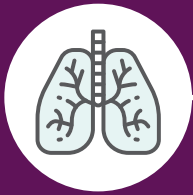


# What's in your differential?



What would you expect if you had a patient exhibiting:

- ▶ Diffuse interlobular septal thickening
- ▶ Sea-blue histiocytes accounting for the majority of alveolar macrophages identified in BAL fluid analysis
- ▶ Hepatosplenomegaly
- ▶ Thrombocytopenia

## It may not be what you think...

**Pulmonologists can play a critical role in the early diagnosis of acid sphingomyelinase deficiency (ASMD)**

- ▶ 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).<sup>1</sup>
- ▶ 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.<sup>1</sup>

BAL=bronchoalveolar lavage.

**sanofi**

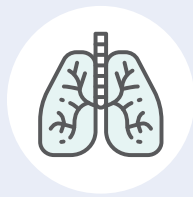
**ASMD**  
ACID SPHINGOMYELINASE DEFICIENCY

# PULMONOLOGISTS ARE ON THE FOREFRONT OF DIAGNOSING ASMD

## Cryptogenic ILD? Multisystemic involvement? Consider ASMD

▶ Interstitial lung disease (ILD) occurs in the majority of patients with ASMD at some time in their lives.<sup>1</sup>

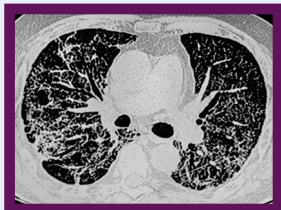
### ILD\* is a hallmark sign of ASMD<sup>1</sup>



**>80%** of patients with ASMD types A/B and B have ILD.<sup>2</sup>

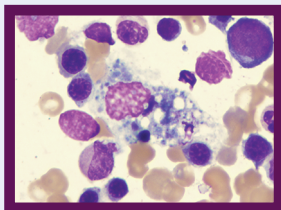
**ILD associated with ASMD can lead to progressive deterioration of pulmonary function.<sup>1</sup>**

▶ A proportion of patients with ILD may progress to oxygen dependence and pulmonary failure.<sup>3,4</sup>



Lipid-laden macrophages often accumulate in the intra-alveolar space, and typical radiologic findings include<sup>3</sup>:

- ▶ Interlobular septal thickening
- ▶ Crazy paving
- ▶ Ground-glass opacities



BAL fluid analysis indicating overwhelming presence of sea-blue histiocytes is another distinctive manifestation that may suggest ASMD.<sup>3</sup>

**Patients with ASMD may present with additional pulmonary signs and symptoms including<sup>2,5,6</sup>:**

- ▶ Frequent respiratory infection (including pneumonia)
- ▶ Shortness of breath
- ▶ Restrictive pattern on pulmonary function tests (PFTs)
- ▶ Pulmonary hypertension

▶ **Other hallmark signs and symptoms of ASMD include splenomegaly, hepatomegaly, thrombocytopenia, and pediatric growth delay.<sup>1</sup>**

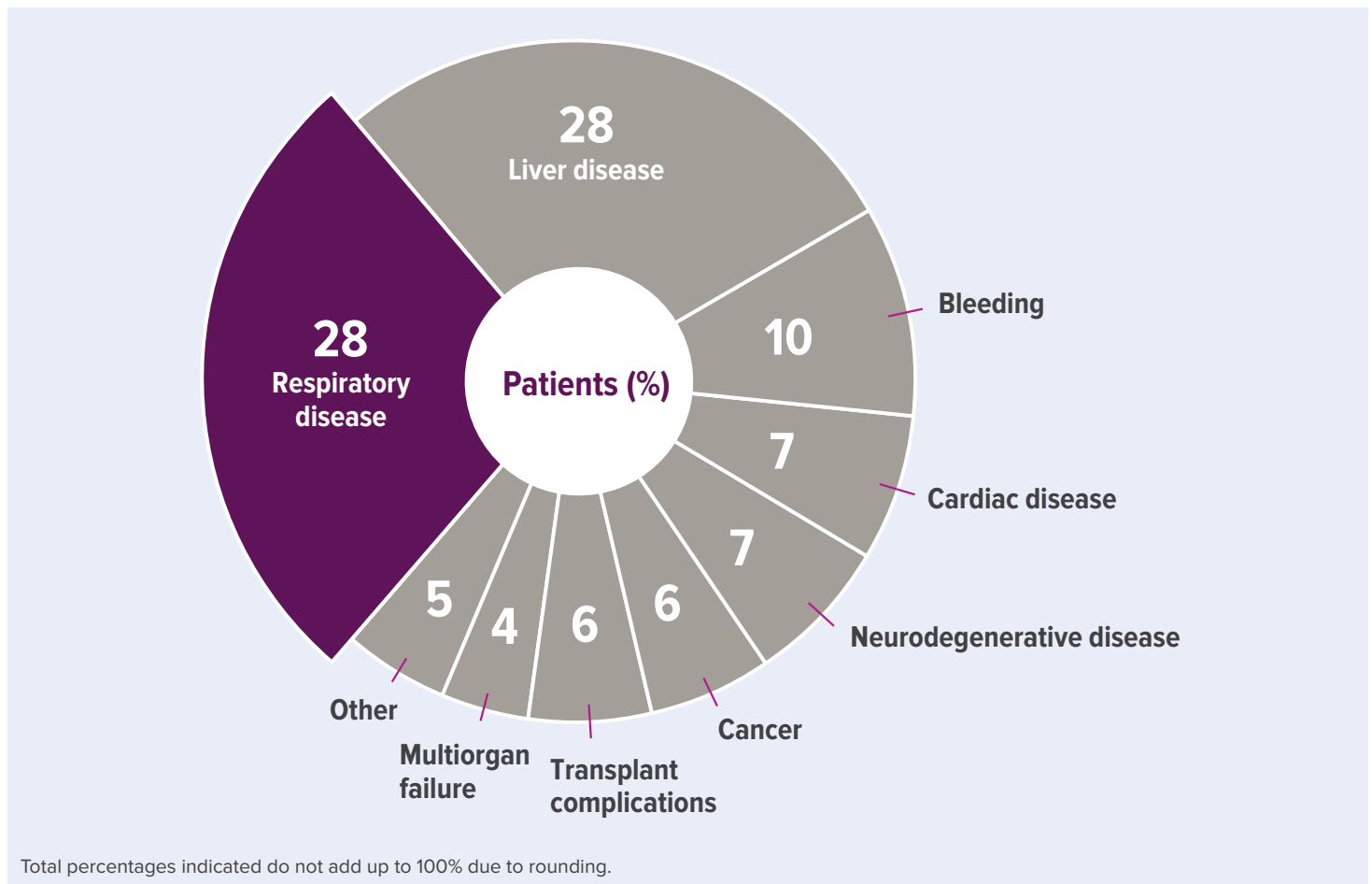
\*ILD is identified through chest radiography and HRCT.<sup>1</sup>  
HRCT=high-resolution computed tomography.

# RESPIRATORY DISEASE: A LEADING CAUSE OF DEATH IN ASMD<sup>7</sup>

## Patients with ASMD can experience significant morbidity and early mortality<sup>7</sup>

- ▶ 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.<sup>8\*</sup>
- ▶ In a global study examining the leading causes of death among patients with ASMD types A/B and B (N=85),<sup>†</sup> among patients who died of respiratory disease (n=23), 48% died in childhood<sup>‡</sup> and 52% died in adulthood.<sup>7</sup>

## Primary causes of death in patients with ASMD types A/B and B<sup>7</sup>



\*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.<sup>8</sup>

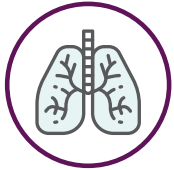
<sup>†</sup>Based on a retrospective global study of 85 patients with ASMD types A/B and B that evaluated the causes of death and disease-related morbidity among patients with ASMD type A/B (n=27) and type B (n=58). Data for 85 patients who died (n=78) or received liver transplant (n=7) were collected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

<sup>‡</sup>Age range: 0.6 to 17 years.<sup>7</sup>

Early diagnosis is imperative for initiating timely management and family screening.<sup>1</sup>

# ASMD SIGNS AND SYMPTOMS OFTEN OVERLAP WITH OTHER LUNG DISEASES

**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<sup>9</sup>**  
**Phenotypic overlap with other pulmonary conditions often leads to diagnostic delays<sup>10</sup>**



**Pulmonary manifestations of ASMD may mimic<sup>2,3,5,11-15</sup>:**

- ▶ Common variable immunodeficiency (CVID)
  - ▶ Pulmonary veno-occlusive disease
  - ▶ Connective tissue disease (CTD)
  - ▶ Telomeropathies
  - ▶ Cystic fibrosis
- ▶ Pneumonia, lymphoid interstitial pneumonia, and other respiratory infections
  - ▶ Lymphangiomyomatosis and lymphangitic malignancy
  - ▶ Pulmonary edema and hypertension
  - ▶ Pulmonary alveolar proteinosis (PAP)

## Differential considerations in ASMD

**Rule out other causes of pulmonary dysfunction<sup>5,11-14,16</sup>:**

- ▶ Lymphatic anomalies
  - ▶ Family history of:
    - ILD
    - Aplastic anemia
    - Early graying
    - Other lysosomal storage diseases
  - ▶ CVID, CTD, PAP, and telomeropathies
- ▶ Infection
  - ▶ Malignancy
  - ▶ Liver disease
  - ▶ Congestive heart failure
  - ▶ Hematologic disease
  - ▶ Advanced pulmonary fibrosis/honeycombing

# UNEXPLAINED ILD? CONSIDER ASMD. TEST TO KNOW

## Diagnostic considerations for patients who may be presenting with ASMD

Alone, these signs may appear isolated, but considered together they may point to ASMD

### Presentation of cryptogenic ILD suggestive of ASMD<sup>1,3,17-19</sup>

#### HRCT features

- ▶ Interlobular septal thickening
- ▶ Crazy paving
- ▶ Splenomegaly and hepatomegaly
- ▶ Ground-glass opacities

#### Pathology features (cryobiopsy/ VATS biopsy, BAL)\*

- ▶ Foamy macrophages/sea-blue histiocytes
- ▶ Foamy epithelial cells

### Other signs and symptoms suggestive of ASMD<sup>2,5</sup>



#### Infants and children

- ▶ Thrombocytopenia
- ▶ Cherry-red macula
- ▶ Developmental delay
- ▶ Hypotonia
- ▶ Low HDL-C
- ▶ Easy bruising/bleeding



#### After childhood

- ▶ Thrombocytopenia
- ▶ Low HDL-C
- ▶ Pathologic fractures
- ▶ Bruising/bleeding

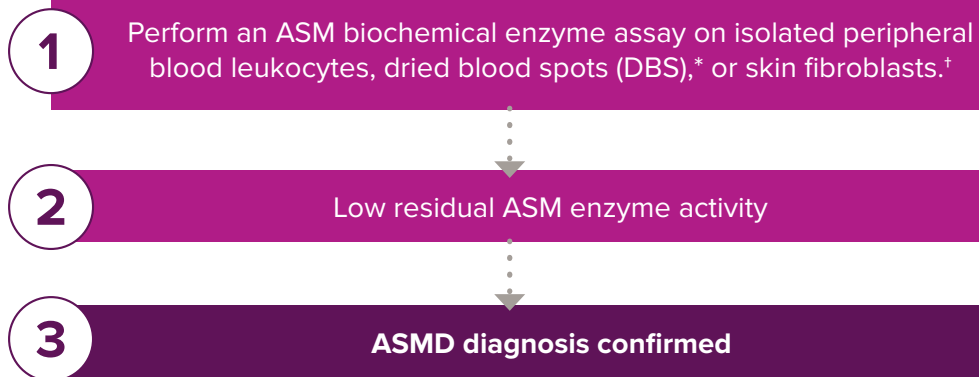
Testing early for ASMD when you see pulmonary manifestations is crucial for symptom management.<sup>1</sup>

\*Possibly avoid biopsies if there are alternatives for diagnosis (due to bleeding risk of patients with platelet dysfunction).<sup>1</sup>  
HDL-C=high-density lipoprotein cholesterol; VATS=video-assisted thoracoscopic surgery.

# TAKE THE STEP TOWARD AN ACCURATE DIAGNOSIS

Diagnostic testing for ASMD can start with a simple blood draw<sup>2,5</sup>

Patients with ASMD have low ASM enzyme activity.



Additional diagnostic confirmation can be achieved using molecular genetic testing.<sup>5</sup>

**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.<sup>1</sup>

\*DBS sample collection is simple and minimally invasive. Limitations of DBS testing include the potential effects of anemia and recent transfusions on results.<sup>5,20</sup>

†Skin fibroblasts or *sphingomyelin phosphodiesterase 1* gene sequencing can be used in equivocal cases.<sup>5</sup>

# 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](http://www.concertgenetics.com) or [www.ncbi.nlm.nih.gov/gtr](http://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
<b>PULMONARY DISEASE PANELS</b>		
Interstitial lung disease panel	30	Blueprint Genetics
Comprehensive pulmonology panel	114	Blueprint Genetics
Pulmonary panel	101	Centogene
PulmZoom: interstitial lung disease	38	DNA Diagnostic Laboratory Johns Hopkins Hospital
Interstitial lung disease panel	24	Prevention Genetics
chILD-SEQ (interstitial lung disease)	48	Seattle Children's Hospital

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: <a href="http://www.blueprintgenetics.com">www.blueprintgenetics.com</a>
Centogene	WB: 1 mL EDTA (lavender) tube; Extracted DNA: 2 µg; DBS: 10 spots; Saliva: Oragene buccal swab	P: 617-580-2102 E: customer.supportUS@centogene.com W: <a href="http://www.centogene.com">www.centogene.com</a>
DNA Diagnostic Laboratory- Johns Hopkins Hospital	WB: 3-6 mL EDTA (lavender); Extracted DNA: call; Saliva: Oragene	P: 410-955-0483 E: ddl@jhmi.edu W: <a href="https://www.hopkinsmedicine.org/dnadiagnostic/">https://www.hopkinsmedicine.org/dnadiagnostic/</a>
Prevention Genetics	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube; DNA also accepted; Saliva: Orange/ GeneFiX	P: 715-387-0484 E: clinicaldnatesting@preventiongenetics.com W: <a href="http://www.preventiongenetics.com">www.preventiongenetics.com</a>
Seattle Children's Hospital	WB: 3 mL EDTA (lavender); Extracted DNA: 5 µg; Saliva: Oragene	P: 206-987-2617 E: labGC@seattlechildrens.org W: <a href="https://seattlechildrenslab.testcatalog.org">https://seattlechildrenslab.testcatalog.org</a>

ACD=acid citrate dextrose; chILD-SEQ=childhood interstitial lung disease sequencing; EDTA=ethylenediaminetetraacetic acid; WB=whole blood.

Cryptogenic ILD?  
Diffuse septal thickening?  
Hepatosplenomegaly?

CONSIDER ASMD

**ASMD is a rare multisystemic condition marked by respiratory disease that can lead to significant morbidity and early mortality<sup>1,7</sup>**



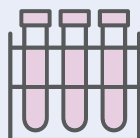
Respiratory disease is a leading cause of death in ASMD.<sup>7</sup>

ILD is a hallmark sign of ASMD.<sup>1</sup>  
Patients may experience<sup>2,5,6</sup>:

- ▶ Frequent respiratory infection (including pneumonia)
- ▶ Shortness of breath
- ▶ Restrictive pattern on PFTs
- ▶ Pulmonary hypertension

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.<sup>9</sup>

**Include ASMD in your differential to enable early diagnosis and timely management<sup>1</sup>**



## 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.<sup>1</sup>

Find more information on ASMD and testing at [ASMDfacts.com/HCP](https://ASMDfacts.com/HCP)

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