UNDERSTANDING BETA–THALASSEMIA

ON A GENETIC LEVEL

A GUIDE FOR PATIENTS AND CAREGIVERS

THE PURPOSE OF THIS BROCHURE

is to help you learn more about how a change at the genetic level can cause beta-thalassemia and how this affects you. Since beta-thalassemia is caused by a change in a gene, it's important to understand the role of genes in your disease.

As you navigate through your experience as someone living with beta-thalassemia or as a caregiver, this information can help you build a deeper understanding of beta-thalassemia. We hope the following topics help you have conversations with your doctor about the goals you are working toward.

NOTE TO THE READER:

This brochure is intended to help you learn more about beta-thalassemia and how to connect with others, including your doctor (if appropriate). Although this brochure is for both people living with beta-thalassemia and caregivers of people with beta-thalassemia, the language throughout uses "you" and "your." As a parent or a caregiver for someone with beta-thalassemia, you can think of "you" as "your loved one."

Actor portrayals throughout. Not real patients or caregivers.

Though the images are of actors, the stories throughout this brochure are inspired by real patients and caregivers living with beta-thalassemia. We are grateful to them for sharing their experiences so that this resource can be as useful as possible to others in the community.

MY THAL. My today.

I'M WORKING HARD TOWARD BECOMING A PASTRY CHEF, BUT SOMETIMES MY TEACHER THINKS I'M JUST BEING LAZY. EVEN WHEN MY THALASSEMIA MAKES ME EXHAUSTED, I WILL NEVER LET THAT BE A REASON TO QUIT.

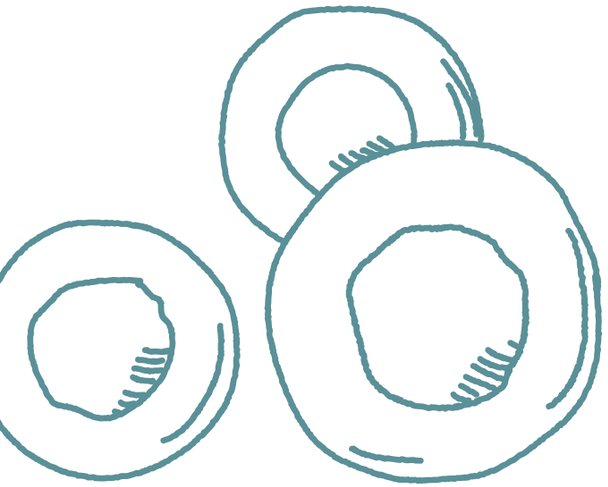
THIS CULINARY PROGRAM IS GONNA TAKE A LOT OUT OF ME, BUT IT'S GONNA BE WORTH IT.

MY DOCTOR AND I ARE WORKING ON WHAT I CAN DO TO MANAGE MY DISEASE AND STILL ACCOMPLISH MY GOALS.

Aiden

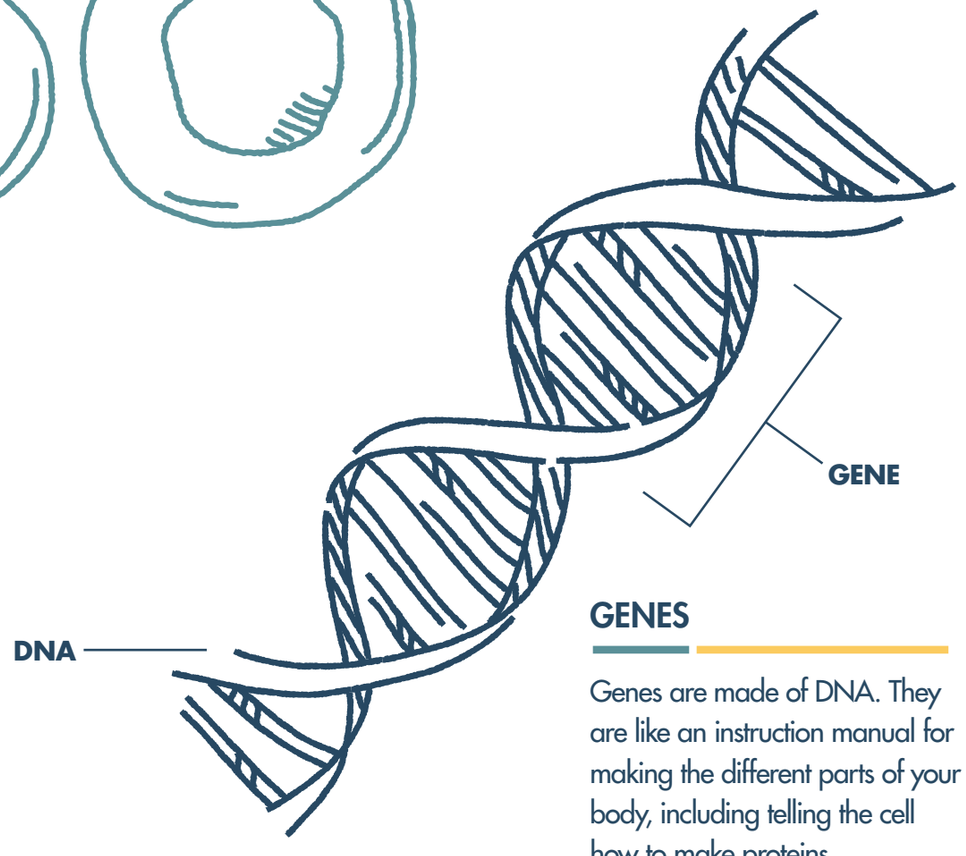
WHERE TO START: CELLS, GENES, PROTEINS, AND YOUR BODY

Let's start by talking about terms—cells, **DNA**, genes, and **proteins**. It is important to know these terms so that you can understand how your body works. Then, you can learn how **genetic diseases** like beta-thalassemia affect the functions of your body.



CELLS

Cells are the building blocks of all living things. Inside cells is DNA, which tells the cell what to do.



GENES

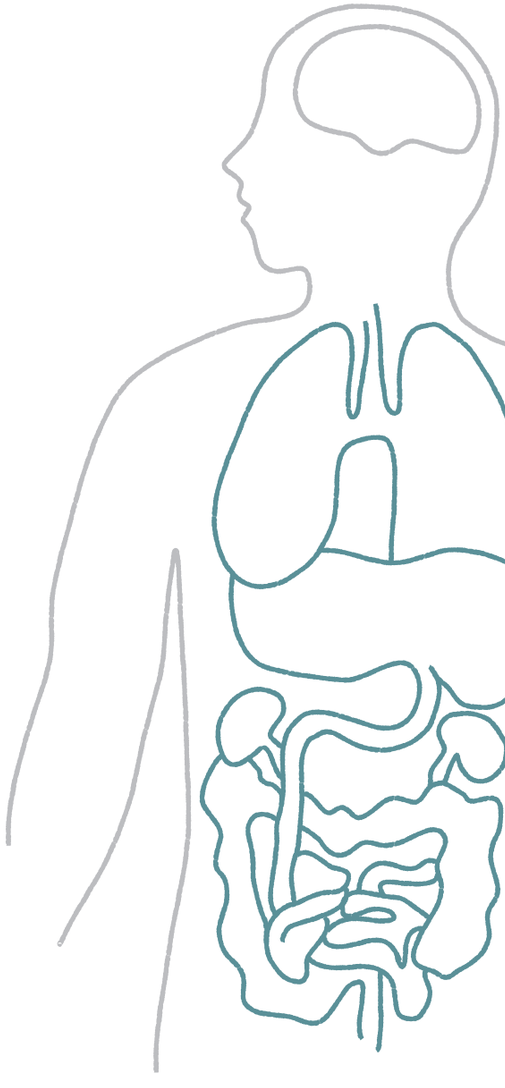
Genes are made of DNA. They are like an instruction manual for making the different parts of your body, including telling the cell how to make proteins.

PROTEINS

Proteins are the workers of the cell. They perform different functions within your body to keep you healthy. Proteins also contribute to the structure, function, and regulation of your organs.

BODY

In order to work properly, your body relies on the ways that cells, genes, and proteins work together. For instance, genes can instruct cells to make protein that facilitate communication between cells in different parts of your body.



GENES AND GENOTYPES

In this section, we will go into more detail about 2 terms we just reviewed: **genes** and **proteins**. To better understand how genes and proteins work together, it may be helpful to first look at an example that is not related to beta-thalassemia: eye color.

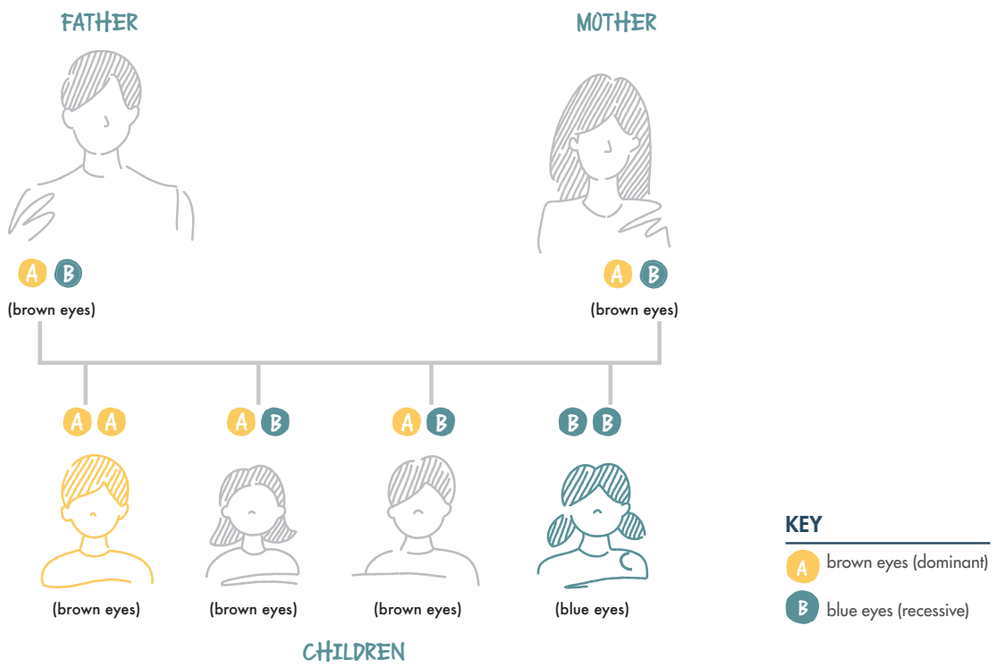
As we said in the previous section, genes provide instructions to your cells. The instructions provided by your unique set of genes tell your cells to make certain proteins; these proteins then create an eye color that is unique to you. In other words, genes instruct cells to make proteins that are involved in the expression of a physical **trait** (like eye color).

People inherit their genes from their parents. This is why children often look like their parents—they share physical traits (and other characteristics) that are determined by the genes they share with their parents.

Genes usually come in pairs: 1 copy of the gene from your mother and 1 copy of the gene from your father. In the example below, the genes are represented by the letters A and B. Each child receives a unique pair of genes, one from each parent. This pair of letters is called a **genotype**.

A genotype can be used to describe the general way a characteristic you inherit will show up in you. However, it is important to remember that your genes are unique to you. Even if you share the same genotype with other people, the inherited characteristic may not show up in the same way.

HOW YOU INHERIT GENOTYPES



To better understand the roles specific genes and genetics play in how your body (or your loved one's body) functions, it's helpful to have conversations with your doctor or read more information from trusted sources.

Talk to your doctor or care team if you are interested in learning more about you or your loved one's specific genotype and how it may affect the severity of your beta-thalassemia.

MY DAUGHTER LOVES PLAYING WITH HER FRIENDS AFTER SCHOOL, BUT SOME DAYS SHE DOESN'T HAVE THE ENERGY. MAYBE WE CAN TALK TO OUR DOCTOR ABOUT HOW SHE CAN BE MORE ACTIVE.

WHY IS THIS IMPORTANT TO KNOW?

Understanding the role that genes, proteins, and genotypes play in your body can help you better understand how beta-thalassemia affects your body in a unique way.

NEXT, WE WILL LEARN MORE ABOUT **HOW BETA-THALASSEMIA AFFECTS YOUR BLOOD**

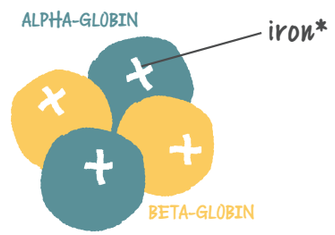
BETA-THALASSEMIA AND BLOOD CELLS

RED BLOOD CELLS AND HEMOGLOBIN

Red blood cells play an important role in your body. Their job is to carry oxygen from the lungs to the cells throughout your body. Oxygen is like your body's fuel—it is used to create energy.

Like all cells, red blood cells rely on a protein within the cell to do the actual work. In red blood cells, this protein is called **hemoglobin**. The hemoglobin in your red blood cells does the work of carrying oxygen throughout your body. When your red blood cells are healthy, each cell is densely packed with hemoglobin.

ADULT HEMOGLOBIN

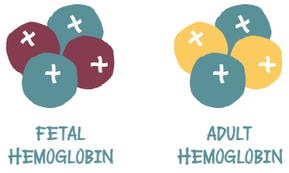


*Iron in globins is part of the **heme** group

HOW HEMOGLOBIN IS FORMED

Immature cells referred to as **blood stem cells** go through several steps to become red blood and other cells. When blood stem cells mature into red blood cells, their genes instruct the cell to begin creating a protein called hemoglobin.

There are 2 main types of hemoglobin that can be found in your body: **fetal hemoglobin** (HbF) and **adult hemoglobin** (HbA). Fetal hemoglobin is made before you are born and consists of a combination of the proteins called gamma-globin and alpha-globin. Fetal hemoglobin has 2 gamma-globin proteins and 2 alpha-globin proteins. The body usually starts making adult hemoglobin shortly after birth. Adult hemoglobin is a combination of 2 beta-globin proteins and 2 alpha-globin proteins.



KEY

- alpha-globin
- gamma-globin
- beta-globin
- iron

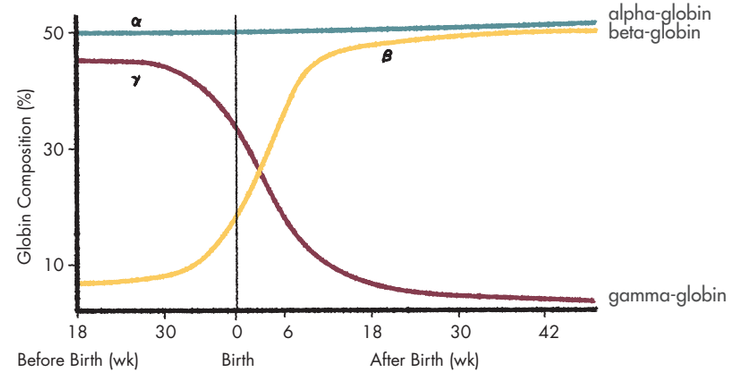
WHAT IS HEMOGLOBIN "SWITCHING"

Both types of hemoglobin help red blood cells carry oxygen, but they function at different times in your life. Fetal hemoglobin mainly functions while a child is in development in the womb. Adult hemoglobin replaces fetal hemoglobin shortly after birth and accounts for most of the hemoglobin from infancy into adulthood.

The transition from fetal hemoglobin production to adult hemoglobin production is known as **hemoglobin switching.**

Both fetal hemoglobin and adult hemoglobin carry oxygen. Fetal hemoglobin holds oxygen more tightly than adult hemoglobin. Because the womb is an environment with a low oxygen pressure, it makes it easier for fetal hemoglobin to deliver oxygen throughout the body as the fetus develops. After birth, however, adult hemoglobin becomes the main form of hemoglobin, as it is better suited to delivering oxygen in the body's new, relatively higher-oxygen-pressure environment.

Each of the proteins that make up adult hemoglobin also contain iron. Iron is an important component of hemoglobin because it is the part of the protein that attaches to oxygen.



Switch from fetal to adult hemoglobin over time

WHAT CAUSES BETA-THALASSEMIA?

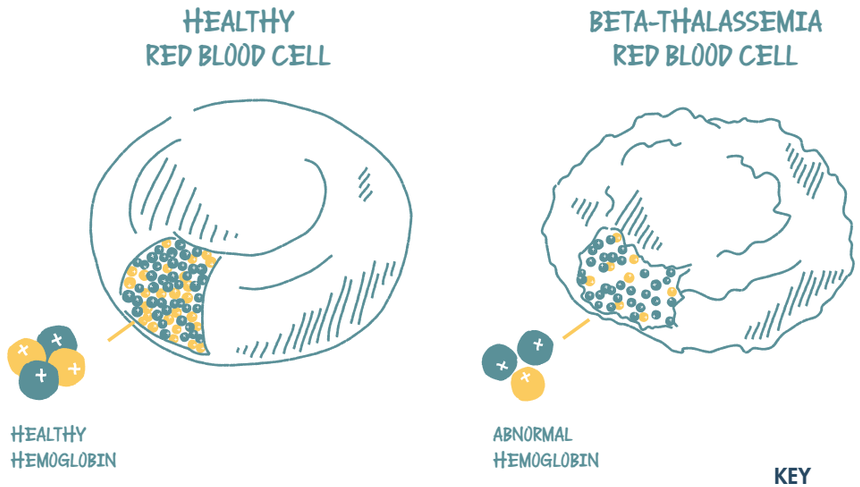
Beta-thalassemia is caused by a change in a specific gene called the ***HBB* gene**.

The *HBB* gene contains the instructions for creating beta-globin (a part of adult hemoglobin). A change in the *HBB* gene can lead to the instructions for beta-globin being incorrect, causing your body to produce reduced amounts of or no beta-globin protein.

IN THE NEXT FEW PAGES, WE WILL TALK ABOUT **HOW BETA-THALASSEMIA AFFECTS HEMOGLOBIN**

HEMOGLOBIN AND BETA-THALASSEMIA

For people with beta-thalassemia, the body doesn't produce enough beta-globin or produces beta-globin that doesn't work properly. This imbalance results in an excess amount of alpha-globin proteins, which clump together and cause your red blood cells to die early. A lack of healthy beta-globin also means that there is less functional adult hemoglobin. Without enough hemoglobin, there may not be enough healthy red blood cells to carry the oxygen you need to the rest of your body. This condition is called **anemia**.



RED BLOOD CELL LIFE SPAN

The red blood cells of a healthy person have a greater life span (approximately 4 months) than the red blood cells of a person with beta-thalassemia.

NORMAL HEMOGLOBIN RANGES BY AGE GROUP

MALE			FEMALE		
2–9 years	10–17 years	≥18 years	2–9 years	10–17 years	≥18 years
11.5–14.5 g/dL	12.5–16.1 g/dL	13.5–18 g/dL	11.5–14.5 g/dL	12–15 g/dL	12.5–16 g/dL

Your hemoglobin level is measured as the amount of hemoglobin in grams (g) per deciliter (dL) of whole blood, with a deciliter being 100 milliliters (mL).

The most common blood test you will have is the complete blood count (CBC). The complete blood count is a series of tests that determine the number of red and white blood cells you have, as well as the level of hemoglobin in your blood. The results from the complete blood count will help your hematologist determine how well your red blood cells are carrying oxygen throughout the body. This will also help your hematologist in determining your level of anemia.

MY SON ENJOYS BEING AROUND OTHERS, BUT DOESN'T ALWAYS HAVE THE ENERGY. MAYBE I CAN TALK TO HIS DOCTOR ABOUT HOW HE CAN BE MORE ACTIVE.

IN THE NEXT FEW PAGES, WE WILL TALK ABOUT **HOW CONSISTENTLY LOW HEMOGLOBIN CAUSED BY BETA-THALASSEMIA CAN AFFECT YOUR BODY**

HOW BETA-THALASSEMIA AFFECTS YOUR BODY

As you just learned, beta-thalassemia is a genetic disease that affects how much hemoglobin your body produces.

Without enough hemoglobin, your organs will not get the oxygen they need to function properly. This means you may have anemia, which can cause a wide range of symptoms, from fatigue and weakness. If severe anemia is left untreated, it can lead to early death.

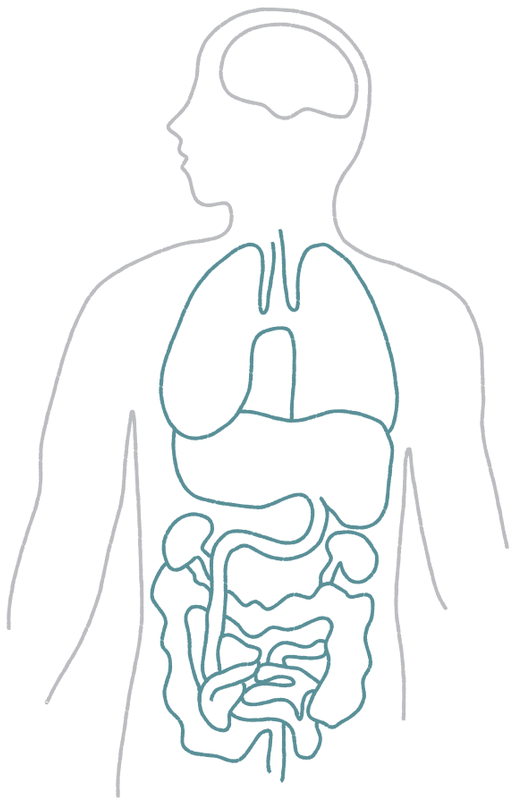
The effects of beta-thalassemia differ from person to person based on how much beta-globin your body is actually producing. Some people with beta-thalassemia may get very sick when they are infants, whereas others do not experience problems until they get older. There are people who can go their whole lives without ever having any symptoms.

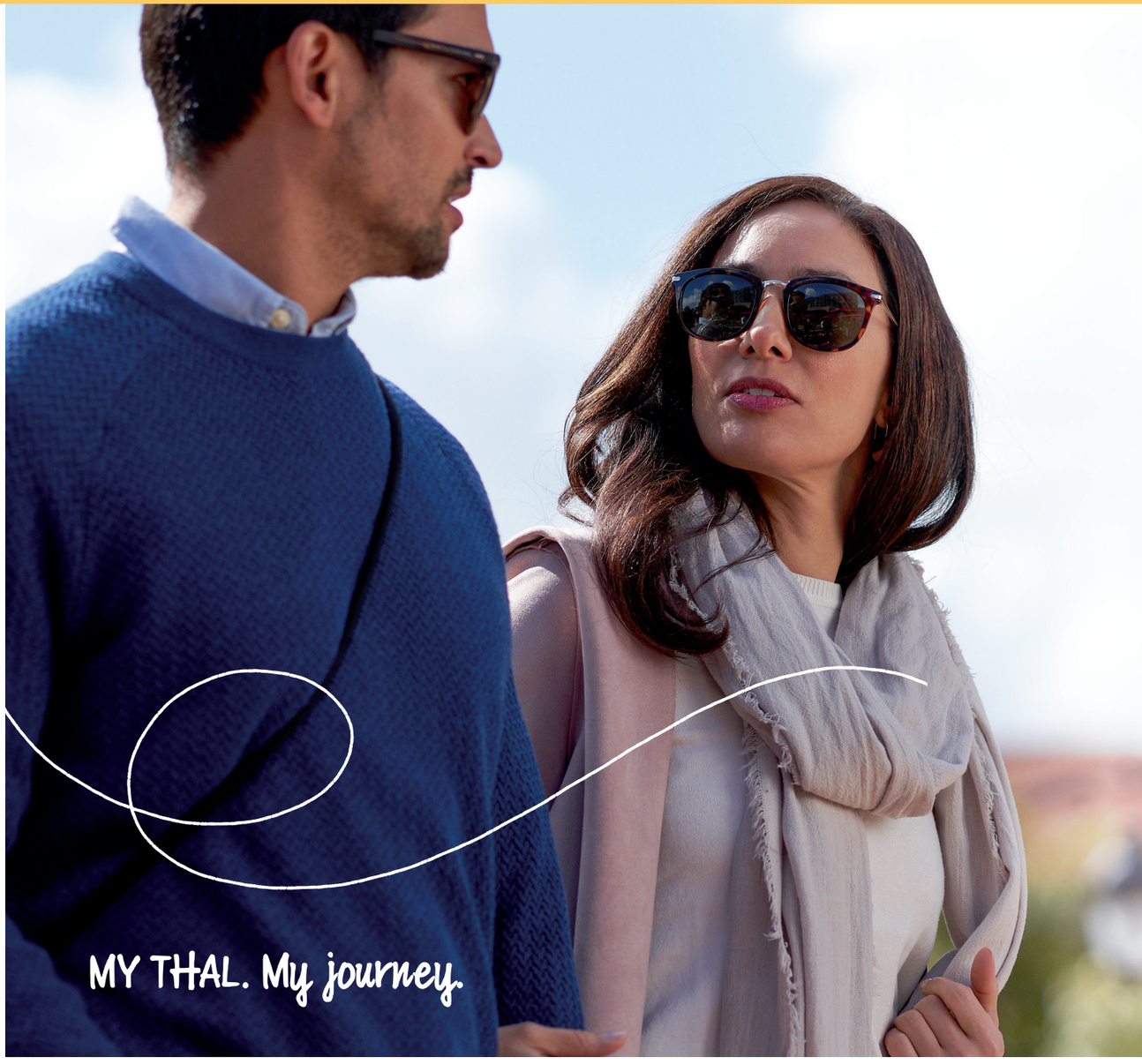
The severity of each person's thalassemia may depend on their particular genotype. This will be discussed further in the next section.

TALK ABOUT YOUR EXPERIENCE

Because beta-thalassemia can be different for different people, it's important to discuss with your doctor how beta-thalassemia affects you and what symptoms you're experiencing.

It may be helpful to discuss how your loved one feels about the potential impact and long-term risks associated with beta-thalassemia. Having candid conversations with them and with their doctor can help you collectively manage expectations, set goals, and make more informed treatment decisions.





I FEEL GUILTY WHEN THE BONE PAIN I EXPERIENCE FROM THALASSEMIA SLOWS ME DOWN ON OUR ADVENTURES. I'M GOING TO CONTINUE TALKING TO MY DOCTOR ABOUT HOW TO PLAN MORE TRIPS FOR US AROUND MY TREATMENT SCHEDULE.

IN THE NEXT FEW PAGES, WE WILL DISCUSS **THE DIFFERENT WAYS OF TALKING ABOUT BETA-THALASSEMIA**

3 WAYS TO TALK ABOUT BETA-THALASSEMIA

It can be confusing to try to understand the different ways people describe beta-thalassemia. Some people try to group similar experiences with beta-thalassemia together, but none of them are perfect. Each person living with beta-thalassemia is completely unique and has their own experience of how the disease affects them. Here are three of the most common ways that people talk about beta-thalassemia:

01

TYPES OF BETA-THALASSEMIA

Historically, beta-thalassemia has been classified into 3 main groups, based on the symptoms a person has and when they first started to show signs of the disease. The 3 main types are:

- **Thalassemia major**
  People show serious symptoms of disease between the ages of 6 months and 2 years; without regular transfusions, most of these people do not survive childhood
- **Thalassemia intermedia**
  People may show symptoms of disease later than those with thalassemia major, possibly not until adulthood, and may have no symptoms or have milder symptoms that either do not require transfusions or only occasionally require transfusions
- **Thalassemia minor**
  (also called "beta-thalassemia trait") Even though these people carry the disease trait (they may, in fact, be called "carriers"), they usually do not have any symptoms, although some people may experience mild anemia

02

GENOTYPES IN PEOPLE WITH BETA-THALASSEMIA

There are nearly 350 different changes in the *HBB* gene that can cause beta-thalassemia. The different changes are grouped and represented by one of the categories shown below, with each letter representing the gene you inherited from each parent. When paired, these categories then create a genotype.

- **beta^0**: no beta-globin is produced
- **beta$^+$**: a reduced amount of beta-globin is produced
- **beta^E**: a reduced amount of beta-globin is produced; this genotype is most common in Southeast Asia

As discussed earlier, genotypes are often written as 2 letters, with 1 letter for the copy of the gene from each parent. People with beta-thalassemia can have any mix of the 3 genotypes described above. They may have 2 copies of beta^0 (known as a beta^0/beta^0 genotype, which is a severe form of beta-thalassemia) or 1 copy or no copies of beta^0 (known as non-beta^0/beta^0 genotypes, which are less severe).

Your genotype can be determined by a blood test and may help your doctor with treatment decisions. Many people with beta-thalassemia learn their genotype when they are first diagnosed. If you're not sure what your genotype is, you can ask your doctor.

03

TRANSFUSION DEPENDENT OR NON–TRANSFUSION DEPENDENT

There are people living with beta-thalassemia who receive regular red blood cell transfusions to help make up for their lack of healthy red blood cells. Some doctors are starting to categorize beta-thalassemia based on whether or not a person depends on regular blood transfusions to survive and function. If a person needs regular transfusions, it is sometimes called transfusion-dependent beta-thalassemia, or TDT. For patients who do not receive regular transfusions, the term non–transfusion dependent beta-thalassemia (or NTDT) may be used.

DO YOU HAVE TDT?

The most straightforward way to talk about your beta-thalassemia may be about whether you receive regular transfusions or not. If you are dependent on transfusions to manage your beta-thalassemia, TDT may be the most direct way to describe your disease.

To help you and your loved one understand what it's like to live and grow up with beta-thalassemia, it can be helpful to talk with others who are living with it and who have more years of experience. Connecting with others can also help to provide perspectives on managing the disease through many different life experiences or changes. Reach out to a patient organization in your area or ask your doctor for connections and recommendations.

NOW THAT YOU KNOW A LITTLE MORE ABOUT THE BASICS OF BETA-THALASSEMIA, WE WILL TALK ABOUT **TREATMENT OPTIONS ON THE NEXT FEW PAGES**

TREATMENTS FOR TRANSFUSION-DEPENDENT BETA-THALASSEMIA (TDT)

For people with TDT, there are currently two standard options for treatment:

- **Regular blood transfusions**, which help with the symptoms of TDT (anemia) but do not address the disease at the genetic level
- **Stem cell transplant**, which addresses TDT at the genetic level and is potentially curative

BLOOD TRANSFUSIONS

Since people with TDT cannot make enough hemoglobin on their own, they require regular **red blood cell transfusions** in order to treat their anemia and keep them alive. Blood from a donor contains working red blood cells that help treat anemia, facilitate normal growth and activity levels, and improve quality of life. The new blood is able to deliver the oxygen (fuel) that their body needs.

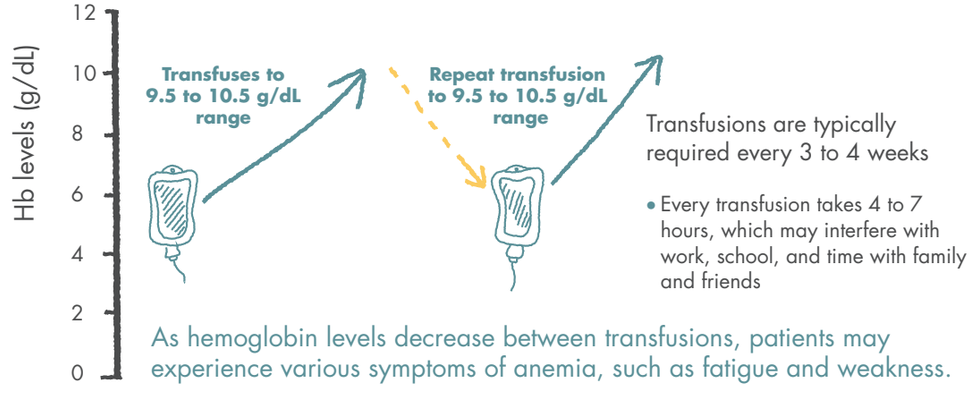
After people with TDT receive a red blood cell transfusion, their hemoglobin levels go up and they usually feel good and energized for a period of time. But once their hemoglobin levels begin to decrease and levels get low, they can start to feel tired and weak, which often means it's time for another transfusion.

To maintain normal levels, they need blood transfusions on a regular basis. It's important for a person with TDT to stay with a transfusion schedule, as symptoms can progressively get worse over time. Guidelines from the Cooley's Anemia Foundation recommend that the target hemoglobin level be maintained in the 9.5 to 10.5 g/dL range, typically accomplished by administering transfusions **every 3 to 4 weeks** for most patients.

As you age and you go through lifestyle changes, you may need to adjust your timing and target hemoglobin levels again. Maintaining a transfusion schedule is a big commitment, but it is necessary for your health. If your body doesn't get the transfusions it needs, your symptoms could progress from weakness and fatigue to some of the more severe ones listed in the "How Beta-thalassemia Affects Your Body" section (page 14).

Listening to your body and reporting any patterns that you notice (like feeling more tired or less energetic) to your doctor will help you work together to determine a transfusion schedule that works for you. Figuring out the right timing, transfusion amount, and target hemoglobin level for your body may not happen at first, but through a strong partnership with your doctor it can come together over time.

CYCLE OF REGULAR RED BLOOD CELL TRANSFUSIONS



Transfusions are typically required every 3 to 4 weeks

- Every transfusion takes 4 to 7 hours, which may interfere with work, school, and time with family and friends

As hemoglobin levels decrease between transfusions, patients may experience various symptoms of anemia, such as fatigue and weakness.

*Patients with TDT are recommended to maintain a pretransfusion hemoglobin level of 9.5 to 10.5 g/dL.

SIDE EFFECTS FROM REGULAR BLOOD TRANSFUSIONS

While regular red blood cell transfusions can help manage the symptoms of TDT, they can contain a lot of iron—sometimes more than your body can process on its own. Over time, the iron from transfusions can build up on top of the excess iron you may have due to beta-thalassemia. This is called iron overload, and the iron collects in organs like your heart, liver, and **endocrine system**. Iron overload can make it difficult for these organs to work properly. For example, iron overload in the endocrine system may cause diabetes as well as fertility issues and other hormonal issues. The iron buildup can also lead to other serious complications, including organ damage and organ failure, if it is not treated effectively.

Monitoring iron levels in the body is an important part of comprehensive TDT care. Iron overload can be monitored through **serum ferritin testing** (a type of blood test). Serum ferritin correlates with how much iron you have stored in your body. A steady decrease in serum ferritin typically indicates a lower amount of iron. However, the measure is not always reliable, as serum ferritin levels may change for a variety of reasons that are not related to iron levels. Magnetic resonance imaging (or MRI) is the gold standard for measuring the amount of iron in your organs: **liver iron concentration (or LIC)** for your liver and cardiac T2* (star) for your heart.

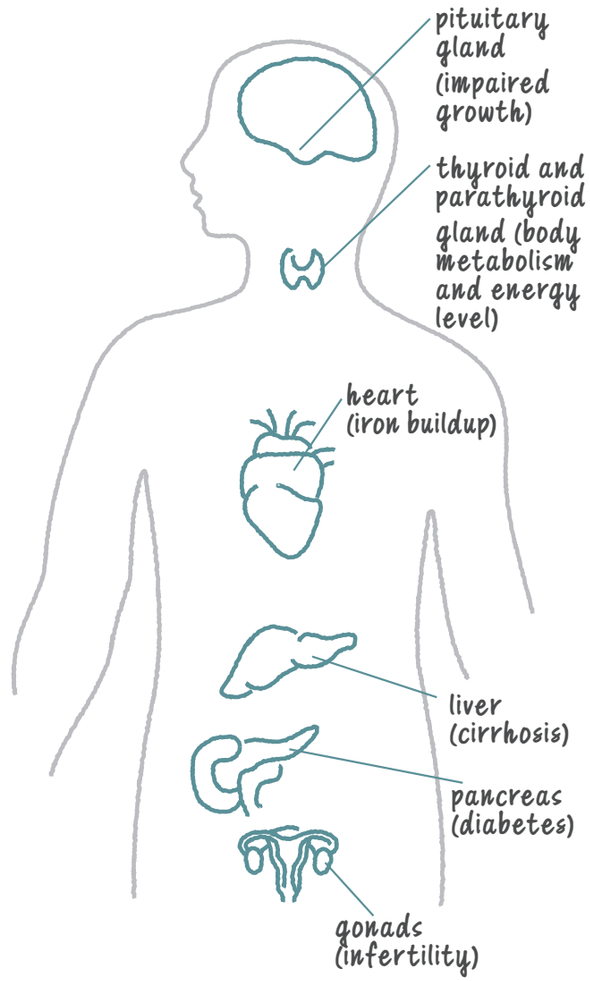
Please note that the information here about treatment is for general educational purposes only. You should always speak to your doctor about the possible risks and side effects associated with treatments for beta-thalassemia.

NOW THAT YOU UNDERSTAND THAT IRON OVERLOAD IS A SIDE EFFECT OF REGULAR BLOOD TRANSFUSIONS, ON THE NEXT FEW PAGES, YOU CAN LEARN **ABOUT MANAGING IRON OVERLOAD**

BLOOD TRANSFUSIONS AND CHELATION THERAPY

HOW CAN IRON OVERLOAD BE TREATED?

You may experience iron overload either as a result of beta-thalassemia or from ongoing red blood cell transfusions. Your doctor may treat iron overload with special medications. This kind of treatment is called **chelation (kee-LAY-shun) therapy**. It is important that you develop a regular routine for taking your medication for chelation therapy throughout your life, as even short periods of not taking your medication can have damaging effects on your body. Talk to your doctor about managing your iron levels and keeping your organs as healthy as possible.



IRON LEVELS

Iron overload from chronic blood transfusions may lead to a buildup of iron in or damage to the heart, liver, and endocrine system.

If needed, your doctor will help you to maintain a chelation schedule to keep your iron levels in check. They will also periodically test your iron levels through an MRI (liver iron concentration) or cardiac T2* (star) or through a blood test called serum ferritin (SF).

If you have questions or are concerned about your iron levels and the effect they may have on your health over time, make sure you discuss it with your doctor.

SPEAKING WITH YOUR LOVED ONE'S DOCTOR

Regular supportive care can help manage complications your loved one with beta-thalassemia experiences. Here are some things to talk about with your loved one and then discuss with their doctor:

- How does your loved one feel after and near the end of their transfusion cycle?
- How long after a blood transfusion until they start to feel weakness, pain, and/or fatigue?
- Has their doctor adjusted their transfusion volume or transfusion schedule since their last growth spurt?
- Has their doctor changed their transfusion volume or transfusion schedule since they started a new activity?
- Have they been able to achieve any new goals?

Their doctor can also tell you more about how to manage their iron levels and develop a comprehensive care plan. It is important to remember that regular red blood cell transfusions do not address the disease at the genetic level.

See more about comprehensive care starting on page 23.

MY SON IS ABOUT TO START FIRST GRADE. I'M ALREADY THINKING ABOUT THE CHALLENGES HE WILL FACE WITH AN ONGOING TRANSFUSION SCHEDULE. I WOULD LIKE TO TALK TO HIS DOCTOR ABOUT HIS OPTIONS.

ON THE NEXT FEW PAGES, WE WILL DISCUSS **ADDITIONAL ASPECTS OF CARE FOR TDT**

STEM CELL TRANSPLANT

A **stem cell transplant** (also called bone marrow transplant [BMT] or allogeneic hematopoietic stem call transplant [allo-HSCT]) is a treatment that may have a curative effect on beta-thalassemia by addressing the disease at the genetic level. Stem cells are most often found in the bone marrow. Blood stem cells have the unique ability to grow and transform into other cells, like red blood cells and white blood cells. A stem cell transplant aims to replace blood stem cells that contain a nonfunctioning *HBB* gene with blood stem cells from a donor who has a working *HBB* gene. A stem cell transplant from a donor adds healthy stem cells to the body.

Before the new cells are added, a form of treatment called conditioning (which is often chemotherapy) is used to make room in the bone marrow for the new cells. Over time, the goal of a stem cell transplant is for the healthy blood stem cells to make their way to the bone marrow and to start making new blood cells; this process is called engraftment.

To receive a stem cell transplant, an appropriate stem cell donor (who may be related or unrelated to the patient) must be identified. This is so that the transplanted cells have the best chance of being accepted by your body. For the most favorable outcome, the donor should be genetically similar to the person receiving the stem cells, with the receiver being less than 14 years old. Generally, siblings are the people who are most genetically similar. About 25% to 30% of people have a **matched sibling donor**.

As you age and you go through life and lifestyle changes, continue to discuss different treatment options with your doctor. If you want to know more about treatments for transfusion-dependent beta-thalassemia (TDT), your doctor can share the benefits and potential risks (some of which may be severe) involved with these options.

LIKELINESS OF A MATCHED SIBLING DONOR

DONOR MATCH

About 25% to 30% of people have a matched sibling donor.

COMPREHENSIVE TDT CARE AND LONG-TERM GOALS

In addition to the standard of care we mention on previous pages, comprehensive care for TDT may be available at a dedicated thalassemia center. This type of care can also include having a team of specialists, including a cardiologist, endocrinologist, and a doctor with expertise in beta-thalassemia. These doctors have specific knowledge that can help you manage all aspects of your TDT and its impacts. Speak to your doctor or reach out to patient organizations to find the location of the dedicated thalassemia center nearest you.

It's important to consider all aspects of beta-thalassemia and to continue discussions with your care team, especially as you age. Whether you need to make a change to your transfusions, are considering other treatment options, or are reaching new milestones in life, it's always a good opportunity to evaluate your long-term goals and discuss them with your doctor.

Here are some examples of when this might happen:

- Changing schools
- Participating in new sports or activities
- Moving or changing primary hematologists (transitioning from pediatric to adult care)
- Living away from home for the first time/going away to college and managing care without daily caregiver support
- Starting a job or career and managing a full-time/regular schedule
- Relationships and family planning
- Taking care of others while taking care of yourself
- Extended travel, time abroad, immersive experiences
- Annual comprehensive care visit

GOALS GUIDE

The Goals Guide, which can be found at **lifewithbetathal.com/resources**, can help you have proactive discussions with your doctor and let them better understand the things you'd like to accomplish. Talk to your doctor today or at your next visit about how you can optimize your treatment to align with your long-term goals.

IN THE NEXT FEW PAGES, WE WILL TALK ABOUT **FINDING THE CARE YOU NEED FOR BETA-THALASSEMIA**

HOW DO I FIND THE SPECIALIZED CARE I NEED?

Building a team of doctors that understand you as a person and as a patient can be challenging for anyone. As someone with beta-thalassemia, or as a caregiver of someone with the condition, you may find it difficult to find doctors who specialize in treating you or your loved one. Despite this, it is recommended that you find a team of doctors who can provide you with comprehensive care that monitors the symptoms and manages the complications of beta-thalassemia before they progress.

Finding the right team of doctors at a practice or hospital may take time. You could start by finding a **primary care physician (PCP)** or **hematologist** who understands beta-thalassemia and with whom you feel comfortable. If you are struggling to find a primary care physician or hematologist who specializes in beta-thalassemia, reaching out to an advocacy organization (like Cooley's Anemia Foundation*) may be helpful. Once you find a PCP or hematologist you trust, ask them to help you fill out the rest of your care team. Depending on your healthcare needs, your care team may also include other specialists, such as:

If you want to build a comprehensive care team with expertise in beta-thalassemia or are looking for a specialist who understands the unique aspects of your disease, start by speaking with your doctor. Patient organizations who support the beta-thalassemia community can also help you find a specialist or other members of your team. You may also want to discuss with your doctor how you can benefit from visiting a comprehensive care center. You can find one at https://www.thalassemia.org/treatment-centers.† Once you have a care team in place, plan for at least 1 comprehensive care appointment every year.

*This advocacy organization is independent from bluebird bio, Inc. and is being shared as a resource only.

†This link will take you to a site that is outside the control of bluebird bio, Inc. This link is provided for informational purposes only and does not imply referral, recommendation or endorsement by bluebird bio as to the qualifications of any person or organization listed or the quality of medical care they may provide. We do not make or imply any endorsement of external websites.

STARTING CONVERSATIONS WITH YOUR DOCTOR

Receiving the care you need will require being open and honest about how you're feeling emotionally and physically. This kind of vulnerability may not be easy for many people. It may even feel uncomfortable at first, but as you build trust and develop a stronger relationship with each doctor, these conversations can get easier. If you need some help starting conversations about how you are feeling today, **think about how you would complete the following sentences:**

- Lately I've been struggling with…
- How can I best prepare for…
- I'd like to know more about…
- I currently manage my beta-thalassemia by…
- I want to start planning for…
- I'm nervous about…
- My long-term goal is to…
- How can I better manage my...
- My next step(s) is/are...

FINDING THE RIGHT DOCTOR FOR YOU

Some relationships in your life may feel more natural or come easier than others. Your relationship with your doctor is no different. Remember that no single doctor is right for everyone. If, over time, conversations like the above continue to feel uncomfortable or you don't feel heard, you might want to think about finding a doctor who is a better fit for you. **It's important that you feel you can trust your doctor with your health and life goals.**

IN THE NEXT FEW PAGES, WE WILL DISCUSS **GETTING THE RIGHT CARE FOR YOUR LOVED ONE**

GETTING THE RIGHT CARE FOR YOUR LOVED ONE

Because beta-thalassemia is a lifelong condition that affects people from childhood through adulthood, you and your loved one's doctor may need to consider their future healthcare needs starting at a young age. This includes ongoing conversations that evaluate how regular red blood cell transfusions impact your loved one's life and their overall health.

To help build engagement, consider your answers to the following lifestyle questions and share them with their doctor:

- How has my loved one's beta-thalassemia and/or regular red blood cell transfusions impacted their performance at work or school?
- How has my loved one's beta-thalassemia and/or regular red blood cell transfusions impacted their ability to participate in certain activities or sports?
- How has my loved one's beta-thalassemia and/or regular red blood cell transfusions affected their ability to travel?
- Overall, do I feel that my loved one's beta-thalassemia and regular red blood cell transfusions have caused them to miss out on small or big things in life?
- How should I talk to my loved one's teachers and our friends and family about beta-thalassemia?

To help evaluate their overall health, ask your doctor about the following:

- How have regular red blood cell transfusions impacted my loved one's health so far?
- How do you expect regular red blood cell transfusions to impact my loved one's health in 5 years? 10 years? And 20 years?
- Is my loved one currently eligible for any advanced treatment options?
- Do you recommend I consider an advanced treatment option for my loved one?

Based on this conversation, you and your doctor can work on a shared set of goals and a long-term treatment plan to help manage your loved one's overall health. This may include a plan to treat with an advanced therapy.

ASSESSING CARE OVER TIME

If you and your doctor are not able to align on a path forward or you are just looking for a different perspective, you can seek the opinion of another doctor. Patient advocacy groups can help put you in touch with a new beta-thalassemia specialist. **Remember, as your loved one's life changes, your needs may change as well.** It's important that you feel you can trust your loved one's doctor with their health and personal goals.

Asha

HER THAL. Our today.

I WANT TO MAKE SURE THAT MY DAUGHTER HAS EVERY OPPORTUNITY TO LIVE HER DREAMS. FOR ME, THAT MEANS GETTING HER THE RIGHT CARE WITH THE BEST DOCTORS FOR HER.

ON THE NEXT FEW PAGES, WE WILL TALK ABOUT **THE LATEST ADVANCEMENTS IN BETA-THALASSEMIA**

EVOLVING BETA-THALASSEMIA

As research continues to evolve, so does our understanding of beta-thalassemia, and treatment options are being developed. In this section, you'll learn more about the focus of current research and why it's important.

PRENATAL SCREENING AND GENETIC COUNSELING

Because beta-thalassemia is a **genetic disease**, it can be identified and diagnosed through **prenatal screening**. This can provide early diagnosis and allow people to better understand how beta-thalassemia can be managed. They may be also be recommended to a genetics counselor who can help screen other family members and identify a match for a stem cell transplant if needed. For more info, talk to your doctor.

MEDICAL EVOLUTIONS

Currently, there are medications adults can pair with red blood cell transfusions to help address some of the symptoms associated with beta-thalassemia.

Several other therapies in development focus on how the body produces hemoglobin and, ultimately, red blood cells. These therapies can potentially modify a person with TDT's ability to produce functional hemoglobin.

GENE THERAPY

Similar to a donor stem cell (or allogeneic) transplant, gene therapy is another treatment option that has the potential to treat beta-thalassemia in some patients. Although it is still being researched, this type of therapy has the potential to change the course of the disease at the genetic level.

There are 2 main types of gene therapy: **gene addition** and **gene editing**

In gene addition, copies of functional genes are added to a cell to help do the work of a defective gene. The addition of functional genes can take place either inside (*in vivo*) or outside of the body (*ex vivo*).

In gene editing, targeted breaks are created in DNA, with or without instructions for how to repair the break. The goal of these breaks is to disrupt or correct the function of a gene.

If you are interested in learning more about gene therapy, you can **visit thegenehome.com** for more information.

KEEP THE CONVERSATIONS GOING

As the understanding of beta-thalassemia evolves and new treatment options are developed, staying informed can give you the information you need to have more meaningful conversations with your doctor about living with beta-thalassemia, your long-term goals, and evolving options.

GLOSSARY

Adult hemoglobin:
consists of 4 protein subunits: 2 subunits of beta-globin, which is produced by the HBB gene, and 2 subunits of a protein called alpha-globin, which is produced by the *HBA* gene

Alpha-globin:
produced by the *HBA* gene, 2 subunits of the alpha-globin make up half of the 4 protein subunits found in adult hemoglobin and also fetal hemoglobin

Beta-globin:
produced by the *HBB* gene, 2 subunits of the beta-globin make up half of the 4 protein subunits found in the adult hemoglobin

Beta-thalassemia:
a genetic blood disorder in which the production of beta-globin is reduced or eliminated

Blood stem cell:
a special cell that has the potential to develop into all of the types of blood cells, including white blood cells, red blood cells, and platelets

Chelation therapy:
medicine that helps to reduce the amount of iron in your body

DNA:
a molecule that is in almost all living things that carries genetic information

Endocrine system:
this system is made up of the glands and organs that produce hormones and release them into the blood so that they can travel to organs and tissues throughout the body

Fetal hemoglobin:
containing 2 alpha and 2 gamma subunits, fetal hemoglobin is the dominant form of hemoglobin in the fetus from conception to birth. It plays a key role in the transportation of oxygen from maternal to fetal circulation

Gamma-globin:
encoded by *HBG1* and *HBG2*, this protein is created in the fetal liver, spleen, and bone marrow. 2 gamma-globin proteins combine with 2 alpha-globin proteins to make up fetal hemoglobin, which is normally replaced by adult hemoglobin shortly after birth

Gene:
a sequence of DNA responsible for controlling inherited traits

Genetic disease:
a disease that is caused by a genetic change

Genotype:
your genetic makeup for a specific any trait, which may be labeled with a pair of letters, each representing the copy of a gene inherited from one of your parents

Heme:
a non-protein component of hemoglobin that binds to globin proteins and iron which can bind or release oxygen

HBB gene:
this gene provides the instructions for making the beta-globin protein

Hemoglobin:
a molecule in your red blood cells that helps to carry oxygen throughout your body; healthy adult hemoglobin contains iron and a balanced amount of beta-globin and alpha-globin proteins

Liver iron concentration (LIC):
a measurement of iron accumulation in the liver. Elevated levels of iron in the liver may lead to liver disease and heart damage

Matched sibling donor:
considered the optimal donor, a matched sibling donor is a histocompatible (HLA) matched relative who is usually a sibling

Protein:
an important component of your cells that is required for the structure, function, and regulation of your body's tissues and organs

Red blood cell:
a hemoglobin-containing cell that carries oxygen throughout your body

Serum ferritin:
a test used to diagnose and monitor iron overload or iron deficiency

Trait:
an inherited characteristic

Transfusion-dependent beta-thalassemia (TDT):
a form of beta-thalassemia that requires regular transfusions of red blood cells

EMMA

MY THAL. My today.

SOMETIMES, THE BONE PAIN I EXPERIENCE FROM THALASSEMIA CAN GET IN THE WAY OF OUR ADVENTURES. I GET FRUSTRATED WHEN IT FEELS LIKE WE'RE NOT ABLE TO DO EVERYTHING WE HAVE PLANNED.

BUT THE IMPORTANT THING IS THAT I'M TRAVELING, AND—EVEN BETTER—I'M TRAVELING WITH HIM. I'M GOING TO CONTINUE TALKING TO MY DOCTOR ABOUT HOW TO PLAN TRIPS FOR US IN EXCITING NEW PLACES.

WHAT ARE THE NEXT STEPS?

NOW YOU HAVE MORE INFORMATION ABOUT YOUR THAL AND HOW IT AFFECTS YOU IN A UNIQUE WAY. ARE YOU READY TO SPEAK TO YOUR DOCTOR ABOUT PLANNING YOUR TOMORROW?

As part of your next step, you will also want to **download a copy of the "Setting Goals With Beta-Thalassemia"** guide while you're visiting **lifewithbetathal.com/resources**. This useful, portable guide will:

- Help you plan for a clear conversation with their doctor about personal goals and their medical team
- Provide an opportunity for you to capture your own personal treatment journey
- Offer you lots of space to write down your future plans and set goals

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