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EXCLUSIVE

Genetic test "screening campaign" may be causing unnecessary alarm, experts warn

A campaign to screen thousands of people for haemochromatosis using direct-to-consumer genetic tests has raised questions over what diagnosis claims are being made and how tests are regulated, report Elisabeth Mahase and Gareth Iacobucci

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The UK National Screening Committee does not recommend screening for haemochromatosis, an inherited condition that causes iron build-up and can damage the liver, joints, pancreas, and heart in adults. It says that although a faulty *HFE* gene is known to cause iron build-up, "this does not happen to every person with the faulty gene" and warned that screening would identify people who may never experience symptoms. There was "no evidence" to suggest that a screening programme was "the best way of helping people with the condition," it concluded after a review in 2021.[1]

But the charity Haemochromatosis UK has been carrying out what it terms "screening programmes" in Northern Ireland since 2021 to see if people have gene mutations associated with the condition, *The BMJ* has learnt. Haemochromatosis is known to be particularly common in Ireland, Scotland, and Wales.[2]

The genetic test used by the charity looks to find people who have mutations on the *HFE* gene. Three of the variations that could be identified—one or two copies of H63D, a single H63D plus a single C282Y variant, or a single C282Y—all point to a low risk of having the condition. The other potential variation—two copies of C282Y—indicates a higher risk of haemochromatosis.

The charity has so far contacted more than 36 000 households in Belfast and Newry to raise awareness of the condition and to offer free genetic testing.[3] It has dispatched around 360 test kits to these areas and has also tested just over 200 people in Derry-Londonderry and Carrickfergus through another free testing campaign.[4] It told *The BMJ* that the screening programme was launched "in response to grassroots, cross community concerns about the observed, high prevalence of genetic haemochromatosis" and that it hopes that this work "can help inform the NHS's response to a condition in which early diagnosis demonstrably improves outcomes."

Overdiagnosis and anxiety

However, clinicians and researchers have expressed concern to *The BMJ* over the campaign, noting that it may be unnecessarily alarming patients by misrepresenting "usually benign" gene variants while also diverting scarce NHS resources away from people with higher risk variants that can lead to serious disease. The NHS in Northern Ireland is currently under extreme pressure,[5] with a deepening GP workforce crisis, large numbers of vacancies throughout the service, and lengthy waiting times.[6]

The BMJ understands that people found to have a single H63D mutation, for example, have been told by the charity that "you have this variant of the condition: carrier H63D."

A letter from Haemochromatosis UK sent to someone who had taken the test, seen by *The BMJ*, says that people found to have a single H63D mutation "have this variant of the condition: carrier H63D." This is despite the charity's guidance to GPs saying that H63D carriers are "very low risk" and "generally do not accumulate enough iron to cause any tissue damage," while most people with two copies of H63D "never develop symptoms or load iron." The guidance also suggests that most variations of these gene mutations that can be detected through the test are low risk and that most people do not usually load iron as a result.[7 8]

The letter from Haemochromatosis UK continues, "We have written to your GP with a copy of your results. Your GP is now aware that you have been genetically tested and what the results are."

The Cambridge consultant hepatologist Bill Griffiths, a former member of Haemochromatosis UK's clinical advisory panel, told *The BMJ*, "You can cause a lot of anxiety if you just offer to screen for this condition randomly and then, when you have the genetic results, you are not very careful about how you relay the result to that person—who may have wanted the test because they felt tired, for example, but did not actually have any evidence of iron overload. Haemochromatosis UK could be creating a lot of overdiagnosis and a lot of anxiety in the process. Furthermore, it detracts from those who genuinely have the condition."

Griffiths, who has been running a haemochromatosis clinic since 2000, said that although there was an access problem for tests, more regulation was needed for this type of screening.

"Genetic testing needs to be interpreted in the context of presence of symptoms and iron indices, to then determine whether the patient has haemochromatosis, whether they are just at risk of the condition, and if so what the risk is," he told *The BMJ*. "And then it's about at what point preventive

measures should be put in place if treatment is not appropriate straight away and what should those measures be exactly. We have seen numerous examples where people have been, in my opinion, ill informed."

In response to concerns, Haemochromatosis UK has said that all letters are drafted by an appropriately qualified and regulated clinician. It adds that, on the basis of feedback[9] from people undergoing screening, it is confident that the campaign has not increased anxiety and that everyone taking the test is able to access a free 45 minute phone or video call appointment with a specialist advanced nurse practitioner, provided by the charity, to discuss their results.

Misleading claims?

On the strength of its screening campaign the charity has also claimed that as many as one in 10 people in Northern Ireland "have the condition, but most are unaware that they do."[10 11] This is based on the number of people found to have one of the gene mutations after taking a supplied test, rather than people who have had the condition diagnosed or are experiencing symptoms. Before this the charity had said that one in 113 people in Northern Ireland had the condition.[12]

David Melzer, professor of epidemiology and public health at the University of Exeter, said, "This clear misreporting of low risk iron variants as always causing disease highlights the need for an evidence based approach to genetic testing and to provide accurate information to people taking tests. It underlines the need for effective regulation of direct-to-consumer genetic tests, and of claims made by those promoting their testing in the media."

Melzer, who has led UK Biobank studies on haemochromatosis,[13] was previously a member of the Haemochromatosis UK clinical advisory group but told *The BMJ* that he had resigned over his concerns.

Jeremy Shearman, consultant hepatologist and gastroenterologist in Warwick with an interest in haemochromatosis, was the inaugural chair of Haemochromatosis UK's clinical advisory panel but stepped down after his tenure ended in 2021. He was not on the charity's clinical advisory panel during the time of the campaign, but he told *The BMJ* that he shared Meltzer's concerns that screening on the basis of genetic tests without measuring iron stores could lead to misdiagnosis with the risk of health anxiety, unnecessary stigma, and "irrational" consumption of healthcare resources.

"We've got to counsel against a naive model of haemochromatosis that anyone who has fatigue and a raised ferritin by definition has the condition. I think genetic testing without assessment of the patient's other risk factors and measures of iron overload is potentially harmful," said Shearman, who currently chairs the national special interest group on haemochromatosis.

He said he believed that the situation was "unfortunate, regrettable . . . and largely avoidable," and he urged the charity to work more closely with clinicians and clinical scientists with experience in the condition. "I'd be very keen to bring anyone interested in haemochromatosis research to the same table so that we can derive consensus on some of these difficult issues," he added.

Haemochromatosis UK has rejected claims that it could be misleading people through the screening campaigns and says that it stands by its numbers, welcoming "requests from accredited researchers to access and explore the dataset themselves."

Better regulation

In 2021 a House of Commons Science and Technology Committee report warned that direct-to-consumer genetic tests could lead to consumers overestimating their risk of an illness or seeking unnecessary treatment.[14] It said that a combination of low public understanding, variable test quality, and the complexity of correctly interpreting genomic results suggested that the "chance of results being inaccurate or misinterpreted was high."

The committee called on the government to subject these tests to pre-market assessment by an external body and to amend current regulation of direct-to-consumer genomic tests to improve the requirements on the information and support provided to consumers.

These direct-to-consumer genetic testing kits fall under the remit of the UK Medical Device Regulations 2002 when they have a medical intended purpose. However, while the Medicines and Healthcare Products Regulatory Agency is the responsible regulator for such medical devices and diagnostics, it does not itself approve them. It relies on the manufacturer to self-declare compliance or be validated and certified by an approved body. It then investigates the device if there are allegations of non-compliance or adverse incident reports that cause concern.[15]

"At risk" families value screening

In a statement on concerns Haemochromatosis UK said, "We recognise that not all clinicians and academics agree on all aspects of the condition, or its treatment . . . Clinical confusion and academic controversy continue to adversely impact patient care. Families at risk well understand the value of preventative healthcare."

The charity also says that it supports thousands of people who experience ill health linked to the lower risk variants. "Some, but not all, clinicians believe that only C282y homozygotes are at risk of ill health," it said. "However, our support community of over 10 000 people routinely report ill health associated with compound heterozygosity (i.e., C282y plus H63d) and H63D homozygosity (i.e., two H63d copies).

"Many people with these variants are already receiving active treatment within the NHS. By accepting an academic narrative that only C282Y homozygotes are at risk of ill health and by not screening for these pathogenic variants, non-C282Y homozygotes are unfairly disadvantaged."

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