Krabbe Newborn Screening

A Family Guide

LEUKODYSTROPHY CARE NETWORK

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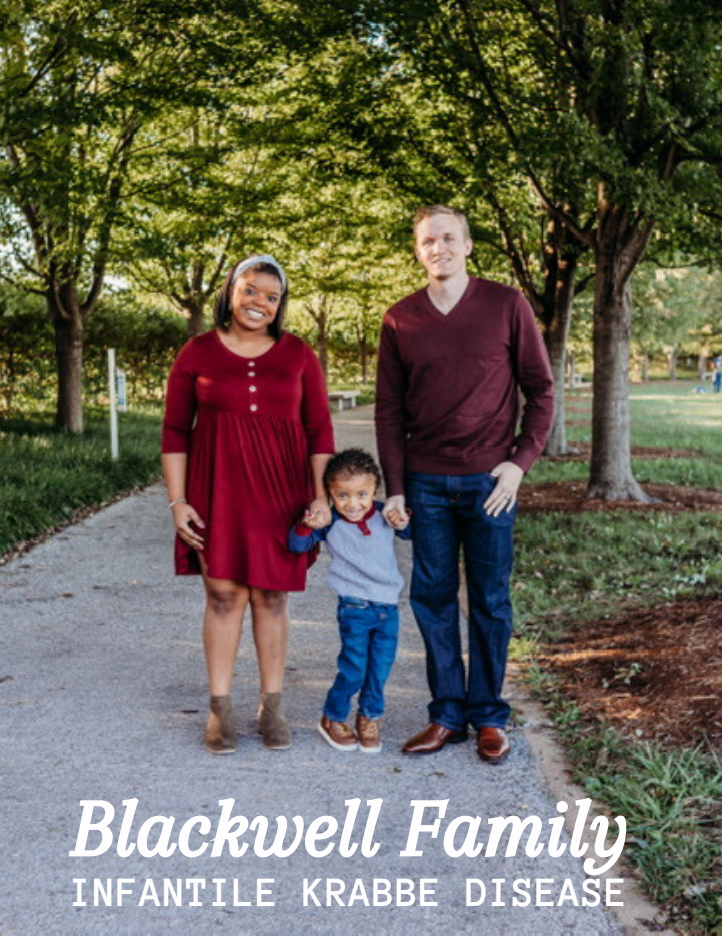


Dear Parent(s):

AS A FELLOW PARENT OF A CHILD DIAGNOSED WITH KRABBE DISEASE VIA NEWBORN SCREENING (NBS), BEFORE YOU BEGIN DIGESTING THE INFORMATION IN THIS GUIDE, I WANT YOU TO KNOW THAT YOUR CHILD'S STORY WILL BE A BEAUTIFUL ONE.

The paralyzing fear and heartache that is consuming you will not last forever. The journey you're about to go on may not be the life you imagined, but it will still be a full one. The dreams you had for your child don't need to disappear, but perhaps adapted to fit the resilient child who will shock you with their ability to overcome. So please, continue to dream and hope and wish for your child, because these current circumstances will not define their future.

Along the way your child will teach you how to fight—for their health, education, your family, your job, and your mental health. As their parent, you will always be the best expert on your child. And when the overwhelm of attending doctors' appointments, therapies and tests feels like too much, know that you have a community of families behind you who have stood where you are. They will be there to grieve with you, celebrate with you, and help guide you on this journey until what once felt overwhelming becomes second nature.

My son was diagnosed via newborn screening five years ago. Receiving his diagnosis shattered our hearts and left us with dozens of unanswered questions. It is our hope that this guide acts as a resource for as you navigate your new normal. Today, my son attends preschool and various therapies throughout the month. He is fun loving, determined, and social. His challenges from this disease have not stolen his joy, and they won't steal your child's either.

With love and hope,

K. Blackwell

KEY INFORMATION

- Newborn screening is **not a diagnostic test**. It is a way to identify infants who could be at risk for Krabbe disease.
- After receiving a positive newborn screening result, your child should be evaluated to determine which of the following categories they fall into:
    a. They may be unaffected and will not have Krabbe disease, known as a "false positive" result.
    b. They may have the form of Krabbe disease with symptoms that start in infancy which requires a rapid referral for treatment.
    c. Or they might be at risk for having Krabbe disease in childhood or later in adult life.
- Although there is no cure, **there is treatment available**. To benefit from treatment, a diagnosis needs to be made.
- Regardless of the outcome of your child's follow-up testing, **there is hope**.
- There are families, medical providers, and advocates who can help support and guide you throughout your family's journey. **You are not alone!**

IMPORTANT TERMS

- **Myelin** ("my-len"): also known as white matter, forms a protective coating around nerves and helps them quickly carry information from one part of the brain and spinal cord to another.
- **Leukodystrophy** ("luke-o-dis-tro-fee"): a group of inherited genetic diseases that damage the myelin, or white matter, of the brain.
- **Psychosine** ("sigh-co-seen"): a toxic substance that builds up in individuals with Krabbe disease. Psychosine collects in the brain and spinal cord and damages myelin.

- **Other names for Krabbe Disease** ("Crab-Ay"): Krabbe Leukodystrophy, Globoid Cell Leukodystrophy, GALC Deficiency. Krabbe is a type of Lysosomal Storage Disorder and Leukodystrophy.

USING THIS GUIDE

Learning your child received a positive newborn screening result can be scary and overwhelming. Although there is a lot of information to take in and process, **this guide is here for you to use at your own pace**. Our aim is to provide you with key information about Krabbe disease and newborn screening and to answer your initial questions.

HIGHLIGHTS

- Krabbe disease is a type of condition called a leukodystrophy. All leukodystrophies affect the white matter or myelin of the brain.
- Krabbe disease is a rare inherited genetic condition.
- **There are different types of Krabbe disease** and each begins at a different age. Babies identified through newborn screening need to have additional testing to determine which type they might have.
- Follow up and confirmatory testing will place the child into one of three categories: **unaffected** or "**false positive**," **infantile**, or **late onset**.
- Babies who have the infantile form of Krabbe disease need to be seen urgently at the medical center your doctor recommends. The goal of newborn screening is to identify these babies so that they can be quickly treated.

PART I

What does a positive newborn screening result for Krabbe disease mean?

What is newborn screening?

Babies born in the United States undergo newborn screening (NBS) within a few days of their birth. The purpose of newborn screening is to **identify babies with certain diseases that can be detected before symptoms begin**. If a definite diagnosis is confirmed early in life, treatment can also start early. Treatments have the potential to significantly limit the negative impact certain conditions may have.

- Each state has its own policies about which diseases are included in its newborn screening panel and what process it follows to determine whether a child is shown to be at risk for a disease.
- Newborn screening is a **screening tool, not a diagnostic test**. Every positive screen needs further testing, or confirmatory testing, to determine whether the disease is actually present and indeed a "true positive." Though great effort is made to minimize "false positives," they do exist.
- An online resource for understanding more about newborn screening can be found at www.babysfirsttest.org.

Why is Krabbe disease on my state's NBS panel?

- The primary goal of Krabbe newborn screening is to find infants who will develop the disease in infancy, so they can immediately be directed to treatment specialists.
- The standard treatment for Krabbe disease is a **hematopoietic (or blood) stem cell transplant (HSCT).*** Although not a cure, a HSCT does make it possible to **significantly slow down or stop the disease's progression**. However, the transplant needs to be done before the onset or at the very start of Krabbe disease symptoms. Once damage to the brain's white matter occurs, it is permanent and cannot be repaired. HSCT has been performed in babies with Krabbe disease for over two decades. More recently, gene therapy has been developed for Krabbe disease and there are now ongoing clinical trials studying gene therapy alone or combined with HSCT. Ask your doctor for more information about the most up-to-date treatment options for your child's specific case and visit www.clinicaltrials.gov.
- Krabbe newborn screening may also identify babies who are at risk of developing the disease later in childhood or adulthood, thus giving their family the opportunity to establish a medical plan of monitoring to detect early signs of the disease. With monitoring, these individuals may be able to receive early treatment if or when it is needed.

*Please see the Clinical Trials section to learn more about other potential options.

What is Krabbe disease?

- Krabbe disease is a type of neurological condition called a **leukodystrophy**. All leukodystrophies are rare inherited genetic diseases that affect the white matter or myelin of the brain. There are more than 50 known types of leukodystrophies.
- **Myelin** normally develops during the first few years of a child's life. It is made up of proteins and fats, and much like the insulating cover on electrical wiring, it forms a protective covering around the nerves. Myelin is responsible for **getting the nervous system's messages quickly from the brain to the body**.
- Krabbe disease is caused by lower than normal levels of an enzyme called galactocerebrosidase (GALC). Without enough GALC, individuals with Krabbe disease cannot break down a naturally occurring toxin found in brain cells called **psychosine**.
- Because psychosine cannot be broken down and eliminated, it builds up, damaging the brain's myelin.
- Symptoms of Krabbe disease appear when myelin damage has occurred and worsen over time as more myelin is affected and the disease progresses.
- See PART II for more details about how Krabbe disease affects the individual.

How are myelin and psychosine measured in Krabbe Disease?

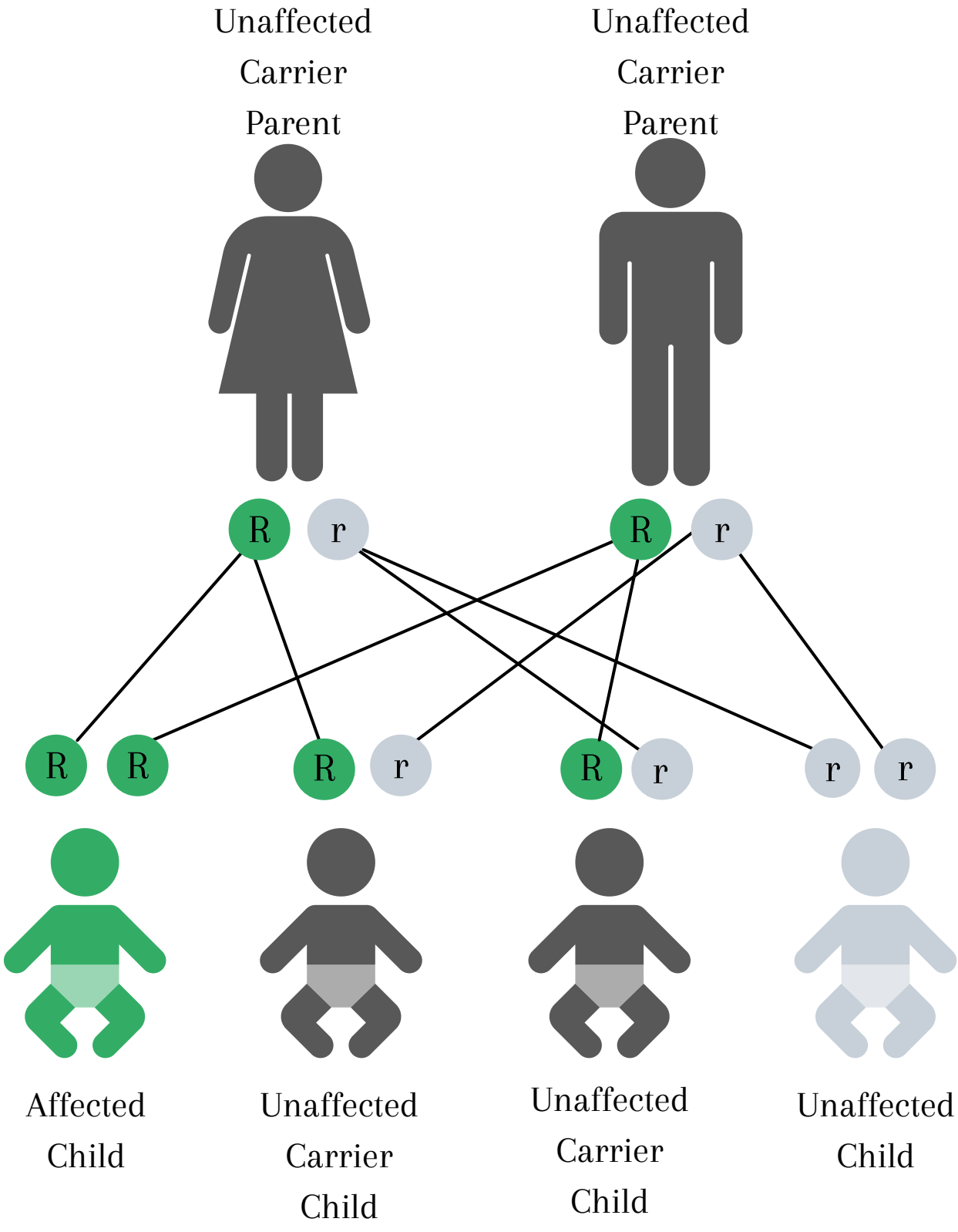
- There are a few ways to evaluate a person's myelin – (1) myelin can be seen on an **MRI scan (magnetic resonance imaging)** of the brain, and (2) it is possible to test how quickly signals travel through someone's nerves by doing a **nerve conduction study (NCS)**. Doctors may recommend performing these tests as a way of monitoring how the myelin is developing or changing over time.
- Psychosine levels can be measured to understand how much of this toxic molecule is in the body and to help predict what form of Krabbe disease might develop. Psychosine is most commonly measured in the blood, and in many states, psychosine levels are measured as part of newborn screening.

How is Krabbe disease inherited?

- In our genetic makeup, we have collections of genes called **chromosomes**. During the process of reproduction, we inherit one set of chromosomes from our mother and the other set from our father.
- **Children born with Krabbe disease have parents who are both "carriers" of the disease**. Being a carrier means that within the parent's own set of chromosomes, one copy of the GALC gene is normal, while the other is abnormal. A child with Krabbe disease will have received two copies of the abnormal GALC gene, one from each parent.
- This type of inheritance is called "**autosomal recessive**."

Genetics

The figure below shows how parents who are carriers have a 25% chance of having a baby who will have two abnormal genes, resulting in a baby with Krabbe disease, where “R” is the abnormal gene and “r” is the normal gene.

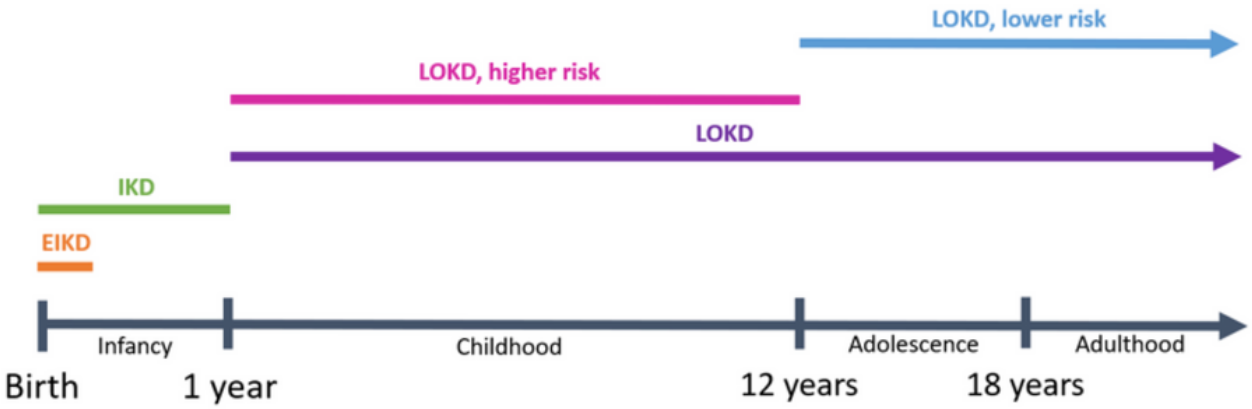


What are the different types of Krabbe Disease?

There are three types of Krabbe disease that are based on the age of disease onset. PART II of this guide goes into detail about how each type affects the child.

- Symptoms start in **infancy** (< 12 months): *Infantile Krabbe disease (IKD)*
  - If an individual has a psychosine level greater than 10 in the newborn period, it is called early Infantile Krabbe Disease. Infants with early IKD should be referred urgently to a transplant center for treatment during the newborn time period.
  - Some infants who do not have a psychosine level greater than 10 may develop Krabbe disease later in infancy (in the first year of life). Infants who develop any symptoms or other findings indicating Krabbe Disease should also be referred urgently to a transplant center for treatment.
- Symptoms start in **childhood, adolescence, or adulthood**: this type is usually split into two categories, based on a patient's risk of disease onset in early childhood:
  - Late Onset Krabbe disease (LOKD) with higher risk for symptoms starting in early childhood
  - Late Onset Krabbe disease (LOKD) with lower risk for symptoms starting in early childhood

Different Forms of Krabbe Disease



What happens at the first appointment following a positive newborn screen for Krabbe disease?

- Regardless of what state you live in, the principles of what needs to be accomplished remain the same. The purpose is to follow up on the newborn screen's initial results and order **confirmatory tests that will place the baby in one of the disease categories** listed above (unaffected, infantile Krabbe disease, or at risk for developing late onset Krabbe disease).
- The experience of bringing a healthy newborn in for evaluation **can feel overwhelming**. Many families find it useful to write down a list of questions prior to their appointment (see PART III for suggested questions). Others find it helpful to bring a second or third adult rather than coming alone. Having a support person join by speaker phone is another option. It may also be possible to record the conversation(s) you have with the specialists at your child's evaluation. Having an extra pair of eyes and ears can help broaden the range of questions asked, and help retain the information that was shared.
- At the **initial clinic appointment**, your provider should go over the specifics of your child's newborn screening results. Typically, the provider will ask about the pregnancy and birth. They will review and gather information about how the child has been eating, sleeping, and interacting. A detailed medical history of family members will usually be discussed including any neurological conditions that may have affected immediate or extended family. In addition, a careful physical exam will typically be completed, focusing on the baby's neurological health and development.
- Lastly, **blood tests will be ordered that will help reach a diagnosis** so that your baby can be placed into one of the possible categories. If they were not already done on your state's newborn screen, your provider may recommend genetic testing and/or psychosine level testing for your child to help with the evaluation. These tests are sent out to specialized labs and results are not immediate. You should make sure to ask your provider when and how they will contact you with the results, and who you should contact with any questions that arise while you wait. In some states, both parents will also have blood drawn for the same genetic testing as your child to help clarify the results.
- If your baby is identified as having the most aggressive form of infantile Krabbe disease, called early infantile Krabbe disease, your providers may discuss a **direct referral to a center performing HSCT and/or gene therapy** to expedite the option to begin treatment as rapidly as possible.

The confirmatory testing for a baby who screens positive for Krabbe disease should place the child into one of the following categories:

Unaffected

- Infants can screen positive for Krabbe disease on newborn screening and then be found to **not have the disease**. This is called a **false positive**.
- This can happen if the baby is a carrier for Krabbe disease or if there are differences in the child's genes that slightly lower the GALC enzyme activity, but not enough to cause Krabbe disease.

Early Infantile Krabbe Disease

- This type of Krabbe disease **requires urgent action if the infant has a high psychosine level**. This is a sub-type of infantile Krabbe disease (IKD).
- Infants whose blood tests indicate they fall into this group should be immediately referred to a qualified transplant specialist for a full evaluation and to begin the process to receive treatment.
- The goal for infants with early infantile Krabbe disease is to receive **transplant in the first 30 days of life**, so it is important to move as quickly as possible.

At risk for developing Krabbe disease during their lifetime (Infantile or Late Onset Krabbe Disease)

- Some babies do not require an urgent referral to a transplant specialist in the first weeks of life, but are **more likely to experience onset of the disease early in life**. If this occurs later in infancy, it is considered IKD and should still result in a referral to a qualified transplant specialist to determine when treatment should be administered.
- **Higher risk for onset in early childhood**: Some babies are more likely to experience onset of the disease in early childhood. Infants determined to have this level of risk will require regular monitoring by a specialist, particularly in the first five years of life (See PART III for more detail on what this monitoring will look like).
- **Lower risk for onset in early childhood**: Some babies are more likely to experience onset of the disease in late childhood, adolescence, or adulthood. Some of these individuals may never develop the disease at all, or if they do, it may be with milder symptoms. Infants determined to have this level of risk will require ongoing monitoring, but **less frequent testing in early life** (see PART III for more detail on what this monitoring will look like).

Regardless of the outcome of your child's testing, know that there is hope, thanks to their early diagnosis and available treatment.

PART II

How does each specific type of Krabbe disease affect the individual?

HIGHLIGHTS

- Krabbe disease is caused by the buildup of a toxin called psychosine. Psychosine causes the **breakdown of myelin**, the insulation that covers nerves.
- If not treated, some babies will develop severe symptoms of Krabbe disease in the first twelve months of life. It is important to identify these babies so that they **are given the opportunity to receive treatment before it is too late**. This form of the disease can start injuring the brain during pregnancy before a baby is born, even though no symptoms may be present.
- Some babies are at risk of developing Krabbe disease later in life (after the first year). These individuals should be **followed by a doctor familiar with the disease** throughout their childhood.
- Symptoms of Infantile Krabbe Disease (IKD) include extreme irritability, difficulty feeding, stiffness and muscle spasms, and seizures. Symptoms of Late Onset Krabbe Disease (LOKD) include mood and behavior changes, seizures, problems with walking, vision loss, and weakness or stiffness in the muscles.

Infantile Krabbe Disease (IKD)

- IKD is the **most severe form** of Krabbe disease.
- The disease begins during pregnancy and symptoms often appear in the first twelve months of a child's life. Some of the most common early symptoms are **irritability, difficulty feeding, and gastrointestinal reflux**.
- Babies with IKD may not gain the expected **developmental skills** or they may lose skills previously achieved.
- If the disease remains untreated, children with IKD may eventually develop abnormal eye movements, loss of motor skills, inability to feed, difficulty seeing or hearing, stiffness and spasms in the muscles, as well as seizures.
- Because IKD is severe and can progress quickly, newborn screening labs and medical care teams work to identify babies at risk for IKD quickly so that they can have the opportunity to receive a stem cell transplant to **help stop progression of the disease**.
- Some babies with IKD may not be eligible for a stem cell transplant. This is usually because a child did not receive newborn screening for Krabbe and has already developed symptoms. Unfortunately, the damage to the brain caused by Krabbe disease is permanent, so a stem cell transplant must be performed before the onset or at the very start of Krabbe disease symptoms.

Late Onset Krabbe Disease (LOKD)

- LOKD is a form of Krabbe disease that may present in childhood, adolescence, or in adulthood. When an infant's newborn screening results put them at risk for LOKD, the medical team should determine if they are at a higher or lower risk for developing LOKD in early childhood or if it is more likely to occur later in childhood, adolescence, or adulthood.

Higher risk for onset in early childhood

- Some common early symptoms of Krabbe disease in early childhood are irritability, loss of sight, difficulty feeding, gastrointestinal reflux, stiffness and spasms of the muscles, and seizures.
- Infants and children may not gain the expected developmental skills or they may lose skills they previously achieved.
- Children in this high-risk category should be closely monitored through regular appointments with a neurological specialist for the first three years of life so that if the onset of disease occurs, it is possible to intervene quickly. (See PART III for a description of the details of monitoring recommendations.)

Lower risk for onset in early childhood

- Infants in this category have a lower risk for developing symptoms in early childhood, but they may develop symptoms later in childhood, in adolescence, or in adulthood. It is also quite possible for these individuals to never develop the disease, or to develop a milder form of the disease.
- Some common symptoms of Krabbe disease later in life include mood and behavior changes, problems with walking, vision loss, weakness or stiffness in the muscles, and abnormal nerve sensations or pain in the arms or legs.
- In late childhood, adolescence, and adulthood, symptoms tend to progress more slowly, so monitoring can occur less often. (See PART III for a description of the details of monitoring recommendations.)

PART III

What comes next?

HIGHLIGHTS

- If a baby is unaffected, or a “false positive,” they do not need any more testing or follow up. They do not have Krabbe disease.
- If a baby has the most severe form of infantile Krabbe disease, called early infantile Krabbe disease, they will **need to visit a special medical team with experience in treating Krabbe disease as soon as possible**, usually before they are 10-15 days old. These babies should be offered a stem cell transplant and/or the option to be considered to participate in a gene therapy clinical trial to treat the disease.
- If a baby is at risk for Late Onset Krabbe Disease, they will need to **visit a neurologist and have testing done regularly**. If the baby’s testing shows early signs of Krabbe disease, they can be offered the possibility of treatment.
- Hunter’s Hope Foundation has created the **Leukodystrophy Care Network (LCN)**. The LCN is a group of Leukodystrophy parents and medical experts from across the country who can be a resource for families. They can help find hospitals and doctors who are experts in Krabbe disease and can be reached at hope@huntershope.org.

After the initial evaluation, what comes next?

The medical history information you provided, the physical exam of your baby, and the results of the bloodwork and confirmatory tests will **determine the correct diagnosis** or category for your baby. There is a great deal of information to process. Family members may vary in how much detail is helpful at any given moment. Please know, however, that **you have the right to a clear and useful explanation of your child’s diagnosis** so that the appropriate next steps can be taken for the best possible outcomes.

An overview of "what comes next" based on category:

Unaffected

- Infants can screen positive for Krabbe disease on a newborn screening panel and be found to not have the disease through confirmatory testing. This is called a **false positive**.
- When this occurs, no further testing or follow up is needed for the baby. The child is **not at risk** for developing Krabbe disease now or in the future.
- In some cases, you may be informed that your baby is a **carrier** which means that they have one abnormal gene, but have no risk of developing Krabbe disease (for more details, see SECTION I: How is Krabbe disease inherited?).

Early Infantile Krabbe Disease

Babies who are in the early infantile Krabbe Disease category should be **referred urgently** to a pediatric stem cell transplant or gene therapy specialist, ideally within the first 10-15 days of life. Further treatment recommendations will be made after that evaluation.

URGENT **Stem Cell Transplant**

You may have more questions about the transplant process, beyond what is covered in this guide. For babies who are recommended to undergo transplant, here is a list of questions that some parents have found helpful to bring to their first appointment:

ASK YOUR DOCTOR:

- How can we be sure our child is sick? They seem healthy?
- What is the difference between a treatment and a cure?
- Are there any clinical trials or additional treatment options currently available?
- For a baby who is recommended to undergo transplant, what are the risks of transplant, and what are the risks of being untreated?
- What is the transplant process like? How long is it? What is the long-term outlook?
- How quickly can my baby be transplanted?
- Is the transplant process covered by insurance? Will someone at the hospital or transplant center coordinate directly with our insurance company?
- How many children with Krabbe Disease have been transplanted? How are those children currently doing post-transplant?
- What is the difference between transplanting our baby at a hospital near our home versus going to a center that has previous experience transplanting more babies with Krabbe disease?
- How will both my child and I, the parent, be supported throughout the transplant process?
- What type of follow up is needed after a transplant?

Late Onset Krabbe Disease

With HIGHER risk for onset in early childhood

- Your child should be followed by a medical provider with **specific expertise in Krabbe disease**, typically a neurologist or geneticist.
- At each visit, in addition to repeat testing, a detailed recent health history and physical examination should be completed. Families can use these appointments to **bring questions or concerns for discussion**. As your child gets older, the frequency of testing slows down. This is because the risk of the more severe forms of Krabbe disease decreases as the child gets older. Krabbe typically does not progress as quickly later in life.
- Your child should have an MRI scan of the head, nerve conduction testing (NCS), and repeated blood tests by two months of age. Other tests may be considered in specific instances to better understand disease risk.
- **Medical follow up** should occur every two to three months with repeated testing occurring approximately every four months until the child turns two years old.
- Between two and three years of age, follow up visits with the specialist and repeat testing can be spread out to every six months, and then can be done yearly between three and twelve years of age, so long as there are no specific symptoms of concern.
- After age twelve years, the individual is seen and tested every two to five years until adulthood.

Questions families have found helpful to bring to their appointments

ASK YOUR DOCTOR:

- Have my child's psychosine levels been measured? If so, what do those results mean?
- What will my child's monitoring schedule look like?
- How will I know if my child is developing Krabbe disease and needs treatment?
- Who will be involved in the medical care team for my child?
- What do we know right now about the long-term outlook for my child?
- Are the any new treatments or clinical trials available?

Late Onset Krabbe Disease

With LOWER risk for onset in early childhood

- Your child should be followed by a medical provider with **specific expertise in Krabbe disease**, typically a neurologist or geneticist.
- At each visit, a detailed recent health history and physical examination should be completed. Families can use these appointments to **bring questions or concerns for discussion**. Since the risk for early childhood onset of the condition is low, testing is not done as frequently as in higher risk situations. This is because the condition typically does not progress as quickly when it begins later in life.
- Your child should have an MRI scan of the head, nerve conduction testing (NCS), and repeat blood tests by 18 months of age. Other tests may be considered in specific instances to better understand disease risk.
- **Medical follow up** and repeat testing should be repeated about every two to five years until adulthood.

Questions families have found helpful to bring to their appointments

ASK YOUR DOCTOR:

- Have my child's psychosine levels been measured? If so, what do those results mean?
- What will my child's monitoring schedule look like?
- How will I know if my child is developing Krabbe disease and needs treatment?
- Who will be involved in the medical care team for my child?
- What do we know right now about the long-term outlook for my child?
- Are the any new treatments or clinical trials available?
- If our family moves in the future, how can we find a new doctor and team to follow our child?

OLDER SIBLINGS
FUTURE CHILDREN

- Because Krabbe disease is an inherited disease, when a child has a positive newborn screen result, many parents think about the **associated risk for their entire family**. Parents may be concerned about their older children or potential future children.
- These are concerns and questions that can be brought up during the initial appointment or when results of testing become available. Some questions may require further testing of family members. It can be helpful to have a **genetic counselor** to help your family move forward with accurate information.

SUPPORT

www.huntershope.org
Leukodystrophy Care Network

- Hunter's Hope was created in 1997 by NFL Hall of Fame Quarterback Jim Kelly, and his wife, Jill, when their infant son, Hunter (2/14/97 – 8/5/05) was diagnosed with Krabbe Disease. For over twenty years, Hunter's Hope has advocated for Krabbe Newborn Screening, and served families with Krabbe and other Leukodystrophies through our programs, which include the Leukodystrophy Care Network (LCN).
- Hunter's Hope is here to help families affected by possible or confirmed leukodystrophy diagnoses through our family programs and the LCN. Whatever stage your family is in, the network seeks to make the way forward a little smoother by providing access to needed information and resources.
- The LCN is made up of parents, medical professionals, and others interested in improving the quality of life for all affected by a leukodystrophy diagnosis.
- In addition to serving as a resource for families, the LCN helps to coordinate national efforts to improve the care and lives of individuals with a leukodystrophy. You can find out more about Hunter's Hope and the LCN at www.huntershope.org.

Research and Clinical Trials

Some families with a child diagnosed with Krabbe disease are interested in participating in available clinical trials for potential new treatment options. If your family would like to explore this avenue, the websites listed below can serve as excellent resources:

- www.clinicaltrials.gov
- www.huntershope.org/family-care/clinical-trials-and-new-treatments/
- Or, email us at hope@huntershope.org for more information about clinical trials.