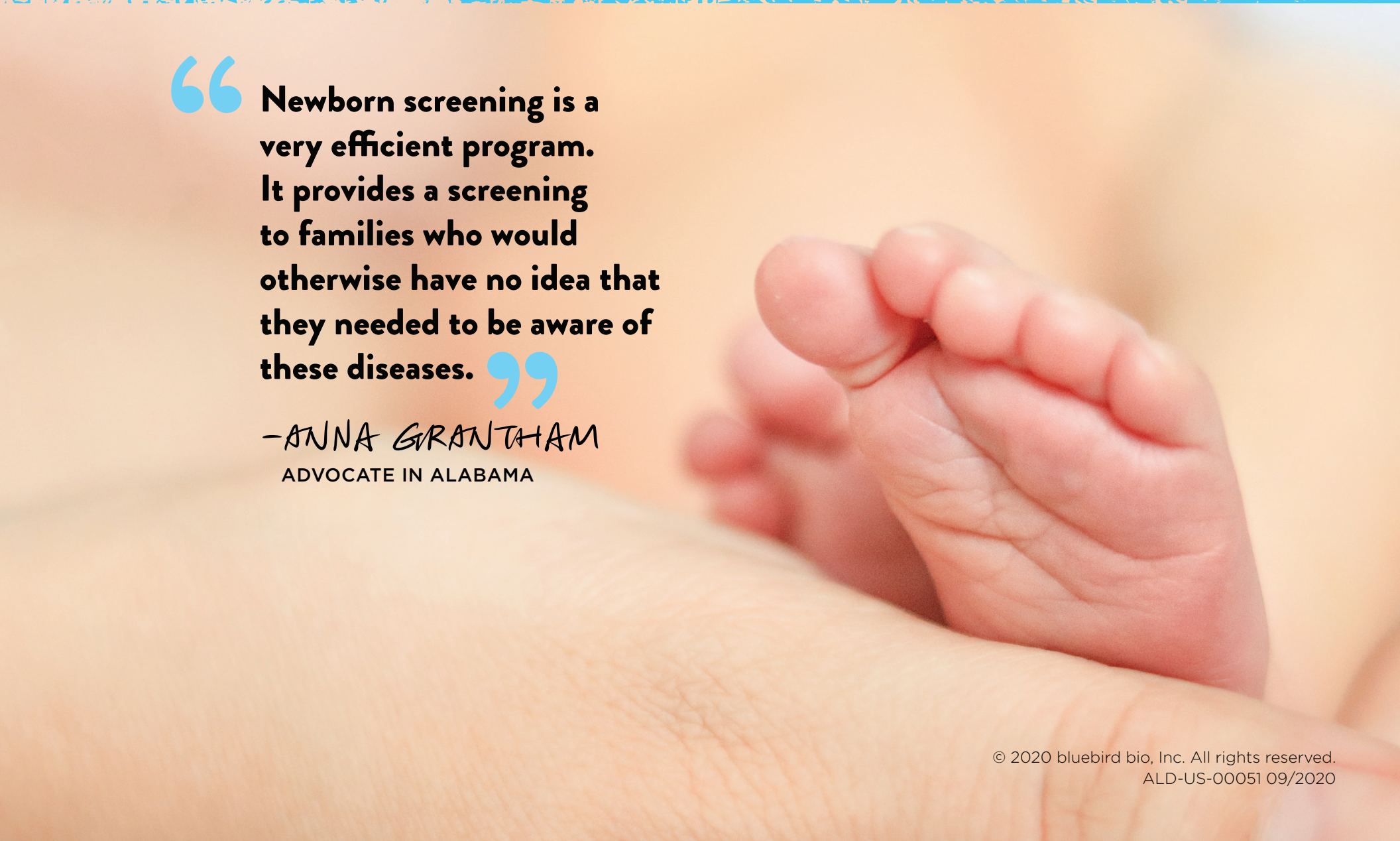
2 what is ALD and what is NBS?

understanding the condition of adrenoleukodystrophy



“Newborn screening is a very efficient program. It provides a screening to families who would otherwise have no idea that they needed to be aware of these diseases.”

–ANNA GRANTHAM
ADVOCATE IN ALABAMA

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What is ALD?

Adrenoleukodystrophy (ALD) is a rare, X-linked genetic disease that occurs in about 1 in 21,000 males and about 1 in 17,000 newborns in the total population. Caused by an underlying mutation in the *ABCD1* gene, a dysfunction in the production of the ALD protein affects the body's ability to break down very long-chain fatty acids (VLCFAs). A build-up of VLCFAs can cause adrenal problems and can potentially lead to brain damage (ALD that progresses to affect the brain is referred to as cerebral ALD).

Everyone's journey with ALD is unique. Some individuals may only experience one manifestation of ALD whereas, for others, these manifestations may overlap during their lifetime.

There are a few main ways ALD can manifest:

- **Asymptomatic:** ALD without signs or symptoms
- **Adrenal insufficiency:** ALD that results in adrenal symptoms such as fatigue, loss of appetite, hyperpigmentation (skin darkening), and belly pain. Most boys with ALD will eventually develop adrenal insufficiency. Although adrenal insufficiency is manageable it can become life-threatening if it is not detected early
- **Adrenomyeloneuropathy (AMN):** ALD that commonly starts in adulthood and affects the spinal cord and nerves
- **Cerebral ALD:** ALD that progresses to affect the brain. The condition can progress very quickly, so early diagnosis is essential.

Cerebral ALD is a severe form of ALD that occurs in about 40% of boys with ALD. In cerebral ALD, the layer of myelin that protects nerves in the brain is broken down. If left undiagnosed or untreated, this can have severe effects. These effects can potentially include significant disabilities, such as an inability to speak or respond, blindness, or even death.

There are a few ways a child may be diagnosed with ALD:

- **Adrenal symptoms**
- **Newborn screening (NBS)**
- **Family history**
- **Neurologic symptoms**

For those who are not diagnosed through NBS, an endocrinologist or geneticist/genetic counselor can confirm an ALD diagnosis by measuring VLCFA levels in blood plasma and testing for a mutation in the *ABCD1* gene. ALD can also occur as a result of a spontaneous mutation. You may hear this form of ALD described as *de novo*.

Progression of cerebral ALD can be effectively stopped if the disease is detected early. **The only currently available treatment option for cerebral ALD is allogeneic-hematopoietic stem cell transplantation (HSCT)**, which optimally occurs at a very early presymptomatic, sometimes early symptomatic, stage of the disease. HSCT is most effective during a narrow therapeutic window, which is often missed due to late diagnosis or misdiagnosis. NBS can provide the earliest opportunity for detection. NBS for ALD provides access to a "window of opportunity" and allows for a timely commencement of treatment.

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What is NBS?

Newborn screening (NBS) is a public health program that screens newborn infants for certain disorders and conditions that may not be immediately apparent at birth. Although NBS identifies the possibility of these disorders, additional lab tests may be needed to confirm diagnosis. For the diseases that are included in NBS panels, early detection can result in manageable and lifesaving outcomes.

Variability in NBS programs is due to a number of factors, including proper funding, available laboratory equipment and resources, and prioritization of conditions included in the screening panel.

NBS starts with a simple blood test

Within a short span of time (roughly 2 to 5 days) **after a baby is born, a physician, nurse, or midwife pricks the newborn's heel (in a process called a heel stick or heel prick)**. Drops of blood are then collected on a card partially made of filter paper (sometimes called a Guthrie card), which preserves the blood for testing. The card also contains a space for information about the baby and the baby's parents' contact information, which is usually filled out before the heel stick. Once the blood spots are dry, the card is ready to be sent to the identified laboratory for analysis. Many labs may keep and store these samples for future need and use. **This is critical, as many of the conditions screened for by NBS need to be diagnosed as quickly as possible.**

A newborn baby receives a heel stick for NBS testing.

Laboratories will analyze the provided samples through a variety of tests including tandem mass spectrometry (MS/MS). MS/MS is the key method for detection of inherited metabolic diseases, a system able to screen for a multitude of diseases very rapidly. With a single dried filter paper blood spot, MS/MS can identify more than 30 inherited metabolic disorders in around 2 to 3 minutes. Thereafter the lab will take time to review and confirm the outcome of the test before communicating the results.

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How does the NBS test for ALD work?

Screening for adrenoleukodystrophy (ALD) involves testing to determine whether there are elevated very long-chain fatty acid (VLCFA) levels. If the results of newborn screening (NBS) testing for ALD are positive, follow-up testing for confirmation is a necessary step before a diagnosis can be made. **Follow-up testing can include genetic testing that looks for alterations in the *ABCD1* gene,** as these mutations are the ultimate cause of ALD.

Both screening for elevated VLCFA levels and genetic testing for the *ABCD1* gene are very accurate in males. **However, neither test can predict what kind of ALD a child will develop.** In females, detection rates for ALD are 80%–85% with VLCFA screening and 100% with genetic testing.

When a positive result occurs, the lab notifies the family's physician and the physician contacts the family. The information provided at the time of diagnosis differs from state to state and country to country. Several patient advocacy organizations have developed helpful informational materials for families whose son or daughter is diagnosed with ALD through newborn screening. Learn more at **ALDNewbornScreening.org**.

> "NBS is a very efficient program. It provides a screening to families who would otherwise have no idea that they needed to be aware of these diseases. This is very common with leukodystrophies because they are so rare. For leukodystrophies, early detection through NBS is really the hope for these families. It is the only way we can ensure these children have a chance at a healthier life."
>
> – ANNA GRANTHAM / advocate in Alabama

What happens after screening?

The NBS test used for ALD **first detects elevated VLCFA levels in a baby's blood at birth.** If VLCFA levels are high, the baby will have to undergo additional testing to confirm a diagnosis of ALD.

Once diagnosed, boys with ALD can undergo possible treatment for any adrenal symptoms they may experience. Most urgently, as there is currently no way to predict which boys with ALD will develop cerebral ALD, NBS allows boys to be identified and monitored before the onset of symptoms of cerebral ALD. **Magnetic resonance imaging (MRI)**, monitoring for the brain changes that indicate cerebral ALD, can lead to improved outcomes, such as life-saving treatment through timely hematopoietic stem cell transplant.

Monitoring using MRI

ALD progresses differently in every child. And although about 40% of boys will develop cerebral ALD, medical guidelines suggest that all boys with ALD should be monitored for progression by having regularly scheduled MRI. MRI provides the earliest opportunity to detect cerebral ALD before any symptoms appear. Early detection of cerebral ALD can have lifesaving results.

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