children can't bear it.

A Comprehensive Understanding of Alagille Syndrome (ALGS)

- IDENTIFYING ALGS
- THE IMPACT OF ALGS
- ASSESSING THE DISEASE
- DIVE EVEN DEEPER

identifying ALGS

What Is ALGS?

ALGS is a rare, life-threatening multisystem disease that often presents in childhood.[1] With ALGS, bile ducts are abnormally narrow, malformed, and reduced in number, which leads to bile accumulation in the liver and, ultimately, progressive liver disease.[2,3]

This autosomal dominant disorder is caused by mutations/deletions in the[1,2,4,5]:

***JAG1* gene**
89% to 95%

and/or

***NOTCH2* gene**
up to 4%

Although 30% to 50% of individuals have an inherited pathogenic variant, the **mutation occurs *de novo* in 50% to 70%** of cases.[6]

The Unbearable Truth

Genetic Interference:
Disruptions in the *JAG1* and *NOTCH2* genes cause defective bile duct morphogenesis and impaired angiogenesis, and abnormalities in skeletal, ocular, cardiovascular, and kidney development.[7]

Who Is Affected by ALGS?

- Affects **males and females equally**[8]
- **≈1 in every 30,000 to 45,000 births**[8]

≈2500 children living with ALGS in the United States[9]

The Unbearable Truth

High-Risk Children:
The child of an affected individual has a 50% risk of inheriting the ALGS-related genetic alteration and developing signs of ALGS.[6]

the impact of ALGS

Affected Areas of the Body

ALGS can affect multiple organs/areas, including[8]:

- Liver
- Kidneys
- Eyes
- Face
- Heart
- Skeleton

> The Unbearable Truth
>
> **A Widespread Disease:**
> ALGS has a broad spectrum of clinical severity, ranging from biochemical liver abnormalities to end-stage liver disease.[2]

Signs + Symptoms

Signs and symptoms of ALGS usually appear in the first 2 years of life.[10]

Cholestatic pruritus is identified as the most bothersome symptom of ALGS. This severe, unrelenting itch is driven by the increase in serum bile acids.[1,2]

> The Unbearable Truth
>
> **More Than Just the Liver:**
> Extrahepatic manifestations can include ocular, skeletal, renal, and cardiovascular abnormalities.[11]

Additional signs and symptoms arising from chronic cholestatic pruritus may include[1,2,11]:

Jaundice

Jaundice affects the majority of patients, presenting in 66% to 87%.

Xanthomas

Xanthomas are common, affecting 30% to 42% of patients and usually appearing at a median of 20 months to 48 months of age.

Failure to thrive and growth deficiencies

Growth impairment, development delay, or failure to thrive has been reported in 50% to 87% of patients.

Diminished quality of life

Cholestatic pruritus is associated with additional symptoms, such as skin damage, sleep problems, mood disturbances, and more.

assessing the disease

Early Diagnosis Is Critical[1]

Diagnosis of ALGS can be challenging due to variable presentation of the clinical manifestations.[12] There is no strong correlation between mutation type, clinical manifestation, and severity.[1,13]

To avoid misdiagnosing ALGS as biliary atresia or another cholestatic liver disease, **3 out of 7 clinical criteria** are required for diagnosis[14*†]:

Hepatic

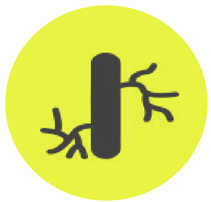
Cardiac

Facial

Ocular

Skeletal

Renal



Vascular

*Absent of molecular diagnosis or family history.
†These do not represent all possible clinical features.

The Unbearable Truth

ALGS in the Family:
The diagnosis of ALGS should also be suspected in individuals who do not meet the full clinical criteria, but do have an affected relative.[6]

assessing the disease (cont'd)

Diagnostic Tools

To establish the extent of disease and needs in an individual diagnosed with ALGS, the following evaluations are recommended[6]:

	EVALUATION	COMMENT
Gastrointestinal	Evaluation by gastroenterologist includes liver function tests and clotting studies	If determined necessary by gastroenterologist, additional studies include serum bile acids, fat-soluble vitamin levels, hepatic ultrasound, Technetium-99m-DISIDA scintiscan, and liver biopsy
Cardiovascular	Complete cardiology evaluation	Includes echocardiogram
Eyes	Ophthalmology evaluation	Look for anterior chamber anomalies
Skeletal	Anteroposterior and lateral chest radiographs to evaluate for presence of butterfly vertebrae	
Renal	Evaluate with renal function studies and renal ultrasound	
Growth	Measurement of growth parameters and plotting on age-appropriate growth charts	
Development	Screening developmental evaluation	More detailed evaluation should be performed if significant delays are identified
Genetics	Genetic testing and consultation with clinical geneticist and/or genetic counselor	

Adapted from Spinner et al. 2000.

Confirming Diagnosis With Genetic Testing

In ALGS, clinical variability in presentation and disease severity can result in underdiagnosis, misdiagnosis, or delayed diagnosis. Genetic testing, therefore, provides valuable confirmation, particularly in milder cases.[1]

Approaches can include a combination of[6]:

- **Gene-targeted testing:**
  Serial single-gene testing or multigene panel
- **Comprehensive genomic testing:**
  Exome sequencing, exome array, or genome sequencing

Learn more about genetic testing at **Eurofins NTD Genetics**.

The Unbearable Truth

A Common Misdiagnosis:
ALGS can often be misdiagnosed as other cholestatic liver diseases, such as biliary atresia, due to significant overlap of biochemical, histologic, and imaging features.[14]

we've only scratched the surface.

Dive even deeper into ALGS at

unbearableALGS.com

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