| **National Institute for Health and Clinical Excellence**<br><br>**Scope on Haemochromatosis**<br>**Document cover sheet** | | | |
|---|---|---|---|
| Date | Version number | Editor | Action |
| 22/01/22 | 1 | Developer team | Post-SHW and SM2 version |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Guideline scope

## Haemochromatosis

The Department of Health in England and NHS England has asked NICE to develop a new guideline on haemochromatosis.

The guideline will be developed using the methods and processes outlined in developing NICE guidelines: the manual.

This guideline will also be used to develop the NICE quality standard for haemochromatosis.

## 1 Why the guideline is needed

Genetic haemochromatosis (GH) is the most commonly inherited condition in Northern Europe. The overall prevalence in the United Kingdom is 1 in 156, with higher rates still in populations of Celtic ancestry. In the vast majority of people with GH, the condition is due to the presence of two copies of a specific mutation in the

high iron (HFE) gene (p.C282Y homozygosity). Very rarely iron loading may be demonstrated in individuals with atypical HFE genotypes (pC282Y/pH63D compound heterozygotes or pH63D homozygotes. GH is a recessive genetic condition, and the gene needs to be inherited from both parents to have the potential of developing the condition.

Clinical manifestations of haemochromatosis depend on several factors such as degree of iron overload, disease stage and severity of organ damage. Signs and symptoms of GH usually appear between the ages of 30 and 60 years. Men are more likely to develop GH at an earlier age. Although the underlying genetic condition is as common in women as men, the condition often presents later due to the regular blood loss associated with menstruation and pregnancy.

The genetic mutation causing GH leads to increased absorption of iron from the diet. As the body has no means by which it can eliminate or excrete iron this builds up, leading to significant iron overload. The liver experiences the heaviest burden of iron overload. Without treatment, excess iron in the liver causes cirrhosis ultimately resulting in liver failure or the development of liver cancer (hepatocellular carcinoma). The condition can also lead to iron deposition in the pancreas, heart, and pituitary gland. A significant number of people with GH report joint pain and some might develop a characteristic pattern of joint damage (haemochromatosis arthropathy).

If GH is diagnosed early, treatment will reduce the risk of serious complications and death. Treatment is by the regular removal of blood (therapeutic venesection/therapeutic phlebotomy). This treatment requires significant time and commitment from the patient to attend treatment sessions and requires regular clinical supervision.

**Current practice**

There is significant variation in current practice. Diagnosis may be based on incomplete clinical data such as borderline tests of iron overload and/or an atypical HFE genotype (i.e., a genotype other than pC282Y homozygosity). Access to venesection can be challenging for some people due to disparity in the availability of services in England, and the amount of time required for treatment. Clinical follow-up

and ongoing monitoring of people with GH, and cascade screening (cascade screening is a mechanism for identifying people at risk for a genetic condition by a process of systematic family tracing) amongst first degree relatives, also varies. Better recognition of people with GH and awareness of how the condition is managed would improve care and reduce associated complications. This guideline aims to improve the management of GH and to improve quality of life for people with GH.

# 2 Who the guideline is for

This guideline is for:

- healthcare professionals providing NHS-commissioned services
- commissioners of health and social care services
- people using services, their families and carers, and the public.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government and Northern Ireland Executive.

## Equality considerations

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to gender, ethnicity, disability and pregnancy.

# 3 What the guideline will cover

## 3.1 Who is the focus?

**Groups that will be covered**

- Adults (18 and over) with suspected or confirmed genetic haemochromatosis.

- Adult first degree relatives (18 and over) of people who have been confirmed with genetic haemochromatosis.

**Groups that will not be covered**

- People with non-HFE genetic iron overload, such as juvenile haemochromatosis and ferroportin disease.
- People with secondary iron overload (e.g., increased iron intake, repeated transfusions, thalassemia, haemoglobinopathies (e.g., sickle disease), congenital haemolytic anaemias (e.g., hereditary spherocytosis) or myelodysplasia).

## 3.2 Settings

**Settings that will be covered**

- All settings where NHS commissioned care is provided.

# 4 Activities, services or aspects of care

**Key areas that will be covered**

We will look at evidence in the areas below when developing the guideline, but it may not be possible to make recommendations in all the areas.

1 Information and support
   - For people with suspected or diagnosed genetic haemochromatosis, non-expressing homozygotes and carriers (and their families and carers) [non-expressing homozygotes defined as pC282Y homozygotes who have not yet developed any symptoms or signs of genetic haemochromatosis; carriers defined as p.C282Y and p.H63D compound heterozygotes who have not yet developed any symptoms or signs of genetic haemochromatosis].

2 Initial identification and assessment of people with suspected genetic haemochromatosis
   - Symptoms and signs
   - Existing comorbidities where genetic haemochromatosis might be the cause (e.g., liver disease, diabetes and musculoskeletal conditions including osteoarthritis and osteoporosis)

- Incidental findings (e.g., raised ferritin, abnormal liver function tests, abnormal findings on imaging of joints or liver)

3 Diagnosis of genetic haemochromatosis

- Initial tests including serum ferritin and transferrin saturation.
- Tests for confirmation of genetic haemochromatosis - HFE mutation analysis (testing for both p.C282Y and p.H63D).
- Investigations for confirmation of iron overload such as liver MRI or liver biopsy (investigations for both p.C282Y homozygotes and p.C282Y and p.H63D compound heterozygotes).

4 Cascade screening

- HFE genotyping (testing for both p.C282Y and p.H63D) for first degree relatives of people with known HFE mutations (index case has to be a p.C282Y homozygote either with or without clinical manifestations).

5 Managing genetic haemochromatosis

Treatment strategies to reduce iron overload (including induction and maintenance phases of treatments separately):

- Treatment strategies such as therapeutic venesection (therapeutic phlebotomy or blood donation), erythrocytapheresis and chelation therapy.
- Treatment end points including ferritin, transferrin saturation and liver iron concentrations.

Additional measures to enhance existing treatments to reduce iron overload:

- Additional measures including dietary modification, use of supplements (iron and vitamin C), proton pump inhibitors, hormonal contraceptives and modification of alcohol intake.

Strategies to prevent progression of disease:

- Strategies to prevent joint disease related to complications of genetic haemochromatosis [treatment/s and additional measures can prevent complications related to genetic haemochromatosis for all organs, the only exception is joint damage].

7 Ongoing monitoring

The frequency and content of monitoring for the following groups:

- people with genetic mutation without iron overload (people identified by cascade screening).
- people with genetic mutation with iron overload and are on treatment
- people with end organ damage.

## Areas that will not be covered

1. Treatment of co-existing conditions.
2. Managing complications related to genetic haemochromatosis.
3. Other rarer genetic conditions, which can mimic genetic haemochromatosis but whose management is significantly different.
4. Secondary haemochromatosis.
5. Management of hyperferritinaemia due to causes other than genetic haemochromatosis.

## Related NICE guidance

### Published

- Type 2 diabetes in adults (2022) NICE 2022 NG28
- Osteoarthritis in over 16s (2022) NICE guideline NG226
- Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome (2021) NICE guideline NG206
- FibroScan for assessing liver fibrosis and cirrhosis in primary care (2020). Medtech innovation briefing [MIB216]
- Thyroid disease (2019) NICE guideline NG145
- Menopause: diagnosis and management (2019) NICE guideline NG23
- Chronic heart failure in adults (2018) NICE guideline NG106
- Fertility problems (updated 2017) NICE guideline CG156
- Fractures (non-complex) (2016) NICE guideline NG38
- Cirrhosis in over 16s (2016) NICE guideline CG50
- Non-alcoholic fatty liver disease (NAFLD) (2016) NICE guideline NG49
- Osteoporosis (2012) NICE guideline CG146
- Alcohol-use disorders: diagnosis and management of physical complications (2017) NICE guideline CG100

- Alcohol-use disorders: prevention (2010) NICE guideline PH24
- Alcohol-use disorders: diagnosis, assessment and management of harmful drinking (high-risk drinking) and alcohol dependence (2011) NICE guideline CG115

**In development**

- Osteoporosis: risk assessment, treatment, and fragility fracture prevention (update). NICE guideline. Publication expected January 2025.
- MRI-based technologies for assessing non-alcoholic fatty liver disease. In development [GID-DG10045]. Publication expected December 2022.

**NICE guidance about the experience of people using NHS services**

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to haemochromatosis:

- Shared decision making (2021) NICE guideline NG197
- Medicines optimisation (2015) NICE guideline NG5
- Patient experience in adult NHS services (2012) NICE guideline CG138
- Service user experience in adult mental health (2011) NICE guideline CG136
- Medicines adherence (2009) NICE guideline CG76

## 4.2 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and personal social services (PSS) perspective, as appropriate.

## 4.3 Key issues and draft questions

While writing this scope, we have identified the following key issues and draft review questions related to them:

1 Information and support for people with suspected or diagnosed genetic haemochromatosis, non-expressing homozygotes and carriers (and their families and carers)

1.1 What information and support is needed by people with suspected or confirmed genetic haemochromatosis, non-expressing homozygotes and carriers and their families or carers?

2 Initial identification and assessment of people with suspected genetic haemochromatosis

2.1 What symptoms and signs are indicative of genetic haemochromatosis?

2.2 What comorbidities are associated with genetic haemochromatosis (e.g., liver disease, diabetes and musculoskeletal conditions including osteoarthritis and osteoporosis)?

2.3 Which incidental findings should prompt diagnostic tests for genetic haemochromatosis (e.g., raised ferritin, abnormal liver function tests, abnormal findings on imaging of joints or liver)?

3 Diagnosis of genetic haemochromatosis

Initial tests:

3.1 What is the diagnostic accuracy of serum ferritin and transferrin saturation tests in genetic haemochromatosis?

3.2 What is the clinical and cost effectiveness of serum ferritin and transferrin saturation tests in the diagnosis of genetic haemochromatosis?

Tests for confirmation of genetic haemochromatosis:

3.3 What is the clinical and cost effectiveness of HFE mutation analysis (testing for both p.C282Y and p.H63D) for confirmation of genetic haemochromatosis?

3.4 What is the clinical and cost effectiveness of liver MRI or liver biopsy for confirmation of iron overload (for both p.C282Y homozygotes and p.C282Y and p.H63D compound heterozygotes)?

4 Cascade screening

4.1 What is the clinical and cost effectiveness of HFE genotyping (testing for both p.C282Y and p.H63D) for first degree relatives of people with known HFE mutations (index case has to be a p.C282Y homozygote either with or without clinical manifestations)?

5 Managing genetic haemochromatosis

Treatment strategies to reduce iron overload (including induction and maintenance phases of treatments separately):

6.1 What is the clinical and cost effectiveness of therapeutic venesection (therapeutic phlebotomy or blood donation), erythrocytapheresis and chelation therapy for the management of genetic haemochromatosis?

6.2 What are the most clinically and cost-effective treatment end points including ferritin, transferrin saturation and liver iron concentrations?

Additional measures to enhance existing treatments to reduce iron overload:

6.3 What additional measures including dietary modification, use of supplements (iron and vitamin C), proton pump inhibitors, hormonal contraceptives and modification of alcohol intake may enhance existing treatments to reduce iron overload?

Strategies to prevent progression of disease:

6.3 What is the clinical and cost effectiveness of strategies to prevent progression of joint disease related to complications of genetic haemochromatosis?

6 Ongoing monitoring

7.1 What should be included in monitoring (e.g., ferritin and transferrin saturation) of people with genetic mutation without iron overload (people identified by cascade screening)?

7.2 What is the optimal frequency of monitoring (e.g., ferritin and transferrin saturation) of people with genetic mutation without iron overload (people identified by cascade screening)?

7.3 What should be included in monitoring (e.g., ferritin, transferrin saturation, quality of life) of people with genetic mutation with iron overload and are on treatment? [monitoring in induction and maintenance phases of each treatment separately]

7.4 What is the optimal frequency of monitoring (e.g., ferritin, transferrin saturation, quality of life) of people with genetic mutation with iron overload and are on treatment? [monitoring in induction and maintenance phases of each treatment separately]

7.5 What should be included in monitoring (e.g., hepatocellular carcinoma surveillance) of people with end organ damage?

7.6 What is the optimal frequency of monitoring (e.g., hepatocellular carcinoma surveillance) of people with end organ damage?

## 4.4 Main outcomes

The main outcomes that may be considered when searching for and assessing the evidence are:

- Health-related quality of life (for example, EQ-5D, SF-36)
- Mortality
- Patient reported outcomes
- Complications of GH (e.g., liver endpoints (transplantation, hepatocellular carcinoma, death)), arthropathy, diabetes)
- Adverse effects of treatments

# 5 NICE quality standards

**NICE quality standards that will use this guideline as an evidence source when they are being developed**

- Haemochromatosis. Publication date to be confirmed.

# Further information

This is the draft scope for consultation with registered stakeholders. The consultation dates are 9 January to 6 February 2023.

The guideline is expected to be published in February 2025.

You can follow progress of the guideline.

Our website has information about how NICE guidelines are developed.