Fabry Findings

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In this issue we focus on Fabry clinical guidelines, the signs and symptoms they include and whether these promote or delay the beginning of treatment for Fabry

What is Fabry?

Fabry is a rare, inherited genetic condition which is estimated to affect around 1 in 100,000 people.[1]

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 (GL-3).[1] Over time, the accumulation of GL-3 in cells causes damage to tissues and organs. Fabry affects many parts of the body and symptoms vary day-to-day and between one person and another.[1]

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

What are clinical guidelines?

Clinical 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 and best practice in caring for their patients.

Why are clinical guidelines important to start treatment in Fabry?

It has been shown that early treatment for Fabry can slow disease progression and prevent organ damage later in life. Physicians make their decision to recommend starting treatment for Fabry based on signs and symptoms described in Fabry guidelines. However, the decision to start treatment is a challenge because it is difficult to predict which of the wide variety of symptoms will develop and when.

When do Fabry symptoms appear?

Symptoms in classic Fabry appear in early childhood and adolescence. In these patients, the α-Gal A enzyme has little or no activity and fats accumulate in most tissues from a young age. Typically, symptoms appear when children are between 3 and 10 years old.[2,3]

Patients with late-onset Fabry present with symptoms later in life, as their α-Gal A enzyme has enough activity to break down some GL-3. Patients typically present with symptoms in one organ at first, usually developing kidney or heart issues in their 40s or 50s.[4,5]

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.[6] Now, we know that Fabry inheritance in women is complicated, and women can experience Fabry in the same way that men do.[7]

Importance of early diagnosis and treatment

Fabry can be difficult to diagnose because symptoms vary between patients. Diagnosis is often delayed and can take an average of 10 years from when the patient noticed the first symptoms to having a diagnosis of Fabry.[8] If Fabry signs and symptoms are recognised promptly, then treatments can start earlier and possibly help delay more serious complications.

There is no cure for Fabry but current treatments may prevent organ damage and greatly improve the quality of life of patients if given early.

Oral chaperone therapy

Chaperones are small molecules that assist enzymes to become functional by helping them fold into the correct shape. Chaperone therapy is a long-term treatment that needs to be started early, and is only suitable for people with a specific mutation of the GLA gene.[8]

Intravenous enzyme replacement therapy (ERT)

ERT is a life-long therapy which replaces missing or deficient α-GaL A enzyme in the body and is given via an intravenous infusion. ERT is suitable for patients with all mutations of the GLA gene but should be started as early as possible. This is particularly important in males with classic Fabry, where it is recommended to start treatment in childhood before symptoms appear.[2]

Fabry guidelines

Although several guidelines exist for Fabry, the benefits of early treatment have led to a change in focus over recent years. Current guidelines used by physicians often recommend starting treatment based on signs and symptoms that may present in late stages of Fabry.[5,9] There is a need for guidelines to include early signs of disease progression to support earlier treatment.[10]

Research news

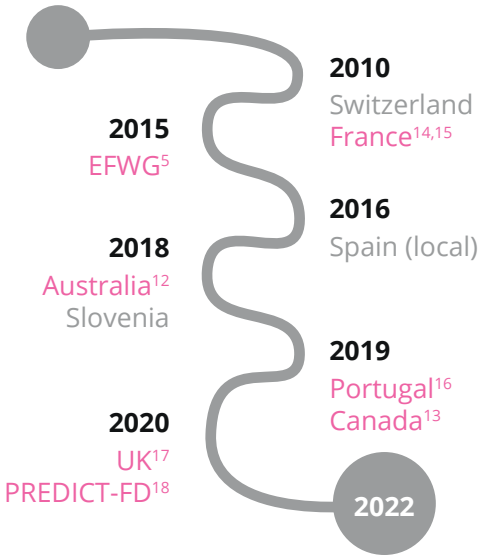
"Do clinical guidelines facilitate or impede drivers of treatment in Fabry disease?" was published in 2022 in ***Orphanet Journal of Rare Diseases***.[11]

The publication

Fabry can vary greatly from person to person so it is difficult to predict which symptoms will develop and when, making the decision to start treatment a challenge. Growing evidence demonstrates that early treatment with Fabry-specific therapy can prevent organ damage later in life. There are many factors that can trigger the decision to begin treatment or act as a barrier to starting treatment.

In 2020, an initiative called **PREDICT-FD** was launched to investigate if 21 Fabry expert physicians from 15 countries could agree on early signs and symptoms of Fabry that would justify starting treatment earlier than currently recommended in practice.[18] The experts identified and agreed on 27 early signs and symptoms of Fabry. These were categorised by those affecting the kidneys, the heart, the brain and nerves, and those symptoms reported by the patient.

In this study, the findings from **PREDICT-FD** were compared with **local and national guidelines** from various countries and with guidance from the **European Fabry Working Group** to find out if there were differences in the signs and symptoms used in the guidelines to start treatment and those agreed in PREDICT-FD. The study also looked at how these differences may delay or accelerate treatment in patients with Fabry.



Timeline of Fabry guidelines included in the study (Published guidelines are shown in pink)

PREDICT-FD stands for PRoposing Early Disease Indicators for Clinical Tracking in Fabry Disease.[18]

European Fabry Working Group (EFWG)

In 2015, a group of physicians involved in the treatment of Fabry throughout Europe known as the EFWG, developed a set of criteria to help physicians make a decision on when to treat Fabry patients.[5]

Local and national guidelines

Some countries have their own 'local' or 'national' sets of guidelines, these contain recommendations on when to start treatment based upon symptoms present in Fabry patients.

Early signs and symptoms of Fabry compared in the study

In the tables below, Fabry signs and symptoms that were present in PREDICT-FD and the EFWG as criteria to start treatment are represented with a tick mark. The number within the bars shows how many of the guidelines also included the symptom. For example, cell damage in the kidneys was agreed to be an early sign of Fabry in the PREDICT-FD study and in 6 out of 8 guidelines but it was not a factor to start treatment in the EFWG.

Kidney sign or symptom	**PREDICT-FD**	**EFWG**	**Guidelines**
Abnormal filtering rate (**GFR**)	✓	✓	6
Albuminuria (ACR)	✓	✓	4
Cell damage	✓		6
Fat accumulation	✓		3
Kidney dialysis or transplant		✓	4
Proteinuria (high levels of protein in the urine)		✓	8
Reduction in GFR rate (using isohexol plasma clearance)	✓		1

GFR stands for glomerular filtration rate, and it measures how well the blood is being filtered by the kidneys

Albuminuria is when there are high levels of the protein albumin in the urine; the results are reported as the albumin-to-creatinine ratio (**ACR**)

Brain and nerves sign or symptom	**PREDICT-FD**	**EFWG**	**Guidelines**
Damage to **white matter** in the brain		✓	2
Neuropathic pain	✓	✓	7
Pain in the stomach and abdomen (gastro-intestinal)	✓		4
Stroke or mini stroke (TIA)	✓	✓	7
Stroke without symptoms seen by MRI			1
Sudden loss of hearing in one ear		✓	3
Sudden loss of vision due to the interrupted flow of blood to the eye's nerve (ischemic optic neuropathy)			1

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

Neuropathic pain is pain that originates from damage to the nerves and includes stabbing, burning or tingling pain

Heart sign or symptom	PREDICT-FD	EFWG	Guidelines
Abnormal **echocardiogram**	✓		6
Abnormal **electrocardiogram** (ECG)	✓	✓	6
Abnormal movement of the heart wall seen during echocardiogram	✓		1
Abnormal pumping of heart (**systolic/diastolic dysfunction**)	✓		5
Cell damage	✓		5
Early thickening of the heart's ventricle (**LVH**)	✓	✓	7
High levels of substances in the blood indicating heart failure	✓		2
High levels of troponin (heart muscle proteins) in the blood	✓		1
Reduced **T1 relaxation time** of heart tissues (cMRI)	✓		4
Signs of scarring or fibrosis in the heart muscle	✓		6
Symptoms of heart disease			1

An **echocardiogram** produces images of the heart to see how well it is functioning, an **electrocardiogram** measures the heart's electrical activity and rhythm

Systolic dysfunction means the heart is not contracting well during heartbeats, **diastolic dysfunction** means it is not relaxing well in between heartbeats

LVH stands for left ventricular hypertrophy, meaning the heart may not be effective at pumping blood because the heart's left lower chamber (the ventricle) has thickened

All tissues have a standard time during which they are relaxed, called **T1 relaxation time**. This is measured with cardiac magnetic resonance imaging (cMRI) which assesses the function and structure of the heart

Sign or symptom reported by the patient and other signs	PREDICT-FD	EFWG	Guidelines
Abnormal sweating or heat/exercise intolerance	✓		2
Angiokeratoma	✓	✓	3
Fever attacks	✓		0
Non-painful gastro-intestinal symptoms (e.g., diarrhoea)	✓	✓	4
Organ biopsy	✓		2
Progression of symptoms	✓		0

Angiokeratomas are purple spots on the skin of the lower back, groin, upper thighs and belly button

Did guidelines agree with PREDICT-FD in the early signs and symptoms that indicate the need to start treatment?

The comparison between PREDICT-FD and other guidelines showed inconsistencies in the recommendations on when to start treatment. In general, recent guidelines coincided the most with early signs and symptoms from PREDICT-FD, and only the four most recent guidelines included recommendations for chaperone therapy, as this was approved several years later than ERT.[8]

KIDNEYS

- Overall, guidelines agreed with early signs and symptoms of kidney damage identified in PREDICT-FD as factors to start treatment. High albumin–creatinine ratio in the urine and early stages of chronic kidney disease were used to inform treatment decisions in most guidelines
- Recommendations to start treatment based on cell damage and levels of filtering rate (GFR) in the kidney varied between guidelines
- Proteinuria tends to appear in later stages of Fabry, so it was not included in PREDICT-FD, but it was included in all other guidelines

HEART

- Guidance on heart signs and symptoms was very different across the guidelines and mostly generic, only guidelines from Canada provided specific criteria for heart damage that coincided with PREDICT-FD
- Early signs of heart damage that could be identified with cMRI varied between national guidelines and were not a factor to start treatment on the EFWG

BRAIN AND NERVES

- Brain and nerve symptoms were excluded from most guidelines, including from PREDICT-FD
- Damage to white matter and sudden hearing loss were excluded from PREDICT-FD but included in other guidelines
- Neuropathic pain, such as stabbing and burning pain, was recognised as an important early sign of Fabry by all guidelines, but not a factor to start treatment
- Painful stomach and abdomen symptoms were noted in PREDICT-FD and in several other guidelines

SIGNS AND SYMPTOMS REPORTED BY PATIENTS

- Most early signs and symptoms included in PREDICT-FD, such as fever attacks, did not feature in other guidelines
- Non-painful gastro-intestinal symptoms were included in PREDICT-FD, the EFWG and four guidelines
- Only PREDICT-FD considered angiokeratomas as an early sign to recommend treatment, while other guidelines only used this symptom for diagnosis

Key drivers of starting treatment in PREDICT-FD, EFWG and other guidelines

All guidelines required a confirmed diagnosis of Fabry before treatment could begin. In PREDICT-FD, the expert group agreed on three key drivers of early initiation of treatment.

"Male sex, young age, and clinical findings, such as severe pain and signs or symptoms of organ involvement"

- All guidelines supported PREDICT-FD, but age referred to men with classic Fabry who should all be offered treatment when showing symptoms
- Guidelines from several countries encouraged therapy for young male patients with classic Fabry who did not show any symptoms (e.g., Portugal's guidelines suggested males with no symptoms aged 8 years old or over could be considered for treatment on an individual basis), while other countries recommended treatment in males with classical Fabry only when symptoms appear
- Australian guidelines focused on specific symptoms that if present would justify initiating treatment, regardless of Fabry type or sex
- Portugal recommended treatment for any paediatric patient who presents with specific signs, such as kidney or heart involvement
- Several guidelines required various signs and symptoms to appear before treatment was recommended for male and female patients with late-onset Fabry (e.g., evidence of kidney and heart involvement or poor brain function)
- Only guidelines from Australia, Canada, Portugal, and the UK recommended chaperone therapy as well as ERT

"Improving clinical outcomes and preventing disease progression"

- UK guidelines were the only ones to acknowledge that although no clinical trial has studied the best time to start treatment, or the group of patients most likely to benefit from it, treatment will be most successful when given early to delay, reverse or stabilise progression

"A family history of Fabry, especially if severe or with major organ involvement or premature death"

- Most guidelines did not mention screening other family members for Fabry once someone had been diagnosed
- Portuguese guidelines required family screening before treatment can commence, and guidelines from the UK and Slovenia included testing other family members as part of the Fabry patient's follow-up by their physician

Barriers to early initiation of treatment in PREDICT-FD, EFWG and other guidelines

The expert group in PREDICT-FD also decided upon two barriers that prevent early start of treatment:

- A lack of consolidated **biomarkers** that can predict which patients will progress and which will respond to treatment
- A misdiagnosis, likely due to a lack of awareness about Fabry

A **biomarker** is a biological molecule found in bodily fluids or tissues that can be used to measure the presence or progression of disease

Impact of PREDICT-FD on early treatment in Fabry

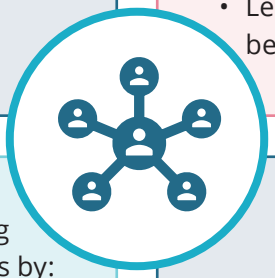
The expert physicians participating in PREDICT-FD agreed on nine potential impacts of the initiative in driving an early start of treatment.

PREDICT-FD may support the consolidation of biomarkers to predict patients who will respond to treatment by:

- Helping to stimulate research into predictive biomarkers
- Leading to modification of national guidelines to include predictive biomarkers

PREDICT-FD may help with the timing of treatment by:

- Helping to improve communication between healthcare professionals and patients
- Helping with earlier initiation of Fabry-specific treatment
- Leading to a consensus on when to begin and end treatment



PREDICT-FD may help with improving patients' management and outcomes by:

- Helping to improve patient outcomes and quality of life
- Helping to improve clinical practice
- Helping to increase awareness amongst healthcare professionals of the need for individualised assessments and multi-disciplinary follow-ups

In addition, PREDICT-FD may support discussions for the reimbursement of treatment

Review of real case medical histories of patients against different guidelines to determine if patients should start treatment

As part of the study, six panel members reviewed 17 anonymised case histories and provided recommendations for treatment initiation based on guidance from their own country, the EFWG, and PREDICT-FD.

In **8** patients, physicians supported the initiation or continuation of treatment regardless of what guidelines they followed

In **3** patients, one physician changed their decision to recommend starting treatment depending on which guideline was applied

In **8** patients, physicians gave varied recommendations to starting treatment depending on which country guideline was applied

Different recommendations were made among physicians in **7** patients based on PREDICT-FD, and in **7** patients based on EFWG

- The experts found greater support for early treatment with PREDICT-FD compared to other guidelines
- However, there was not always total agreement between the experts on when to begin treatment, indicating that there were differences in how guidelines were interpreted and the need to standardise the criteria

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