This brochure features real patients who have been compensated for their participation.

LOOK CLOSER TO

SEE WHAT THALASSEMIA IS HIDING

Even if you don't receive regular transfusions, thalassemia may come with serious risks.
Learn more about these risks and what you can do about them.

Contents

Nothing in this brochure is intended as medical advice. For medical advice, please contact your healthcare team.

What is thalassemia?

Thalassemia is a group of rare inherited blood conditions. It affects the production of a protein called hemoglobin

- Hemoglobin is a key part of red blood cells (RBCs). Hemoglobin holds onto oxygen and delivers it to cells throughout the body. Cells use oxygen to function
- In thalassemia, hemoglobin is not made properly. As a result, healthy RBCs cannot be made properly

Thalassemia results in chronic anemia that can last throughout life

- The type of anemia resulting from thalassemia is not the same as iron-deficiency anemia. Iron-deficiency anemia occurs when the body does not have enough iron to make RBCs

Whom does thalassemia affect?

- Thalassemia affects both men and women
- Thalassemia can affect people of many different backgrounds but is more common among people of African, Asian, Mediterranean, or Middle Eastern descent
- The name *thalassemia* comes from Greek: *thalassa* means sea and *emia* means related to blood

In healthy adults who do not have thalassemia, hemoglobin levels typically range from 14 g/dL to 18 g/dL in men and 12 g/dL to 16 g/dL in women.

What causes thalassemia?

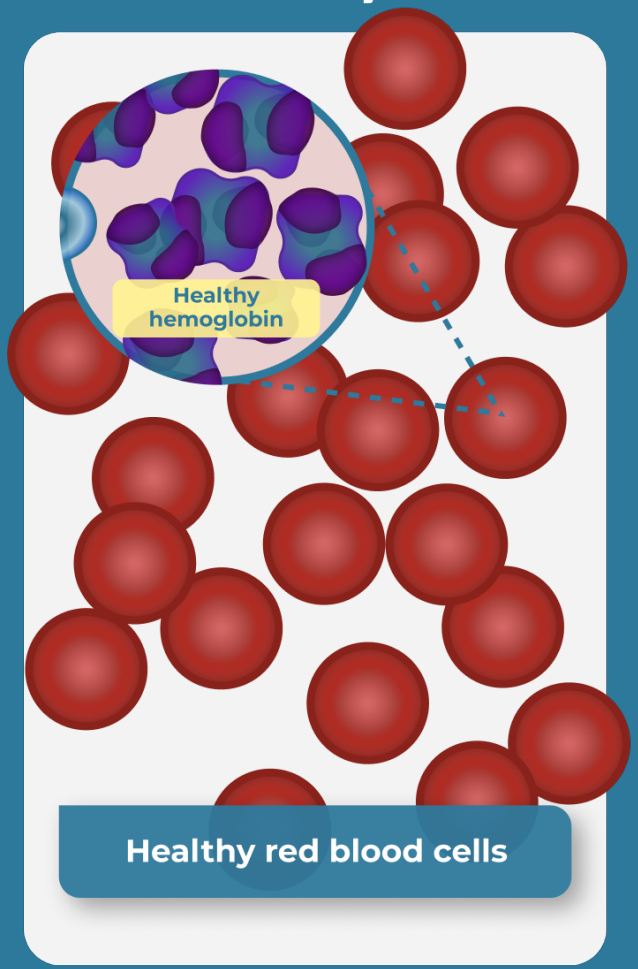
In thalassemia, there are changes to the genes that instruct the body to make hemoglobin

- Hemoglobin is made up of 4 subunits called globins—2 alpha (α) globins and 2 beta (β) globins
- In alpha-thalassemia, the alpha units of hemoglobin are missing or damaged. In beta-thalassemia, the beta units of hemoglobin are missing or damaged. In both types, hemoglobin is not produced properly, and RBCs are not healthy

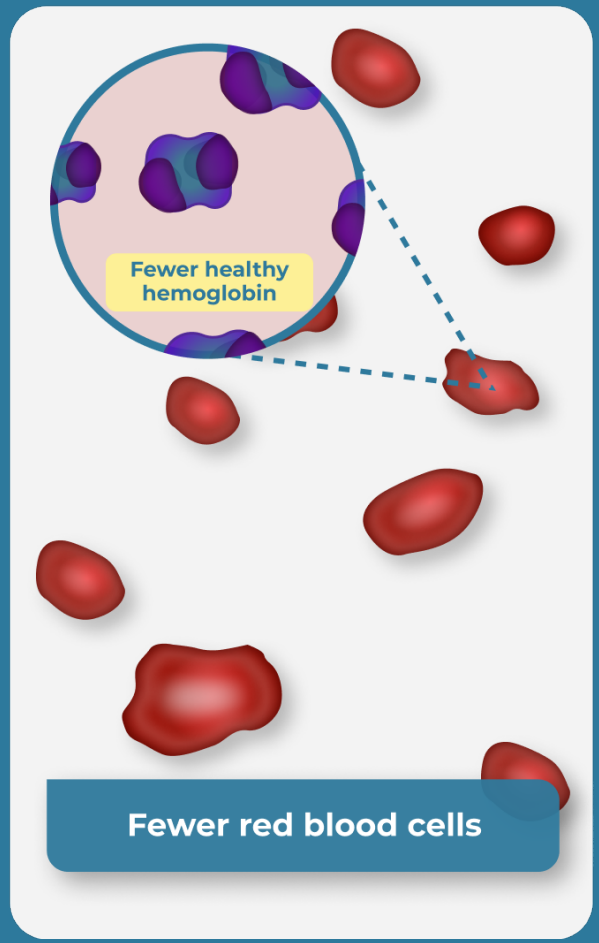
When red blood cells do not have enough energy (ATP) within, they don't develop properly (ineffective erythropoiesis) or break down sooner than normal (hemolysis). This can lead to low hemoglobin, which results in chronic anemia.

Currently, there are no medications for all types of thalassemia that address both the proper production of red blood cells and their survival.

Blood not affected by thalassemia



Blood affected by thalassemia



For illustrative purposes only.

The life span of healthy RBCs is about **120 days**

The life span of thalassemia RBCs is about **17-33 days**

In thalassemia, the shorter lifespan of RBCs can cause chronic anemia symptoms and can also lead to serious complications.

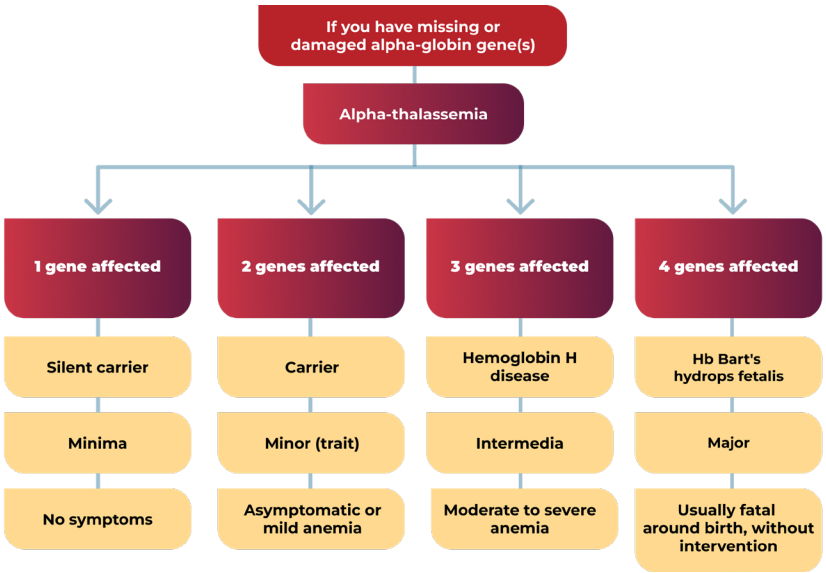
How is thalassemia described?

There are many ways to describe thalassemia

Alpha-thalassemia and beta-thalassemia refer to genetics and inheritance pattern.

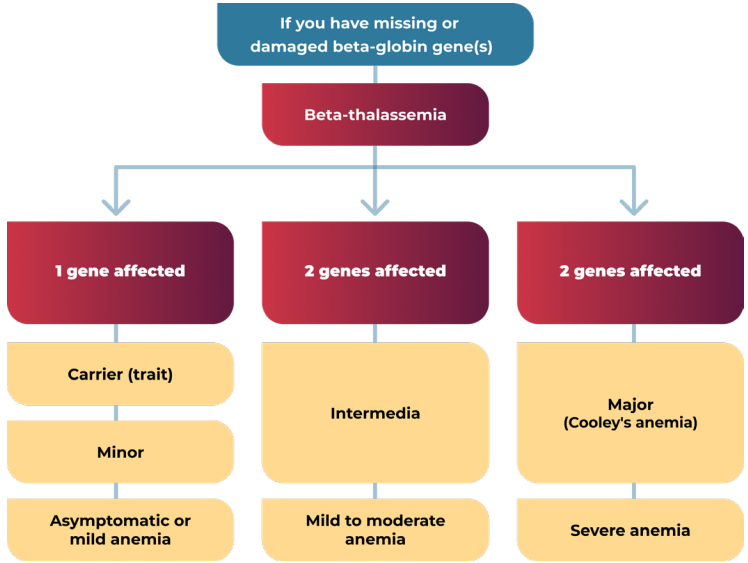
Alpha-thalassemia is caused by changes to alpha-globin genes

- 4 genes provide instructions for making alpha-globin
  - In alpha-thalassemia major, all 4 alpha-globin genes are affected
  - In alpha-thalassemia intermedia, 3 of 4 alpha-globin genes are affected
  - In alpha-thalassemia trait, 1 or 2 of 4 alpha-globin genes are affected; if only 1 alpha-globin gene is affected, a patient is sometimes called a 'silent carrier'



Beta-thalassemia is caused by changes to beta-globin genes

- 2 genes provide instructions for making beta-globin
  - In beta-thalassemia major and beta-thalassemia intermedia, both globin genes are affected
  - In beta-thalassemia minor, 1 beta-globin gene is affected



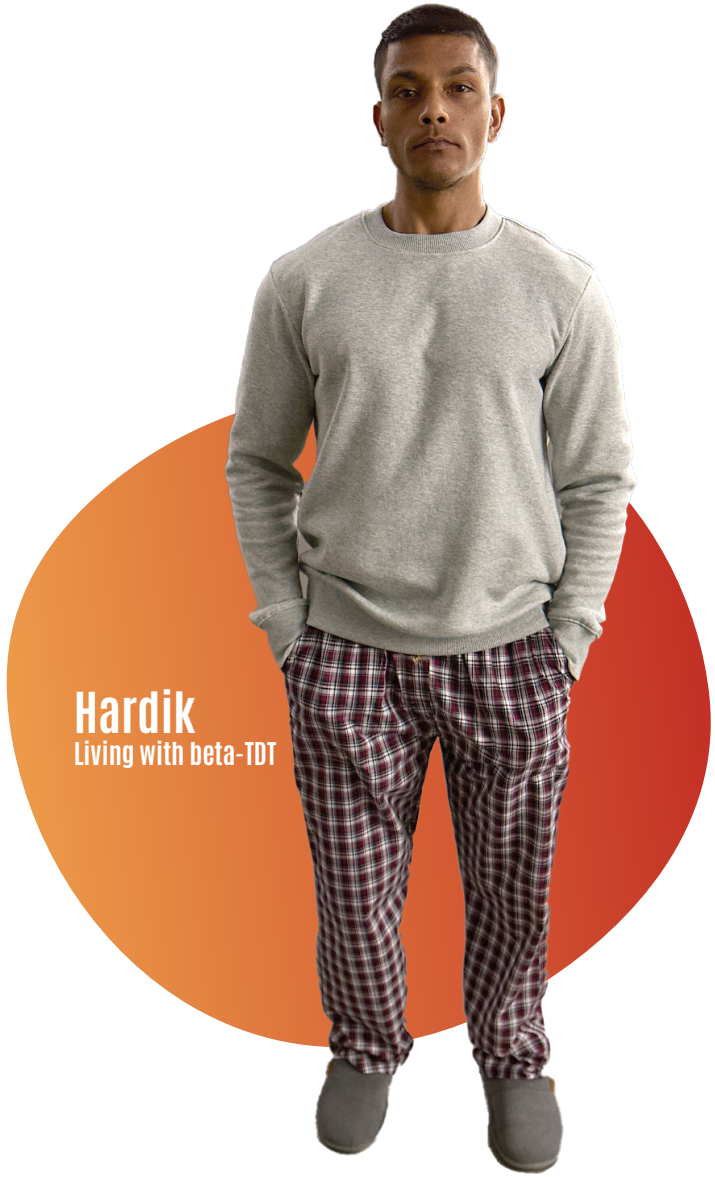
A genetic counselor can provide information about testing for thalassemia type, education about inheritance patterns, and can discuss personalized family planning with you.

How is thalassemia described?

Thalassemia major, thalassemia intermedia, thalassemia minor, and thalassemia trait refer to genetics and severity of anemia.

More recently, experts have begun to describe thalassemia based on transfusion status: transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT)

- Thalassemia that requires regular blood transfusions for survival may be referred to as TDT. For example, a person living with thalassemia who receives transfusions every 3 weeks may be considered to have TDT
- Thalassemia that does not require regular blood transfusions for survival may be referred to as NTDT
- Those who have NTDT may receive transfusions from time to time or not at all
- People with NTDT may require more frequent transfusions over time, and transition to TDT



While there are many ways to describe thalassemia, in both TDT and NTDT, all share in common the body's inability to produce adequate amounts of healthy hemoglobin and healthy red blood cells.

What are the symptoms of thalassemia?

Symptoms of thalassemia may vary from person to person.

Check off any of the symptoms below that you are experiencing so you can share the information with your care team.

Common symptoms include:

- [ ] Fatigue
- [ ] Weakness
- [ ] Shortness of breath
- [ ] Dizziness and fainting
- [ ] Paleness
- [ ] Headaches

Other symptoms include:

- [ ] Yellowing of skin and eyes
- [ ] Possible pain in stomach area due to enlargement of the spleen or liver
- [ ] Changes in facial bones
- [ ] Dark urine
- [ ] Poor appetite
- [ ] Difficulty focusing

> "Doctors often will say I'm not sick enough... but I know there must be something I can do to feel better."
>
> *— Real patient living with thalassemia*

It's important for all people living with thalassemia to be aware of and share any symptoms with their care team.

How is thalassemia managed?*

People with thalassemia may require supportive therapies:

Blood transfusion

- The goal of a blood transfusion is to replenish healthy red blood cells (RBCs) and hemoglobin
- Some people require transfusions for survival. Others may need them from time to time, or in situations when the body is stressed (for example, illness or pregnancy)
- Whether or not someone receives transfusions and how frequently should be discussed with a healthcare professional

Iron chelation therapy

- The goal of iron chelation therapy is to help remove excess iron from the body
- Excess iron in the body can happen because of thalassemia itself and/or transfusion therapy

Folic acid supplementation

- Folic acid is a vitamin needed to make healthy RBCs

Spleen removal (less commonly performed)

- The spleen may become enlarged because it is working hard to break down thalassemic RBCs. Spleen removal may be considered to increase RBC counts

Early and regular monitoring for ALL types of thalassemia is critical. Thalassemia experts recommend regular monitoring for complications in all people living with thalassemia, whether they have non–transfusion-dependent thalassemia or transfusion-dependent thalassemia.

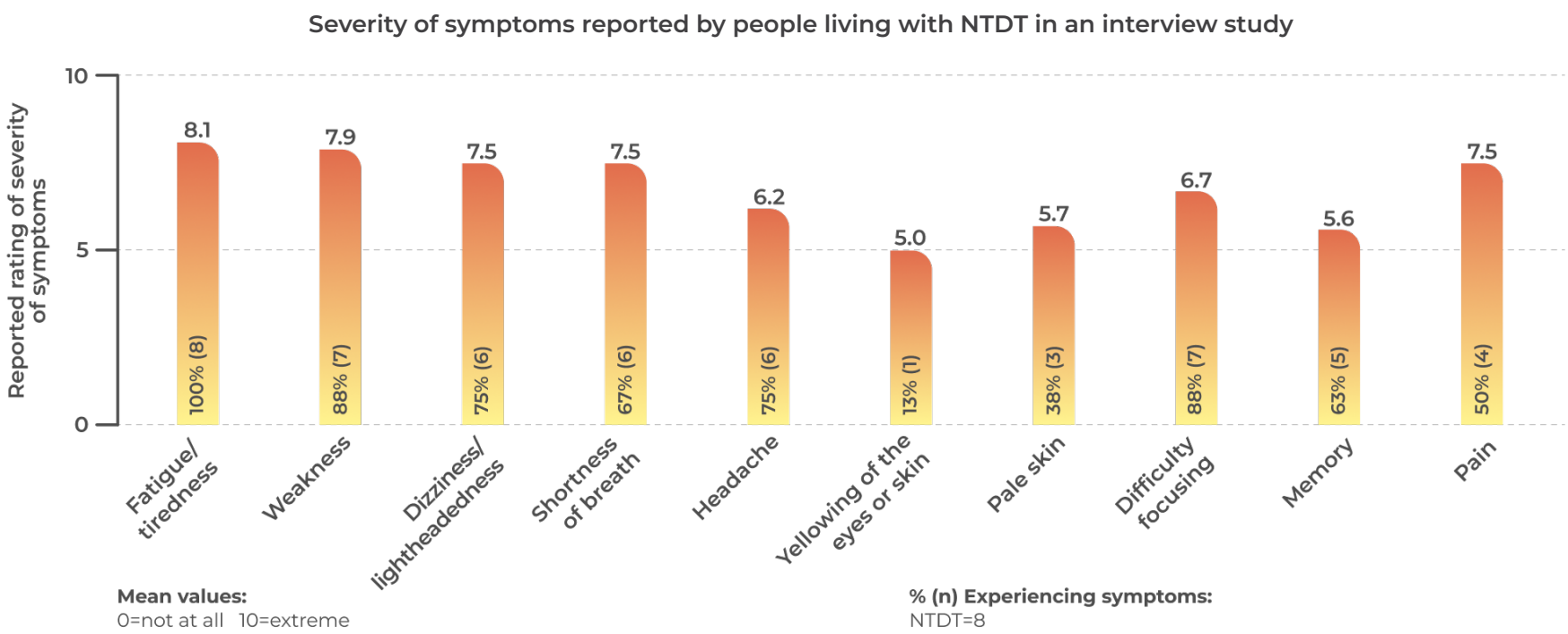
*This is not medical advice. Please consult with your doctor.

Jesse
Living with alpha-TDT†

†Transfusion-dependent alpha-thalassemia

Monitoring helps you and your care team identify and potentially prevent complications.

What symptoms do people with non-transfusion-dependent thalassemia (NTDT) report despite current management strategies?



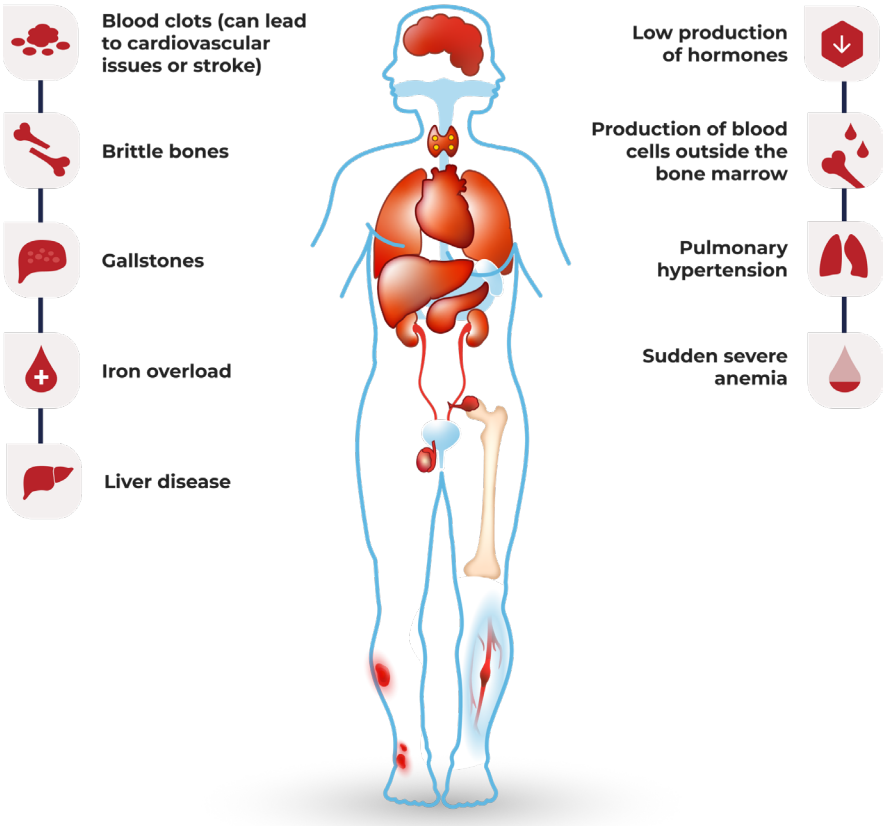
Study design: 18 Transfusion-dependent thalassemia (TDT) patients (5 alpha-thalassemia and 13 beta-thalassemia) and 8 NTDT patients with alpha-thalassemia who had made no changes to their thalassemia treatment for at least 6 months were interviewed about symptoms, impact, quality of life, and transfusion dependence via open-ended, semi-structured interviews. Symptom severity was rated by patients on a scale from 0-10. 0 meant no severity of symptoms and 10 meant extreme severity of symptoms.

Mean symptom severity among participants reporting the symptom were calculated from responses.

"Some symptoms like shortness of breath and bone pain are easy to see, but there are ones that are less visible. My spleen was enlarged so I had it removed, my gallbladder failed, I have osteoporosis, iron overload. Thalassemia damages your organs inside as well if not monitored and managed correctly."

Mary Jo
Living with beta-TDT, previously beta-NTDT

What are some complications that can occur in people living with non-transfusion-dependent alpha-thalassemia?



This is not a complete list of possible complications.
For medical advice, please consult with your doctor.

Chronic anemia can be associated with many thalassemia complications.

Some complications can lead to end-organ damage and can be life-threatening if not properly monitored and managed.

For more information, scan the QR code to visit RethinkThalassemia.com.

Monitoring helps you and your care team identify and potentially prevent complications.

Blood clots: Several things that happen in thalassemia can add up to you getting a dangerous blood clot that lodges in a blood vessel, where it can cause a block in blood flow to the heart or a stroke in the brain. For patients who do not receive regular transfusions, this can be more common.

Brittle bones: Most blood cells are made in the bone marrow (the spongy material inside bones). In patients with thalassemia, it can expand due to increased demand for red blood cells, which causes your bones to widen. This can make your bones thin and brittle, increasing the chance of broken bones.

Gallstones: Gallstones are one of the most prevalent complications. They are a result of the breakdown of red blood cells (hemolysis), one of the key processes driving thalassemia.

Hemolysis: The destruction of red blood cells which leads to the release of hemoglobin from within the red blood cells into the blood plasma.

Ineffective erythropoiesis: When the body tries to make red blood cells, but they don't develop properly.

Iron overload: People with thalassemia who receive regular transfusions, as well as those who do not receive regular transfusions, can get too much iron in their bodies either from frequent blood transfusions or from the disease.

This means a lot of iron is moving around in the blood. When iron builds up, it collects in places like the heart, liver, and endocrine organs and can make it hard for these organs to work properly.

Liver disease: When iron deposits into the liver, it can lead to fibrosis (scarring of the liver) and cirrhosis (severe scarring, which can prevent proper functioning).

Low production of hormones: Hormones are chemicals the body produces and uses to regulate almost every organ and function. Due to anemia or iron overload, thalassemia can result in lower production of certain hormones. This can be associated with a number of conditions, including growth delays, delayed puberty, thyroid problems, and diabetes.

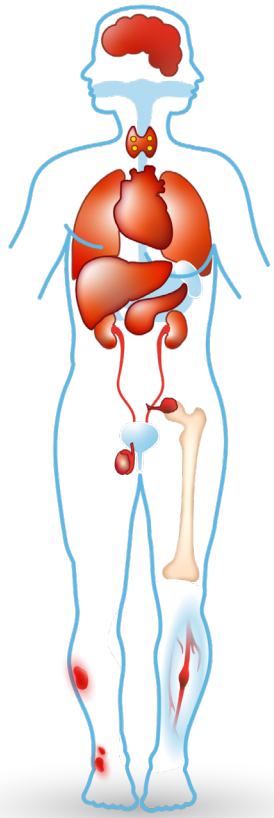
Production of blood cells outside the bone marrow: This can occur in all types of thalassemia when red blood cells are not produced properly in the bone marrow. This can lead to enlargement of organs such as the spleen and liver or formation of masses next to the spine.

Pulmonary hypertension: A type of high blood pressure in the lungs. The breakdown of red blood cells (hemolysis) can cause it, and so can iron overload.

Sudden severe anemia: A "hemolytic crisis" or sudden drop in hemoglobin with signs of red blood cell destruction can occur in people with alpha-thalassemia. This can happen as a result of an infection with high fever.

What are some complications that can occur in people living with non-transfusion-dependent beta-thalassemia?

- Blood clots (can lead to cardiovascular issues or stroke)
- Brittle bones
- Heart failure
- Iron overload
- Leg ulcers



- Liver disease
- Low production of hormones
- Production of blood cells outside the bone marrow
- Pulmonary hypertension

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Heart failure: The heart muscle can't pump enough blood to meet the body's needs for blood and oxygen. In thalassemia, heart complications are one of the major concerns. Several things might cause heart disease. Heart disease can progress to heart failure and possibly death.

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Leg ulcers: Anemia results in reduced oxygen delivery to tissues like the skin, making it easier for ulcers, or sores, to develop.

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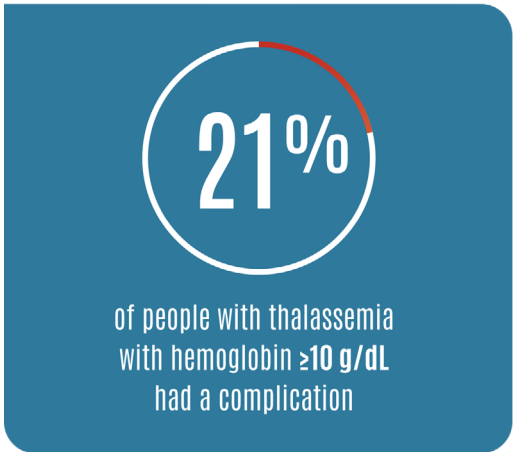
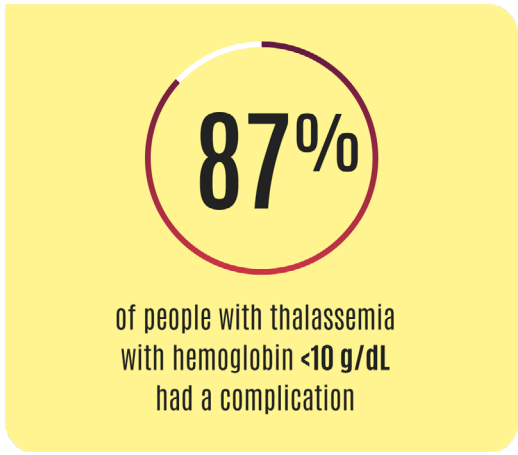
Production of blood cells outside the bone marrow: This can occur in all types of thalassemia when red blood cells are not produced properly in the bone marrow. This can lead to enlargement of organs such as the spleen and liver or formation of masses next to the spine.

Pulmonary hypertension: A type of high blood pressure in the lungs. The breakdown of red blood cells (hemolysis) can cause it, and so can iron overload.

In people not receiving regular blood transfusions, those with more severe anemia were more likely to have serious health issues

In a 10-year study of 53 patients with beta-thalassemia intermedia, those with more severe anemia were more likely to have serious health issues.





In this study, all patients had beta-thalassemia intermedia (non–transfusion-dependent thalassemia). Complications evaluated in the study included liver disease, abnormal formation of blood cells outside bone marrow, diabetes, brittle bones, low production of sex hormones, blood clots, pulmonary hypertension, and low levels of thyroid or parathyroid hormone.

In healthy adults who do not have thalassemia, hemoglobin levels typically range from 14 g/dL to 18 g/dL in men and 12 g/dL to 16 g/dL in women.

In people with beta-thalassemia

An increase of 1 g/dL in hemoglobin may be associated with a reduced risk of future serious complications, such as a stroke, organ damage, and blood clots.*

People with higher levels of iron in their blood (measured by ferritin) may have a higher risk of thalassemia complications. In a 10-year study of patients with non–transfusion-dependent beta-thalassemia, those with:

- Ferritin levels of 800 ng/mL and up had the highest risk of complications.
- Ferritin levels above 300 to under 800 ng/mL had lower risk of complications
- Ferritin level 300 ng/mL or below had no complications

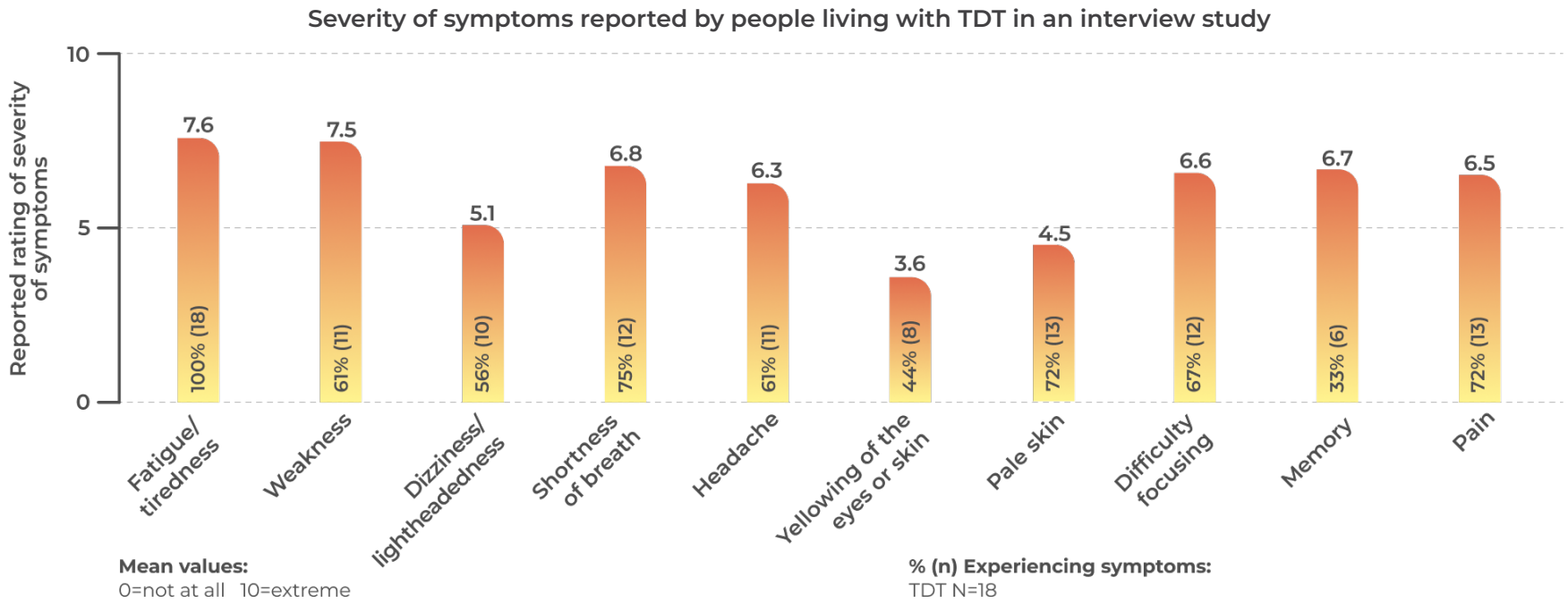
In healthy adults without thalassemia, ferritin levels typically range from 30 to 300 ng/mL.

*This is not medical advice. Please consult with your doctor.

Getting your hemoglobin and ferritin† levels checked is an important part of regular monitoring.

†A measure of iron in the blood.

What symptoms do people with transfusion-dependent thalassemia (TDT) report despite current management strategies?



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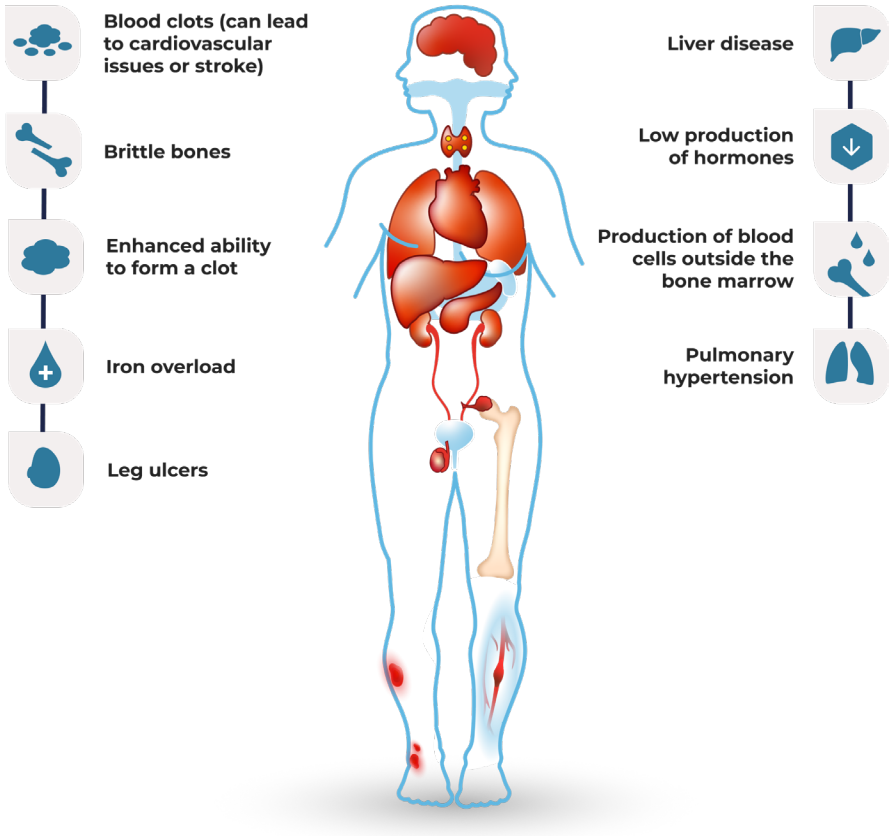

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Pulmonary hypertension: A type of high blood pressure in the lungs. The breakdown of red blood cells (hemolysis) can cause it, and so can iron overload.

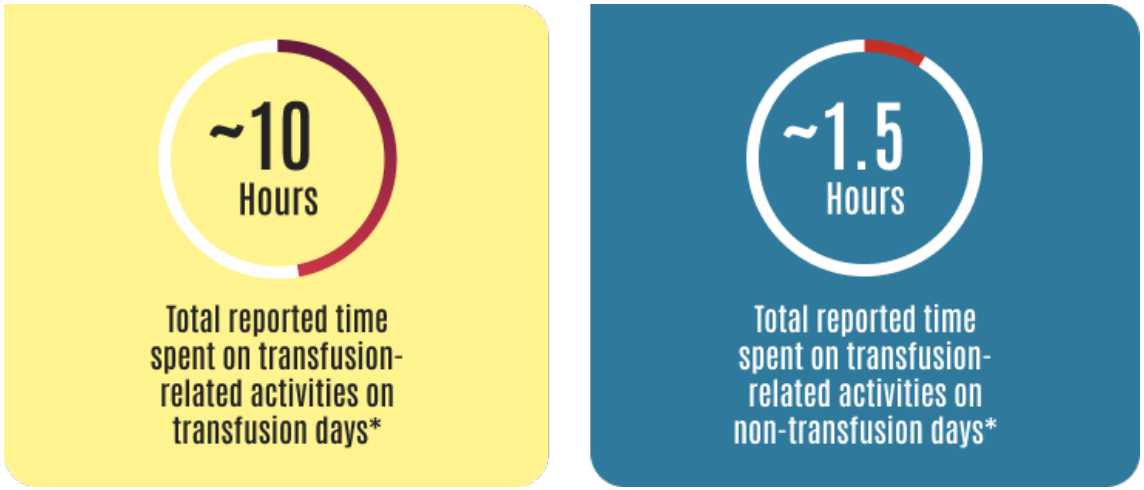
What are some ongoing challenges of transfusion-dependent thalassemia (TDT)?

Complications

- While one goal of blood transfusions is to reduce the risk of thalassemia complications, people who receive transfusions can still experience them. These complications can be caused by either the thalassemia itself or by the blood transfusions.
    - In a 10-year study of people with transfusion-dependent beta-thalassemia, 76% developed at least 1 complication
- In beta-TDT, greater transfusion burden (defined as more frequent transfusions or more units transfused) was associated with more complications
- While there are limited studies in people with transfusion-dependent alpha-thalassemia, people with alpha-TDT may experience complications similar to those with beta-TDT

Study design: In this study, 612 people living with TDT were followed from their first hospital admission or outpatient appointment in 2009 until death in hospital, last hospital admission, or last outpatient appointment in 2018.

Impact of transfusions on daily life



Study design: In this study, 85 adults living with TD beta thalassemia and 4 caregivers of adolescents living with TD beta thalassemia provided data using a smartphone application. Data included information about their health-related quality of life, symptoms, and TD thalassemia management over a period of 90 days.

People with TDT can experience a substantial impact on quality of life and work productivity. The ability to reduce the number of transfusions or the number of units transfused may help reduce the burden of transfusions.

"I feel sometimes like I'm stuck in this never-ending loop of blood transfusions. I live my life constantly in this same three-week loop, and I can't escape it. It's like I am two different people: There's Hardik before a blood transfusion, and Hardik after a blood transfusion. Those are two very different people we're talking about. Depending on where you are on that timeline, it really affects your ability to take care of things for others when you're trying to just take care of yourself."

Hardik
Living with beta-TDT

Working with a care team

Thalassemia is a complex condition that may involve more than your blood

Because thalassemia affects everyone differently, care teams may be unique to each person's needs. The care team may also change over time to continue to suit individual needs and circumstances.

- Hematologists are experts in blood disorders. They specialize in monitoring blood health and treatment. Some hematologists specialize in thalassemia. They can work with other specialists when needed (for example, a cardiologist to check your heart or an endocrinologist to check for diabetes or thyroid conditions)
- There are also centers that specialize in thalassemia across the country. Some people with thalassemia visit a thalassemia center once a year or more. A thalassemia expert from the center can work with their local hematologist or primary care doctor
- Finding a hematologist whom you trust can help you feel confident that the complex needs of your thalassemia are being met. Asking your primary care doctor for a referral may be a good first step

This is not intended as medical advice. For medical advice, please contact your healthcare team.

OTHER MEMBERS OF YOUR TEAM MAY INCLUDE:

Primary care physician (PCP)

Nutritionist

Cardiologist

Endocrinologist

Psychiatrist/ psychologist

Nurse specialist

Remember that you and your family are key players in your health and well-being. Partner with your care team by communicating your symptoms and how they impact your life to determine the best thalassemia management approach.

What support is available for people living with thalassemia?

While thalassemia is a rare condition, it's important to know you are not alone

- There are communities of people living with thalassemia who interact in a variety of ways:
  - Meeting one-on-one, in person, or over the phone—or engaging more anonymously online
- There are a number of organizations that provide support and education to individuals and families living with thalassemia. Here are some that might be a fit for you:
  - Cooley's Anemia Foundation: www.thalassemia.org
  - National Organization for Rare Disorders (NORD): www.rarediseases.org
  - Thalassaemia International Federation: www.thalassaemia.org.cy

"When I first started talking about thalassemia openly, my parents were a little wary. They were afraid of what other people would say, especially other family members. After we got over that initial bump, they were okay, and today they're super supportive."

— Yasmeen, living with beta-TDT

There are many options to connect with others. By actively participating in a thalassemia community, you can help yourself and people like you.

How can myAgios® Patient Support Services help?

myAgios is a customized support program for people living with thalassemia. As a part of the program, myAgios Clinical Nurse Educators (CNEs) can help you and your family learn more about thalassemia, with support that meets each individual's needs:

Thalassemia Education

- Help you prepare for your next discussion with healthcare providers and related professionals
- Provide an overview of thalassemia, including the cause, symptoms, and complications
- Explain and help you understand the latest research about thalassemia

Individualized Support

- Meet in person or virtually at a time that is convenient for you
- Provide emotional support and listen to understand your experience
- Identify how to best support you and help you set goals to thrive with thalassemia

Community Connections

- Share invites to educational webinars and in-person events to hear from thalassemia specialists and other patients
- Inform you about ways to interact with the thalassemia community, including social media and advocacy groups
- Connect you with other patients and caregivers who may have similar experience living with thalassemia

CNEs are employees of Agios Pharmaceuticals and do not provide medical advice.
For medical advice or treatment-related questions, please talk to your healthcare team.

Call 1-877-77-AGIOS (1-877-772-4467) or scan the QR code on the left for personalized support from a myAgios Clinical Nurse Educator.

Helpful topics for discussion with your care team

Here are some questions and observations that could be helpful when talking to your care team:

- [ ] Here are symptoms I'm experiencing and how often they make me miss out on activities
- [ ] These are activities I'm no longer or rarely able to do based on my symptoms
- [ ] How often should my hemoglobin and ferritin levels be checked?
- [ ] What is the plan for regular screenings and tests?
- [ ] Are there specific signs of complications I should be aware of?
- [ ] Are there any new treatments or clinical trials available that might be suitable for me?
- [ ] What are the potential complications we should be monitoring for?
- [ ] What is the plan for monitoring and tests?
- [ ] How should I manage symptoms or complications between appointments?

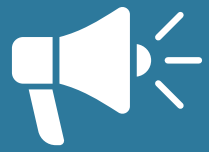
Being open about your health concerns is a bold and rewarding move.

Arming yourself with knowledge can help you feel more confident to share your concerns and ask questions.

Talk to your care team. Share your symptoms and develop a monitoring plan that's right for you.

UNDERSTAND YOUR THALASSEMIA

- All types of thalassemia (NTDT, TDT, alpha- and beta-thalassemia) can cause symptoms
- All types of thalassemia (NTDT, TDT, alpha- and beta-thalassemia) can have serious complications



ADVOCATE FOR YOURSELF

- It's important for anyone living with thalassemia to have a regular monitoring plan to identify, potentially prevent, and actively manage thalassemia complications

GATHER A TEAM YOU TRUST

- It's important to build a comprehensive care team to assist with your overall monitoring and care plan

For support and resources about thalassemia, scan the QR code on the left to go to RethinkThalassemia.com. You can also contact a myAgios® Clinical Nurse Educator at 1-877-77-AGIOS (1-877-772-4467).

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