Plain Language Summary of Publication

Future Rare Diseases

Plain language summary of the International Collaborative Gaucher Group Gaucher Risk Assessment for Fracture score in people living with Gaucher Disease Type 1

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Summary

How to say (double click sound icon to play sound)...

- **Alglucerase:** al-GLOO-seh-rays
- **Beta-glucosidase:** BAY-tuh-GLOO-koh-SIH-days
- **Gaucher disease:** go-SHAY diz-EEz
- **Glycosphingolipids:** GLY-koh-SFIN-go-LIH-pids
- **Imiglucerase:** IH-mih-GLOO-seh-rays

What is Gaucher disease?

Gaucher disease is a rare, inherited genetic condition. People with Gaucher disease have two non-working copies of a gene called *GBA1*, which contains the instructions for producing an enzyme called beta-glucosidase. Beta-glucosidase breaks down excess fatty substances called glycosphingolipids, that help maintain our cells in good working order. People with Gaucher disease do not make enough beta-glucosidase, so glycosphingolipids build up in their organs, causing complications. There are different types of Gaucher disease but most people in the Western world with Gaucher disease have type 1 (shortened to GD1). Typical complications in GD1 include having a larger spleen and liver, blood problems, and increased risk of bone problems. Bone problems, including fractures, are one of the main causes of pain and disability for people with GD1, and can impact their quality of life. Treatments such as enzyme replacement therapy (also called ERT) can reduce fracture risk but do not prevent them completely.

What was the aim of this study?

In this study, researchers looked at a new assessment score called the Gaucher Risk Assessment for Fracture (also known as GRAF). The aim was to evaluate how well the GRAF could predict future fracture risk in adults with GD1 who were receiving ERT.

What were the findings of this study?

The risk of future fractures in adults with GD1 was higher in women, and among people who had a history of bone pain or had their spleens removed as part of their treatment. Risk was also higher if people had a longer time between being diagnosed and starting treatment, and/or were older when they started ERT. The study also found that the GRAF score performed as well as other fracture risk tools used in the general population. These findings support the use of the GRAF score alongside bone density measurements and other risk factor assessments to help doctors and people with GD1 understand the risk of having a fracture after starting ERT.

Who is this article for?

This summary was written for patients and their caregivers, patient advocates, and healthcare professionals who are interested in GD1 and the risk of bone problems when receiving ERT for Gaucher disease.

Who sponsored the International Collaborative Gaucher Group (ICGG) Gaucher Registry and this study?

Both the International Collaborative Gaucher Group (ICGG) Gaucher Registry (NCT00358943) and this study were sponsored by Sanofi.

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Where can I find the original article on which this summary is based?

You can read the full article called 'The International Collaborative Gaucher Group GRAF (Gaucher Risk Assessment for Fracture) score: a composite risk score for assessing adult fracture risk in imiglucerase-treated Gaucher disease type 1 patients' published in the journal *Orphanet Journal of Rare Diseases* for free at:
https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01656-6

What is Gaucher disease?

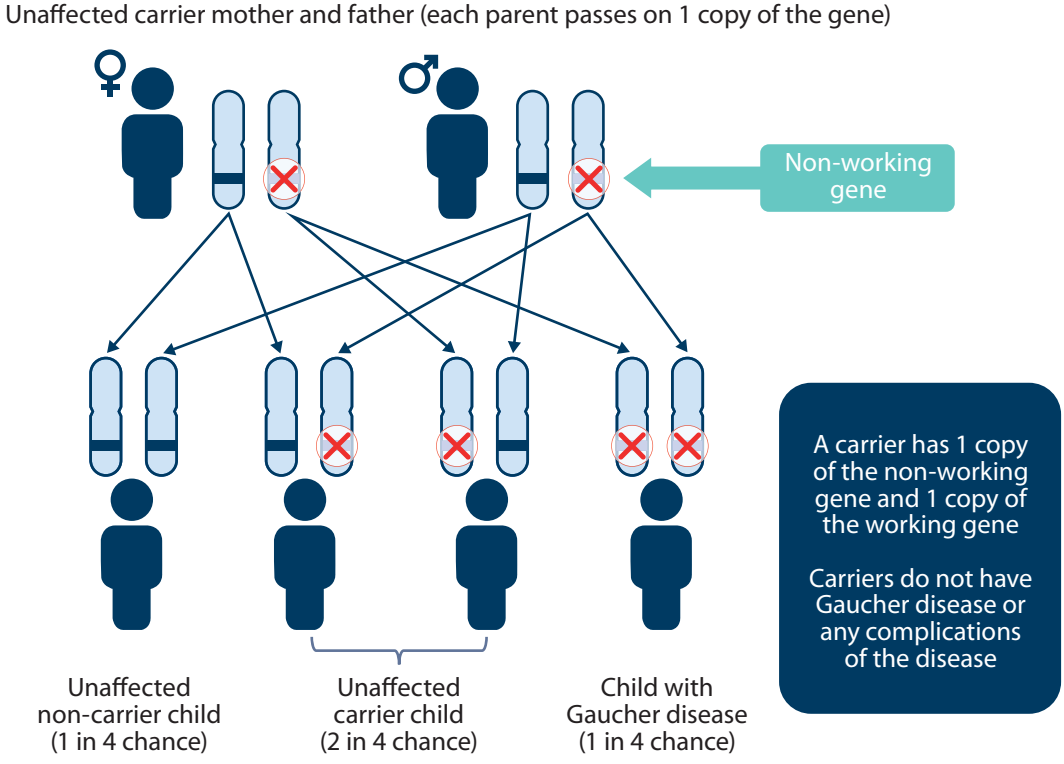
Gaucher disease is a rare genetic condition. People with Gaucher disease have two non-working copies of a gene called *GBA1* that is passed down from each parent to their child (inherited).

People who inherit a non-working copy of the *GBA1* gene from one parent and a working copy from the other parent are known as carriers. Carriers do not have Gaucher disease, or any complications associated with the disease, but can pass the non-working copy of the gene on to their children.

What are genes?

- A substance in our cells called DNA contains the instructions needed to build and maintain our bodies
- A section of DNA containing the instructions to make a particular protein (substances that do most of the work in our cells and body) is called a gene. Genes give us our unique features such as eye colour
- Non-working versions of genes can cause diseases such as Gaucher disease; these are known as 'genetic diseases'

How do people get Gaucher disease?



Children of an individual with Gaucher disease will inherit a non-working copy of the *GBA1* gene but will not have the disease, or could have Gaucher disease themselves if they also inherited a non-working copy from their other parent.

The *GBA1* gene gives cells the instructions to make an enzyme called beta-glucosidase, which breaks down fatty substances in the body known as glycosphingolipids (this is different from good or bad cholesterol).

Glycosphingolipids are important building blocks of our cells and help to maintain cells in good working order. As cells in our bodies regularly need to be broken down and replaced, glycosphingolipids from these cells are also removed.

As people with Gaucher disease have two non-working copies of the *GBA1* gene, their bodies make too little of the enzyme beta-glucosidase. This means that glycosphingolipids are not removed appropriately, and can build up in various organs, such as the spleen or liver.

This causes a wide variety of different complications, depending on the organs affected.

What is Gaucher disease type 1?

Gaucher disease can be described as three types: type 1, type 2, or type 3. Rather than being separate from one another, these types represent a wide range of complications that people with Gaucher disease can have.

Many of the complications are similar across the three types but can affect each person with Gaucher disease differently. One known difference between the types is that people with Gaucher disease type 2 (which occurs in infancy and is fatal early in life) or 3 (with onset in childhood or adolescence) can have certain specific problems with their central nervous system (brain) early in life. People with Gaucher disease type 1 (known as GD1) do not have the same central nervous system problems but may have numbness or weakness in limbs (peripheral neuropathy) or develop Parkinson's disease when middle-aged or older.

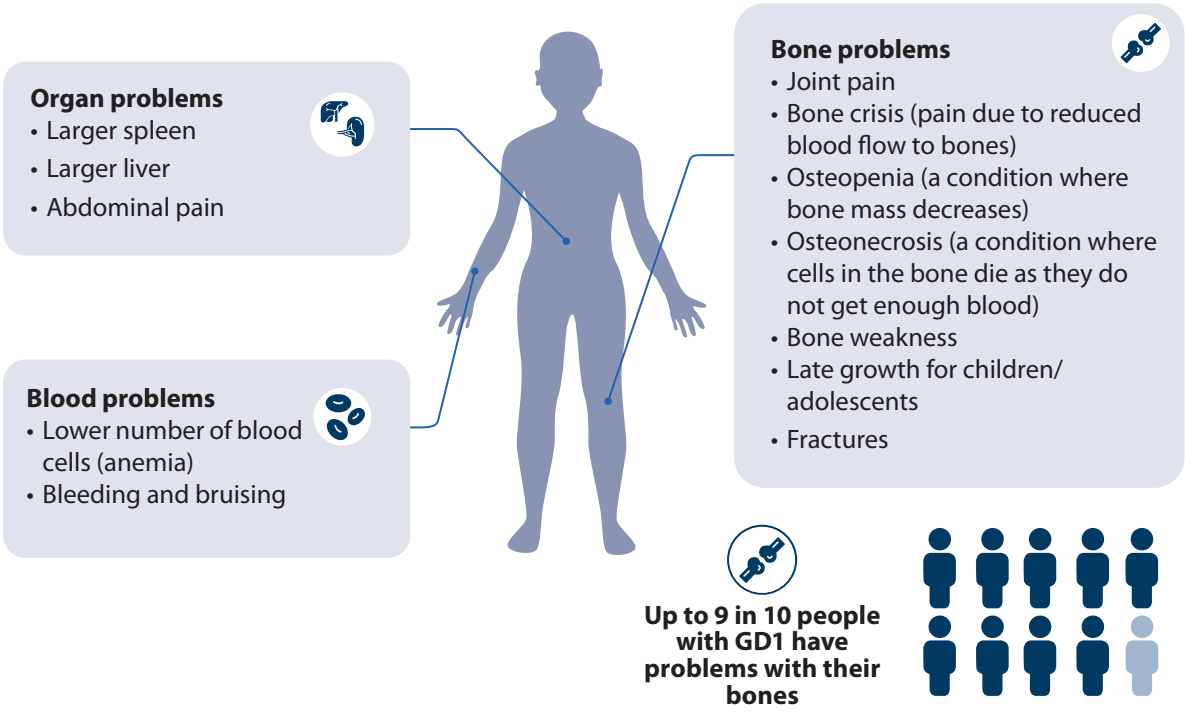
GD1 is the most common form of Gaucher disease in the Western world (Gaucher disease type 3 is the most common form in non-Western countries, such as China, Egypt, India, and Japan). The type of complications seen among people with GD1, and how severe complications are, can vary for each person.

How many people have Gaucher disease?

Gaucher disease is classified as a rare disease

Up to **1** in every **40,000** people are born with Gaucher disease

What are the common complications seen in GD1?



Bone problems are one of the main complications of GD1 and are a major cause of pain, disability, and reduced quality of life. Almost all people with GD1 are at risk of bone problems, such as fractures. These can happen in people with GD1 at any age.

There is currently no treatment that will cure Gaucher disease. The main goal of treatment for GD1 is to help people have a better quality of life by managing complications they have from GD1 and reducing the build-up of glycosphingolipids in organs. People with GD1 may be treated with medicines that replace the enzyme that is not working (beta-glucosidase) with a working version by regular infusions (where medicines are given directly into the bloodstream using a needle). This therapy is called enzyme replacement therapy (ERT). Studies have shown ERT is effective at improving complications of GD1, including bone health. However, people receiving ERT can still be at risk of developing fractures.

What did this study look at?

In this study, researchers wanted to know if a newly developed assessment, called the Gaucher Risk Assessment for Fracture (GRAF), could help them predict (tell them) how likely it is that a person with GD1 might have a fracture in the future.

- The GRAF is based on characteristics (factors) that researchers know might make someone with GD1 more likely to develop a fracture in adulthood.
- It includes assessments that doctors regularly record for people with GD1.

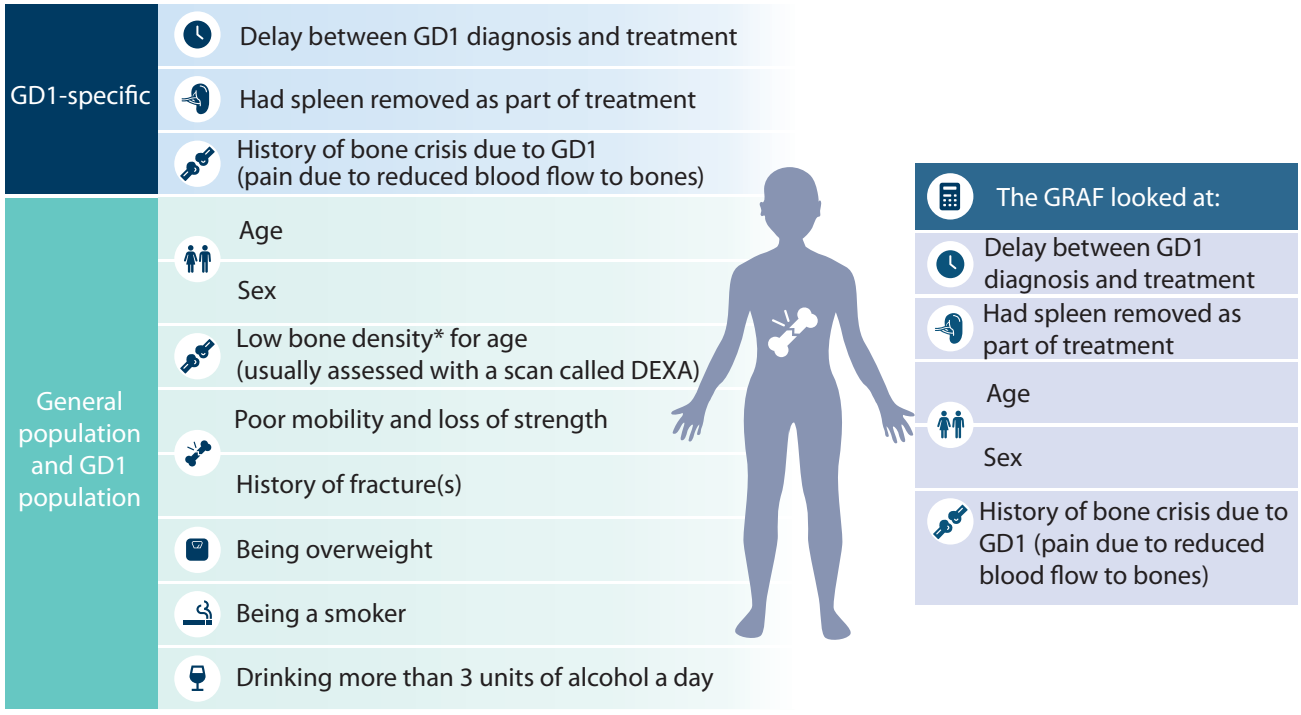
To find out how good the GRAF was at predicting fractures in adulthood, researchers looked at information (data) on people with GD1 from a database called the **International Collaborative Gaucher Group (ICGG) Gaucher Registry**. The published data from this registry was anonymised, meaning no one could be identified in the study.

- The researchers used historical data from people who had previously received treatment with ERTs (imiglucerase or alglucerase) as their first treatment for GD1 (although alglucerase is no longer available as a treatment).
- These data would help the researchers understand if any factors, such as delaying starting treatment, were likely to increase someone's chance of having a fracture, even though they were receiving an ERT.
- As they wanted to understand the chance of a fracture in adulthood, the researchers did not include information from people who had a first fracture before the age of 18 years.

More information on the ICGG Gaucher Registry can be found under '**Where can I find more information about this study?**' at the end of this article.

The GRAF looks at factors that are likely to increase the chance of a person with GD1 having a future fracture

Factors that increase the chance of having a fracture



*Bone density is how full of calcium your bones are, and is one way to measure bone strength

It is useful for doctors and researchers to know if the GRAF is effective at assessing fracture risk because:

- The underlying reasons for fractures in people with GD1 are different from those that lead to fractures in the general population. People with GD1 often have thinning of their bones and can have problems with the shape, form, and strength of their bones that make them more likely to have a fracture, in particular hip and spine fractures, compared with people who do not have GD1. Fractures may also take longer to heal and are less likely to fully repair in people with GD1 (although modern bone surgery to fix fractures is generally successful). Because of these reasons, it is helpful to have an assessment that is specifically for those with GD1.
- It might be useful when other assessments, such as bone scans, are not available.
- It might help doctors and people with GD1 make decisions about starting treatment with an ERT earlier.

How was the GRAF score calculated?

In this study, a person's GRAF score was calculated by taking each of the five factors (see infographic: '**The GRAF looks at factors that are likely to increase the chance of a person with GD1 having a future fracture**') and coming up with a single score for an individual at the time of starting ERT.

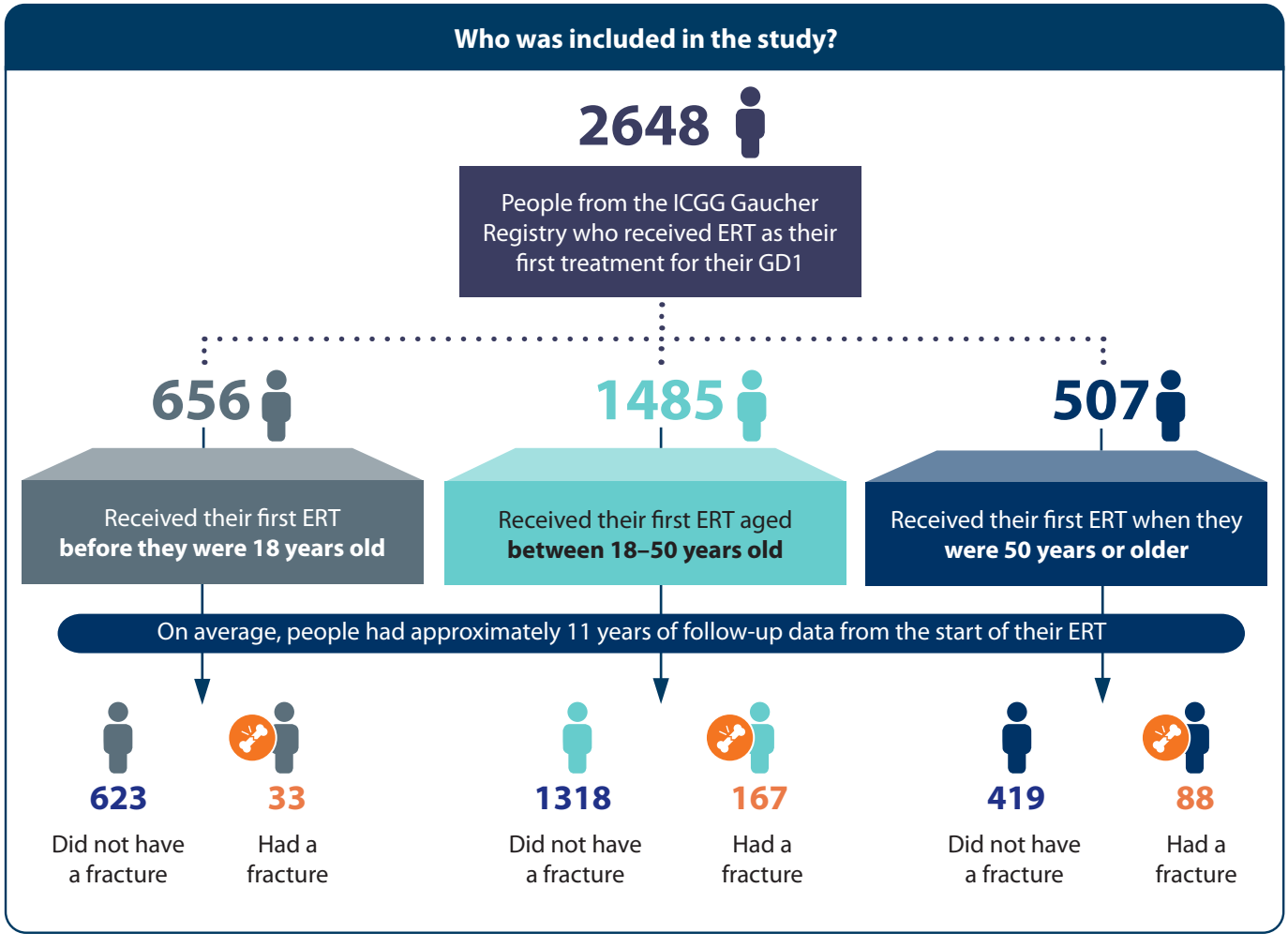
To calculate this, all five factors were put together into a statistical model, and that model assigned each factor a value (score) based on how well it predicted future fracture risk (e.g., the longer it took for someone to receive treatment after their diagnosis, the higher the value this factor was given).

- These values were different for each age group, as the age of when someone started ERT treatment can influence how likely they were to have a future fracture.

Each of the five values were then added together to produce a total GRAF score for a given individual.

- In each age group, based on their GRAF score, people were considered to be at low, medium, or high risk of having a fracture in the future.

Who took part in this study?



For people within each age group, we looked at factors that possibly increased fracture risk

Had a longer time between diagnosis and starting treatment

Were older when they started ERT treatment

Had their spleen removed before they started ERT treatment

Had reported bone crisis before they started ERT treatment

Were female

In each age group, some factors were associated with an increased chance of having a fracture

Received their first ERT **before they were 18 years old**

- No individual factors increased risk

Received their first ERT aged **between 18–50 years old**

- Had a longer time between diagnosis and starting treatment
- Were older when treatment was started
- Had their spleen removed before they started ERT treatment
- Had bone crisis before they started ERT treatment

Received their first ERT when they **were 50 years or older**

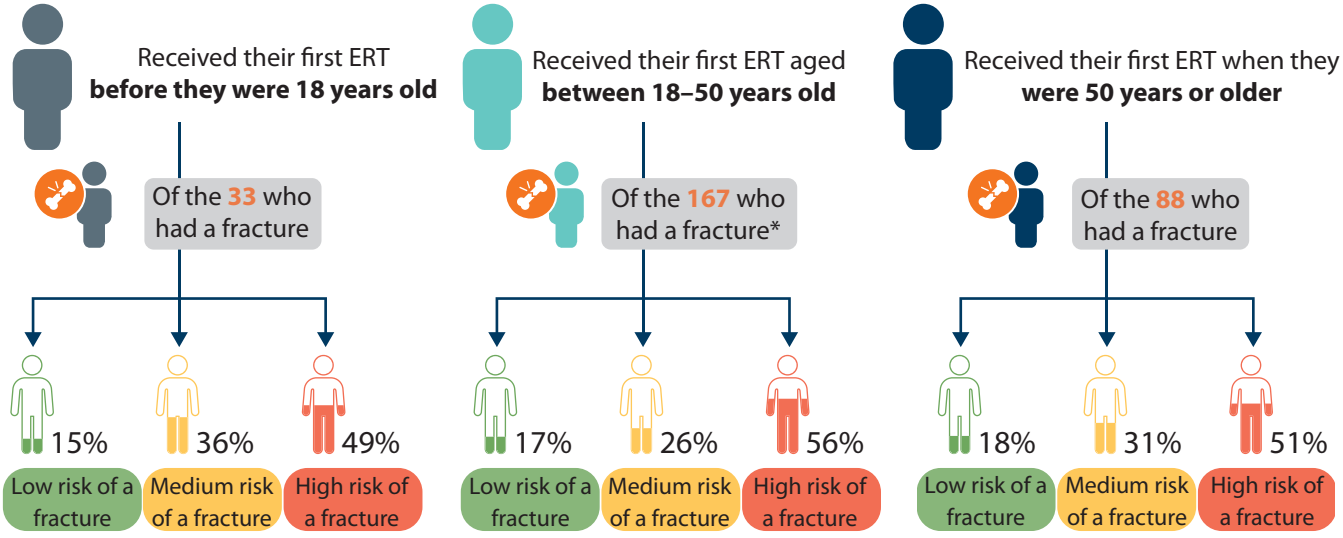
- Had a longer time between diagnosis and starting treatment
- Were older when treatment was started
- Had bone crisis before they started ERT treatment
- Were female

What were the main results of this study?

1 Overall the GRAF score was associated with fracture risk People who had a fracture had a higher GRAF score on average

For each 1-point increase in GRAF score, people were nearly **3 times more likely to have a fracture**

In each age group and based on their GRAF score, people were considered to either be at low, medium or high risk of having a future fracture



*Percentages may not add up to 100% due to rounding

2 Having a higher GRAF score predicted a higher chance of having a fracture after 10 years

The risk that people in each age group would have a fracture 10 years after starting treatment was predicted based on their GRAF score

	Received their first ERT **before they were 18 years old**	Received their first ERT aged **between 18–50 years old**	Received their first ERT when they **were 50 years or older**
GRAF score group	**Chance of having a fracture 10 years after starting treatment**		
Low risk	3%	5%	10%
Medium risk	6%	6%	15%
High risk	9%	14%	26%

Risk of fracture remained low for people with GD1 who had either:

Low-risk GRAF score

Started ERT earlier

What do the results of the study mean?

The GRAF, as an assessment for people with GD1, was found to perform as well as other fracture risk tools that are used in the general population.

The GRAF can be used along with bone density measurements and other known risk factor assessments to help doctors and people with GD1 understand their risk of fracture after starting an ERT such as imiglucerase, or if they started alglucerase in the past (alglucerase is no longer available as a treatment).

- By understanding an individual's potential future fracture risk, doctors and people with GD1 can discuss personalised disease management.

The GRAF score may also help doctors and people with GD1 make decisions on when to start treatment with an ERT based on their future risk of a fracture. For example, if fracture risk is high, doctors may advise people with GD1 to start treatment sooner.

Are there any plans for future studies?

Once more data have been collected in the ICGG Gaucher Registry, the researchers will look at including other measurements such as the bone density measurement scan, dual-energy X-ray absorptiometry (DEXA), and individual GRAF scores to help assess fracture risk.

Where can I find more information about this study?

Original article

The original article is called 'The International Collaborative Gaucher Group GRAF (Gaucher Risk Assessment for Fracture) score: a composite risk score for assessing adult fracture risk in imiglucerase-treated Gaucher disease type 1 patients' and was published in the journal *Orphanet Journal of Rare Diseases*. You can read the full article for free here: https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01656-6

The ICGG Gaucher Registry is a voluntary database that collects medical information on people with Gaucher disease. Information in the registry is used to improve understanding of Gaucher disease and learn more about treatments for the disease. As of October 2021, 6812 people with Gaucher disease across more than 60 countries worldwide have been enrolled in the registry, 5832 of whom have GD1.

- All people in the registry gave consent to their doctor for their information to be part of the ICGG Gaucher Registry and to be used in studies.
- The registry includes participants' information such as sex and age, medical history, medical management, clinical outcomes, and any treatments they have had.

Trial registration site

More information on the ICGG Gaucher Registry can be found at:

- https://www.registrynxt.com/
- or by typing the study number, NCT00358943, into the search bar of the ClinicalTrials.gov website at: https://www.clinicaltrials.gov/

Further information and educational resources

Available treatments and more information about Gaucher disease can be found at:

- https://www.gaucherdisease.org/
- https://www.thinkgenetic.com/diseases/gaucher-disease/treatment/4032
- https://rarediseases.org/rare-diseases/gaucher-disease/
- https://www.thinkgenetic.com/diseases/gaucher-disease

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