Newborn Screening for Krabbe Disease

A Summary of the Evidence and Advisory Committee Decision

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EXECUTIVE SUMMARY

This summary reviews the information the federal advisory committee used when deciding whether to recommend adding Krabbe disease to the Recommended Uniform Screening Panel (RUSP) in 2023.

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. These problems can worsen very quickly without treatment, especially if they arise in the first 6 months of life. Babies affected by Krabbe disease in their first year usually die in early childhood.

Treatment for Krabbe disease

Doctors may recommend hematopoietic stem cell transplant as a treatment for Krabbe disease. This treatment can lower risk of death in early childhood and help with some symptoms but does not cure Krabbe disease. For babies with severe Krabbe disease, doctors recommend treatment by 6 weeks after birth. Children at risk for later-onset Krabbe disease may get treatment if symptoms arise.

Detecting Krabbe disease in newborns

Newborn screening for Krabbe disease 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 Krabbe disease. Sometimes, the second step checks the blood for gene changes linked to Krabbe disease. Newborns whose screening results reveal higher risk for Krabbe disease should see a specialist right away.

Public health impact

Experts think that screening all newborns in the US would find about 70 babies with or at risk for Krabbe disease each year. Not all of these would have Krabbe disease or need treatment. About 15 of these babies would have the most severe Krabbe disease type. Treatment would prevent about 10 babies from dying in early childhood, though many treated children would still have some level of disability.

Committee decision

The Committee voted in 2023 not to recommend adding Krabbe disease to the RUSP. The Committee noted gaps in what is known about how well HSCT works, the risks of HSCT in very young babies, and the outcomes of late infantile Krabbe disease found by screening babies. Krabbe disease may be reconsidered for the RUSP in the future.

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, 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 2022, the ACHDNC requested a new evidence review based on progress in screening and treatment. This summary presents key information the ACHDNC used to decide whether to recommend adding Krabbe disease to the RUSP in 2023. It will answer these questions:

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

Krabbe (pronounced crab-AY) disease is a rare genetic condition affecting the nervous system. People with Krabbe disease 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 Krabbe disease, the GALC enzyme does not work properly. When this happens, certain fats—including a toxic fat 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.

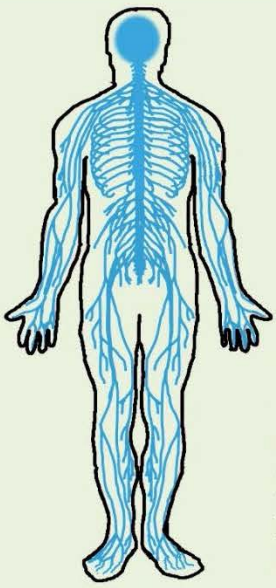
How common is Krabbe disease?

- Krabbe disease is rare. Without newborn screening, about 1 out of every 100,000 children receives a diagnosis of Krabbe disease.
- The actual number of people with Krabbe disease might be higher than this number. The number does not count some people who develop health problems later in life or those with the condition who do not get a diagnosis.

What kinds of health problems does Krabbe disease cause?

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

Figure 1: Health Problems from Krabbe Disease.



Development problems
Damage to the nervous system from Krabbe disease can cause problems with development. Some babies and children with the disease have slowed mental or physical development.

Movement problems
Damage to the nervous system from Krabbe disease can cause muscle weakness and stiffness and interfere with movement. This leads to problems with head and body control, sitting, walking, eating, and breathing. Babies and children with Krabbe disease can lose movement skills as the condition gets worse. These problems can result in death.

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

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 early infantile, late infantile, juvenile, and adult. The early and late infantile types, in which health problems start before 3 years of age, are the most common.

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
Early infantile	0 to 6 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.
Late infantile	7 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 KRABBE DISEASE

How is 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 early or late infantile Krabbe disease. 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 Krabbe 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 Krabbe disease would otherwise be missing.

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

HSCT helps most when done before major problems from Krabbe disease start. For babies with severe Krabbe disease in early infancy, this can be in the first 6 weeks of life. Children at risk for later-onset Krabbe disease are monitored by specialists and may receive treatment if serious symptoms arise. 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 procedure. 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 Krabbe disease. 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 Krabbe disease, HSCT is usually more dangerous than helpful.

FINDING NEWBORNS WHO HAVE KRABBE DISEASE

How are newborns screened for Krabbe disease?

Newborn screening for Krabbe disease 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 Krabbe disease, 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 Krabbe disease. 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 fat (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 toxic fat levels or gene changes, the baby is at higher risk for Krabbe disease.

When a baby is at higher risk for Krabbe disease, 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 Krabbe disease work?

Screening works well to find babies who might have Krabbe disease. Using the 2-step screening described above works better than either step alone. Screening cannot diagnose Krabbe disease, but it can find the high-risk babies who need more tests or to see a specialist.

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

Doctors refer newborns whose screening results show high Krabbe disease 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 fat (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.

Health problems from Krabbe disease do not always start during early infancy, and doctors sometimes cannot tell when or if a healthy-looking baby with Krabbe disease will develop signs or symptoms. Doctors monitor all babies with the condition to see when or if they need treatment. Monitoring involves testing to check how the brain responds to sounds or patterns and how well nerves carry brain messages. Doctors may take pictures of the brain with special scanners or test the blood or brain fluid for certain problems. Babies at higher risk for Krabbe disease need monitoring more often than those at lower risk.

What are some of the benefits and risks of newborn Krabbe disease screening?

Table 2 lists benefits and harms of newborn screening for Krabbe disease.

Table 2: Benefits and Harms of Screening.

Benefits	Harms
• Earlier detection and more direct diagnosis of Krabbe disease.	• False reassurance for families of babies who whose screening results mean low risk for Krabbe disease but who actually have the condition.
• Earlier access to treatment (HSCT). Although HSCT is not a cure, it can lower the risk of childhood death and help with certain symptoms for some babies.	• Potential for treatment when it is not needed. • Earlier exposure to treatment risks. HSCT for Krabbe disease must be done earlier (within the first 6 weeks of life) than is common for other conditions.
• Earlier monitoring for babies at risk for Krabbe disease who do not need treatment right away.	• Some babies are monitored for months or years but never get a diagnosis. • Little is known about how ongoing monitoring affects families.

Does early diagnosis or treatment help patients with Krabbe disease?

Yes, especially for babies with early or late infantile Krabbe disease. Earlier diagnosis allows earlier treatment.

Treatment (HSCT) works best when babies receive it before signs or symptoms of Krabbe disease start. Babies with early infantile Krabbe disease need treatment within the first 6 weeks after birth. Babies with late infantile Krabbe disease need treatment before major signs or symptoms appear (between 6 and 36 months of age). Without screening, many babies do not get a diagnosis until it is too late for treatment to help.

Treatment with HSCT before signs or symptoms arise can extend life for babies with Krabbe disease. Experts need to learn more to know for sure how much it helps with other health problems.

PUBLIC HEALTH IMPACT

How would newborn Krabbe disease screening affect the health of the country?

Experts think that screening all newborns in the US would find about 70 babies with or at risk for Krabbe disease each year.

- About 15 of these would be babies with infantile Krabbe disease found in time to receive treatment. Treatment would prevent 10 of these children from dying in early childhood, though many treated children would still have some level of disability.
- Screening would find about 22 babies at high risk and 33 babies at low risk for other types of Krabbe disease each year. These babies would need continued monitoring by specialists, because making a diagnosis for Krabbe disease can be difficult. Some of these babies would never get a diagnosis of Krabbe disease.

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

- At the time of the report, 10 states screened newborns for Krabbe disease. These states were Georgia, Illinois, Indiana, Kentucky, Missouri, New Jersey, New York, Ohio, Pennsylvania, and Tennessee.
- More than 80% of programs estimated that adding newborn Krabbe disease screening would take less than 3 years.

ADVISORY COMMITTEE DECISION

What did the Committee recommend?

The ACHDNC voted in February 2023 not to recommend adding Krabbe disease to the RUSP. The ACHDNC recognized the severity of Krabbe disease. However, it also noted gaps in what is known about the condition. In March 2023, the ACHDNC Chair sent a letter to the nominators with the decision describing the evidence gaps

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

What happens next?

The people who nominated Krabbe disease for the ACHDNC to consider may nominate Krabbe disease again at a later time.

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 Krabbe disease 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 full Krabbe disease evidence report.
  - The Committee's letter to the nominators recommending not to add Krabbe disease to the RUSP at this time.

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."
Krabbe disease	A rare genetic condition causing problems with the nervous system.
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 *Evidence-Based Review of Newborn Screening for Krabbe Disease: Final Report (03/13/2023)*. This report was commissioned by the ACHDNC. It reviewed data on Krabbe disease screening and treatments in children through January 10, 2023. The report included both published and unpublished research. To read the report, visit this page.