Newborn Screening for Infantile Krabbe Disease

A Summary of the Evidence and Advisory Committee Decision

Expedited Review Report Date: 1 February 2024

This summary was prepared under a contract to Duke University from the Maternal and Child Health Bureau of the Health and Resources and Services Administration (Contract Number: 75R60223F34007 under 75R60221D00001/75R60221F34001).

EXECUTIVE SUMMARY

This summary reviews the information the federal advisory committee used when deciding whether to recommend adding Infantile Krabbe disease to the Recommended Uniform Screening Panel (RUSP) in 2024.

About the condition

Krabbe disease is a rare condition that affects about 1 out of every 100,000 people. People with Krabbe disease have too little of an enzyme called GALC. This leads to death of nerve cells, including those in the brain. Krabbe disease causes health problems, like severe irritability and trouble moving. Most babies with Krabbe disease have the infantile form, and are affected in the first 12 months after birth. Infantile Krabbe disease (IKD) is the most severe form, causing health problems that worsen quickly and lead to death in early childhood without treatment.

Treatment for Infantile Krabbe disease

Doctors may recommend hematopoietic stem cell transplant (HSCT) as a treatment for IKD. This treatment can lower risk of death in early childhood and help with some symptoms, but does not cure Krabbe disease. For babies with IKD, doctors recommend treatment by 6 weeks after birth before major signs of disease.

Detecting Infantile Krabbe disease in newborns

Newborn screening for IKD can be included with routine newborn screening. There are a few steps in screening. The first step uses the same dried blood spots collected to screen for other conditions to check for low GALC enzyme levels. The second step checks the spots for high levels of psychosine, a substance that builds up in IKD. Sometimes, the second step will also include a check for gene changes linked to Krabbe disease. Newborns whose screening results reveal higher risk for IKD should see a specialist right away.

Public health impact

Screening all newborns in the US is expected to find about 11 babies with Infantile Krabbe disease each year. About 10 of these babies with IKD would likely be treated with an HSCT. Of the babies who receive an HSCT, 1 baby would likely die within 100 days and the others would be alive at 2.5 years but have some level of disability.

Committee decision

The ACHDNC voted in 2024 to recommend adding Infantile Krabbe disease to the RUSP. The ACHDNC noted the benefit of early treatment with HSCT at increasing survival of babies with IKD, although other health problems may remain.

ABOUT THIS SUMMARY

What is newborn screening?

Newborn screening is a public health service that can change a baby's life. Newborn screening involves checking all babies to find those few who look healthy but who are at risk for one of several serious health conditions that benefit from early treatment.

Certain serious illnesses can be present even when a baby looks healthy. If the baby does not receive screening for these early in life, diagnosis may be delayed. Treatment started later might not work as well as earlier treatment. Newborn screening programs have saved the lives and improved the health of thousands of babies in the United States (US).

Who decides what screening newborns receive?

In the US, each state decides which conditions to include in its newborn screening program. To help states determine which conditions to include, the US Secretary of Health and Human Services provides a list of conditions recommended for screening. This list is called the Recommended Uniform Screening Panel (RUSP). Progress in screening and medical treatments can lead to new opportunities for newborn screening. To learn how a condition is added to the RUSP, see **Box A**.

What will this summary tell me?

In 2010 and in 2023, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) reviewed data on newborn screening and did not recommend adding Krabbe disease to the RUSP. In 2023, the ACHDNC requested a new review of evidence for early detection of Infantile Krabbe disease (IKD). This summary presents key information the ACHDNC used to decide whether to recommend adding IKD to the RUSP in 2024. It will answer these questions:

- What is Infantile Krabbe disease (IKD)?
- How is IKD treated?
- How are newborns screened for IKD?
- Does early diagnosis or treatment help patients with IKD?
- What is the US public health impact of newborn IKD screening?
- Did the ACHDNC recommend adding IKD to the RUSP?

Box A: Adding a Condition to the RUSP

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), makes a recommendation to the US Secretary of Health and Human Services about adding specific conditions to the RUSP. The ACHDNC bases its decision on a review of the condition, the screen, the treatment, and the ability of newborn screening programs to check for the condition. To learn more about the ACHDNC, visit this website.

UNDERSTANDING THE CONDITION

What is Infantile Krabbe disease?

Infantile Krabbe (pronounced crab-AY) disease (IKD) is a rare genetic condition affecting the nervous system within the first year of life. People with IKD are born with a change in a single gene called *GALC*. Normally, this gene makes the GALC enzyme, which helps break down fats in the nervous system. In people with IKD, the GALC enzyme does not work properly. When this happens, certain chemicals—including a toxic chemical called psychosine—build up. This leads to the death of nerve cells, including those in the brain. This causes health problems that can lead to death in early childhood.

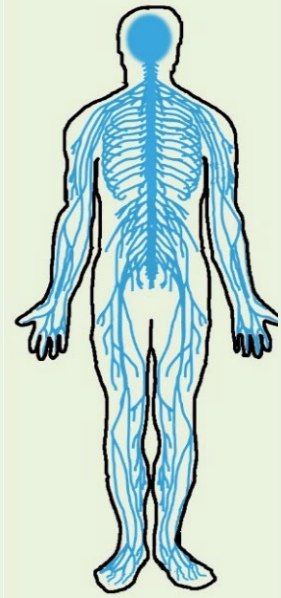
How common is Infantile Krabbe disease?

- IKD is rare. Without newborn screening, about 1 out of every 100,000 children receives a diagnosis of IKD.

What kinds of health problems does Infantile Krabbe disease cause?

Without treatment, IKD causes severe health problems that affect the nervous system. These problems can impact development, movement, and other things (Figure 1).

Figure 1: Health Problems from Infantile Krabbe Disease.



Development symptoms

Damage to the nervous system from infantile Krabbe disease can cause problems with development. Babies with this disease have slowed mental or physical development.

Movement symptoms

Damage to the newvous system from infantile Krabbe disease can cause muscle weakness and stiffness and interfere with movement. This leads to probelsm with head and body control, sitting, walking, eating, and breathing. Babies with infantile Krabbe disease can lose movement skills as the disease gets worse. Without treatment, these problems can result in death in early childhood.

Other symptoms

Damage to the nervous system from infantile Krabbe disease can cause other symptoms. These can include severe irritability, difficulty eating, seizures, or problems with vision or hearing.

Are there different types of Krabbe disease?

Yes. Experts currently describe 4 types based on when health problems from Krabbe disease start. These types are infantile, late infantile, juvenile, and adult. The infantile and later infantile types, in which health problems start before 3 years of age, are the most common and serious types.

Experts are still learning about Krabbe disease. They may change how to describe types of Krabbe disease in the future.

When do Krabbe disease symptoms develop?

Babies are born with Krabbe disease, but the timing and type of health problems it causes can vary. Health problems include both signs (problems observed by a doctor, nurse, or parent) and symptoms (problems observed by a patient). Table 1 shows when health problems may appear for each type.

Table 1: Timing of Signs and Symptoms.

Type	Age When Signs or Symptoms Start	Details
Infantile	0 to 12 months	• Babies with this type have the most severe signs and symptoms. • Signs or symptoms usually appear around age 4 months. Nervous system changes begin before babies show health problems. • On average, babies with this type live for about 1.5 years.
Later infantile	13 to 36 months (3 years)	• Children with this type have severe signs and symptoms. • Signs or symptoms usually appear around age 14 months. • On average, children with this type live for about 9.5 years.
Juvenile	37 to 180 months (15 years)	• Children with later-onset Krabbe disease often have milder signs and symptoms. • Signs or symptoms usually appear around age 4 years. • About 80% of people with this type live past the age of 16 years.
Adult	Later than 180 months (15 years)	• Adults with later-onset Krabbe disease often have milder signs and symptoms. • Signs or symptoms usually appear around age 32 years, but this can vary. • Almost 90% of people with this type live past the age of 19 years.

TREATMENT FOR INFANTILE KRABBE DISEASE

How is Infantile Krabbe disease treated?

There is no cure for Krabbe disease. Whether and when a baby needs treatment depends on many things, like how severe symptoms are when a baby is diagnosed.

Doctors recommend hematopoietic stem cell transplantation (HSCT) as treatment for babies with IKD. HSCT is sometimes called a "bone marrow transplant." It works by using cells from a donor who does not have Krabbe disease. There are a few different ways to get these cells from a donor, like umbilical cord blood from a newborn or bone marrow cells from an older donor. When transfused (transferred) into the blood of a baby with IKD disease, these donor cells grow and develop within the baby's body. They travel to the baby's bone marrow and throughout the body. They make the GALC enzyme that a baby with IKD disease would otherwise be missing.

HSCT is not a cure for IKD. It can lower the risk of death in early childhood and may also help with some symptoms. Outcomes for babies with IKD who get HSCT vary. Some children who get HSCT still need feeding tubes and wheelchairs.

HSCT helps most when done before major problems from IKD start. Doctors recommend that babies with IKD receive HSCT in the first 6 weeks of life. Families offered HSCT talk to specialists about whether this treatment is right for their child.

Experts are studying other possible treatments for Krabbe disease.

What are the risks of treatment for Krabbe disease?

HSCT is a serious treatment. It has a short-term risk of serious infections and other complications. HSCT can lead to major health problems or death due to infection, side effects of medicine, or new cells from the bone marrow transplant attacking the body. Later risks of HSCT include problems with bone growth and trouble conceiving children.

Risks from HSCT depend on a few things, like how well bone marrow cells from the donor match those of the baby with IKD. How much HSCT helps also depends on a few things, like the baby's signs and symptoms at the time of treatment. Once a baby has serious health problems from IKD, HSCT is not effective.

FINDING NEWBORNS WHO HAVE INFANTILE KRABBE DISEASE

How are newborns screened for Infantile Krabbe disease?

Newborn screening for IKD can be included with other routine newborn screening. Most newborn screening begins when a doctor or nurse collects a few drops of blood from a baby's heel and dries them onto a special piece of paper. The hospital sends these "dried blood spots" to the state's newborn screening program. The program uses a laboratory to check the dried blood spots for many conditions.

To screen for IKD, laboratories use special equipment to measure the levels of the GALC enzyme in the dried blood spots. Low levels of the GALC enzyme mean a higher risk for IKD. Babies with low GALC enzyme levels need a second screening step, which can happen in a few ways. Most often, the second step checks the dried blood spots for high levels of a toxic chemical (psychosine) that builds up when the GALC enzyme does not work well. Sometimes, the second step checks the blood for certain changes in the baby's *GALC* gene. When screening finds high levels of psychosine or certain gene changes, the baby is at higher risk for IKD.

When a baby is at higher risk for IKD, the baby needs more tests. The newborn screening program works with the baby's doctor to help the baby get the right tests or see a specialist right away.

How well does screening for Infantile Krabbe disease work?

Screening works well to find babies who might have IKD. Using the 2-step screening described above, with GALC and psychosine level testing can identify babies at high risk for IKD. Screening cannot diagnose IKD, but it can find the babies who need more tests or to see a specialist in a timely manner.

What happens if newborn screening indicates a high risk for Infantile Krabbe disease?

Doctors refer newborns whose screening results show high IKD risk for more testing. Testing starts with a doctor's exam and blood tests. Doctors retest things that were checked during newborn screening, like GALC enzyme levels, toxic chemical (psychosine) levels, or changes in the *GALC* gene. Some changes in the *GALC* gene can help doctors predict when signs or symptoms will start. Doctors also examine the baby in the clinic and test for other neurological problems.

To be effective, HSCT for IKD must be done before signs of disease start in the first 6 weeks of life. Doctors begin talking with parents about the risks and benefits of HSCT shortly after IKD is confirmed.

What are some of the benefits and risks of newborn IKD screening?

Table 2 lists benefits and harms of newborn screening for IKD.

Table 2: Benefits and Harms of Screening.

Benefits	Harms
• Earlier detection and more direct diagnosis of IKD.	• Screening and follow-up testing require taking blood, which can cause pain. • The timing of IKD problems can be hard to predict from screening and require close monitoring
• Earlier access to treatment (HSCT).	• Earlier exposure to possible treatment risks. • HSCT for IKD must be done earlier (within the first 6 weeks of life) than is common for other conditions. • The early timing for HSCT may cause families anxiety in decision-making.
• Early HSCT can lower the risk of childhood death and help with certain symptoms for some babies.	• Early HSCT is not a cure. • Early HSCT may not help with all symptoms which may appear. • Little is known about longer term outcomes of HSCT.

Does early diagnosis or treatment help patients with Infantile Krabbe disease?

Yes, earlier diagnosis of IKD allows earlier treatment.

Treatment with HSCT works best when babies receive it before health problems develop. Babies with infantile Krabbe disease need treatment within the first 6 weeks after birth. Without screening, many babies with IKD do not get a diagnosis until it is too late for treatment to help.

Treatment with HSCT before health problems start can extend life for babies with IKD. Experts need to learn more to know how much it helps with other health problems.

PUBLIC HEALTH IMPACT

How would newborn IKD screening affect the health of the country?

Experts think that screening all newborns in the US would find about 11 babies with or at risk for Infantile Krabbe disease each year.

- About 11 of these would be babies with infantile Krabbe disease found in time to receive treatment. About 10 of the 11 babies would receive early treatment with HSCT, and at least 1 family would decline treatment.
- Of the 10 babies receiving HSCT, about 9 would survive to 30 months of age. One baby would be expected to die from HSCT treatment by 30 months.
- Without IKD newborn screening, 1 of 11 babies would be diagnosed in time to receive treatment and survive to 30 months of age. Eight babies with IKD would not be identified early with clinical detection, and would die before reaching 30 months of age.

What is the status of newborn Krabbe disease screening in the US?

- At the time of the report, 11 states screened newborns for Krabbe disease. These states were Georgia, Illinois, Indiana, Kentucky, Missouri, New Jersey, New York, Ohio, Pennsylvania, South Carolina and Tennessee.
- 2 of the 11 states (New Jersey and Ohio) do not use the 2-step screening for both GALC and psychosine levels that experts recommend for IKD screening.

ADVISORY COMMITTEE DECISION

What did the Committee recommend?

The ACHDNC recognized the severity of IKD and the benefit of early treatment. The ACHDNC voted in January 2024 to recommend adding Infantile Krabbe disease to the RUSP by first screening for low GALC enzyme level and then checking if the psychosine level was 10nM or more. In July 2024, the Secretary HHS added Infantile Krabbe Disease to the RUSP with 2-step screening of GALC and psychosine levels.

The ACHDNC may consider other types of Krabbe disease for the RUSP again in the future. To do so, it would need more data about Krabbe disease.

What happens next?

Each state can decide whether to screen newborns for Krabbe disease. To screen for any condition, states must be prepared. They must have the right equipment and systems in place. They also must have specialists to work with families to determine if a baby has the condition and, if so, the best treatment.

If a state decides to add IKD to its newborn screening program, the state will work to put the needed screening and follow-up services in place.

Box B: Where Can I Learn More?

Follow the links below to learn more.

- To learn more about Krabbe disease, visit the National Institutes of Health Krabbe Disease website.
- Visit the Committee's website to learn more about:
  - Nominating conditions to the RUSP.
  - The Infantile Krabbe disease evidence report.
  - The Committee's letter to the Secretary HHS recommending adding Infantile Krabbe disease to the RUSP.
  - The Secretary HHS letter to the ACHDNC adding Infantile Krabbe disease to the RUSP.

HELPFUL INFORMATION

Glossary

Term	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. The committee that oversees the RUSP.
Dried blood spot	A drop of blood taken from a baby's heel, dried onto a special piece of paper, and used to screen for many conditions.
GALC gene	Certain changes in this gene cause Krabbe disease.
GALC enzyme	An enzyme that helps break down fats in the nervous system. This enzyme does not work properly in people with Krabbe disease.
HSCT	Hematopoietic stem cell transplantation. A treatment for Krabbe disease that provides the body with the GALC enzyme that would otherwise be missing. Also called a "bone marrow transplant."
IKD	Infantile Krabbe Disease, a rare genetic condition causing severe problems with the nervous system in the first 12 months of life.
Psychosine	A toxic fat that can kill cells in the nervous system.
RUSP	Recommended Uniform Screening Panel. The list of conditions recommended for newborn screening.
Secretary of Health and Human Services	The head of the US Department of Health and Human Services. This person decides whether to add conditions to the RUSP.
Sign	A health problem observed by someone other than a patient, like a parent, doctor, or nurse.
Symptom	A health problem observed by a patient.
Specialist	A doctor with expertise in a certain area of medicine.
US	United States.
Transfused	Transferred into the blood.

Source

The information in this summary is based on the *Expedited Evidence-Based Review of Newborn Screening for Krabbe Disease Final Report: February 1, 2024* This report was commissioned by the ACHDNC. It reviewed data on Infantile Krabbe disease screening and treatments in children from January 10, 2023 through November 22, 2023. The report included both published and unpublished research. Relevant conference abstracts to be presented in February 2024 but not yet published were provided by experts for the expedited review. To read the report, visit this page.