Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency

A Summary of the Evidence and Advisory Committee Decision

Report Date: 02 June 2022

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: 710067-0922-00 under 75R60221D00001/75R60221F34001).

EXECUTIVE SUMMARY

This summary reviews the information the federal advisory committee used when deciding whether to recommend adding Guanidinoacetate methyltransferase (GAMT) deficiency to the Recommended Uniform Screening Panel (RUSP) in 2022.

About the condition

GAMT deficiency is a rare condition. It is caused by changes in the *GAMT* gene. Fewer than 1 out of every 100,000 people in the United States (US) have this condition. People with GAMT deficiency have too little creatine and too much guanidoacetate (GUAC). They have serious brain and muscle problems that get worse over time without treatment.

Treatment for GAMT deficiency

There is no cure for this condition. Early diagnosis allows early monitoring and treatment. The main treatment is supplements that are taken by mouth for life. Treatment can also include diet changes. Early treatment may help with or even prevent symptoms.

Detecting GAMT deficiency in newborns

Newborn screening for GAMT deficiency can be included with routine newborn screening for other conditions in the first few days of life. It measures the levels of creatine and GUAC. This process uses the same dried blood spots already taken for screening of other conditions. Newborns with low creatine and high GUAC levels are at a higher risk for GAMT deficiency. They need more testing to know if they have this condition and to find the right treatment.

Public health impact

Experts think that screening all newborns in the US would find about 7 babies with GAMT deficiency each year. This is fewer than 1 out of every 100,000 children born.

Committee decision

The Committee voted in 2022 to recommend adding GAMT deficiency to the RUSP. As of January 2023, the RUSP recommends that state newborn screening programs include GAMT deficiency.

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 2021, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) requested an evidence review of newborn screening for Guanidinoacetate methyltransferase (GAMT) deficiency. This summary presents key information that the Committee used to decide whether to recommend adding GAMT deficiency to the RUSP. It will answer these questions:

- What is GAMT deficiency?
- How is GAMT deficiency treated?
- How are newborns screened for GAMT deficiency?
- Does early diagnosis or treatment help patients with GAMT deficiency?
- What is the public health impact of newborn GAMT deficiency screening in the US?
- Did the Committee recommend adding GAMT deficiency to the RUSP?

Box A: Adding a Condition to the RUSP

A committee, called 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 Committee 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 GAMT deficiency?

GAMT deficiency is rare. It is caused by changes in the *GAMT* gene. Normally, the *GAMT* gene makes an enzyme with the same name. The GAMT enzyme makes creatine. Creatine helps the brain and body get the energy they need.

People get 1 copy of the *GAMT* gene from each parent. GAMT deficiency occurs when both copies of this gene do not work. When this happens, people cannot make enough creatine. They also have too much guanidinoacetate (GUAC), which is used to make creatine. This causes serious health problems.

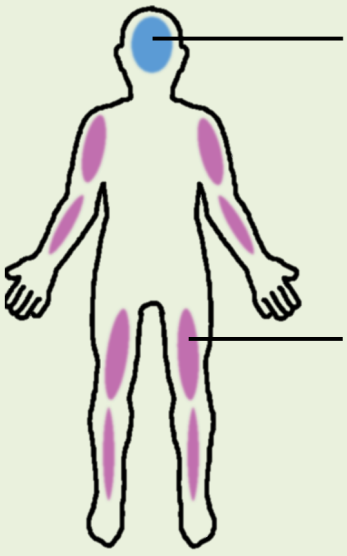
How common is GAMT deficiency?

- GAMT deficiency is rare. Currently, fewer than 1 out of every 100,000 people in the US are diagnosed with GAMT deficiency.
- This number is based on people who have symptoms and are diagnosed without newborn screening. Not everyone with this condition is diagnosed, so the actual number of people with GAMT deficiency might be higher.

What kinds of health problems does GAMT deficiency cause?

Without treatment, GAMT deficiency causes serious problems with the brain and muscles. These problems get worse over time (Figure 1).

Figure 1: GAMT Deficiency Symptoms.



Brain symptoms
Without treatment, GAMT deficiency causes many problems with the brain and how it develops. People with this condition can have problems with cognitive abilities, speech and language, and behavior. Many will also have seizures.

Muscle symptoms
People with GAMT deficiency can have weak muscles and poor motor skills if they do not get treatment. Problems can include trouble walking and unwanted muscle movement.

When do GAMT deficiency symptoms develop?

The timing and type of problems caused by this condition may vary from person to person. Table 1 shows when symptoms may arise without screening and treatment.

Table 1: Symptom Timing and Type.

Age	Symptom	Details
Birth	Signs do not show	• Before birth, creatine comes from the mother. • Parents and doctors cannot tell just by looking if a baby has this condition.
Infancy	Brain and muscle symptoms	• After birth, the creatine from the mother disappears. Without treatment, symptoms will begin. • Symptoms usually do not start until after 3 months of age.
Early childhood through adulthood	Worsening brain and muscle symptoms	• Without treatment, most people with GAMT deficiency will have serious problems with cognitive abilities, speech and language, behavior, and movement. These problems will get worse over time. Many people will also have seizures. People with GAMT deficiency can live as long as those without the condition.

TREATMENT FOR GAMT DEFICIENCY

How is GAMT deficiency treated?

There is no cure for GAMT deficiency. People who have it need treatment for their whole lives.

The main treatment is supplements that are taken by mouth. Some supplements increase creatine. Others lower GUAC. Diet changes, like eating less protein, can also help.

Doctors check a baby's levels of creatine and GUAC during treatment. This makes sure that any supplements and diet changes are working.

What are the risks of treatment for GAMT deficiency?

Treatment for GAMT deficiency is generally safe.

FINDING NEWBORNS WHO HAVE GAMT DEFICIENCY

How are newborns screened for GAMT deficiency?

Newborn screening for GAMT deficiency can be included with other routine newborn screening in the first few days of life. 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 GAMT deficiency, laboratories use special equipment to measure the levels of creatine and GUAC in the dried blood spots.

When a newborn has low levels of creatine and high levels of GUAC, the baby needs more tests. The newborn screening program works with the baby's doctor when screening results mean that the baby needs other tests or to see a specialist.

How well does screening for GAMT deficiency work?

Screening works well to help find babies with GAMT deficiency. False positives are rare. Screening cannot diagnose GAMT deficiency, 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 GAMT deficiency?

Doctors refer newborns whose screening results show high risk for more testing. This may involve more tests on dried blood spots, urine tests, and an exam by a special doctor. Tests may also look at the baby's *GAMT* gene. Some babies might need a special type of brain scan to check their creatine or GUAC levels.

What are some of the benefits and risks of newborn GAMT deficiency screening?

Table 2 lists the benefits and risks of newborn GAMT deficiency screening as of 2022.

Table 2: Benefits and Risks of Screening.

Benefits	Risks
• Earlier detection and diagnosis of babies with GAMT deficiency.	• Some babies found from newborn screening do not have GAMT deficiency. All babies with low creatine and high GUAC levels need more testing. • Blood is taken for screening and follow-up testing. This can cause pain.
• Earlier treatment. This may help with or even prevent the disease process.	• There are few, if any, risks of treatment.
• More time to plan for the future.	• More worry about the future.
• Health counseling and family planning for family members.	• Some people do not want to know genetic risks. Some families do not like to share health details.
• Peace of mind for the families of babies with normal creatine and GUAC levels.	• Undue worry for the families of babies with low creatine and high GUAC levels during newborn screening who do not have GAMT deficiency after more testing.

Does early diagnosis or treatment help patients with GAMT deficiency?

Early diagnosis allows early monitoring and treatment. This can improve the health of people with GAMT deficiency.

Box B: Where Can I Learn More?

Follow the links below to learn more.

- To learn more about GAMT deficiency, visit the National Institutes of Health GAMT deficiency website.
- Visit the Committee's website to learn more about:
  - Nominating conditions to the RUSP.
  - The full GAMT deficiency evidence report.
  - The ACHDNC recommendation to the Secretary to add this condition to the RUSP.

PUBLIC HEALTH IMPACT

How would newborn GAMT deficiency screening affect the health of the country?

Experts think that screening all newborns in the US for this condition would find about 7 babies each year. This is fewer than 1 out of every 100,000 children born.

Without screening, diagnosing GAMT deficiency can take time. Babies will not have symptoms right away. Newborn screening may allow for diagnosis in the first weeks of life. This is when treatment could work best.

What is the status of newborn GAMT deficiency screening in the US?

- Two states, Utah and New York, screened newborns for GAMT deficiency at the time of the report. One state (Michigan) had approved screening but had not started as of April 2022.

ADVISORY COMMITTEE DECISION

What did the Committee recommend?

The Committee voted in May 2022 to recommend adding GAMT deficiency to the RUSP. The Committee based its decision on the ability of screening to find babies with GAMT deficiency and evidence that early treatment was better than later treatment. The Committee also considered if newborn screening was feasible and if state newborn screening programs were ready. In January 2023, the US Secretary of Health and Human Services accepted the Committee's recommendation. The RUSP now recommends that state newborn screening programs include GAMT deficiency.

What happens next?

Each state will decide whether to screen newborns for GAMT deficiency. 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 GAMT deficiency to their newborn screening program, they will work on getting the needed screening and follow up services in place for that state.

HELPFUL INFORMATION

Glossary

Term	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. The committee that oversees the RUSP.
Creatine	A substance made by the GAMT enzyme. Creatine helps the brain and body get the energy they need. People with GAMT deficiency have too little creatine.
Deficiency	A lack of something. People with GAMT deficiency do not have enough working GAMT enzyme.
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.
False positive	When screening wrongly shows that a person could have a condition.
GAMT deficiency	Guanidinoacetate methyltransferase deficiency. A rare condition that affects the brain and muscles.
GAMT enzyme	An enzyme made by the *GAMT* gene. The GAMT enzyme makes creatine.
GAMT gene	The gene that causes GAMT deficiency. People with this condition have 2 copies of this gene that do not work.
GUAC	Guanidoacetate. A substance used by the GAMT enzyme to make creatine. People with GAMT deficiency have too much GUAC.
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.
Specialist	A doctor with expertise in a certain area of medicine.
Supplement	A substance that can be taken by mouth to improve health. Vitamins and minerals are types of supplements.
US	United States.

Source

The information in this summary is based on the *Evidence-Based Review of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency: Final Report (06/2/2022)*. This report was commissioned by the ACHDNC. It reviewed data on GAMT deficiency screening and treatments in children through April 1, 2022. The report included both published and unpublished research. To read the report, visit this page.