased towards internet users. Nevertheless, the results still show that the internet is an important source of support for people with GH. This finding is consistent with interview studies where people with GH state that the internet was a source of support that they turned to that helped them better understand their diagnosis.[22]

Work from this and previous surveys indicates that the internet and online support groups are an important source of support for people living with GH. Increasingly people are turning to the internet to learn more about health conditions and as a source of support.[74, 75] However, despite the ease of access, the quality of information and support provided can vary.[75, 76] It is important therefore, to ensure that online sources of information provide high-quality and reliable information.

In summary our work suggests that:

- It is important to ensure that all clinicians who might work with people who have GH (not just specialist consultants) have a good understanding of the condition
- The internet is a vital source of information for people with a poorly understood condition such as GH, so making sure that sources of information on the internet that might be recommended to people with GH are reliable and valid will be important for clinicians

STRENGTHS AND LIMITATIONS

This survey allowed us to collect up-to-date information on the experience of symptoms, diagnosis, treatment and support in a very large sample of people with GH. Although no attempt is made to attribute symptoms to GH, the data provides valuable information on symptoms experienced by people with the condition.

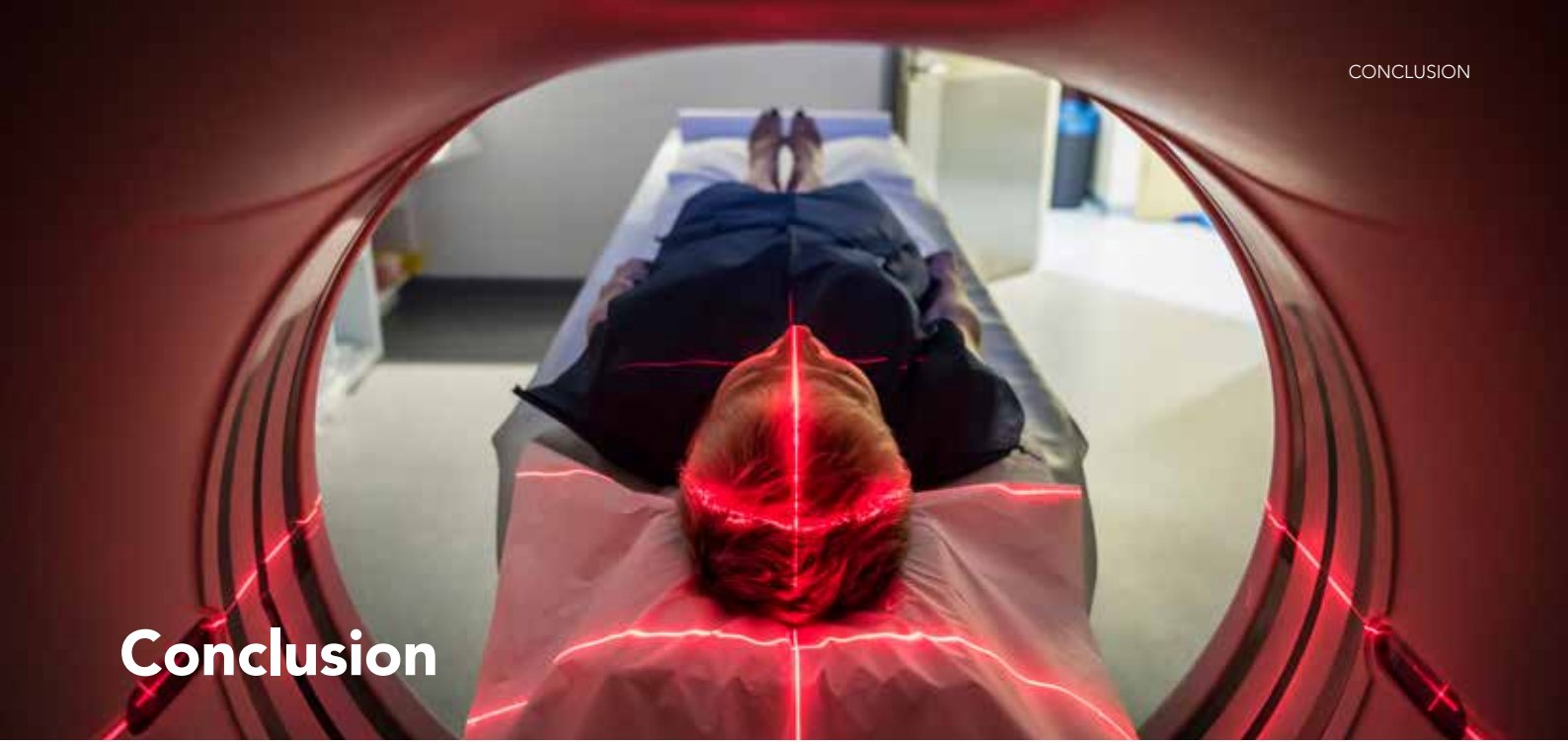
In interpreting the results, it is important to note the limitations of a self-report survey that relies on patient recall, which may not always be accurate. Firstly, because the sample was self-selecting, mostly recruited through patient support groups and limited to those with access to the internet, it may not be representative of people with GH. The fact that the sample might not be representative is indicated by the fact that a much lower percentage of people reported having the C28CY homozygous abnormality than we might normally expect, and a much higher percentage of women were in our sample than we might normally expect.

Secondly, the questions used were broad and not validated and there may be variation in respondents' interpretation of questions and response items. This should be kept in mind particularly when looking at prevalence data. It also limited our ability to compare findings with published prevalence data.

In addition, it is possible that our respondents may have had other conditions that we were unable to account for. Since the survey is cross sectional, collecting data at one point in time, no inferences can be made about cause and effect.

Finally, there was missing data in some of the questions. However, we have tried to be as transparent as possible about this within the report.

Despite the limitations, the importance of this survey should not be underestimated and the recommendations we make are based both on this survey and previous research in this field.



Conclusion

The 2017 HUK survey provided us with a unique opportunity to examine the perception of symptoms, research priorities, information about treatment and the perception of support in a worldwide sample of 1,998 adults living with GH.

The results from the survey have raised awareness of the problems that people living with haemochromatosis experience, and highlighted areas where future research can be developed to help improve the lives of people living with this condition. In the following two sections, we detail our principal findings and present our key recommendations.

PRINCIPAL FINDINGS

- The research has shown us that many people with GH report experiencing issues with arthritis or joint pain and fatigue
- When we grouped people according to their experience of symptoms we found three distinct groups:
  Group 1 (48.7%): Who report persistent fatigue and joint pain
  Group 2 (36.6%): Who report no or low symptoms
  Group 3 (14.7%): Who report persistent and painful symptoms
- Most people who have undergone or are undergoing treatment report that de-ironing helps improve their experience of many haemochromatosis-related symptoms
- Many people with GH in the UK report receiving tests that are in line with the clinical recommendations of Fitzsimons et al.,[1] although our analysis does indicate there is still a relatively high percentage of people who report not getting the tests that they need. For instance, 40% of respondents in the UK indicated that they did not have transferrin saturation measured as a part of their routine monitoring. As these clinical recommendations are very recent, this emphasizes the need for us to promote them amongst clinicians
- Within the UK most people rated the support and information they receive from their consultant and venesection staff as excellent or very good. However, people felt the knowledge of their GP was only adequate
- Within the UK people indicated that their main sources of support with their haemochromatosis were HUK, the internet and their consultant
- Conducting the survey and writing the associated report has allowed us to come up with a series of key recommendations

KEY RECOMMENDATIONS

From conducting this survey and reviewing existing literature, we suggest the following recommendations. These are discussed in more detail below:

- Recommendation 1: We need to improve awareness of GH and current clinical recommendations
- Recommendation 2: We need more clinical research to better characterise the symptoms associated with GH
- Recommendation 3: We need more research to better understand the impact of GH-related symptoms on people living with GH
- Recommendation 4: We need more work to understand why individual differences in treatment may exist

Glossary of terms

Chelation: a drug therapy that removes metals from the body.

Erythrocytapheresis: a process where red blood cells are separated from other components of the blood.

Ferriscan®: a liver MRI scan where specific data is interpreted to tell us about the amount of iron in the liver.

Fibroscan®: a liver elastography measurement that tells us about the degree of stiffness of the liver.

Heterozygote (noun), heterozygous (adj.): A person with one mutated and one normal copy of a given gene. This means that they may carry associated conditions and are referred to as 'carriers'.

C282Y: The mutation most commonly associated with genetic haemochromatosis.

Homozygote (noun), Homozygous (adj.): A person with the same mutation on both copies of a gene, for example, both copies of the *HFE* gene having the C282Y mutation.

Iron overload: when people have too much iron in their body. This is determined by looking at their levels of serum ferritin and transferrin saturation.

Liver function test: a group of blood tests that give an indication of how well the liver is functioning.

Serum ferritin: iron storage protein that gives an indication of the amount of iron stored in all body tissues.

Transferrin saturation: transferrin can be thought of as an 'iron transporter' in the blood. Transferrin saturation tells us how much availability there is for iron transport in the blood. When this is higher than 50%, the level of iron in the body could be toxic.

Venesection: also referred to as phlebotomy. This is where blood is removed from the body in order to reduce the amount of iron in the body. It is the most commonly used treatment for haemochromatosis.

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Appendix I: Table of studies that have examined symptoms in people with haemochromatosis

Author Year of study Countries of study	Participant characteristics	Sampling	How were symptoms assessed?	Symptoms examined (percentage of sample affected)
Allen et al. (6) Baseline 1990-1994 and follow-up 2004-2006 Australia	1,290 people with haemochromatosis Median age 63.2 to 66.6 (depending on genotype) 58.8% male	Population screening (n=23,484)	Clinical records and questionnaire	**C282Y/C282Y (n=203)** Fatigue (19.1%) History of arthritis medication (11.8%) Abnormal metacarpophalangeal joints (18.3%) Hepatomegaly (1.9%) History of liver disease (7.9%) Diabetes (1.5%) **C282Y/H63D (n=242)** Fatigue (13.5%) History of arthritis medication (5.8%) Abnormal metacarpophalangeal joints (20.1%) Hepatomegaly (4.3%) History of liver disease (5.6%) Diabetes (2.0%) **H63D HOMOZYGOUS/HETEROZYGOUS (n=146)** Fatigue (15.9%) History of arthritis medication (7.5%) Abnormal metacarpophalangeal joints (15.7%) Hepatomegaly (1.9%) History of liver disease (6.9%) Diabetes (4.8%) **C282Y HETEROZYGOUS/WILDTYPE (n=698)** Fatigue (14.3%) History of arthritis medication (4.6%) Abnormal metacarpophalangeal joints (11.6%) Hepatomegaly (2.7%) History of liver disease (5.2%) Diabetes (1.9%)
Adams et al. (5) 1997 France, Canada	410 people with haemochromatosis Mean age 49 (11-82) 59.5% male	Retrospective study in two clinics	Clinical history, clinical tests	Impotence (40%) Fatigue (38%) Skin pigmentation (38%) Arthritis (29%) Cirrhosis (22%) Diabetes (14%) Asymptomatic (27%)
Bardou-Jacquet et al. (18) Baseline 1989 and follow-up 2010 France	226 people with haemochromatosis (C282Y/C282Y) Mean age 44.4 56.8% male	Participants registered in haemochromatosis database	Self-report	Chronic fatigue (37.0%) Joint problems (16.5%) Severe fibrosis (6.1%) Diabetes (1.8%)

Author Year of study Countries of study	Participant characteristics	Sampling	How were symptoms assessed?	Symptoms examined (percentage of sample affected)
Brissot et al. (7) Year of survey not specified, publication was 2011 USA, France, Ireland, UK	210 people with haemochromatosis Mean age 46.3 (SD 12.1) 55% male	Convenience sampling	Self-report	AT DIAGNOSIS Fatigue/anemia (74%) Joint pain (55%) Loss of libido (30%) Skin discolouration (25%) Heart problems (21%) Hair loss (20%) Liver problems (16%) Loss of period (9%) None (14%) CURRENT Fatigue/anemia (60%) Joint pain (50%) Loss of libido (23%) Skin discolouration (12%) Heart problems (12%) Hair loss (11%) Liver problems (10%) Loss of period (5%) None (19%)
Buetler et al. (17) 2002 USA	768 people with genetic mutations Haemochromatosis-specific demographics not reported	Population screening (n=41,038)	Self-report questionnaire	CONTROLS (NO mutations) General health limited (41.4%) Arthropathy (41.6%) Impotence (35.9%) Fatigue (26.5%) Arrhythmias (25.1%) Depression (18.2%) Abdominal pain (9.6%) Diabetes (8.4%) Darkening of skin (7.6%) Weight loss (7.3%) Hair loss (5.9%) Liver problem/hepatitis (4.1%) C282Y/C282Y mutation General health limited (41.9%) Arthropathy (36.3%) Fatigue (27.4%) Impotence (26.8%) Arrhythmias (25.0%) Depression (17.7%) Abdominal pain (8.1%) Liver problem/hepatitis (8.1%) Hair loss (7.3%) Weight loss (6.5%) Diabetes (5.6%) Darkening of skin (1.6%) C282Y/H63D mutation General health limited (42.9%) Arthropathy (42.9%) Impotence (40.4%) Fatigue (26.4%) Arrhythmias (26.3%) Depression (17.7%) Abdominal pain (10.1%) Diabetes (7.4%) Weight loss (7.1%) Hair loss (4.9%) Liver problem/hepatitis (3.7%) Darkening of skin (5.1%)

Author Year of study Countries of study	Participant characteristics	Sampling	How were symptoms assessed?	Symptoms examined (percentage of sample affected)
Camancho et al.(19) Date of survey unknown but published in 2017 (this is probably the same survey as Richette et al completed in 2006) France	306 people with haemochromatosis Median age 60.0 (IRQ 53 to 68 years) 52.6% male	Convenience sampling (through Association Hémochromatose France)	Self-report	**C282Y/C282Y (n=266)** Joint pain (88.4%) Asthenia (79.3%) Osteoarthritis (53.4%) Cardiac disease (15.4%) Diabetes (15.4%) **C282Y/H63D (n=40)** Joint pain (77.5%) Asthenia (82.1%) Osteoarthritis (32.5%) Cardiac disease (10%) Diabetes (17.8%)
Haemochromatosis UK (2) 2005 Country unknown	Unknown	Unknown	Self-report	Joint pain (72%) Chronic fatigue (57%) Chest pains, cardiomyopathy, shortness of breath (53%) Mood swings, depression and anxiety (52%) Impaired sexual dysfunction (42%) Skin discolouration (34%) Abdominal pain (27%) Loss of body hair (25%) Liver disease (23%) Menstrual problems (15%) Diabetes (13%)
McDonnell et al.(8) 1996-1997 20 countries (90% North America)	2,851 participants 99% White 62% male	Convenience sampling	Self-report	Extreme fatigue (45.5%) Joint pain (43.5%) Impotence or loss of libido (25.8%) Skin bronzing (25.7%) Heart fluttering (23.8%) Depression (20.8%) Abdominal pain (20.3%)
Olynyk et al. (9) 1994 Australia	16 C282Y/C282Y participants Mean age 55.8 (30-74) 43.8% male	Population screening (n=3,011)	Clinical tests and clinical records	Arthritis (37.5%) Skin pigmentation (37.5%) Liver problems (31.3%)
Richette et al. (20) 2006 France	306 people with haemochromatosis Mean 60.1 ± 13 52.6% male	Convenience sampling (through Association Hémochromatose France) 304 age and sex matched controls recruited from medical clinics	Self-report	**GH at diagnosis:** Joint pain (51.5%) Asthenia (57.9%) Liver disease (18.4%) Cardiac disease (10.0%) Diabetes (5.2%) **GH at time of survey:** Joint pain (86.9%) Asthenia (79.7%) Liver disease (27.1%) Cardiac disease (15.8%) Diabetes (9.8%) **Age and sex matched controls:** Joint pain (43.1%) Asthenia (31.9%) Liver disease (1.3%) Cardiac disease (9.2%) Diabetes (7.9%)

Author Year of study Countries of study	Participant characteristics	Sampling	How were symptoms assessed?	Symptoms examined (percentage of sample affected)
Sahinbegovic et al.(10) 2005-2008 Country unknown	199 participants Mean age 55.9 (25-79) 67.3% male	Convenience sampling across 7 clinics	Self-report and clinical tests	Joint pain (72.5%) Bony enlargement (65.8%) Swollen joints (13.6%)

This table was put together after a literature review, which was not done systematically. There is a possibility that some studies may be missed out, however the goal with this work was to summarise some of the studies that have been done for the report.

Appendix II: Additional information about analysis of survey

Data was categorised as described below and presented descriptively as frequencies. The following inferential statistics were used within this report:

- Chi-squared analyses which allowed us to compare frequencies between different groups
- Logistic regression analyses which allowed us to ascertain the odds of one group experiencing an event when compared to a reference group
- Latent Class Analysis which allowed us to identify meaningful groups who shared a high likelihood of responding similarly to the same questions

PARTICIPANT CHARACTERISTICS

We presented the frequencies of the characteristics of people within the sample in terms of the following:

Age (Q11): Calculated as date of survey completion minus date of birth. Age was categorised as 18-30, 40-49, 50-59, 60-69, 70+.

Gender (Q12): Categorised as male or female.

Ethnicity (Q14): Categorised as White Northern European, White Other or Other (due to the low number of people who responded Asian/Asian British or Black/African/Caribbean/Black British or Other or mixed ethnic group, anyone who responded positively to any of these items was characterised as 'Other').

Genetic mutation information (Q13): One copy of C282Y, two copies of C282Y, one copy of H63D, two copies of H63D, one copy of C282Y and one copy of H63D, unknown (not had genetic test or still awaiting results) or other (unlisted mutation).

Length of time since diagnosis (Q122): Calculated as the date of survey completion minus the reported date of diagnosis. This was then categorised as <1 year, 1-5 years or 5 + years.

SYMPTOMS: EVER EXPERIENCED

Note: Mental health issues have been renamed as psychological or cognitive difficulties for the sake of this report.

To determine the prevalence of ever experiencing symptoms, we examined the following questions: Whether ever experienced: Fatigue (Q15); Arthritis or joint pain (Q22); Abdominal pain (Q29); Mental health issues (Q36); Sexual health issues (Q44); Menstrual problems in women only (Q56); Skin problems (Q63); Breathing or heart problems (Q71); Hair loss (Q78); Liver problems (Q85); Pituitary dysfunction (Q93); Diabetes (Q99 and 100); Cancers (Q106).

Anyone who answered 'yes' to one of these questions was classified as having experienced that symptom. Anyone who answered 'no' was classified as not having experienced that symptom.

SYMPTOMS: CURRENTLY EXPERIENCED

To determine the prevalence of symptoms currently experienced, we asked this question: "On a scale of 0-10 how would you rank the problem of any [symptom asked about] you currently suffer?" This was examined for: Fatigue (Q17); Arthritis or joint pain (Q24); Abdominal pain (Q31); Mental health issues (Q40); Sexual health issues (Q47); Menstrual problems in women only (Q59); Skin problems (Q67); Breathing or heart problems (Q74); Hair loss (Q81); Liver problems (Q89); Pituitary dysfunction (Q95); Diabetes (Q102).

Participants could endorse any of the following for these symptoms:

0 No impact, pain or problems
1 Mild symptoms, not distressing
2 Irritating and sometimes painful symptoms, easily relieved
3 More persistent symptoms, occasionally interfering with day-to-day life, less easily relieved
4 Very persistent symptoms, regularly interfering with work and family life
5 Very persistent symptoms, interfering with work and family life most days
6 Very persistent symptoms, interfering with your life every single day
7 Painful, persistent symptoms which affect your life most days and are not relieved by medication
8 Painful, persistent symptoms which affect your quality of life every day and are not relieved by medication
9 Extremely painful, persistent symptoms which affect your quality of life every day, with no relief
10 Seriously painful, debilitating, disabling or life threatening symptoms

For each of these symptoms we categorised participants as the following, according to the score that they accorded that symptom: none or mild (0-2), persistent (3-6) or painful (7-10).

It is important to note that for this analysis we stratified by current treatment.

N.B. We conducted additional analyses for arthritis/joint pain when it was at its worst and this was categorised as above. Where we explored frequencies regarding the location of joint pain or arthritis, we did this using the responses specified in Q25.

CURRENT TREATMENT

To identify different treatment groups we used Q126:

This was categorised as not treated (responded newly diagnosed and treatment not yet started or stopped treatment or diagnosed with no treatment intended), de-ironing (responded undergoing de-ironing) or maintenance (responded in maintenance).

WHETHER DE-IRONING IMPROVED SYMPTOMS

To examine this we looked at the following questions: Fatigue (Q15); Arthritis or joint pain (Q22); Abdominal pain (Q29); Mental health issues (Q36); Sexual health issues (Q44); Menstrual problems in women only (Q56); Skin problems (Q63); Breathing or heart problems (Q71); Hair loss (Q78); Liver problems (Q85); Pituitary dysfunction (Q93); Diabetes (Q99 and 100); Cancers (Q106).

We only examined people who responded 'yes' to ever experiencing that symptom. This variable was then categorised as: Improved (responded ceased or better) or No difference or worse (responded no different or worse).

We conducted a Latent Class Analysis to examine clusters of symptoms. The analysis is described below:

Firstly, we created categories of all currently experienced symptoms by splitting each symptom up by experience of that current symptom being none or mild (0-2), persistent (3-6) or painful (7-10).

We then ran a Latent Class Analysis on all symptoms where 25% or more participants responded that they had ever experienced that symptom. Latent Class Analysis uses mathematical modelling to group categorical and/or continuous variables into classes based on likelihood estimates (77-79). These classes represent groupings of data where people responded similarly, so in the case of this analysis it would allow us to see groupings of people who report having similar symptoms.

Following this we ran a Chi-squared analysis to examine different patient characteristics, treatment, other symptoms and health conditions (predictors) to see how they are associated with symptom cluster (outcome).

DIAGNOSIS AND HEALTHCARE

We ran descriptive analyses to examine the frequencies of the following in those people who were from the UK:

Diagnosis-related issues: Prompt for diagnosis (Q113); who made formal diagnosis (Q114); tests offered at time of diagnosis (Q125); time from presentation of symptoms to diagnosis (Q115) categorised as <5 years, or 5 or more years.

Testing-related issues: Obtaining genetic test for self (Q119); obtaining genetic test for family members (Q120)

Treatment and care-related issues: Understanding from Doctor, level of support from healthcare team and skills and understanding of team providing venesection (all Q127); issues with venesection (Q129); main sources of information and support (Q131); treatment (Q121).

Additional analyses: We also ran additional analyses which are contained and explained within the Appendices.

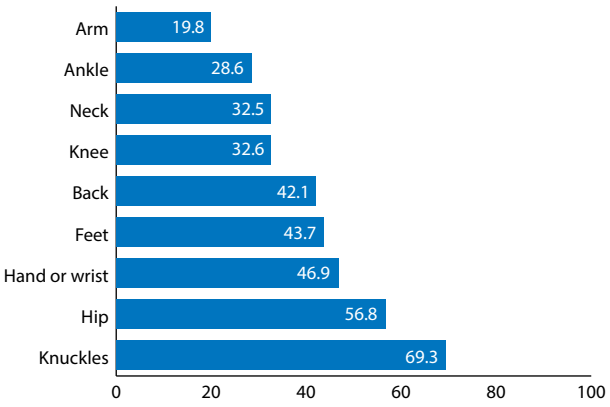
STATISTICAL SOFTWARE

We used SPSS to conduct the majority of analyses with Latent Gold being used to conduct the Latent Class Analysis.

Appendix III: Additional analyses on ever experiencing symptoms

Figure 1: Joint pain or arthritis

Location of joint pain or arthritis in people who reported experiencing joint pain or arthritis (n=1,481)



This analysis is limited to those people who responded positively to having either joint pain and/or arthritis. Thus, all presented proportions indicate the proportion of people with joint pain and/or arthritis experiencing pain in that particular location. Responses were limited to those areas asked about, and people could respond positively to more than one location.

Table A: Psychological or cognitive difficulties

In total 1,260 people responded positively to ever having had one or more of the psychological or cognitive difficulties asked about in the survey (n.b. in the survey these were called 'mental health issues'). The frequencies below represent people having ever experienced these issues.

Type of mental health issue	Frequency	% of sample
None	380	22.10
Forgetfulness or 'brain fog'	1,039	60.44
Short term memory loss	544	31.65
Dementia	2	0.001
Mood swings	513	29.84
Short temper	618	35.95
Paranoia	177	10.30
Fear of other people	188	10.93
Anxiety	558	32.46
Depression	652	37.93

Frequencies are based off the total number of people who answered this question (n=1,719)

Table B: Cancer

In total, 276 people in the sample responded positively to having a diagnosis of cancer. The types of cancer that people reported having are listed below. People could endorse more than one type of cancer. People were identified with a type of cancer if they responded positively to the following: diagnosed and then treated successfully, diagnosed and currently treated and/or diagnosed and untreatable.

When we examined how many people had a *current diagnosis* of at least 1 cancer we found that 25 people (1.55%) had a current diagnosis of cancer.

Type of cancer	Frequency	% of sample
No cancer	1,341	82.22
Brain	9	0.55
Ocular	1	0.06
Mouth	6	0.37
Oesophagus	1	0.06
Lung	3	0.18
Breast	35	3.85
Stomach	1	0.06
Liver	9	0.55
Kidney	8	0.49
Pancreas	3	0.18

Type of cancer	Frequency	% of sample
Blood	3	0.18
Skin	54	3.31
Bone Marrow	1	0.06
Bladder	5	0.30
Colon	13	0.80
Prostate	16	2.26
Testicular	3	0.42
Thyroid	8	0.49
Womb	31	3.41
Lymphoma	7	0.43

For breast and womb cancer, the frequency was calculated based on the total number of women who responded to this question (n=909) and for testicular and prostate cancer the frequency was calculated based on the total number of men who responded to this question (n=707).

Table C: Sexual health issues

In total, 943 people responded positively to ever having experienced a sexual health issue. Participants were asked to identify which issue they were having in additional questions and responses are included below.

Type of sexual health issue	Frequency	% of sample
None	688	41.70
Erectile dysfunction (men only)	281	39.41
Loss of libido (women)	546	58.40
Loss of libido (men)	239	33.52

In total, 1,650 people answered this question of whom 713 were men and 935 were women. These numbers were used to calculate frequencies.

Table D: Breathing or heart issues

In total, there were 978 people who endorsed having a minimum of one issue with breathing or heart problems. The specific issues that participants endorsed are listed below. As people could not endorse a 'none' response for this question, we included anyone who answered 'no' to the question about ever experiencing heart or breathing problems and who did not endorse any of the specific items as none.

Type of breathing or heart issue	Frequency	% of sample
None	625	38.99
Shortness of breath in day-to-day living	279	17.40
Shortness of breath under light/more exertion (e.g. a brisk walk)	527	32.88
Chest pains	234	14.60
Tingling and/or numbness	372	23.20
Arrhythmia	405	25.27
Formally diagnosed cardiomyopathy	33	2.06

In total, 1,603 people responded to this question. Frequencies are based off this.

Table E: Skin issues

In total, 1,141 people responded that they had issues with their skin. The specific issues that participants endorsed are listed below. People could endorse more than one issue.

Type of skin issue	Frequency	% of sample
None	470	29.17
Skin discolouration (tanning or bronzing)	450	27.93
Skin discolouration (yellowing)	73	4.53
Skin discolouration (greying or paling)	143	8.88
Blotchiness and/or rashes	392	24.33
Overly sensitive to touch	191	11.86
Itchiness	730	45.31
Diagnosed psoriasis	109	6.77

Frequencies are based off the total number of people who answered this question (n=1,611).

Table F: Location of skin issues

In addition to answering questions about the type of skin issues they experienced, participants could also endorse questions pertaining to the areas that these issues occurred.

Location of skin issue	Frequency	% of people reporting skin issues
Head/face	673	58.98
Arms/hands	656	57.49
Abdomen	320	28.04
Genitalia	163	14.29
Legs/feet	648	56.79

Frequencies based off the number people who reported having skin issues (n=1,141).

Table Gi: Diabetes

In total, 129 people responded that they had diabetes. The specific types of diabetes are listed below.

Type of diabetes	Frequency	% of sample
None	1,493	92.05
Type 1 diabetes	13	0.80
Type 2 diabetes	116	7.15

Frequencies based off the number people who reported having diabetes (n=1,622)

Table Gii: Bronzed diabetes

As an additional analysis we explored the number of people with type 2 diabetes, who also exhibited bronzing or skin discolouration (as 'bronze diabetes' was typically considered as the clinical presentation of haemochromatosis). We excluded people with a diagnosis of type 1 diabetes from this analysis.

Diabetes and bronzing	Frequency	% of sample
No diabetes No bronzing	423	51.46
Diabetes No bronzing	29	3.53
No diabetes Bronzing	397	48.30
Diabetes Bronzing	33	4.01

Frequencies based off the number of people who answered the question pertaining to whether they had diabetes and experienced tanning or bronzing (n=822)

Table H: Hair loss

In total, there were 536 people who endorsed having a minimum of one issue with hair loss. The specific issues that participants endorsed are listed below.

As people could not endorse a 'none' response for this question, we included anyone who answered 'no' to the question about ever experiencing hair loss and who did not endorse any of the specific items, as none.

Location of hair loss	Frequency	% of sample
None	1,092	67.08
Hair loss from the head (other than normal male balding)	337	20.70
Facial hair	43	2.64
Body hair (mild or patchy)	248	15.23
Body hair (complete)	27	1.66
Alopecia due to iron overload	13	0.80
Alopecia due to another cause	16	0.99

Frequencies are based off the total number of people who answered this question (n=1,628)

Table I: Liver problems

In total, 656 people reported having one or more of the issues listed below. As people could not endorse a 'none' response for this question, we included anyone who answered 'to my knowledge I have not experienced any liver problems' to the question about their experience of liver problems and who did not endorse any of the specific items below, as none.

Type of liver problem	Frequency	% of sample
None	855	56.59
Diagnosed but asymptomatic	236	15.62
Abdominal pain associated with the liver	186	12.31
High liver fat or fatty liver disease	307	20.32
Enlarged liver	125	8.27
Liver fibrosis	81	5.36

Type of liver problem	Frequency	% of sample
Liver cirrhosis	81	5.36
Liver cancer	8	0.53
Liver transplant	3	0.20

Frequencies are based off the total number of people who answered this question (n=1,511)

Appendix IV: Additional analyses on current symptoms

We firstly wanted to ascertain whether the experience of current symptoms was affected by age. We therefore looked at the prevalence of each symptom across three age categories: 18-39, 40-59 and 60 or older (categories were based off those used in McDonnell et al.).

We firstly examined the association of age with perceived severity of symptoms, using Chi-squared analysis (see Table A).

Table A: Association of age with current symptoms

		Aged 18-39	Aged 40-59	Aged 60 or older	X2, p-value
Current arthritis or joint pain	None or mild (0-2)	82 (50.9%)	272 (35.8%)	249 (38.3%)	13.99, p=.007
	Persistent (3-6)	54 (33.5%)	302 (39.7%)	255 (39.2%)	
	Painful and persistent (7-10)	25 (15.5%)	186 (24.5%)	146 (22.5%)	
Current fatigue	None or mild (0-2)	56 (30.6%)	312 (39.7%)	353 (53.6%)	51.82, p<.001
	Persistent (3-6)	99 (54.1%)	313 (39.9%)	218 (33.1%)	
	Painful and persistent (7-10)	28 (15.3%)	160 (20.4%)	88 (13.4%)	
Current abdominal pain	None or mild (0-2)	89 (61.0%)	437 (67.2%)	476 (81.4%)	57.54, p<.001
	Persistent (3-6)	47 (32.2%)	167 (25.7%)	98 (16.8%)	
	Painful and persistent (7-10)	10 (6.8%)	46 (7.1%)	11 (1.9%)	
Current psychological or cognitive difficulties	None or mild (0-2)	72 (41.9%)	392 (52.9%)	465 (74.5%)	101.78, p<.001
	Persistent (3-6)	81 (47.1%)	258 (34.8%)	135 (21.6%)	
	Painful and persistent (7-10)	19 (11.0%)	91 (12.3%)	24 (3.8%)	
Current sexual health issues	None or mild (0-2)	67 (51.9%)	400 (61.0%)	399 (68.1%)	24.94, p<.001
	Persistent (3-6)	53 (41.1%)	176 (26.8%)	145 (24.7%)	
	Painful and persistent (7-10)	9 (7.0%)	80 (12.2%)	42 (7.2%)	
Current menstrual problems	None or mild (0-2)	39 (52.0%)	280 (77.6%)	280 (97.2%)	99.03, 0<.001
	Persistent (3-6)	24 (32.0%)	57 (15.8%)	5 (1.7%)	
	Painful and persistent (7-10)	12 (16.0%)	24 (6.6%)	3 (1.0%)	
Current skin problems	None or mild (0-2)	99 (71.2%)	479 (70.4%)	468 (74.4%)	4.23, p=0.38
	Persistent (3-6)	36 (25.9%)	166 (24.4%)	132 (21.0%)	
	Painful and persistent (7-10)	4 (2.9%)	35 (5.1%)	29 (4.6%)	

		Aged 18-39	Aged 40-59	Aged 60 or older	X2, p-value
Current breathing or heart problems	None or mild (0-2)	91 (71.7%)	435 (68.5%)	468 (77.9%)	16.74, p=.002
	Persistent (3-6)	32 (25.2%)	155 (24.4%)	101 (16.8%)	
	Painful and persistent (7-10)	4 (3.1%)	42 (7.1%)	32 (5.3%)	
Current hair loss	None or mild (0-2)	76 (85.4%)	464 (87.5%)	517 (91.8%)	7.04, p=.13
	Persistent (3-6)	9 (10.1%)	48 (9.1%)	33 (5.9%)	
	Painful and persistent (7-10)	4 (4.5%)	18 (3.4%	13 (2.3%)	
Current liver problems	None or mild (0-2)	68 (81.9%)	460 (83.6%)	529 (92.5%)	23.60, p<.001
	Persistent (3-6)	11 (13.3%)	62 (11.3%)	32 (5.6%)	
	Painful and persistent (7-10)	4 (4.8%)	28 (5.1%)	11 (1.9%)	
Current pituitary dys-function	None or mild (0-2)	51 (82.3%)	424 (94.4%)	488 (97.0%)	29.09, p<.001
	Persistent (3-6)	9 (14.5%)	16 (3.6%)	10 (2.0%)	
	Painful and persistent (7-10)	2 (3.2%)	9 (2.0%)	5 (1.0%)	
Current diabetes	None or mild (0-2)	59 (90.8%)	419 (92.1%)	475 (95.0%)	6.34, p=.18
	Persistent (3-6)	4 (6.2%)	24 (5.3%)	21 (4.2%)	
	Painful and persistent (7-10)	2 (3.1%)	12 (2.6%)	4 (0.8%)	

We then wanted to determine whether the experience of current symptoms was affected by treatment status. To do this we compared the experience of symptoms across each possible response to the question on treatment, using Chi-Squared analysis (see Table B).

Table B: Current experience of symptoms stratified by treatment status

		Initial de-ironing	Maintenance	Treatment stopped	Newly diagnosed not yet treated	Diagnosed with no treatment intended	X2, p-value
Current arthritis or joint pain	None or mild (0-2)	80 (32.1%)	373 (40.2%)	10 (27.8%)	25 (40.3%)	36 (52.9%)	23.66, p=.003
	Persistent (3-6)	114 (45.8%)	350 (37.8%)	10 (27.8%)	22 (35.5%)	23 (13.2%)	
	Painful and persistent (7-10)	55 (22.1%)	204 (22.0%)	16 (44.4%)	15 (34.2%)	9 (13.2%)	
Current fatigue	None or mild (0-2)	91 (35.3%)	469 (49.0%)	8 (21.1%)	15 (23.8%)	34 (47.2%)	40.45, p<.001
	Persistent (3-6)	122 (47.3%)	341 (35.6%)	19 (50.0%)	36 (57.1%)	23 (31.9%)	
	Painful and persistent (7-10)	45 (17.4%)	147 (15.4%)	11 (28.9%)	12 (19.0%)	15 (20.8%)	

		Initial de-ironing	Maintenance	Treatment stopped	Newly diagnosed not yet treated	Diagnosed with no treatment intended	X2, p-value
Current abdominal pain	None or mild (0-2)	151 (71.6%)	623 (75.0%)	16 (53.3%)	32 (61.5%)	44 (72.1%)	12.53, p=.13
	Persistent (3-6)	52 (24.6%)	170 (20.5%)	12 (40.0%)	17 (32.7%)	15 (24.6%)	
	Painful and persistent (7-10)	8 (3.8%)	38 (4.6%)	2 (6.7%)	3 (5.8%)	2 (3.3%)	
Current psychological or cognitive difficulties	None or mild (0-2)	124 (50.4%)	595 (65.7%)	18 (50.0%)	21 (35.0%)	41 (58.6%)	41.53, p<.001
	Persistent (3-6)	94 (38.2%)	246 (27.2%)	16 (44.4%)	31 (51.7%)	21 (30.0%)	
	Painful and persistent (7-10)	28 (11.4%)	64 (7.1%)	2 (5.6%)	8 (13.3%)	8 (11.4%)	
Current sexual health issues	None or mild (0-2)	151 (68.0%)	519 (63.7%)	17 (50.0%)	25 (51.0%)	37 (64.9%)	11.44, p=.12
	Persistent (3-6)	57 (25.7%)	215 (26.4%)	11 (32.4%)	19 (38.8%)	16 (28.1%)	
	Painful and persistent (7-10)	14 (6.3%)	81 (9.9%)	6 (17.6%)	5 (10.2%)	4 (7.0%)	
Current menstrual problems	None or mild (0-2)	101 (84.9%)	339 (86.3%)	13 (76.5%)	21 (65.6%)	37 (68.5%)	Not reported as not enough observations in cells
	Persistent (3-6)	11 (9.2%)	36 (9.2%)	4 (23.5%)	7 (21.9%)	13 (24.1%)	
	Painful and persistent (7-10)	7 (5.9%)	18 (4.6%)	0	4 (12.5%)	4 (7.4%)	
Current skin problems	None or mild (0-2)	160 (70.5%)	643 (74.2%)	19 (55.9%)	39 (75.0%)	46 (70.8%)	7.67, p=.47
	Persistent (3-6)	55 (24.2%)	190 (21.9%)	13 (38.2%)	11 (21.2%)	15 (23.1%)	
	Painful and persistent (7-10)	12 (5.3%)	33 (3.8%)	2 (5.9%)	2 (3.8%)	4 (6.2%)	
Current breathing or heart problems	None or mild (0-2)	158 (70.9%)	608 (75.0%)	19 (55.5%)	34 (65.4%)	43 (78.2%)	11.27, p=.19
	Persistent (3-6)	49 (22.0%)	161 (19.9%)	12 (35.3%)	15 (28.8%)	11 (20.0%)	
	Painful and persistent (7-10)	16 (7.2%)	42 (5.2%)	3 (8.8%)	3 (5.8%)	1 (1.8%)	

		Initial de-ironing	Maintenance	Treatment stopped	Newly diagnosed not yet treated	Diagnosed with no treatment intended	X2, p-value
Current hair loss	None or mild (0-2)	165 (88.2%)	647 (90.1%)	27 (100%)	35 (85.4%)	44 (93.6%)	Not reported as not enough observations in cells
	Persistent (3-6)	18 (9.6%)	52 (7.2%)	0	2 (4.9%)	2 (4.3%)	
	Painful and persistent (7-10)	4 (2.1%)	19 (2.6%)	0	4 (9.8%)	1 (2.1%)	
Current liver problems	None or mild (0-2)	170 (86.7%)	660 (89.7%)	27 (93.1%)	28 (75.7%)	38 (82.6%)	12.21, p=.14
	Persistent (3-6)	19 (9.7%)	52 (7.1%)	1 (3.4%)	7 (18.9%)	7 (15.2%)	
	Painful and persistent (7-10)	7 (3.6%)	24 (3.3%)	1 (3.4%)	2 (5.4%)	1 (2.2%)	
Current pituitary dys-function	None or mild (0-2)	155 (93.4%)	594 (96.1%)	23 (100%)	25 (89.3%)	41 (93.2%)	Not reported as not enough observations in cells
	Persistent (3-6)	9 (5.4%)	15 (2.4%)	0	2 (7.1%)	3 (6.8%)	
	Painful and persistent (7-10)	2 (1.2%)	9 (1.5%)	0	1 (3.6%)	0	
Current diabetes	None or mild (0-2)	156 (95.1%)	590 (93.8%)	21 (84.0%)	27 (93.1%)	43 (100%)	Not reported as not enough observations in cells
	Persistent (3-6)	6 (3.7%)	29 (4.6%)	2 (8.0%)	1 (3.4%)	0	
	Painful and persistent (7-10)	2 (1.2%)	10 (1.6%)	2 (8.0%)	1 (3.4%)	0	

Appendix V: Latent Class Analysis of current symptoms

To derive groups of symptoms we used a technique called Latent Class Analysis. This allowed us to identify symptom 'clusters' among survey respondents. The clusters represent groups of people who have a similar pattern of symptoms, such that those people who are in the same group have very similar patterns of symptoms to each other, whilst having as different a pattern of symptoms as those in the other groups as possible. In other words, this analysis allows us to see groupings of people who report having similar symptom profiles.

The first part of this analysis involved identifying the optimal number of groups needed to best reflect the data. To do this we examined model fit indices (log-likelihoods and Bayesian Information Criteria). The number of optimal groups was selected by determining the lowest value for the Bayesian Information Criteria (BIC) and log-likelihood (LL) while also having parsimony with the lowest number of parameters. The 3 cluster fit was determined to be the best fitting model as it had the lowest BIC value and the lowest number of parameters.

This data indicated that the best model was one with three groups (see Table A).

Table A: Model fit criteria

		LL	BIC(LL)	Npar
Model1	1-Cluster	-5729.4165	11568.0925	16
Model2	2-Cluster	-5112.3220	10395.3618	25
Model3	3-Cluster	-4982.6015	10197.3793	34
Model4	4-Cluster	-4962.6501	10218.9349	43
Model5	5-Cluster	-4944.4472	10243.9874	52
Model6	6-Cluster	-4923.1410	10262.8335	61
Model7	7-Cluster	-4917.1380	10312.2858	70

LL: Log-likelihood
BIC: Bayesian Informational Criteria.
Npar: Number of parameters

Once the optimal number of groups was determined, we then examined the characteristics of each of the groups that we had identified so that we could characterise the symptoms each group presented. The data that we used to do that is presented in Table B.

Table B: Characteristics of groups identified using Latent Class Analysis

		Group 1 (48.7%)	Group 2 (36.6%)	Group 3 (14.7%)
Current liver problems	None or mild (score 0-2)	0.8919	0.9958	0.5449
	Persistent (score 3-6)	0.0932	0.0042	0.2621
	Painful (score 7-10)	0.0149	0	0.193
Current skin problems	0-2 none or mild	0.7672	0.8981	0.3179
	3-6 persistent	0.2184	0.0994	0.5006
	7-10 painful	0.0143	0.0025	0.1814
Current breathing and/or heart problems	0-2 none or mild	0.7716	0.966	0.1569
	3-6 persistent	0.2143	0.0337	0.4864
	7-10 painful	0.0141	0.0003	0.3567
Current fatigue	0-2 none or mild	0.2939	0.9098	0.0156
	3-6 persistent	0.5721	0.0892	0.2986
	7-10 painful	0.134	0.0011	0.6858
Current abdominal pain	0-2 none or mild	0.7554	0.9815	0.2304
	3-6 persistent	0.2307	0.0184	0.5293
	7-10 painful	0.0139	0.0001	0.2403
Current psychological or cognitive difficulties	0-2 none or mild	0.5729	0.9669	0.1643
	3-6 persistent	0.3667	0.0328	0.4778
	7-10 painful	0.0604	0.0003	0.3579
Current sexual health issues	0-2 none or mild	0.6511	0.8954	0.2161
	3-6 persistent	0.2913	0.0997	0.421
	7-10 painful	0.0576	0.0049	0.3629
Current arthritis or joint pain	0-2 none or mild	0.2264	0.7692	0.0224
	3-6 persistent	0.5307	0.2187	0.2824
	7-10 painful	0.243	0.0121	0.6951

Green: Group had a high probability of responding that symptom currently had a low/mild impact on life (score of 0-2 on question).
Yellow: Group had a high probability of responding that symptom currently had a persistent impact on life (score of 3-6 of question).
Red: Group had a high probability of responding that symptom currently had a painful impact on life (score of 7-10 on question).

For this analysis, survey respondents were asked to rate on a scale from 0-10 their current experience of various symptoms. For the sake of identifying meaningful groups we only included those symptoms where a minimum of 25% of respondents reported ever experiencing that symptom. As this analysis relies on survey respondents having data for all symptoms, there were 924 people included in this analysis.

Finally, to examine whether there were differences between groups for a variety of sociodemographic, treatment and health-related characteristics, we conducted Chi-squared analyses (see Table C). We found that the group who had persistent and painful symptoms were significantly younger than other groups, and were more likely to have had 5 or more years between noticing symptoms to time of diagnosis, were less likely to be in maintenance and were more likely to have ever experienced cancer and pituitary dysfunction. In comparison the group with no symptoms were significantly older, more likely to have been diagnosed for 5 or more years, more likely to have a shorter time between noticing symptoms to diagnosis, less likely to not be currently treated and less likely than other groups to have ever experienced pituitary dysfunction.

Table C: Sociodemographic, treatment and health-related characteristics of symptom groups.

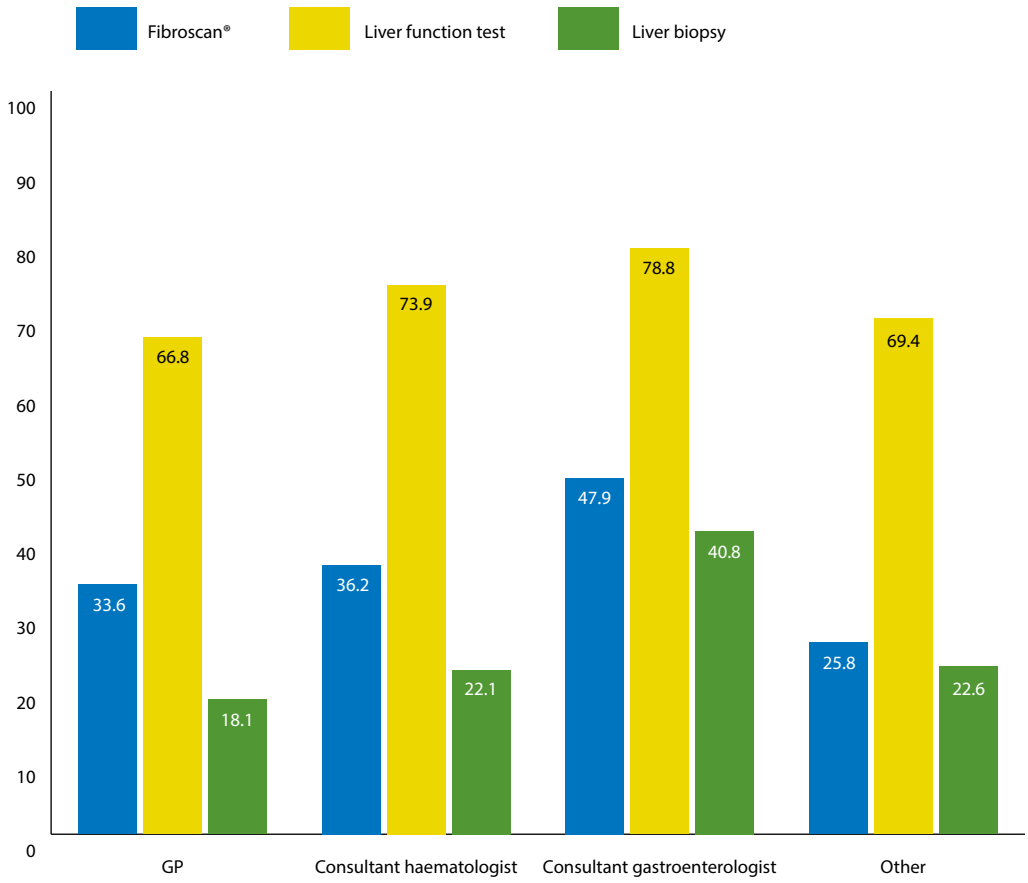
		Group 1: Persistent fatigue or joint pain	Group 2: No symptoms	Group 3: Persistent and painful symptoms
Age ***	18-39	29 (6.5%)	20 (5.8%)	9 (6.8%)
	40-59	214 (47.9%)	140 (40.6%)	84 (63.6%)
	60 or older	204 (45.6%)	185 (53.6%)	39 (29.5%)
Sex ***	Female	268 (60.0%)	157 (45.5%)	73 (55.3%)
	Male	179 (40.0%)	188 (54.5%)	59 (44.7%)
Years since diagnosis	1 or less	103 (25.9%)	68 (22.6%)	34 (30.4%)
	1 to 4 years	142 (35.7%)	92 (30.6%)	38 (33.9%)
	5 or more years	153 (38.4%)	141 (46.8%)	40 (35.7%)
Time between noticing symptoms to diagnosis ***	Less than 5 years	345 (86.0%)	285 (94.1%)	84 (74.3%)
	5 or more years	56 (14.0%)	18 (5.9%)	29 (25.7%)
Current treatment ***	Currently undergoing de-ironing	93 (60.8%)	267 (46.8%)	45 (49.5%)
	Currently undergoing maintenance	37 (24.2%)	238 (41.8%)	25 (27.5%)
	Treatment stopped	14 (3.5%)	3 (1.0%)	6 (5.5%)
	Treatment not yet started	14 (3.5%)	7 (2.3%)	10 (9.2%)
	No treatment intended	17 (4.2%)	15 (5.0%)	5 (4.6%)
Cancer ***	Yes	75 (17.0%)	62 (18.2%)	38 (30.2%)
	No	367 (83.0%)	279 (81.8%)	88 (69.8%)
Diabetes	Yes	41 (9.2%)	35 (10.4%)	19 (14.6%)
	No	403 (90.8%)	303 (89.6%)	111 (85.4%)
Pituitary dysfunction ***	Yes	28 (6.3%)	7 (2.1%)	15 (11.7%)
	No	416 (93.7%)	334 (97.9%)	113 (88.3%)

While the total number of survey respondents included in the Latent Class Analysis was 924, it should be noted that there was additional missing data for the predictors examined in this analysis. Therefore, the total number of survey respondents included in each Chi-squared analysis ranged from 924 (gender) to 681 (years since diagnosis).

Appendix VI: Additional analyses on diagnosis and treatment

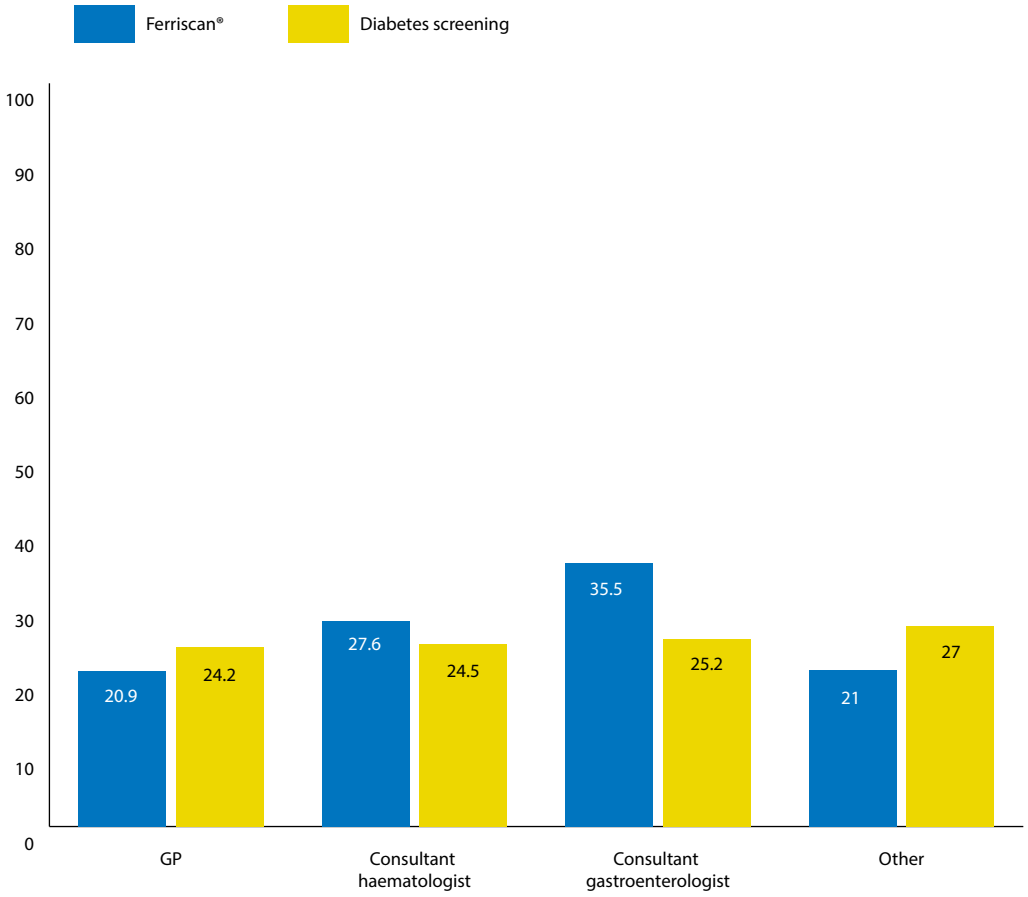
To determine whether being diagnosed by different professionals might be associated with differences in the care offered at diagnosis, we examined the frequency of people who were offered liver tests, Fibroscans and/or diabetes screening at diagnosis, stratified by the type of health professional who made their diagnosis (see Figures 1 and 2).

Figure 1: Proportion of people offered liver tests at diagnosis based on who made diagnosis



Results were analysed with Chi-squared tests. Results indicated that there was a significant difference between groups for the likelihood of being offered a Fibroscan® ($X^2(3, n=690)=13.71$, $p<.01$) or liver biopsy ($X^2(3, n=710)=27.24$, $p<.001$). However, there was no significant difference between groups in the likelihood of being offered a liver function test.

Figure 2: Proportion of people offered additional tests based on who made diagnosis



Results were analysed with Chi-squared tests. Results indicated that there was a significant difference between groups for the likelihood of being offered a Ferriscan® (X2(3, n=699)=11.31, p<.01). However, there was no significant difference between groups in the likelihood of being offered a diabetes test (X2(3, n=622)=0.27, p=.97).

To determine whether the information and support offered at diagnosis differed by the healthcare professional who made the diagnosis, we examined the differences in the frequencies of people being offered different sources of support, stratified by who made the diagnosis (see Table A).

Table A: Sources of support accessed by patients based on who made the diagnosis

	GP N(%)	Consultant haematologist N(%)	Consultant gastroenterologist N(%)	Other N(%)	X2, p-value
None of tests specified	109 (34.4%)	122 (36.3%)	86 (38.2%)	62 (43.4%)	3.61, p=.31
Dietary advice	85 (26.8%)	115 (34.2%)	71 (31.6%)	45 (31.5%)	4.28, p=.23
Counselling	14 (4.4%)	15 (4.5%)	14 (6.2%)	13 (9.1%)	5.20, p=.16
Links to HUK	121 (38.2%)	131 (39.0%)	83 (36.9%)	43 (40.1%)	3.70, p=.30
Reading material	116 (36.6%)	125 (37.2%)	82 (36.4%)	43 (30.1%)	2.46, p=.48
Blood donation information	35 (11.0%)	61 (18.2%)	21 (9.3%)	8 (5.6%)	19.01, p<.001

DIFFICULTIES WITH VENESECTION AND RATING OF NURSE/DOCTOR WHO PERFORMS VENESECTION

To ascertain whether those people who rated the skill of the nurse/doctor who performed their venesection as poor or inadequate was associated with difficulties in having venesection carried out, we examined the rating of venesection staff with difficulties that were asked about (see Table B). We did not include skill level of venesection staff within this analysis as it was a repetition of the rating question.

Table B: Association of skill level of staff who perform venesection with issues with venesection (n=882)

	Excellent, good or adequate skill level of venesection nurse/doctor	Poor or inadequate skill level of venesection nurse/doctor	X2, p-value
Experienced no issues with venesection	567 (68.1%)	14 (28.0%)	33.82, p<.001
Difficulty finding suitable veins	76 (9.1%)	16 (32.0%)	26.39, p<.001
Need for additional support	48 (5.8%)	6 (12.0%)	3.19, p=.07
Travel required or location of service	98 (11.8%)	10 (20.0%)	2.97, p=.09
Accessibility issues	9 (1.1%)	4 (8.0%)	15.55, p<.001
Appointment availability	88 (10.6%)	10 (20%)	4.24, p<.05

Authored by The University of Surrey.
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