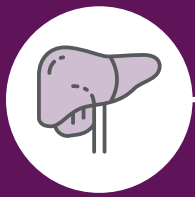


What's in your differential?



What would you expect if you had a patient exhibiting:

- ▶ **Hepatomegaly without cholestasis**
- ▶ **Low HDL-C**
- ▶ **Abnormal liver enzymes**
 - Elevated transaminases
 - Elevated kPa without elevated BMI
 - Elevated GGT
 - Elevated bilirubin levels
 - Elevated alkaline phosphatase

It may not be what you think...

Hepatologists and pediatric gastroenterologists can play a critical role in the early diagnosis of acid sphingomyelinase deficiency (ASMD)¹

- ▶ Historically known as Niemann-Pick disease types A, A/B, and B, ASMD is a genetic disease caused by a deficiency in the enzyme acid sphingomyelinase (ASM).²
- ▶ Deficiency in ASM enzyme activity leads to intracellular sphingomyelin accumulation that can result in progressive multiorgan damage and shortened life span in both adult and pediatric patients.²

BMI=body mass index; GGT=gamma-glutamyl transferase; HDL-C=high-density lipoprotein cholesterol; kPa=kilopascal.

sanofi

ASMD
ACID SPHINGOMYELINASE DEFICIENCY

HEPATOLOGISTS AND PEDIATRIC GASTROENTEROLOGISTS ARE ON THE FOREFRONT OF DIAGNOSING ASMD¹

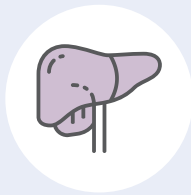
Cryptogenic liver disease? Multisystemic involvement? Consider ASMD

► Patients with ASMD are at risk for liver disease.¹

- In ASMD, sphingomyelin accumulates in macrophages (Kupffer cells) and hepatocytes, transforming them into clusters of foamy cells.¹
- This accumulation can lead to progressive liver dysfunction.^{1,2}

Key hepatic and gastric signs of ASMD

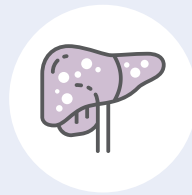
In patients with ASMD types A/B or B²⁻⁵:



Hepatomegaly

>70%

Patients often present with liver volume >1.5 MN.



Liver fibrosis

88%

Hepatomegaly is associated with liver fibrosis, which may progress to cirrhosis and even liver failure in some patients.



Gastrointestinal issues*

>75%

*Symptom prevalence data for gastrointestinal issues are for patients with all ASMD types.⁵

Patients with ASMD may also be at risk of cirrhosis, portal hypertension, and variceal bleeding.¹

Additional hepatic signs and symptoms include^{2,3}:

► **Abnormal liver chemistry tests**

► **Dyslipidemia**

- Elevated total cholesterol
- Elevated LDL-C
- Low HDL-C
- Elevated VLDL-C
- Elevated triglycerides

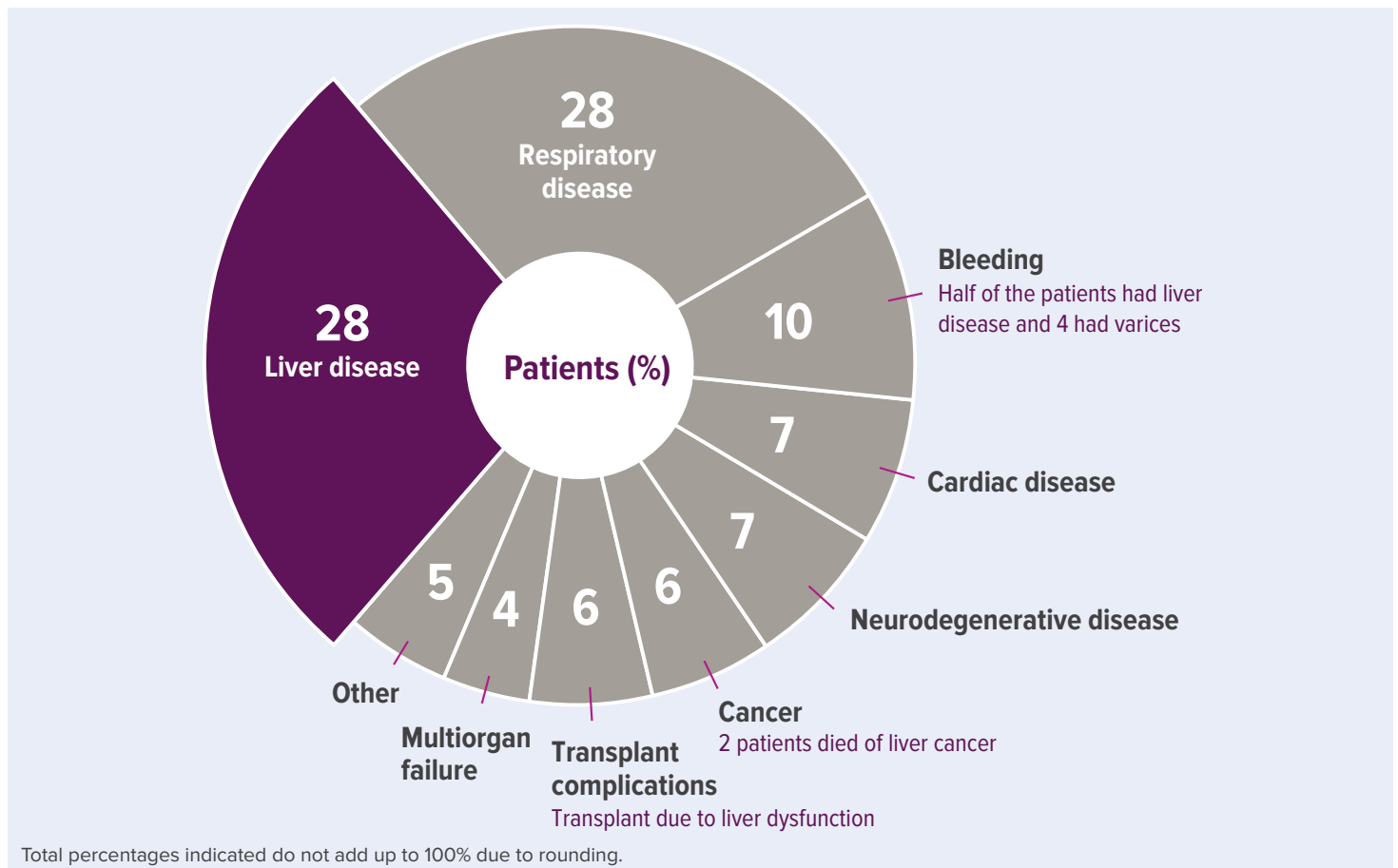
- **Other hallmark signs and symptoms of ASMD include splenomegaly, interstitial lung disease, thrombocytopenia, and pediatric growth delay.²**

LIVER DISEASE: A LEADING CAUSE OF DEATH IN ASMD⁶

Patients with ASMD can experience significant morbidity and early mortality⁶

- ▶ Life expectancy at birth for the ASMD type A/B or B cohort was 37 years compared to 79 years for the general US population in 2018.^{7*}
- ▶ In a global study examining the leading causes of death among patients with ASMD types A/B and B (N=85),[†] among patients with terminal liver disease (n=23), 52% died or had a transplant in childhood[‡] and 48% died in adulthood.^{6§}

Primary causes of death in patients with ASMD types A/B and B⁶



*This observational, multicenter, retrospective cohort study included medical chart records retrieved from 25 medical centers in the US. The study included pediatric, adolescent, and adult patients (n=110) with ASMD non-type A (including type B, type A/B, or unspecified), surviving or deceased, with retrievable information from the US hospital medical records and the first date of evidence of ASMD, defined as either first symptom onset or a diagnosis of ASMD types B or A/B (whichever came first) between January 1, 1990, and February 28, 2021. Eligible medical chart records were abstracted to collect the evaluation criteria, including demographics, medical and developmental history, and mortality data, and characterized using descriptive statistics. Life expectancy at birth was computed post hoc as the area under the survival curve.⁷

†Based on a retrospective global study of 85 patients with ASMD types A/B and B that evaluated the causes of death and disease-related morbidity among patients with ASMD type A/B (n=27) and type B (n=58). Data for 85 patients who died (n=78) or received liver transplant (n=7) were collected by treating physicians (n=27) or abstracted from previously published case studies (n=58).⁶

‡Age range: 2.5 to 18 years.⁶

§Age range: 21 to 67 years.⁶

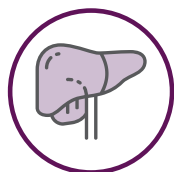
- ▶ **Liver disease was also a common comorbidity in patients whose primary causes of death were listed as respiratory, cardiac, or multiorgan failure.⁶**

Early diagnosis is imperative for initiating timely management and family screening.²

ASMD SIGNS AND SYMPTOMS OFTEN OVERLAP WITH OTHER LIVER DISEASES¹

Missed diagnoses and diagnostic delays are common for patients with ASMD. In ASMD types A/B or B, patients can experience delays of up to ~10 years⁸

Phenotypic overlap with other hepatic conditions often leads to diagnostic delays¹



Hepatic manifestations of ASMD may mimic⁹:

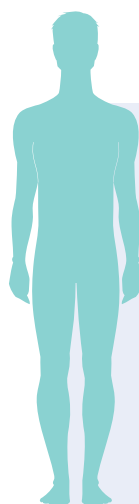
- ▶ Nonalcoholic fatty liver disease (NAFLD)
- ▶ Autoimmune hepatic disease
- ▶ Chronic hepatitis B
- ▶ Cryptogenic cirrhosis
- ▶ Lysosomal acid lipase deficiency

Consider ASMD in patients presenting with liver abnormalities including:



In pediatric patients^{2,4,9}:

- ▶ Both dyslipidemia and abnormal LFTs
- ▶ Hepatosplenomegaly without cholestasis or obesity
- ▶ Apparent fatty liver disease and elevated liver enzymes without obesity

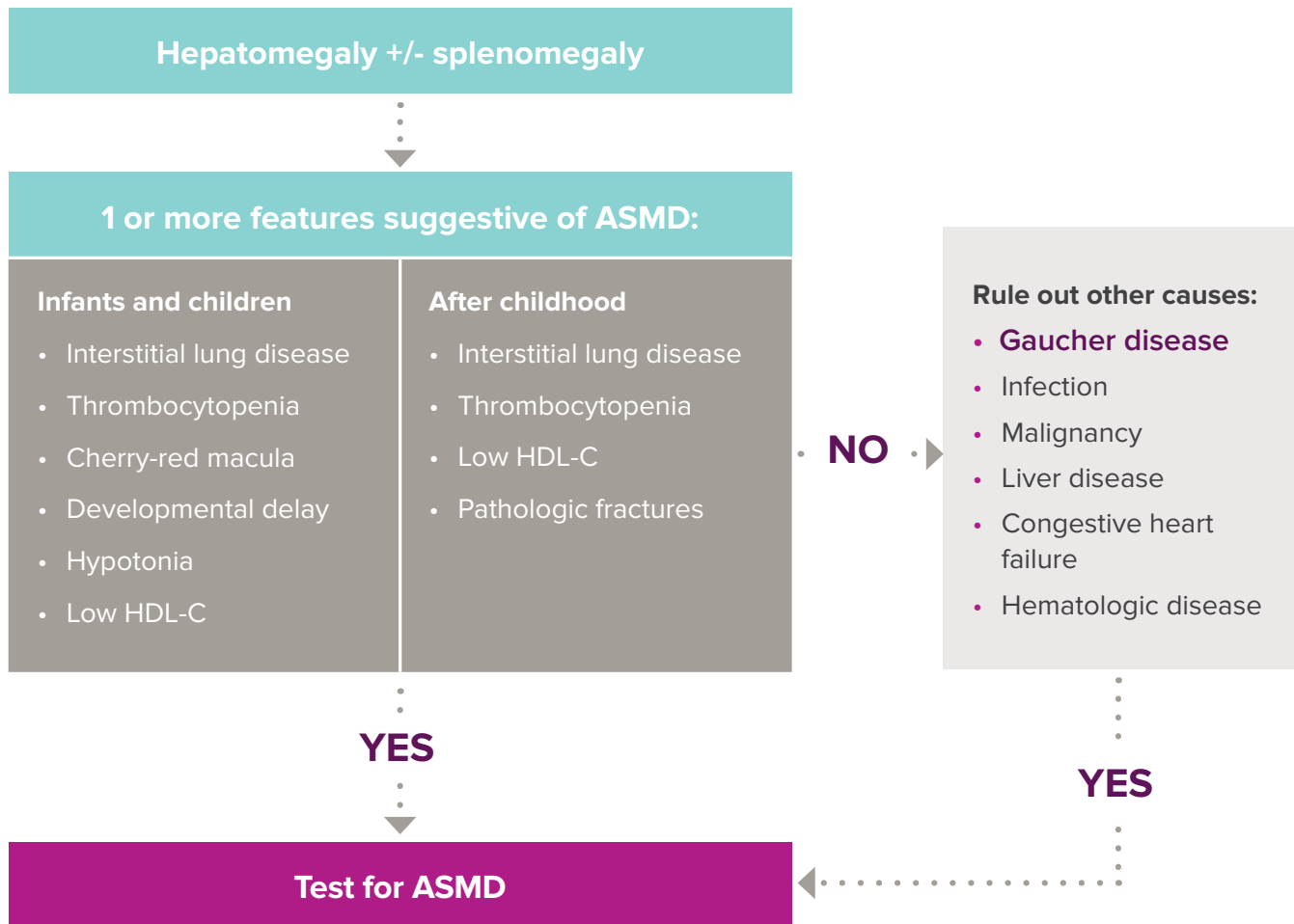


In adult patients^{9,10}:

- ▶ Cryptogenic liver disease with splenomegaly
- ▶ Fatty liver disease (NASH, NAFLD) with abnormal lipid profiles

IN ASMD, HEPATOMEGALY AND SPLENOMEGALY OFTEN PRESENT FIRST²

A diagnostic approach for ASMD based on expert guidelines⁹

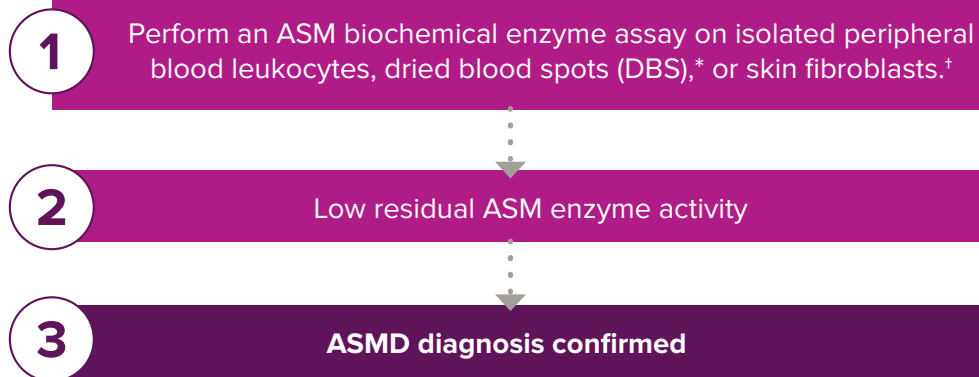


Include ASMD in your differential when considering diseases that have similar signs or symptoms.²

TAKE THE STEP TOWARD AN ACCURATE DIAGNOSIS

Diagnostic testing for ASMD can start with a simple blood draw^{3,9}

Patients with ASMD have low ASM enzyme activity.



Additional diagnostic confirmation can be achieved using molecular genetic testing.⁹

APRIL
Living with
ASMD type B

ASMD is a progressive disease. An early and accurate ASMD diagnosis can enable appropriate and timely symptom management efforts from a multidisciplinary care team.²

*DBS sample collection is simple and minimally invasive. Limitations of DBS testing include the potential effects of anemia and recent transfusions on results.^{9,11}

†Skin fibroblasts or *sphingomyelin phosphodiesterase 1* gene sequencing can be used in equivocal cases.⁹

MULTIGENE PANEL TESTING OPTIONS FOR ASMD

Some laboratories offering ASMD testing are listed below. There may be other laboratory tests appropriate for your patient and this is not an endorsement of any one laboratory. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Consult each laboratory for a full range of options. Content is current at time of printing and tests may not be available in all states; please contact the specific laboratory to confirm test availability and all logistics. Sanofi does not review or control the content of non-Sanofi websites. These listings do not constitute an endorsement by Sanofi of information provided by any other organizations.

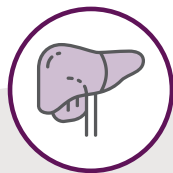
Test	# of genes	Lab
LIVER DISEASE PANELS		
Cholestasis NGS panel	52	Blueprint Genetics
Metabolic liver failure panel	16	Blueprint Genetics
Liver disease panel	72	Cincinnati Children's Hospital Medical Center, Molecular Genetics Lab
Cholestasis NGS panel	72	Fulgent Genetics
Cholestasis panel	70	Prevention Genetics
Mirum cholestasis test	77	Prevention Genetics
Liver disease panel	47	University of Chicago

Lab	Sample requirements	Contact
Blueprint Genetics	WB: 1 mL EDTA (lavender) tube; Extracted DNA: 2 µg; Saliva: Oragene	P: 650-452-9340 E: support.us@blueprintgenetics.com W: www.blueprintgenetics.com
Cincinnati Children's Hospital Medical Center, Molecular Genetics Lab	WB (preferred): 3-5 mL EDTA (lavender), 1 mL infants; Saliva: Oragene; Extracted DNA: 10 µg	P: 513-636-4474 E: LabGeneticCounselors@cchmc.org W: www.cincinnatichildrens.org/service/g/geneticsgenomics-diagnostic-lab
Fulgent Genetics	WB: 2 x 4 mL EDTA (lavender); Extracted DNA: 3 µg; Saliva: Oragene	P: 626-350-0537 E: info@fulgentgenetics.com W: www.fulgentgenetics.com
Prevention Genetics	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube; DNA also accepted; Saliva: Oragene/ GeneFiX	P: 715-387-0484 E: clinicaldnatesting@preventiongenetics.com W: www.preventiongenetics.com
University of Chicago	WB: 3-10 mL EDTA (lavender); Extracted DNA: please call; Saliva: Oragene; Buccal: please call	P: 888-824-3637 E: ucglabs@genetics.uchicago.edu W: https://dnatesting.uchicago.edu/our-tests

Cryptogenic liver disease?
Abnormal liver enzymes?
Hepatosplenomegaly?

CONSIDER ASMD

ASMD is a rare multisystemic condition marked by liver disease that can lead to significant morbidity and early mortality^{2,6}



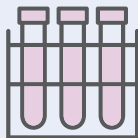
Liver disease is a leading cause of death in ASMD.⁶

Hepatomegaly and liver fibrosis are key hepatic signs of ASMD.² Patients may also exhibit⁴⁻³:

- ▶ Abnormal liver chemistry tests
- ▶ Cirrhosis
- ▶ Dyslipidemia

Missed diagnoses and diagnostic delays are common for patients with ASMD. In ASMD types A/B or B, patients can experience delays of up to ~10 years.⁸

Include ASMD in your differential to enable early diagnosis and timely management²



SUSPECT ASMD? TEST TO KNOW

Diagnostic testing can start with a simple blood draw: confirm a diagnosis of ASMD with an ASM biochemical enzyme assay.²

Find more information on ASMD and testing at ASMDfacts.com/HCP

References: 1. Wasserstein M, Dionisi-Vici C, Giugliani R, et al. Recommendations for clinical monitoring of patients with acid sphingomyelinase deficiency (ASMD). *Mol Genet Metab*. 2019;126(2):98-105. 2. Geberhiwot T, Wasserstein M, Wanninayake S, et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). *Orphanet J Rare Dis*. 2023;18(1):85. 3. McGovern MM, Avetisyan R, Sanson BJ, Lidove O. Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis*. 2017;12(1):41. 4. McGovern MM, Wasserstein MP, Giugliani R, et al. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. *Pediatrics*. 2008;122(2):e341-e349. 5. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of illness in acid sphingomyelinase deficiency: a retrospective chart review of 100 patients. *JIMD Rep*. 2018;41:119-129. 6. Cassiman D, Packman S, Bembi B, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): literature review and report of new cases. *Mol Genet Metab*. 2016;118(3):206-213. 7. Pulikottil-Jacob R, Dehipawala S, Smith B, et al. Survival of patients with chronic acid sphingomyelinase deficiency (ASMD) in the United States: a retrospective chart review study. *Mol Genet Metab Rep*. 2023;38:101040. 8. Doerr A, Farooq M, Faulkner C, et al. Diagnostic odyssey for patients with acid sphingomyelinase deficiency (ASMD): exploring the potential indicators of diagnosis using quantitative and qualitative data. *Mol Genet Metab Rep*. 2024;38:101052. 9. McGovern MM, Dionisi-Vici C, Giugliani R, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. *Genet Med*. 2017;19(9):967-974. 10. Maurice J, Manousou P. Non-alcoholic fatty liver disease. *Clin Med*. 2018;18(3):245-250. 11. Trifonova OP, Maslov DL, Balashova EE, Likhov PG. Evaluation of dried blood spot sampling for clinical metabolomics: effects of different papers and sample storage stability. *Metabolites*. 2019;9(11):277.