# Fabry Findings

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Fabry International Network

**In this issue we focus on guidelines for the personalised management of classic Fabry: treatment and care tailored to the individual for better outcomes.**

## What is classic Fabry?

Fabry is a rare, inherited genetic condition which is estimated to affect around **1 in 100,000 people**. Fabry is caused by a **mutation** in the **GLA gene**, which leads to a reduction or absence of an enzyme called α-galactosidase A (α-Gal A), used to break down a particular type of fat in the body known as globotriaosylceramide (Gb-3). Over time, the accumulation of Gb-3 in cells causes damage to tissues and organs.[1]

A **mutation** is the permanent change in a DNA sequence that makes up a gene.

The **GLA gene** provides instructions for the body to make the α-Gal-A enzyme.

Individuals with classic Fabry have little or no α-Gal A enzyme activity and Gb-3 accumulates in most tissues from a young age. Symptoms usually start between 3 and 10 years of age.[2, 3] In contrast, those with some enzyme activity generally develop symptoms later in life. This late-onset Fabry often presents as kidney or heart issues in the person's 40s or 50s.[4, 5]

## The symptoms of classic Fabry

Early symptoms include burning pain in the hands and feet (known as acroparesthesia), sweating less and clusters of red or dark blue spots on the skin (known as angiokeratomas). Headaches, stomach pains and diarrhoea and tiredness are also common. In time, the build up of Gb-3 can damage the heart, kidneys and lead to stroke.[6]

# Classic Fabry in men and women

In the past, women were thought to be 'asymptomatic carriers' of Fabry, meaning that they can pass Fabry on to their children without experiencing any symptoms themselves.[7] Now, we know that Fabry inheritance in women is complicated, and women can experience Fabry in the same way that men do, although the severity of their symptoms tends to be more varied.[8]

# Fabry specific treatment

Two types of Fabry specific treatment are available: enzyme replacement therapy and oral chaperone therapy.

## Intravenous enzyme replacement therapy

Enzyme replacement therapy (ERT) is a life-long treatment that replaces missing α-GaL A enzyme in the body and is given via an intravenous infusion. It is suitable for those with any Fabry mutation of the GLA gene.[2] Two forms of ERT are available, agalsidase alfa and agalsidase beta.

## Oral chaperone therapy

Chaperones are small molecules that help enzymes to work. Chaperone therapy is a long-term treatment taken as a tablet and is only suitable for people with a specific mutation of the GLA gene.[9] Migalastat is a chaperone therapy for Fabry.

# Why are guidelines important for the management of Fabry?

Guidelines are a set of recommendations written for healthcare professionals to help diagnose and treat a medical condition. Guidelines are an important way for the medical community to share knowledge to improve care for their patients.

# Research news

"An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease" was published in 2022 in ***Molecular Genetics and Metabolism***.[10]

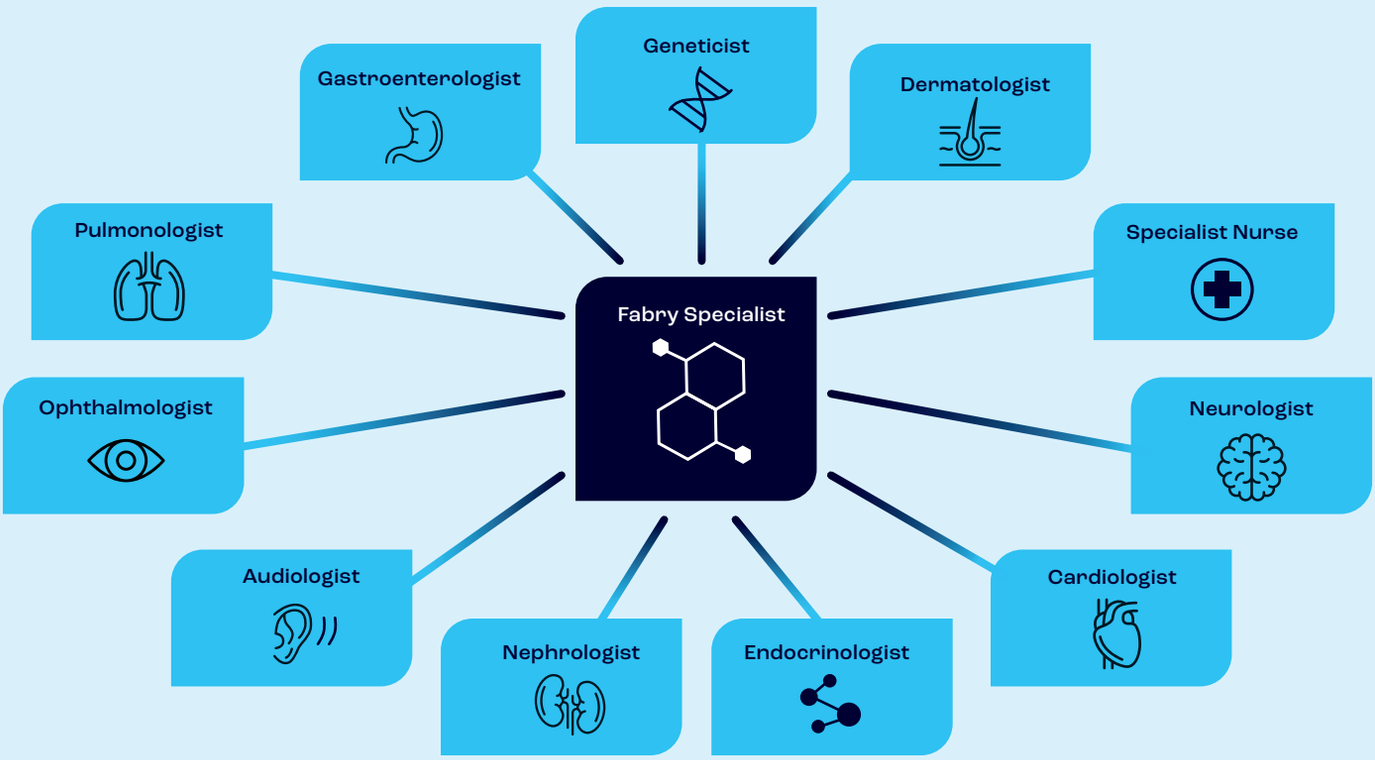
## The publication

In December 2020, an international group of 25 experts in the management of Fabry met to develop these new recommendations and guidance. They are based on 388 published studies of treatment for Fabry including clinical trials, registries and reports on small groups or individual patients.

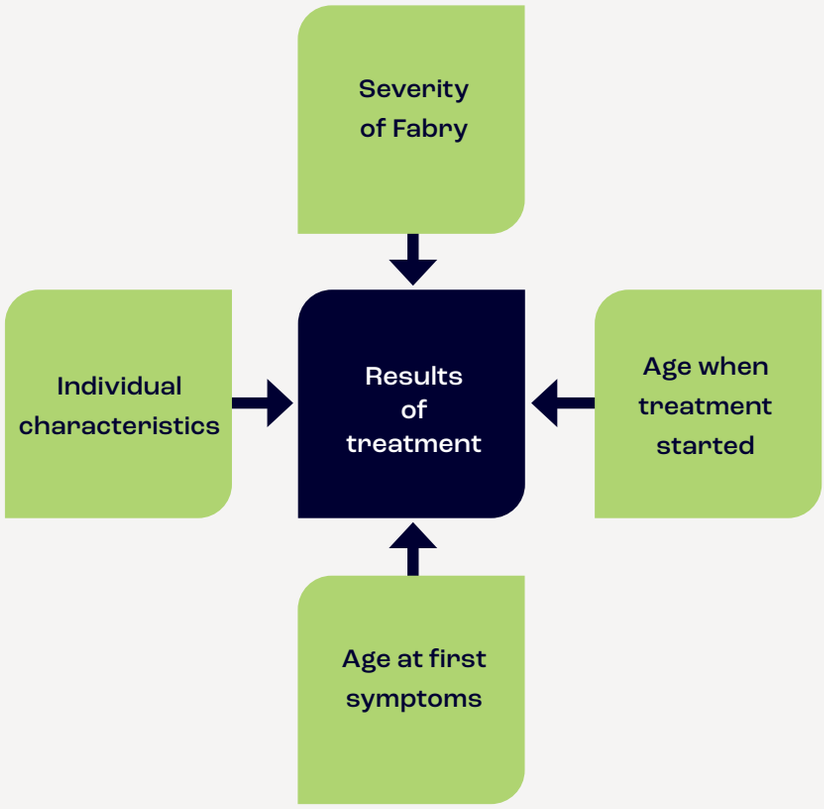
## Ensuring care and treatment is right for the individual

Fabry is a chronic disease that affects many parts of the body and therefore it is important that an overall medical care plan is in place to coordinate the many different specialists that may need to be involved in an individual's care.[11, 12]

To achieve the best care for those with Fabry, both the disease, and how it affects the individual need to be considered.



As the effects of Fabry vary from person to person, the plan must also take into account the specific health needs of the individual. Results of treatment can vary and may depend on the individual, how severe their Fabry is, when they developed symptoms and when they started treatment. It is therefore important to monitor the effects of treatment and to make adjustments for individuals based on how well they are responding to their treatment.

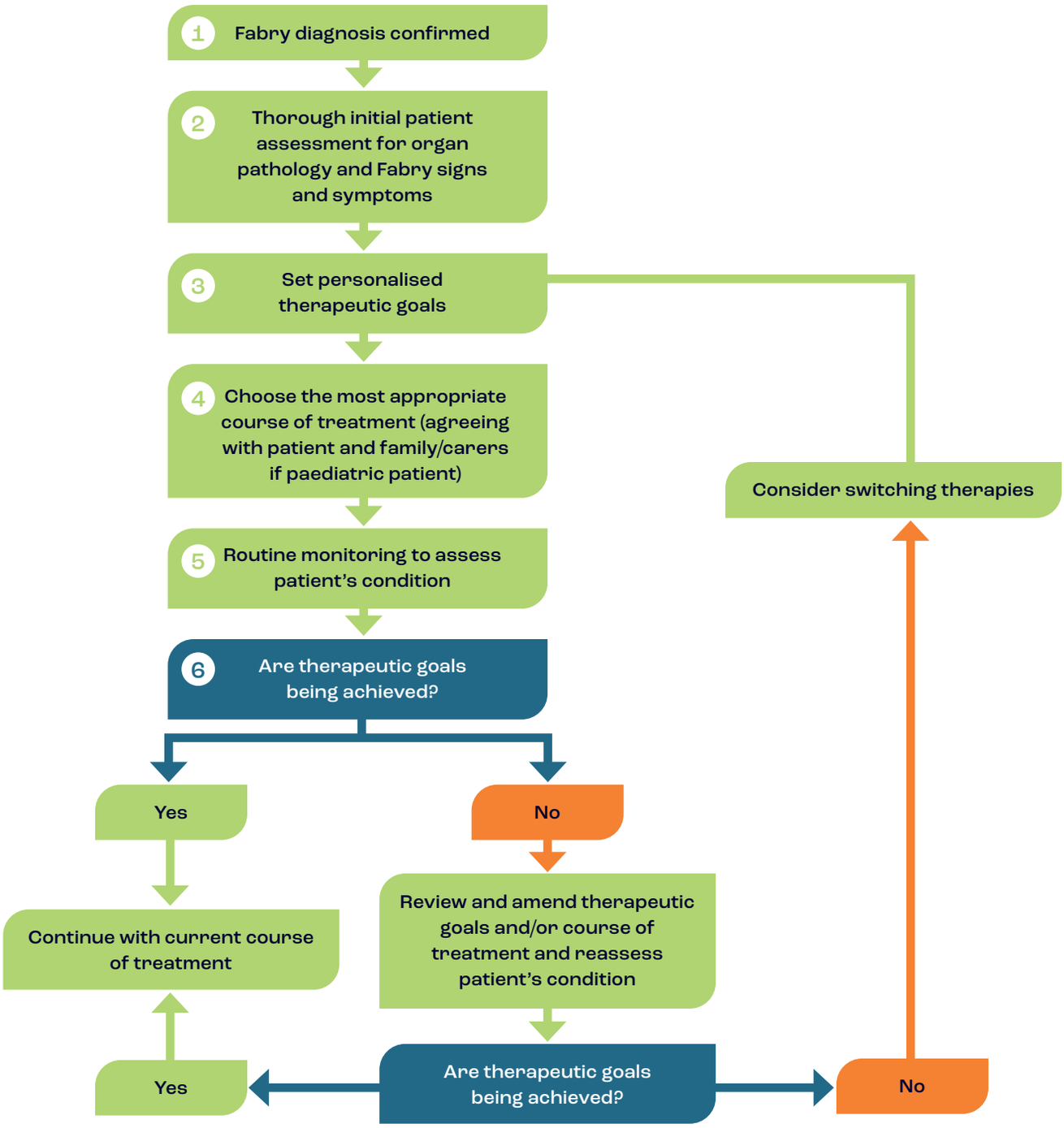



# The recommendations

As the range of symptoms of Fabry can vary greatly from person to person, treatment goals need to be tailored to the individual. Regular monitoring is essential to track the impact of Fabry on organs, such as the heart and kidneys and to determine how effective treatment is.

Using routine monitoring of patients alongside clinical recommendations reduces the burden of Fabry and improves patient care and quality of life.

Optimal patient care can be achieved by early diagnosis, carefully choosing the treatment strategy for patients according to their Fabry signs and symptoms and ensuring timely treatment initiation. Continued monitoring and assessment of clinical status are essential to this process. The authors propose methods for monitoring and caring for someone with Fabry from diagnosis as below.



## 1 Confirm the diagnosis of Fabry

Genetic testing should be performed in both males and females as part of the diagnosis. Referral to a geneticist or genetic counsellor to identify family members at risk of Fabry and to suggest they are tested is recommended.

Those with a confirmed diagnosis should be referred to a psychologist or social worker to improve the sharing of information about the diagnosis and what it means for the patient.

## 2 Thorough patient assessment

Following diagnosis, the first step is to thoroughly assess the person for signs and symptoms of Fabry, including any effects it may be having on their organs. Various tests may be used to achieve this and are listed on page 9.

These tests are used to determine the individual's health and how Fabry may be affecting their health. They serve as a baseline for measuring any progression of Fabry and how well any treatments are working when the tests are repeated at a later date. The tests also provide information about what type of treatment is needed.

The interpretation of some tests and predicting how Fabry may progress can be more difficult in female patients with classic Fabry than in male patients. Fabry may progress more slowly in female patients. Kidney failure can occur at a similar age in men and women but it is 10–20 times less likely in females with classic Fabry compared to males with classic Fabry.

Therefore, treatment and monitoring decision-making in female patients should take into account their individual genetics (how the GLA gene is expressed), as this usually determines the disease course in females.

## 3 Set personalised therapeutic goals

The overall goals in the management of Fabry should be to optimize treatment with both Fabry-specific treatment (ERT or chaperone therapy) and other suitable therapies to limit organ damage, reduce the risk of progression to severe or life-threatening events, and control symptoms.

## 4 Choose the most appropriate course of treatment

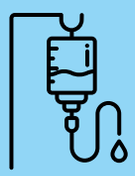
An appropriate treatment plan should be discussed and agreed with the patient and their family. Treatment should be started as soon as possible after a confirmed diagnosis as this may slow progression and stabilize the disease.

**Real world evidence** from the **Fabry Registry** has confirmed that early identification of Fabry makes early treatment possible and reduces the impact of heart, kidney and brain complications. The number of **severe clinical events** in those with classic Fabry was reduced after treatment with ERT (agalsidase beta).[13] Similar data for oral chaperone therapy has not been published yet.

**Real-world evidence** on treatment for Fabry comes from the experience of those treated by their usual doctors and not as part of a clinical trial.

**The Fabry Registry** is an international database that monitors clinical data of both treated and untreated Fabry patients regarding disease onset, progression, and treatment.

**Severe clinical events** refer to heart events, stroke, kidney failure, or death.



The burden of treatment and its impact on quality of life need to be considered by doctors. For example, home infusions of ERT should be made available where possible to avoid lengthy travel to the clinic.

Patients are not always offered supportive therapy (e.g. for pain) or psychological support and the authors suggest that these should be provided immediately after diagnosis when needed.[14, 15]

## 5 Assess patients' clinical status through regular monitoring

Details of the tests that are suitable for monitoring are listed on page 9. In the recommendations they are used to determine if the goals of treatment (therapeutic goals) for the patient are being reached.

Some of the tests and measures make use of **biomarkers**. These are various substances present in the blood, body fluids or tissues. The amount of substance present gives a measure of the presence or progression of disease and response to treatment. For example, in Fabry, a rise in the level of **lyso-Gb3** in the blood indicates that the disease is progressing.

A **biomarker** is a measurable substance which shows a biological condition or process responsible for signs and symptoms of disease. They can be measured with samples found in bodily fluids or tissues.

**Lyso-Gb3** is a biomarker for Fabry. Its levels in the blood are measured to understand the progress of the condition and effect of treatment.

## 6 Are therapeutic goals being achieved?

If the patient's treatment is meeting the goals that have been set, their treatment plan continues.

If goals are not being met, then the Fabry specific treatment and any supportive therapies are reviewed and adjusted to provide better management of Fabry for the patient. If the adjusted treatment is working well, it is continued. If not, then switching to another treatment may be considered.

# Fabry specific treatment

The authors presented the results from treatment studies that had taken place between 2009–2011.

## Switching from agalsidase beta to agalsidase alfa

Due to the worldwide shortage of ERT agalsidase beta in 2009, some patients were switched to the other available ERT, agalsidase alfa. In a series of switch studies, with a follow-up period up to 3 years, the results showed that:[16–18]

- The use of the regular approved dose of agalsidase beta was associated with stable kidney function (as measured by eGFR)
- The use of a reduced dose of agalsidase beta or switching to agalsidase alfa resulted in:
    - a decline in kidney function (as measured by **eGFR**)
    - an increase in the **Mainz Severity Score Index (MSSI) scores**
    - more frequent pain attacks, chronic pain, and stomach or intestinal pain

**eGFR** stands for the estimated glomerular filtration rate. It is a measure of how well the kidneys are working.

**Mainz Severity Score Index (MSSI) scores** evaluate the severity of Fabry signs and symptoms and observe patients' response to ERT. A higher score indicates more severe symptoms.

A smaller study in Latin America found no change when switching from agalsidase beta to agalsidase alfa in terms of heart or kidney function or disease severity score for at least two years after the switch.[19]

## Agalsidase alfa vs agalsidase beta

A study in four major treatment centres in Europe and America found that:[20]

- There was no difference in the number of clinical events in patients treated with agalsidase alfa compared to agalsidase beta
- A greater response to agalsidase beta was seen in some markers of Fabry (e.g. level of lyso-Gb3 in the blood)
- In these centres, patients with more severe disease (classic males) were mostly treated with agalsidase beta, whereas patients with later-onset Fabry or females were mostly treated with agalsidase alfa

## ERT vs chaperone therapy

A clinical trial compared patients on ERT (agalsidase alfa and agalsidase beta) to patients on migalastat:[21]

- ERT and migalastat had similar effects on kidney function, although the study population was not representative of patients with classic Fabry
- There was a significant reduction in one of the markers of Fabry disease (the **LVM index**) with migalastat compared to ERT
- Lyso-Gb3 levels in the blood remained low and stable in patients switched from ERT to migalastat

**Left ventricular mass index (LVM index)** is a useful measure to predict heart events. Higher values indicate changes in the heart that could affect its function.

## Migalastat after ERT treatment or no treatment

A real-world study looked at clinical outcomes in patients with both classic and later-onset Fabry over two years:[22]

- The results of markers of disease were mixed, showing some improvement in the heart (decrease in LVM index), but a worsening in the kidney (yearly loss of eGFR)
- Fabry symptom severity (MSSI) scores were stable in males, but increased in females
- Some males had an increase in lyso-Gb3 levels
- **NT-proBNP** increased over two years in females

**NT-proBNP** is a substance released in the body when the walls of the heart are stretched or there is a large amount of pressure on the heart.

Another study in 2019 looked at patients treated previously with ERT or patients that had not received ERT who were then treated with migalastat for more than two years:[23]

- Data showed that patients had stable kidney function for up to 8.6 years, regardless of treatment status, sex or Fabry type
- The patients in this study were not considered to be representative of those with classic Fabry as 75% were female and had normal kidney function

# Monitoring recommendations

The authors recommend the following measures to monitor the progress of Fabry and response to treatment.

### Fat build-up

**Lyso-Gb3 level**

- Lyso-Gb3 builds-up in the blood of people with Fabry
- It is a useful biomarker because high levels are associated with progression of Fabry symptoms
- It can be used to monitor response to ERT in males since levels decrease after treatment
- It is less useful for females because their starting levels of lyso-Gb3 are usually lower than males
- It may not be useful for monitoring response to therapy in those treated with chaperone therapy, particularly for females and late-onset patients

**Clinical recommendation**

- Monitor levels at **baseline** then every 6-12 months after starting treatment or switching treatments
- Other organ-specific biomarkers need to be used for monitoring, especially in females and patients on chaperone therapy

**Baseline** evaluation involves the clinical assessment of the patient following diagnosis and before treatment is started.

## Immune system

**Neutralising antibodies: anti-drug antibodies – usually immunoglobulin G (IgG)**

- Those treated with ERT may develop antibodies to the treatment (anti-drug antibodies)
- This is usually seen in males with classic Fabry who produce little or no α-Gal A enzyme themselves
- The enzyme delivered by ERT is recognised as a foreign substance by the immune system and anti-drug antibodies are produced
- These antibodies generally develop within 3–6 months of starting ERT
- They are sometimes called neutralising antibodies as they may reduce the effectiveness of treatment, leading to an increase in lyso-Gb3 levels

**Clinical recommendation**

- Monitor anti-drug antibodies together with lyso-Gb3 levels in those receiving ERT
- Monitor IgG at baseline before ERT, then at intervals of 3–6 months for the first 18 months of treatment and every 6 months thereafter until two negative results are confirmed
- Frequency of monitoring should be tailored to the patient's needs

## Heart

**ECG (electrocardiogram)**

- ECG can detect early signs of Fabry affecting the heart such as **bradycardia**

**CMR (cardiac magnetic resonance)**

- **CMR** can be used to assess a number of heart biomarkers including the **inter-ventricular septal wall thickness (IVSWT), left ventricular mass (LVM) index** and **T1 mapping**

**ECHO (echocardiogram)**

- ECHO is useful for diagnosing and monitoring **cardiomyopathy**
- It can be used to measure the **IVSWT** and **LVM index**

**Biomarkers**

- **T1 mapping** is a biomarker that reflects the build up of Gb3 and lyso-Gb3 and may predict changes in **LVM**
- **NT-proBNP** levels in the blood are elevated in those where Fabry is affecting the heart
- Hs-cTnT is a biomarker for damage to the heart muscle

**Clinical recommendation**

Assessing the level of heart involvement is important. Thorough assessment should include tests such as **ECG**, **CMR** and **ECHO**. Testing for biomarkers of heart disease may also be useful.

- CMR should be performed at diagnosis in those over 25 years of age or if **left ventricular hypertrophy (LVH)** or **arrhythmia** is present in those aged 25 or under
- If the initial assessment is normal, CMR should be performed every 5 years or more frequently, if clinically indicated, to monitor the response to treatment
- If a patient is receiving ERT and has mild **LVH**, **CMR** should be performed every 2–3 years, or if a patient is receiving ERT and had moderate or severe **LVH**, **CMR** should be performed annually
- Perform **ECHO** at diagnosis and then every 2-3 years in those aged 18 years or under and every year in those aged over 18 years
- **T1 mapping** is useful in assessing disease progression in Fabry
- NT-proBNP and Hs-cTnT are important for heart disease staging in Fabry

An **ECG** or **electrocardiogram** is a test to measure the electrical activity of the heart and its rhythm.

**Bradycardia** is a slower than normal heart rate.

**CMR (cardiac magnetic resonance)**, also known as a cardiac MRI, involves a scan which assesses the function and structure of the heart.

The **inter-ventricular septal wall** refers to the wall of tissue separating the left and right ventricles (lower chambers) of the heart. **Inter-ventricular septal wall thickness (IVSWT)** is an important measure as thicker walls can interfere with the heart's ability to pump blood.

**Left ventricular mass (LVM) index** is calculated by dividing the weight of the left ventricle of the heart by body surface area. Higher values indicate changes in the heart that could affect its function.

**T1 mapping** is a technique used in cardiac magnetic resonance and can be used to assess signs of heart disease.

An **echocardiogram (ECHO)** produces images of the heart to see how well it is functioning.

**Cardiomyopathy** is chronic disease of the heart muscle where the heart chamber walls are stretched, thickened or stiff.

**Left ventricular hypertrophy (LVH)** is when the heart's left lower chamber (the ventricle) has thickened, meaning the heart may not be effective at pumping blood.

**Arrhythmia** is an irregular heart rhythm.

## Kidneys

### Albuminuria

- An early sign of kidney damage and used to monitor the deterioration of kidney function (nephropathy)
- Males with classic Fabry usually develop albuminuria in their teens or 20s
- Monitoring **albuminuria** is preferred over **proteinuria** as an indicator of kidney disease as it can be detected earlier

### Estimated glomerular filtration rate (eGFR)

- **eGFR** can be used to assess the progression of kidney disease
- The **eGFR** rate checks how well the kidneys are filtering the blood to remove waste and excess fluid. These tiny filters are called glomeruli and the test estimates how much blood passes through the glomeruli each minute

### Clinical recommendation

- Early treatment with ERT preserves kidney function in patients with classic Fabry and regular monitoring of kidney function is therefore important
- Combining ERT or chaperone therapy, when appropriate, with other kidney protective therapies is also recommended

**Albuminuria** is when there are high levels of the protein albumin in the urine.

**Proteinuria** is a high level of protein in the urine and is an indicator of kidney disease.

The **eGFR** rate checks how well the kidneys are filtering the blood to remove waste and excess fluid. These tiny filters are called glomeruli and the test estimates how much blood passes through the glomeruli each minute.

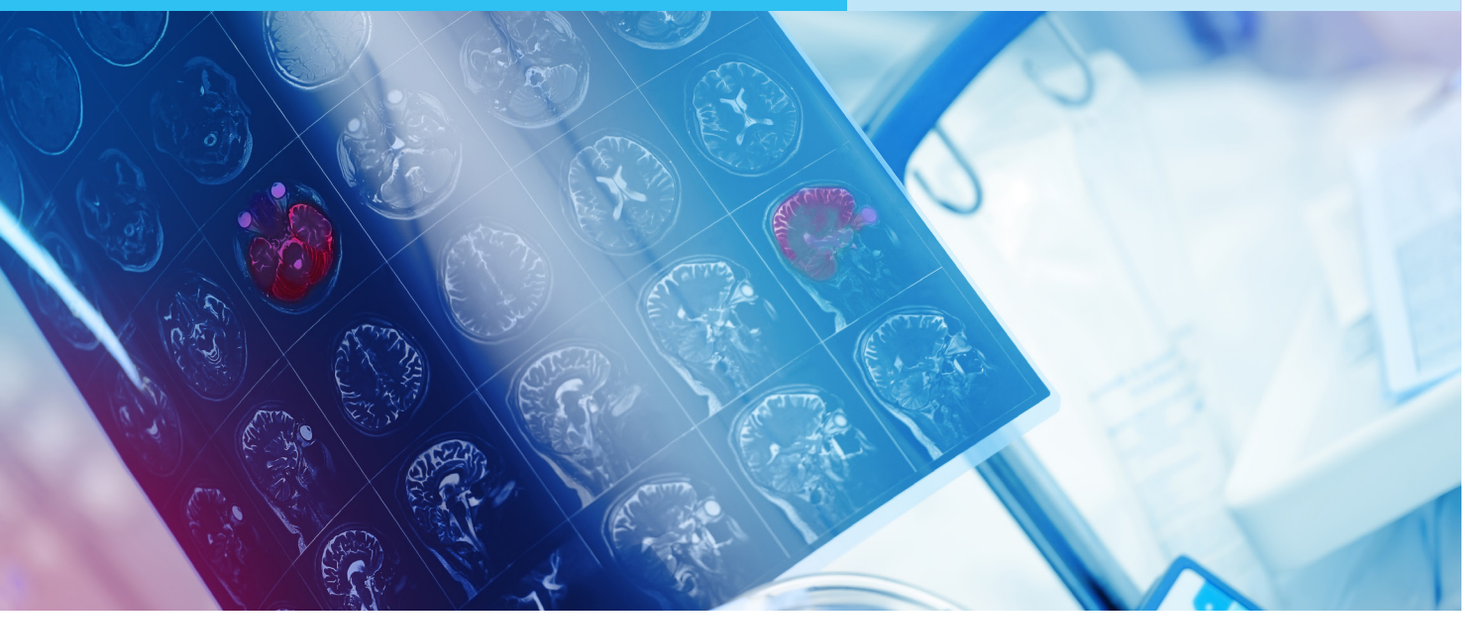
## Brain

**Brain magnetic resonance imaging (MRI)**

- Issues with the brain's blood flow can affect males and females with Fabry
- **MRI**s help identify issues such as **TIA**s and strokes, **white matter** lesions, small bleeds in the brain and the abnormal shape of a brain artery
- Stroke could be the first serious symptom of Fabry and is often caused by **atrial fibrillation**
- Healthcare professionals should be aware that Fabry can potentially cause stroke for patients aged 20–50 years

**Clinical recommendation**

- Brain **MRI** should be performed at the first assessment in males aged over 20 years and females over 30 years, then at least every 3–5 years
- Even though ERT does not cross the blood brain barrier, ERT should be started immediately after a confirmed diagnosis of Fabry to slow or stop disease progression in the kidneys, heart and brain which could cause a stroke



**Magnetic resonance imaging (MRI)** is a technique to create anatomical images useful for disease detection, diagnosis and monitoring.

**TIA** stands for transient ischaemic attack. It is sometimes called a mini stroke.

**White matter** lays in the deepest tissues of the brain and is made up of millions of nerve fibres that connect the whole of the brain together. Some lesions in this area can be considered normal as a person ages, but they can damage pathways in the brain leading to complications such as issues with balance, memory, and walking.

**Atrial fibrillation** is a condition that causes an irregular heart rate.

## Gastrointestinal

**Radiological examination**

- Used to investigate blood flow and movement of food through the digestive system

**Doppler scan**

- Can assess damage to blood vessels

**Endoscopy**

- Used to see signs of damage or inflammation to the lining of the **gastrointestinal system**

Bowel **biopsy**

- To look for deposits of Gb3

**Clinical recommendation**

- Patients should be referred to a gastroenterologist for radiological examination, **Doppler scan** or **endoscopy/biopsy**

**Radiological examination** is a test using radiation or other imaging techniques.

A **Doppler scan** is a type of ultrasound scan that detects blow flow in the body.

The **gastrointestinal system** is the pathway of the digestive system which includes the mouth, throat, oesophagus, stomach, small intestine, large intestine, rectum, and anus.

A **biopsy** is a medical procedure that involves taking a small sample of body tissue so it can be examined under a microscope.

An **endoscopy** is a procedure where a flexible tube with a light and camera at the end is used to look inside the body.

## Eyes

**Clinical recommendation**

- Patients should be referred to an ophthalmologist for monitoring
- A baseline assessment is needed followed by check ups as required

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