Newborn Screening for X-linked Adrenoleukodystrophy

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 X-linked adrenoleukodystrophy (X-ALD) to the Recommended Uniform Screening Panel (RUSP) in 2015.

About the condition

X-ALD is a rare disorder caused by a change in a single human gene. Studies of patients with symptoms suggest that about 2-3 out of every 100,000 people have X-ALD. People with X-ALD do not have enough of a protein that helps the body break down certain types of fats. Babies with X-ALD look normal. There are different types of X-ALD that can cause problems with the adrenal glands, brain, and spinal cord. Without treatment, these problems can worsen quickly and cause death during childhood. X-ALD usually affects boys more severely than girls.

Treatment for X-ALD

There is no cure for X-ALD. Early diagnosis allows early monitoring and treatment for babies with X-ALD. Available treatments include cortisol replacement and human stem cell transplant. The treatment a patient needs depends on many factors, like the type of X-ALD.

Detecting X-ALD in newborns

Newborn screening for X-ALD can happen along with routine newborn screening for other conditions in the first few days of life. Newborn screening for X-ALD measures levels of a certain fatty acid. This process uses the same dried blood spots already collected to screen for other disorders. Newborns with high fatty acid levels are at higher risk for X-ALD. They need more testing and evaluation to diagnose the condition.

Public health impact

Based on what is known about screening and the risk of being born with X-ALD, experts think that screening all newborns in the United States for X-ALD would find about 143 babies with the condition each year (about 3.6 out of every 100,000 children born). It would prevent up to 64 cases of serious disability/death and up to 44 deaths due to the disease each year.

Committee decision

The Committee voted in 2015 to recommend adding X-ALD to the RUSP. As of 2016, the RUSP recommends that state newborn screening programs include X-ALD.

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 identify 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 illnesses early in life, a diagnosis may be delayed. Later treatment 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 2014, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) requested an evidence review of newborn screening for X-linked adrenoleukodystrophy (X-ALD). This summary presents key review information that the Committee used to make its decision about whether to recommend adding X-ALD to the RUSP. It will answer these questions:

- What is X-ALD?
- How is X-ALD treated?
- How are newborns screened for X-ALD?
- Does early diagnosis or treatment help patients with X-ALD?
- What is the public health impact of newborn X-ALD screening in the US?
- What did the Committee decide about adding X-ALD 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 X-ALD?

X-ALD is a rare genetic disorder. People with X-ALD have a change in a single gene called ABCD1. Normally, this gene makes a protein that helps the body break down types of fats, known as very long chain fatty acids (VLCFAs). In people with X-ALD, the ABCD1 gene does not work properly. When the ABCD1 gene does not work properly, VLCFAs build up in the body and cause health problems.

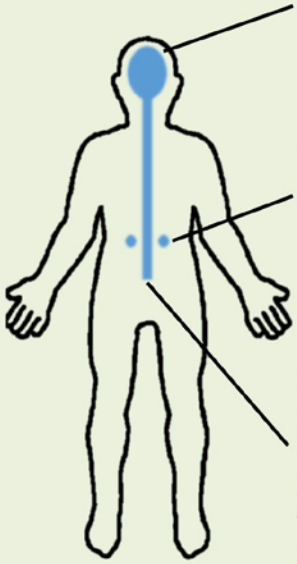
How common is X-ALD?

- X-ALD is a rare disorder. About 2-3 out of every 100,000 children receives a diagnosis of X-ALD.
- This estimate is based on the number of people who develop symptoms and receive a diagnosis without newborn screening. Not everyone with X-ALD is diagnosed, so the estimate might be low.
- Girls with the genetic change causing X-ALD do not always develop the disorder.

What kinds of health problems does X-ALD cause?

X-ALD can damage the adrenal glands, brain, and spinal cord (Figure 1). X-ALD symptoms can look different in different people, even for people with the same ABCD1 gene change. Boys typically have more severe symptoms than girls.

Figure 1: X-ALD Symptoms



Brain symptoms
Brain cells have a coating made of special cells that acts like insulation on a wire. This coating is called myelin. Myelin can disappear in X-ALD, causing problems with thinking, behavior, or even the ability to walk or communicate. The brain symptoms of X-ALD can lead to death.

Adrenal symptoms
The adrenal glands normally make hormones, including cortisol. X-ALD may damage the adrenal gland so that it does not make enough cortisol. Cortisol helps protect the body from stress, like that caused by infections. When cortisol levels in the body are low, the body cannot respond to this stress. This symptom can lead to problems like low blood pressure, low blood sugar, and death.

Spinal cord symptoms
Like brain cells, nerves in the spinal cord normally have a protective coating that can disappear because of X-ALD. This causes symptoms like leg stiffness, weakness, and pain and, in severe cases, lower body paralysis.

Are there different types of X-ALD?

Doctors classify X-ALD into 3 overlapping types based on symptoms. Patients with X-ALD can have one or more of the following types:

- **Adrenocortical insufficiency**: People with this type of X-ALD have adrenal gland problems only.
- **Cerebral ALD**: People with this type have problems affecting the brain. Many also have problems with their adrenal glands. This is the most serious type of X-ALD. It affects 1 out of every 2 or 3 people with X-ALD and is most common in young boys.
- **Adrenomyeloneuropathy**: People with this type of X-ALD have spinal cord problems. They may also have problems with their adrenal glands.

A patient's type (or types) of X-ALD may change over time.

When do X-ALD symptoms develop?

The timing and type of problems caused by X-ALD vary between different people. Table 1 explains when X-ALD symptoms may arise.

Table 1: Symptom Timing and Type.

Age	Symptom	Details
Birth	No symptoms	• X-ALD is present at birth, but most babies with the disorder have no visible symptoms. Parents and doctors cannot tell by looking if a baby has X-ALD.
Childhood	Adrenal symptoms	• Most boys with X-ALD develop these symptoms as children or young adults. They can begin during the first year of life and may occur before other problems. The risk for these symptoms is lifelong.
	Brain symptoms	• These symptoms appear between ages 2 and 10 years in boys with cerebral ALD. They get worse quickly. Without treatment, many boys lose the ability to walk and talk and can die within 3 years of symptoms starting.
Adulthood	Spinal cord symptoms	• These symptoms appear in the 30s or 40s. • Girls with the genetic change causing X-ALD may never develop symptoms. If they do, symptoms typically do not develop until mid- to late adulthood.

TREATMENT FOR X-ALD

How is X-ALD treated?

There is no cure for X-ALD. Treatments focus on treating the problems caused by the disorder.

- **Cortisol Treatment**

  Cortisol treatment helps with adrenal problems in X-ALD. People whose adrenal glands do not make enough cortisol may take cortisol in one of a few ways, depending on their health. During stress or illness, these people need more cortisol than their bodies can make. People with adrenal problems from X-ALD need cortisol treatment throughout life. This treatment does not help with brain or spinal cord problems from X-ALD.

- **Hematopoietic Stem Cell Transplantation (HSCT)**

  HSCT treatment is also called a "bone marrow transplant." HSCT can slow or even stop brain problems from worsening in X-ALD. HSCT replaces the bone marrow in a patient with the bone marrow from a donor who does not have X-ALD. The new bone marrow makes blood cells with a working ABCD1 gene and protein for breaking down VLCFAs. HSCT is not right for all children with X-ALD. Only children with brain symptoms get HSCT. HSCT does not help with adrenal or spinal cord problems from X-ALD.

What are the risks of treatment for X-ALD?

Cortisol therapy is safe. People who need cortisol therapy have careful adrenal and treatment monitoring to make sure their treatment is appropriate.

HSCT is a serious medical procedure. It leads to a temporary risk of serious infections and can cause other complications. Risks depend on several different things, like the match between the HSCT ("bone marrow") donor and the person with X-ALD. Because of these risks, HSCT can lead to death. Families offered HSCT should talk to specialists about whether this treatment is right for their child.

FINDING NEWBORNS WHO HAVE X-ALD

How are newborns screened for X-ALD?

Newborn screening for X-ALD can happen along 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 disorders.

To screen for X-ALD, laboratories use a machine called a tandem mass spectrometer to measure how much of the VLCFA (fatty acid) is in the dried blood spots. High levels of VLCFAs mean a higher risk for X-ALD.

When a newborn has high VLCFA levels, the baby needs more tests. The newborn screening program works with the baby's doctor when screening results mean that the baby should receive other tests or see a specialist to tell for sure if the baby has X-ALD.

How well does screening for X-ALD work?

Screening identifies babies with high VLCFA levels. After further testing, some of these babies receive a diagnosis of X-ALD. Others do not have X-ALD but do have other serious health problems that also raise VLCFA levels. Screening cannot diagnose X-ALD, but it can determine which babies need more tests or to see a specialist.

Experts think that screening detects all boys at risk for X-ALD. Screening does not find all girls with X-ALD, because some of these girls do not have high VLCFA levels at birth. Experts in the field and newborn screening programs continuously work to make screening better.

What happens if newborn screening indicates a high risk for X-ALD?

Doctors refer newborns at high risk for X-ALD for more testing. This testing involves measuring VLCFAs in the blood to determine if the newborn has X-ALD. Doctors may test whether there is a change in the ABCD1 gene. They also might run other tests, like measuring how well the adrenal gland works or taking pictures of the brain with a special scanner known as magnetic resonance imaging (MRI).

Problems caused by X-ALD usually do not happen in very young children. Therefore, doctors monitor patients after diagnosis to see if they need treatment. This monitoring includes checking the adrenal function and taking pictures of the brain once or twice each year. People with X-ALD need monitoring for problems throughout life.

What are some of the benefits and risks of newborn X-ALD screening?

Table 2 describes the benefits and risks of newborn X-ALD screening as of 2015.

Table 2: Benefits and Risks of Screening.

Benefits	Risks
● Earlier identification and evaluation of babies at high risk for X-ALD.	● Some babies identified from newborn screening do not have X-ALD. All babies with high VLCFA levels need more tests.
● Earlier symptom monitoring.	● Newborns with X-ALD may not show symptoms for years or decades.
● Earlier treatment.	● Earlier exposure to treatment risks.
● More time to plan for the future.	● More anxiety about the future.
● Health counseling and family planning for family members.	● Sometimes, people do not want to know genetic risks. Some families do not like to share health information.
● Reassurance for the families of babies who do not have high VLCFA levels.	● In some cases, girls with X-ALD do not have high VLCFA levels. Screening would offer false reassurance for these girls.

Does early diagnosis or treatment help patients with X-ALD?

Researchers have not yet determined exactly how much **early diagnosis** from newborn screening improves health for patients with X-ALD.

However, early diagnosis before symptoms develop allows **early monitoring and treatment** – and these can improve outcomes for people with X-ALD. Babies diagnosed early, like after a relative develops X-ALD, have fewer brain problems and longer lives than similar babies not diagnosed early.

- **Early monitoring**

  X-ALD symptoms are unpredictable and arise at different times for different people. Early monitoring gives patients the best chance of detecting and treating symptoms as soon as they arise.

- **Early cortisol treatment**

  Although we do not know how much early cortisol treatment helps in X-ALD, it works in other disorders that cause adrenal problems. Delaying this treatment in X-ALD may cause worse symptoms.

- **Early HSCT treatment**

  HSCT works better in patients with mild brain symptoms. HSCT has risks, so only boys with clearly worsening brain symptoms get this treatment. Early monitoring is the best way to find boys who can benefit from HSCT.

Box B: Where Can I Learn More?

Follow the links below to learn more about information from this summary.

- To learn more about X-ALD, visit the National Institutes of Health X-ALD website.
- Visit the Committee's website to learn more about:
  - Nominating a Condition to the RUSP.
  - Full X-ALD evidence report.
  - The ACHDNC's recommendation to the Secretary to add X-ALD to the RUSP.

PUBLIC HEALTH IMPACT

How would newborn X-ALD screening affect the health of the country?

Based on what is known about screening and the risk of being born with X-ALD, experts think that screening all newborns in the US for X-ALD would do the following:

- Find about 143 babies with X-ALD each year (about 3.6 out of every 100,000 children born).
- Prevent between 17 and 64 cases of serious disability or death due to X-ALD each year.
- Prevent between 7 and 44 deaths due to X-ALD each year.

Without screening, diagnosing X-ALD can take 10 years or longer after symptoms develop. Sometimes, the diagnosis is never made. Newborn screening for X-ALD allows diagnosis early in life before symptoms arise.

What is the status of newborn X-ALD screening in the US?

- At the time of the report, one state (New York) screened newborns for X-ALD. Three more (California, Connecticut, and New Jersey) had requirements to start.
- Most states estimated that newborn X-ALD screening could begin 1 to 3 years after funding became available.

ADVISORY COMMITTEE DECISION

What did the Committee recommend?

The ACHDNC voted in 2015 to recommend adding X-ALD to the RUSP. The Committee based its decision on the ability of screening to find babies with X-ALD and early treatment being better than later treatment. In 2016, the US Secretary of Health and Human Services recommended that all newborns receive X-ALD screening.

To screen for any condition, states must be prepared. They must have the right equipment and procedures. There must also be specialists who can work with families to determine whether a baby has the condition and, if so, the best treatment.

HELPFUL INFORMATION

Glossary

Term	Definition
ABCD1	The gene responsible for causing X-ALD.
Adrenocortical insufficiency	A type of X-ALD in which the adrenal glands do not produce enough hormones.
Adrenomyelo-neuropathy	A type of X-ALD in which people have spinal cord symptoms.
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. The committee that oversees the RUSP.
Cerebral ALD	A type of X-ALD in which people have brain symptoms. This type is the most severe and primarily affects children.
Dried blood spot	A drop of blood that is collected from a baby's heel, dried onto a special piece of paper, and used to screen for many disorders.
HSCT	Hematopoietic stem cell transplantation. An X-ALD treatment that provides a working copy of the ABCD1 gene. Also called a bone marrow transplant.
MRI	Magnetic resonance imaging. A scanner that takes pictures of the brain.
Myelin	A coating on brain cells that can disappear in X-ALD. This causes problems with thinking, behavior, and walking or communicating.
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 specific area of medicine.
Tandem mass spectrometer	A machine that measures substances in dried blood spots.
VLCFAs	Very long chain fatty acids. The substances in food that people with X-ALD cannot break down.
X-ALD	X-linked adrenoleukodystrophy. A rare genetic disorder that affects the adrenal glands, spinal cord, and brain.

Source

The information in this summary comes from the report *Newborn Screening for X-Linked Adrenoleukodystrophy (X-ALD): A Systematic Review of Evidence* (14 October 2015), commissioned by the ACHDNC. The report reviewed evidence on X-ALD screening and treatments in children through July 2015. It included both published and unpublished research. To see a copy of the report, visit this page.