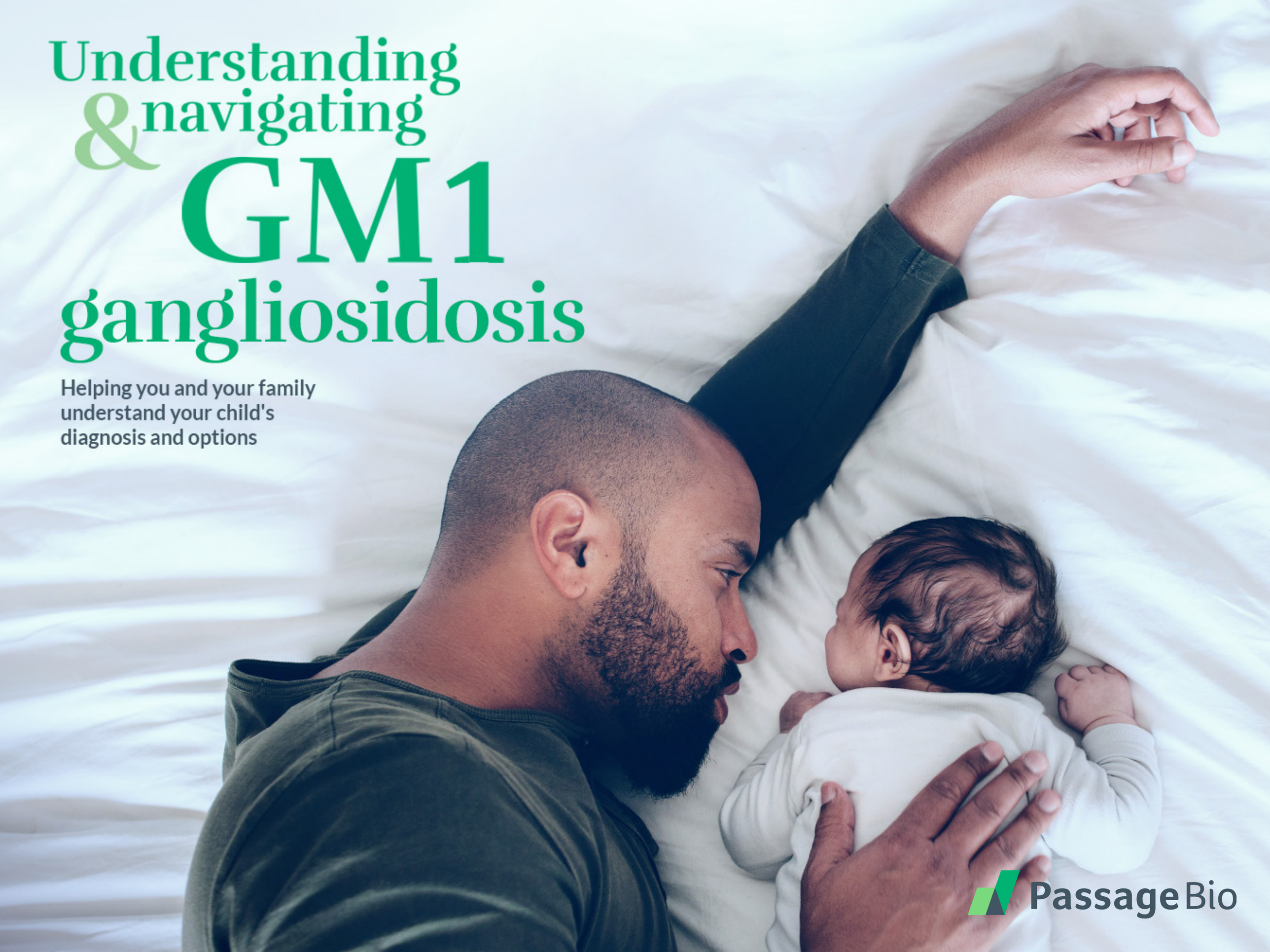
Understanding & navigating GM1 gangliosidosis

Helping you and your family understand your child's diagnosis and options



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What is GM1 gangliosidosis?

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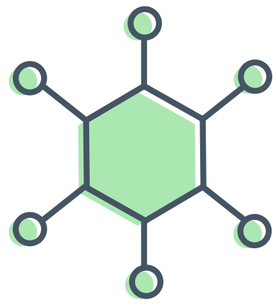
GM1 gangliosidosis is a rare, inherited genetic disorder that causes a variety of symptoms

GM1 gangliosidosis occurs when a person has very low amounts of a vital enzyme, β-galactosidase (referred to as β-gal). This enzyme affects nerve cells (called neurons) in the brain and spinal cord, components of the central nervous system (CNS). This results in a number of symptoms that may lead parents to believe that their child needs medical attention.

GM1 gangliosidosis is most common and severe in babies younger than 1 year old but can affect people of all ages

Anyone born with GM1 gangliosidosis has low amounts of β-gal, even if symptoms do not appear until later in childhood.



The severity of GM1 gangliosidosis is generally determined by how much of the β-gal enzyme is active within the cell

Typically, there is less β-gal activity in the youngest patients, which means they will generally have a more severe form of the disease.

GM1 gangliosidosis is estimated to affect 1 in 100,000 to 200,000 babies born.

What are the signs and symptoms?

The signs and symptoms of GM1 gangliosidosis impact people differently depending on the age at which symptoms appear and how severe they are. Symptoms can differ based on the type of GM1 gangliosidosis.

The most common, severe, and progressive form of the disease is early onset infantile (Type 1).

Age of onset	Symptoms
 **Early onset infantile (Type 1)** Symptoms appear by 6 months of age	• Limpness (hypotonia) • Delays in development • Feeding difficulties • Skeletal abnormalities Damage to the CNS occurs rapidly, with the inability of muscles to relax, deafness, and blindness often seen by 1 year of age.
 **Late onset infantile (Type 2a)** Symptoms appear between 6 months and 2 years of age	• Seizures • Lag in motor and learning skills • Failing to meet developmental milestones and/or losing of milestones that have been achieved Overall, symptoms are similar to those of early onset infantile GM1 gangliosidosis, but disease progression is slower.
 **Juvenile (Type 2b)** Symptoms appear from 2 to 5 years of age	• Abnormalities in movement • Change in the ability to speak clearly • Abnormal eye movements
 **Adult (Type 3)** Symptoms may appear at 3 years of age or older, although they may appear in adults 20 to 40 years of age	Weakness in the arms and legs progresses over time, leading to the inability to walk without assistance and slurred speech.

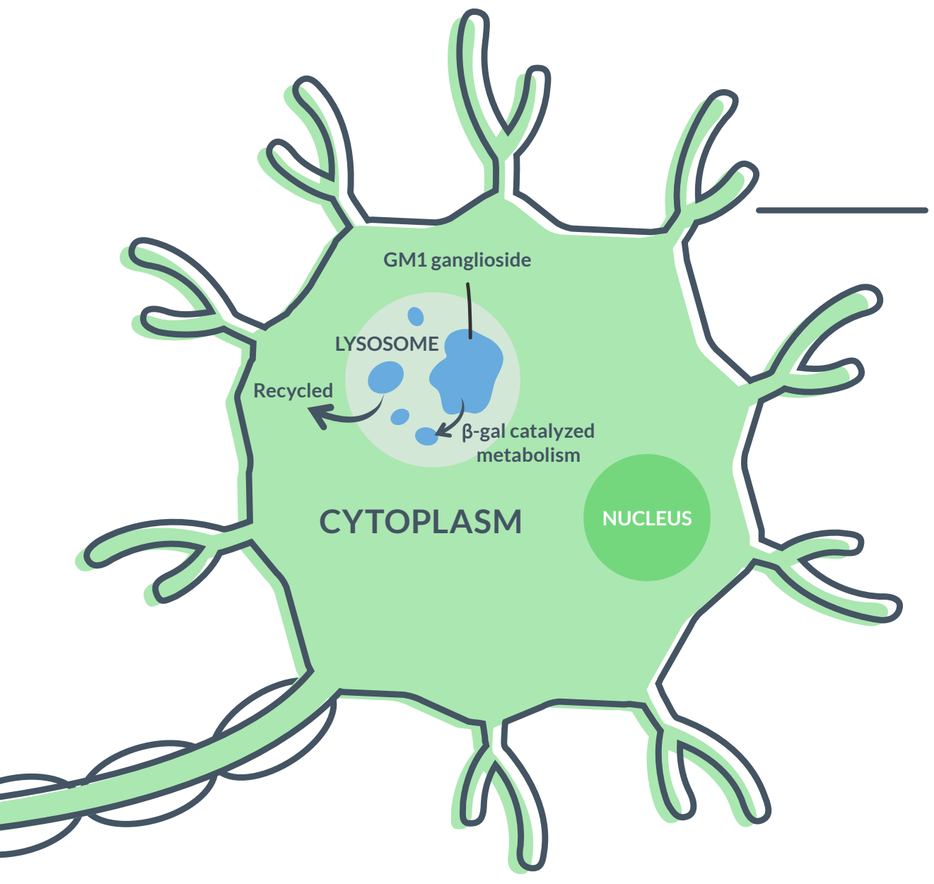
What causes GM1 gangliosidosis?

GM1 gangliosidosis is referred to as a “lysosomal storage disorder.”

Like other diseases in this group of disorders, GM1 gangliosidosis involves small compartments called “lysosomes” inside cells found in the nerves, liver, heart, etc. Lysosomes contain various enzymes that break down (or metabolize) larger molecules into smaller components for reuse or recycling elsewhere in the cell. This avoids the buildup of too many of these components within the cell.

In GM1 gangliosidosis, the function of lysosomes is disrupted by genetic mutations

The galactosidase beta 1 (*GLB1*) gene provides the cells of the nervous system with instructions on how to make the enzyme β-gal. The body needs β-gal to process a key fatty acid (or lipid) known as GM1 ganglioside.

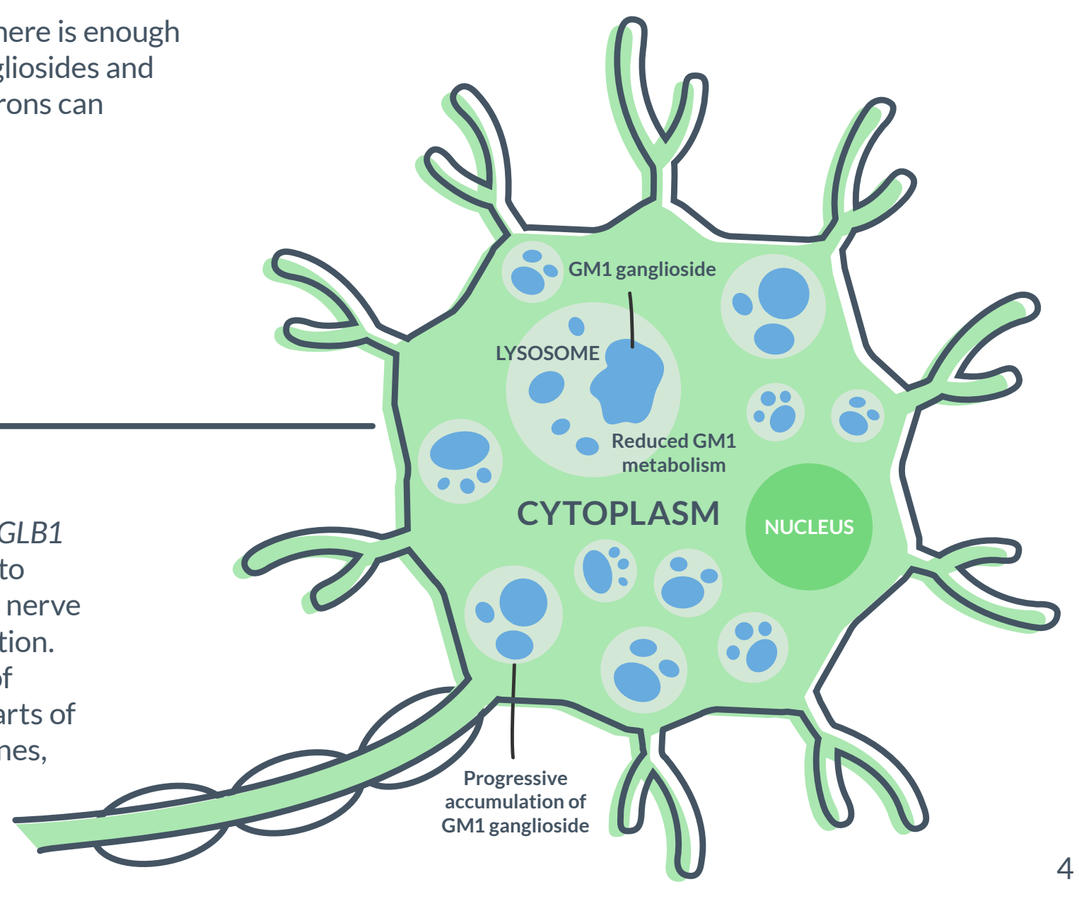


Healthy nerve cell with normal function

In patients with healthy *GLB1* genes, there is enough β-gal enzyme to metabolize GM1 gangliosides and keep them at normal levels so the neurons can function properly.

GM1 gangliosidosis nerve cell with harmful buildup

Without enough β-gal enzyme due to *GLB1* mutations, GM1 ganglioside builds up to harmful levels within the lysosomes of nerve cells, ultimately destroying nerve function. Lack of β-gal can also lead to buildup of other damaging substances in other parts of the body, including the eyes, heart, bones, liver, and spleen.



Who is at risk?

GM1 gangliosidosis is passed down from parents to their children

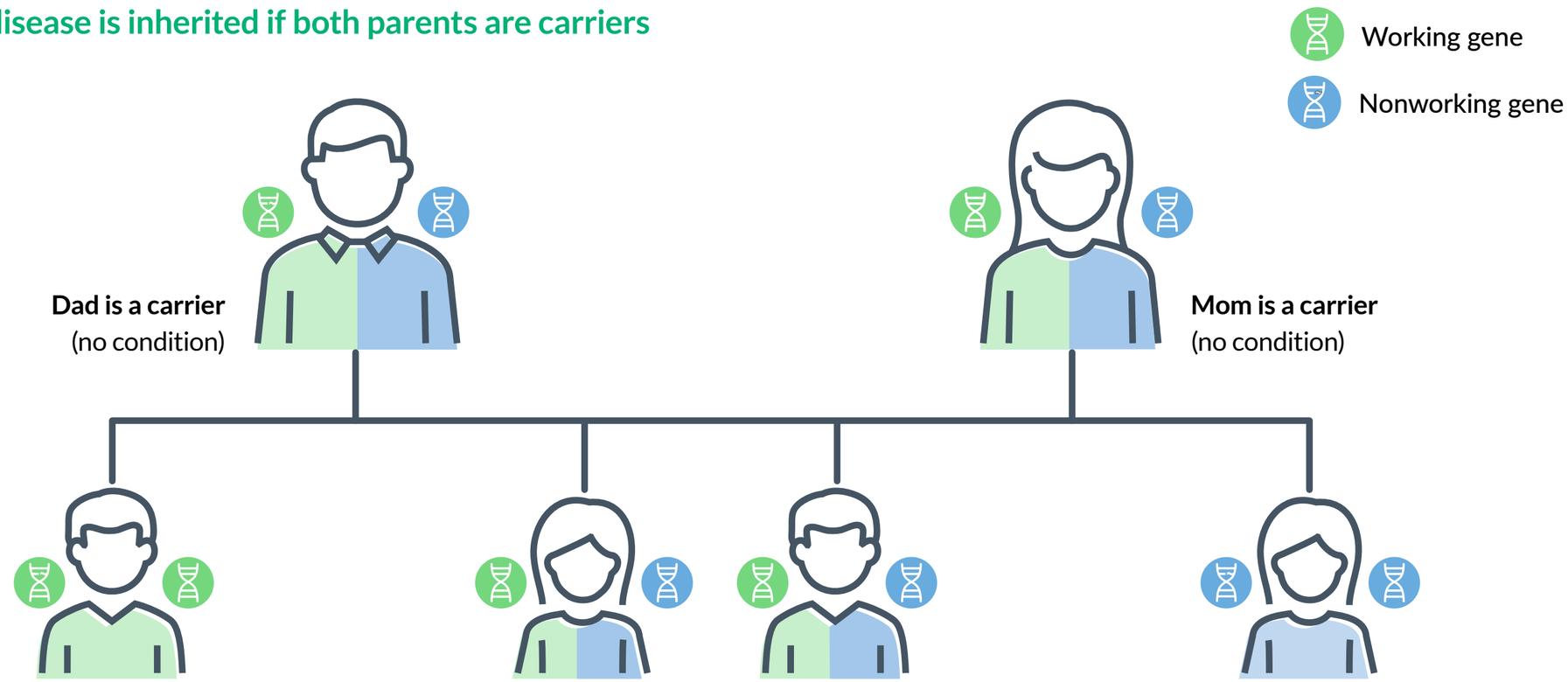
Every person has two copies of the *GLB1* gene. If one of those two copies is a mutation, the person is a "carrier" of GM1 gangliosidosis.

- Healthy *GLB1* gene
- Mutated *GLB1* gene

In a carrier, the one remaining normal copy of the *GLB1* gene is sufficient to produce enough β-gal for normal functioning. This means the carrier may not have the symptoms of the disease.

- Healthy *GLB1* gene
- β-gal

How the disease is inherited if both parents are carriers



Condition not present

25% chance for the child to receive two functioning copies of the healthy gene and not have GM1

Carrier

50% chance for the child to be a carrier but not have GM1

Has condition

25% chance for the child to receive TWO mutated copies of the *GLB1* gene, which means the child would have GM1

How is GM1 gangliosidosis diagnosed?

Early diagnosis is critical due to rapid nervous system progression.

The presence of GM1 gangliosidosis symptoms indicates that there is ongoing, progressive disease activity. This is why early diagnosis is so important, especially for patients with the more progressive infantile types of the disease.

Signs that may lead to a diagnosis of infantile forms of GM1 gangliosidosis

The process often begins when parents or physicians notice symptoms that are commonly associated with the disease, such as poor muscle strength, limpness, the inability to sit up and crawl, poor feeding and failure to thrive, and the presence of a “cherry red spot” in the back of the eye that is seen during an eye exam.

Signs that may lead to a diagnosis of juvenile or adult GM1 gangliosidosis

GM1 gangliosidosis should be considered when there is new or worsening muscle weakness, slurred speech, lack of balance or coordination, other movement disorders, and/or a reduced ability to learn or comprehend.

What tests are needed for a diagnosis?

If a doctor suspects that a patient has GM1 gangliosidosis, a number of tests can be used to confirm a diagnosis.

Various forms of imaging

- Neuroimaging to visualize the nervous system structure and function
- Other imaging techniques, including X-rays, abdominal ultrasound, and echocardiogram

Blood tests

Used to evaluate patient's level of β-gal activity

Genetic testing

Used for determining if there are mutations in the *GLB1* gene

Currently, there are no approved disease-modifying treatments available for patients with GM1 gangliosidosis.

What types of specialists care for someone with GM1 gangliosidosis?

While there are no approved disease-modifying treatments available for patients with GM1 gangliosidosis, patients may be managed with symptomatic and supportive care from specialists, including:

Neurologist

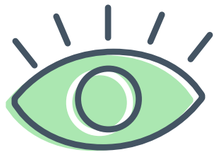
Developmental pediatrician

Gastroenterologist

Cardiologist

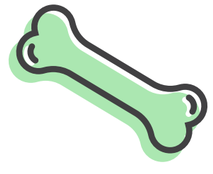
Physiatrist/Physical therapist

Geneticist or metabolic specialist



Ophthalmologist

Pulmonologist



Orthopedist

Speech language pathologist

With limited treatment options for GM1 gangliosidosis, it is important to consider the role of clinical trials.

What is a clinical trial?

Clinical trials are research studies where doctors see if a potential treatment is safe and effective in people

The effectiveness, or ability of a treatment to help people, is often called efficacy. Doctors who work on clinical trials are called Principal Investigators, or PIs. People choose to be in clinical trials because they may benefit from the potential treatment being studied or because they want to help answer a specific health question.

Imagine-1
A Clinical Trial for GM1 Gangliosidosis

Passage Bio is conducting an investigational clinical trial called IMAGINE-1 to collect data about the potential safety, effectiveness, and dosing of a gene therapy for patients with GM1.

Learn more about the IMAGINE-1 Trial at **GM1Study.com**

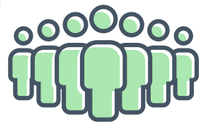
How a potential treatment gets approved

All of the prescription therapies available to you today have been studied in clinical trials before approval.

1.

Scientists gather lots of evidence that a potential treatment could help treat a disease or disorder.

2.



PIs study the potential treatment in people with the disease. There are often 3 phases of clinical trials:

- Phase 1 tests safety and dose
- Phase 2 tests effectiveness and safety
- Phase 3 tests effectiveness and safety in a larger group of patients

In rare diseases, where there are low numbers of patients and limited treatment options, researchers often combine phases to answer more questions in a smaller group of patients. For example, you may see a trial labeled as Phase 1/2. This can speed up the time it takes to get treatments people need approved.

3.

Study results are evaluated to determine whether the potential treatment significantly benefits people with the disease.

4.

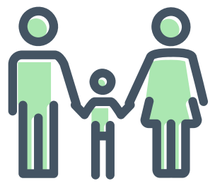
The Food and Drug Administration (FDA) and other government agencies around the world assess the results of potential treatments and approve only those treatments that show safety and efficacy.

You and your family are not alone

There are communities dedicated to fighting GM1 gangliosidosis. These organizations are committed to helping children with GM1 gangliosidosis, supporting families, furthering research, and broadening awareness.

GM1 gangliosidosis patient advocacy organizations can help you and your family:

Understand your child's options for care



Connect with physicians, experts, and other families

Establish a community of logistical and emotional support

Identify financial assistance programs

Cure GM1 Foundation
A nonprofit patient advocacy group that provides support and resources for families caring for a child with GM1 gangliosidosis

National Tay-Sachs & Allied Diseases Association (NTSAD)
A nonprofit patient advocacy group that is focused on research, forging collaboration, fostering community, and supporting families

Passage Bio is committed to transforming lives

Patients drive every decision we make, from which therapies to pursue to how we will pursue them. We focus on developing effective treatments that are desperately needed for CNS disorders, like GM1 gangliosidosis.

We believe that collaboration is important. We are committed to working with patient advocacy groups that are also committed to transforming lives.

For more information about Passage Bio and our work to develop an effective treatment for GM1 gangliosidosis, please visit us at **PassageBio.com**.

If identified quickly, patients with GM1 gangliosidosis may be eligible for clinical trials, so early diagnosis is critical

If you would like more information, please talk with a healthcare professional or send inquiries to Passage Bio at **patientservices@passagebio.com**.

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