Consensus clinical management guidelines for Acid Sphingomyelinase Deficiency (Niemann-Pick disease types A, B and A/B)

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Abstract

Background: Acid sphingomyelinase deficiency (ASMD) is a rare autosomal recessive disorder caused by mutations in *SMPD1* gene. This rarity contributes to misdiagnosis, delayed diagnosis and barriers to good care. There is no published national or international guideline for diagnosis and management of patients with ASMD. For these reasons, we at INPDR have developed a clinical guideline that define standard of care for ASMD patients

Methods: The information contained in these guidelines was obtained through a systematic review of the literature and the experiences of the authors in their care of patients with ASMD. We adopted the Appraisal of Guidelines for Research & Evaluation (AGREE II) system as method of choice for the guideline development process.

Results: The clinical spectrum of ASMD, although a continuum, varies substantially with subtypes ranging from a fatal infantile neurovisceral disorder to an adult-onset chronic visceral disease. We made 39 conclusive statements and scored them according to level of evidence, strengths of recommendations and expert opinions. In addition, this guideline has identified gaps in the knowledge that must be filled by future research.

Conclusion: This guideline can inform care providers, care funders, patients and their carers about best clinical practice and lead to a step change in the quality of care for patients with ASMD.

Background

Acid sphingomyelinase deficiency (ASMD; alternatively known as Type A, B and A/B Niemann-Pick disease, OMID# 257200 and 607616) is an ultra-rare multisystem genetic disorder caused by pathogenic variants of *SMPD1* gene. Clinical features, time of onset and severity can vary greatly among the subtypes and even within families bearing identical genetic alterations. At the severe end of the spectrum, the disease is generally progressive in nature and can result in premature death. At the milder end, patients may be oligosymptomatic and a diagnosis can be easily overlooked. The rarity of the disease and the scarcity of expertise contribute to misdiagnosis, delayed diagnosis and barriers to adequate care. This may lead to inadequate or inappropriate care, patients' and families' loss of confidence in the healthcare system and disempowerment, even though the diagnosis of ASMD, particularly type B and A/B, is compatible with improved quality of life if a diagnosis is made promptly and appropriate supportive management is instituted. There is a disease modifying enzyme replacement therapy recently has received regulatory approval in many countries but as yet the mainstay of management is symptomatic supportive therapy using multi-disciplinary and multi-professional teams of experts. There are no national or international standard operating procedures to improve the care of ASMD patients, and hence the Niemann-Pick disease (NPD) community, represented by the International Niemann-Pick Disease Registry (INPDR), has initiated and sponsored the development of comprehensive disease management guidelines to provide a resource for the multi-disciplinary team, and to support patients and

their primary professional caregivers on the current diagnosis, treatment, monitoring and outcome measures for patients with ASMD. This document represents a general guideline, which in the opinion of the authors can inform care providers about the needs of patients with ASMD in order to provide equitable and improved care, define standard of care for ASMD patients, identify knowledge gaps, foster shared care arrangements between expert centres and family physicians, and empower patients. The guidelines encompass management of patients suspected or diagnosed with ASMD disease at any age. These guidelines should be of value to: a) specialist centres, other hospital-based medical teams and other staff involved with the care of ASMD patients, b) family physicians and other primary caregivers and c) patients and their families. It was developed by experts with extensive experience of European, North and South American healthcare systems and populations. However, they might equally be applicable to any country that operates similar healthcare services. It is anticipated that implementation of these guidelines will lead to a step change in the quality of care for patients with ASMD.

Results And Discussion

1. DEFINITION, EPIDEMIOLOGY AND PATHOPHYSIOLOGY

i. What is ASMD

Statement 1

Acid sphingomyelinase deficiency is due the deficient activity of the enzyme acid sphingomyelinase (ASM). ASM is a lysosomal lipid hydrolase required to degrade the sphingolipid, sphingomyelin, into ceramide and phosphocholine. A deficiency of this enzyme results in sphingomyelin accumulation, representing the underlying pathologic defect.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (94%), mostly agree (6%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Statement 2

ASMD is a multisystemic, mostly progressive and potentially life limiting autosomal recessive disorder with age of onset varying from first day/months of life to adulthood.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

ii. Inheritance and historical notes

ASMD is inherited as an autosomal recessive trait that results from the reduced activity of acid sphingomyelinase (ASM) due to loss-of-function variants in *SMPD1*, the gene encoding ASM (1). To date, over 250 *SMPD1* variants have been described in ASMD patients, that result in a wide range of clinical phenotypic severity (2) (3). Carrier individuals who inherit only one pathogenic *SMPD1* allele will be clinically normal. If two carrier individuals have children, each offspring has a 1:4 chance of being affected. There is some evidence indicating that *SMPD1* may be paternally imprinted (preferentially expressed from the maternal chromosome), but it is not known if this has any impact on the ASMD phenotype (4). The first infant with this disease was described in 1914 by the German pediatrician, Albert Niemann (5). More such patients were reported, and detailed pathological studies were conducted in 1922–1927 by Ludwig Pick (6). These infants followed a rapidly neurodegenerative course leading to death within 3 years of age. In 1946, Pfändler and Dusendschon described 2 adult brothers with similar pathologic findings, but distinguishable from Niemann's patients by a later onset of disease symptoms and the lack of central nervous system (CNS) manifestations (7). Over the years, the disease became known as "Niemann-Pick Disease" (NPD). In 1958, Crocker and Farber published a review of 18 cases of NPD, showing that there was a wide variability in age of onset and clinical expression, and in the level of sphingomyelin storage in tissues (8). This led Alan Crocker (1961) to delineate these patients into four subtypes (types A-D). Type A (corresponding to the original patients described by Niemann and Pick) was characterized by severe, early CNS deterioration and visceral and cerebral sphingomyelin storage. Type B showed a chronic course with marked visceral involvement and visceral sphingomyelin storage, but with a sparing of the nervous system. Patients with Type C and D (the latter corresponding to patients from Nova Scotia) were characterized by a subacute nervous system involvement with a moderate and slower course, as well as milder visceral storage. We now know that the latter patients have a different disease caused by mutations in two genes involved in cholesterol cellular trafficking, *NPC1* or *NPC2* (9) (10) (11). In 1966, Brady and associates demonstrated a severe deficiency in acid (lysosomal) sphingomyelinase activity in tissues from patients with type A (12), a finding soon extended to type B. Intermediate phenotypes were subsequently described in patients with ASM deficiency, and these became known as Type A/B NPD (13). The next step was the identification of the gene encoding acid sphingomyelinase, *SMPD1*, together with that of pathogenic variants in patients, confirming that Niemann-Pick disease types A and B were allelic disorders (1). The disease is now referred to as ASMD to better describe these patients and distinguish them from those with Type C NPD (14). The original Type A patients are classified as the **infantile neurovisceral type**; Type B patients are referred to as the **chronic visceral type**, and patients with Type A/B are referred to as the **chronic neurovisceral type**.

iii. How common is ASMD deficiency

Statement 3: *ASMD is a pan-ethnic ultra-rare, autosomal recessive metabolic disorder, with an estimated global prevalence of ~ 1:100,000–1,000,000 births. There is a higher frequency of some specific SMPD1 pathogenic variants in certain ethnic populations with disease incidence as high as ~ 1:40,000.*

- Strength of recommendation: 1
- Level of evidence: B

- Experts' opinion: completely agree (69%), mostly agree (25%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

The most extensive genetic screening for ASMD has been performed in the Ashkenazi Jewish population, where the carrier frequency is estimated to be between ~ 1:100 to 1:200 based on screening for three common "Type A" NPD mutations (predicting a disease prevalence between ~ 1:40,000 and 1:200,000) (15) (16). Several other studies have estimated carrier or disease frequencies in specific populations, and the results are highly variable. In part, this may be due to founder effects and the incidence of consanguinity. In addition, most of these estimates are based on data from lysosomal storage disease testing laboratories rather than from population-based screening (17) (18) (19) (20). More accurate determination of the true disease incidence must await additional screening data in different populations.

iv. Why is ASMD sometimes referred to as a "Jewish Genetic Disease"?

The first infant with ASMD described by Niemann was of Ashkenazi Jewish descent (5). Subsequently, other infants with similar pathology were identified, many of whom were also Ashkenazi Jews (8). Based on these observations, ASMD type A was labeled a "Jewish Genetic Disease" and common type A ASMD variants are included on most Jewish Genetic Disease screening platforms throughout the world. However, patients with all forms of ASMD have been reported from a large number of countries and ethnicities. In fact, the vast majority of affected individuals are not of Ashkenazi descent.

v. How many living ASMD patients are there?

Historically, ASMD is challenging to recognize, likely leading to under diagnosis. In part, this is due to limited awareness within the medical community, the wide-ranging phenotype, and overlap with other, more common conditions. In addition, the number of laboratories offering testing for ASMD activity has been scarce. It is currently estimated that several thousand ASMD patients may be living worldwide based on the number of diagnosed cases and limited information on the disease incidence from sources such as Orphanet, which cites a prevalence of 1–9/1,000,000 in Europe. ASMD is probably underestimated and it is unknown how many cases remain undiagnosed and the true incidence of the disease in various populations remains to be elucidated.

vi. Pathophysiology

Why is ASMD considered a lysosomal storage disorder?

ASMD is a complex lysosomal lipid storage disease that leads to cellular dysfunction in multiple organs. Since the disease initiates in lysosomes, a number of abnormalities may be directly linked to the dysfunction of these organelles, including defects in endocytosis/exocytosis, autophagy, and macromolecule turnover.

The exact pathophysiology of ASMD is insufficiently understood. The primary organs impacted in all subtypes of ASMD are the liver, spleen, lung and haematopoietic systems. The initial accumulation of lysosomal sphingomyelin leads to the accumulation of other lipids in lysosomes, the most prominent of which is cholesterol (21) (22) (23). Other lipids derived from sphingomyelin, such as ceramide and molecules that derive from it (e.g., sphingosine), or lysosphingomyelin (sphingosylphosphorylcholine), as well as glycosphingolipids and bis (monoacylglycero) phosphate, also accumulate (23). Over time, as lysosomes recycle to the cell membrane, these lipids distribute to other compartments, causing a wide range of secondary cellular abnormalities. These may include plasma membrane signaling abnormalities that trigger inflammation and apoptosis, respiration abnormalities due to mitochondrial defects, and abnormalities in nuclear transport. Ultimately, it is hypothesised that chronic inflammation and signaling defects in ASMD cells can lead to tissue fibrosis and/or organ failure.

Are all cell types impacted in ASMD?

Other than mature erythrocytes, all cells have lysosomes. As such, all cells will be impacted by the deficiency of ASM. However, cells of the monocyte/macrophage system are actively involved in phagocytosis and have abundant lysosomes, and are therefore impacted the most in ASMD. Typical histologic images of reticuloendothelial organs, including the liver and spleen, reveal large numbers of lipid-laden macrophages infiltrating throughout the tissues (6). The same is true in the lung, where these cells may be found in airways as well as in interstitial tissue. Other organs impacted in ASMD include the heart, skeletal system, lymphatic and haematopoietic systems, and in some patients, the CNS (24) (25) (26). In these latter patients, storage can be found in glia cells as well as neurons.

2. CLINICAL SIGNS AND SYMPTOMS

i. How is ASMD classified

Statement 4

The clinical manifestation and life expectancy of ASMD patients varies substantially according to the subtypes. ASMD broadly can be divided into infantile neurovisceral ASMD (NPD type A); chronic neurovisceral ASMD (NPD A/B; NPD B variant) and chronic visceral ASMD (NPD type B). While the grouping of patients into designated subtypes is helpful, ASMD patients present with a wide range of phenotypes along a continuum disease spectrum.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (100%), mostly agree (0%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Historically, patients with ASMD presenting with severe infantile neurovisceral disease have been categorized as NPD type A, whereas those who have primarily visceral disease have been classified as NPD type B. However, some patients may have protracted neurovisceral disease (16) (27) (28) (29) and

are described in the literature as variant NPD type B, NPD type A/B, or intermediate NPD (14). It has increasingly become apparent that many patients may not be easily classified, and even within subtypes there is substantial variability. For example, within the chronic, visceral disease subtype (NPD type B), there are patients diagnosed as young children with severe liver, pulmonary and/or splenic disease, and other patients who are diagnosed as adults with much milder disease, without clinical progression over years (29) (30) (31). Within the chronic neurovisceral phenotype some patients experience developmental delay, ataxia, and/or progressive neurologic deterioration, while others may exhibit learning or behavioral abnormalities without any evidence of progression (32). Thus, the designated nosology is a useful tool, but the disease exhibits a continuum of phenotypes. A newer classification system and how it relates to the traditional designations is shown in Table 1.

Table 1
Classification of patients with ASMD

	Infantile Neurovisceral (ASMD type A)	**Chronic Neurovisceral (Intermediate ASMD, ASMD A/B, Variant ASMD B)**	**Chronic Visceral (ASMD type B)**
Phenotype	Infantile onset of severe neurodegeneration with progressive psychomotor deterioration	Visceral features of NPD B as well as neurologic findings including ataxia, variable degrees of developmental delay and peripheral neuropathy	Chronic progressive multi-system or oligosymptomatic, stable disease with no or little neurologic involvement
Natural History	Relentless progression of neurologic and visceral disease and death typically by 3 years of age	Wide spectrum of disease manifestations and severity. Patients live past early childhood, sometimes into adulthood	Wide spectrum of disease manifestations and severity. Sometimes oligosymptomatic. Survival usually extends well into adulthood and may even be normal. Patient may remain stable for years.

ii. What is the clinical presentation in Infantile Neurovisceral ASMD type A?

Statement 5

Early development of hepatosplenomegaly in infancy with initial achievement of developmental milestones until about 6 months of age followed by progressive neurological deterioration starting in the first year of life, especially if associated with a macular cherry red spot, should raise the suspicion of a lysosomal storage disorder including ASMD type A.

- Strength of recommendation: 1
- Level of evidence: B

- Experts' opinion: completely agree (73%), mostly agree (27%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

ASMD type A is the most severe form of ASMD and has a relatively uniform natural history characterized by severe progressive neurodegenerative manifestation in the first year of life with hepatosplenomegaly, development arrest and hypotonia and death typically by 3 years of age (28) (29). Most infants present with hepatosplenomegaly at 2–4 months of age(28) followed by onset of neurologic symptoms at a median age of 7 months, developmental arrest by 10 months of age and then rapidly progressing neurodegeneration with deterioration of behavioral, language and gross and fine motor skills. Patients show progressive hypotonia with loss of deep tendon reflexes, whereas cranial nerve function remains largely intact. Macular cherry-red spots are detectable in most infants by 12 months. These infants suffer from failure to thrive due to insufficient intake of calories resulting from worsening hypotonia, weakened suck and gastrointestinal symptoms. All infants develop progressive respiratory symptoms with frequent respiratory infections secondary to aspiration, and most die of respiratory failure. Massive hepatosplenomegaly is typically present, and most infants have significant hepatic dysfunction or liver failure. Abnormal laboratory values include elevated liver enzymes, low HDL cholesterol and progressive decreases in hemoglobin values and platelet counts. (Table 2)

iii. What is the clinical presentation in Chronic Visceral ASMD type B?

Statement 6

The onset of ASMD type B is variable, from childhood to adulthood. Patients with ASMD type B have extensive phenotypic heterogeneity in disease manifestations, from asymptomatic to polysymptomatic. Progression of disease can vary considerably and stability can also be seen in attenuated older patients. The most common symptoms at initial presentation are splenomegaly and hepatomegaly. Common historical symptoms and complaints may include bleeding, shortness of breath, pulmonary involvement, joint and/or limb pain, bruising, headaches, diarrhea and bone fractures. Interstitial lung disease, abnormal blood counts and/or atherogenic lipid profile can be seen.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (63%), mostly agree (25%), partially agree (13
- %), mostly disagree (0%) and completely disagree (0%).

Being a rare disease and having variable phenotypic manifestations lead to misdiagnosis of ASMD, especially in the later onset group (type B). The systemic involvement in later onset ASMD (types A/B and B) can present anytime from early childhood to adulthood and sometimes requires a high index of suspicion to make a diagnosis.

iv. What are the neurologic features in patients with Chronic Neurovisceral variant (ASMD A/B or intermediate ASMD?)

Statement 7

Patients with variant forms of ASMD have an intermediate phenotype between A and B, with important somatic manifestations outlined in statement 6 and a slowly progressive neurological disease ranging from mild hypotonia or hyporeflexia to severe progressive neurologic abnormalities such as loss of motor function, ataxia and cognitive decline. In these patients, the onset of neurologic disease is later in life than in patients with ASMD type A and is more indolent.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (56%), mostly agree (44%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Patients with variant forms of ASMD have been described in several reports (33) (34) (13) (35) (24) (29) (36) (37) (38). In a prospective study of 64 patients with ASMD type B who underwent detailed neurologic and ophthalmologic examinations, 19 (30%) had neurological abnormalities, suggesting that patients with a phenotype that includes neurological manifestations constitute a significant proportion of ASMD patients (36). The most common abnormalities were mild hypotonia and/or hyporeflexia. Some patients had cognitive impairment (mental deterioration or expressive language delay) and/or other moderate to severe neurological symptoms (36). In some cases the onset of neurological and neuropsychiatric symptoms is subtle and insidious. Worsening neurological symptoms and signs after an initial period of normal development would be a clue. Similarly, in a report of 25 Czech and Slovak patients with ASMD who did not demonstrate the classic ASMD type A phenotype, 16 (64%) had neurologic symptoms (13). In this series, 12 of the 16 patients had the p.Q294K mutation in homoallelic or heteroallelic form, and 10 of those had a protracted neurovisceral phenotype (13). p.W393G is a variant found in south-east Europe (Sinti and Romanies background); these patients frequently show neuropsychiatric symptoms.

Table 2
Classification of patients with ASMD

	Acute Neurovisceral; NPD-A	Chronic Neurovisceral, NPD-A/B	Chronic Visceral; NPD-B
Hepatosplenomegaly	+	+	+
Proatherogenic lipid profile	+	+	+
Delayed growth and puberty		+	+
Thrombocytopenia	+	+	+
Interstitial lung disease	+	+	+
Skeletal involvement	+	+	+
Liver disease	+	+	+
Cherry Red Macula	+	Some patients	Some patients
Hypotonia	+	Some Patient	Absent
Neurodegeneration	Rapidly progressive	Slowly progressive	Absent

v. What are the visceral manifestations of ASMD?

Statement 8

Splenomegaly is one of the most common disease manifestations of ASMD and often the first obvious sign of the disease. Most patients have radiologic evidence of interstitial lung disease.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (63%), mostly agree (31%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Splenomegaly, which results from infiltration by lipid-laden macrophages (39), can be massive and may be a surrogate marker of disease severity because of its correlation with other disease parameters (40) (41).

Hepatomegaly is another common visceral manifestation. Elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin can be seen (41). A systematic analysis of liver biopsies from adult patients with ASMD type B revealed the presence of liver fibrosis in most patients, some of whom had frank cirrhosis in the absence of any clinical symptoms of liver failure (26). Patients homozygous for the *SMPD1* p.A359D mutation associated with moderate to severe ASMD type B, have a

high incidence of clinically relevant liver disease due to progressive cirrhosis (42). Hepatic involvement that may lead to slowly progressive liver failure and in some circumstances/cases fulminant liver failure has been reported (37). In addition to respiratory disease, liver failure is a common cause of death in patients with ASMD type B (43). Hepatosplenomegaly is one of the commonest manifestations of ASMD and the differential diagnosis would include primary liver disorders including chronic Hepatitis B and other infections, lymphoma and other malignancies, other storage disorders like Gaucher disease, lysosomal acid lipase deficiency (LAL-D) and Niemann-Pick type C disease. Diagnostic work-up for Gaucher disease, LAL-D and NPC should regularly and simultaneously include ASMD.

Most patients (41) (44) have evidence of interstitial lung disease by chest radiography and high-resolution computed tomography. However, there is no strong correlation between radiologic findings, respiratory symptoms and the results of pulmonary function tests (44). Therefore, imaging studies are not sufficient in the evaluation of pulmonary disease in ASMD type B and must be interpreted in conjunction with functional testing and the clinical status of the patient. Among patients with functional pulmonary disease, the most common finding is low DL_{CO} followed by restriction of forced vital capacity, which are impaired gas exchange and consistent with restrictive lung disease. Overall, respiratory disease is one of the most common manifestations and a leading cause of death in patients with ASMD type B (43) (37). The combination of hepatosplenomegaly with interstitial lung disease is a useful pointer to the possibility of a multiorgan disease like ASMD. In adults, sarcoidosis is a common cause of interstitial lung disease with multiorgan involvement, but the breathlessness in sarcoidosis would often be far greater for the same extent of radiological changes than in ASMD. The fibrosis in sarcoidosis is often upper lobe predominant and hepatosplenomegaly if present much less obvious. Pulmonary fibrosis can be the main manifestation of other lung disease such as idiopathic fibrosis and pulmonary alveolar proteinosis with minimal hepatosplenomegaly as an additional feature (29).

Dual X-ray Absorptiometry scans to measure bone mineral content (BMC) and bone mineral density (BMD) (45) demonstrate that pediatric patients have significant decreases in adjusted mean BMC and BMD at the lumbar spine, hip and femoral neck compared with a cohort of healthy age-matched subjects. In addition, adults with ASMD type B may have osteopenia or osteoporosis at one or more sites according to the World Health Organization classification of BMD (45). Thus, skeletal involvement may be a feature of ASMD.

Most patients also have an atherogenic lipid profile characterized by low HDL cholesterol, high total cholesterol, high triglycerides and high LDL and very low-density lipoprotein cholesterol compared with age- and gender-matched control subjects. In a study of pediatric patients with ASMD, including 10 with type A and 30 with type B, all patients displayed abnormal fasting lipid profiles (46). Furthermore, electron beam tomography of the coronary arteries performed in 18 NPD type B patients revealed positive calcium scores (range 1.4–34.5) in 10 patients, which in patients < 18 years of age suggests the presence of early atherosclerosis (47). It has been reported that Electrocardiogram abnormalities may be present, although with none specific findings such as sinus bradycardia, left ventricular hypertrophy and conduction abnormalities (47). Mild valvar heart diseases are reported in a few patients with ASMD (47). In general,

there is no strong evidence of primary involvement of the heart in ASMD, but further studies are warranted.

vi. What are the haematologic findings in ASMD?

Statement 9

Patients with ASMD have a variable degree of thrombocytopenia, leukopenia and anemia.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (63%), mostly agree (38%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Mild thrombocytopenia is the most common haematologic abnormality in ASMD. Bleeding episodes may include recurrent epistaxis sometimes requiring repeated cauterizations. Significant bleeding events that have been reported include subdural haematoma, hematemesis, hemoptysis, hemothorax, excessive bleeding after tonsillectomy and adenoidectomy resulting in a blood transfusion, menorrhagia and uterine bleeding that required a hysterectomy (41). Anemia and leukopenia also may be present (41). Bleeding disproportionate to injury or after surgical procedures and easy bruising due to thrombocytopenia are more common than anemias.

vii. What is the impact of ASMD on growth?

Statement 10

Growth restriction is common in children with ASMD. Many patients diagnosed with ASMD in childhood have below average height and weight particularly during adolescence. Typically, height and weight is within normal range by adulthood.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (50%), mostly agree (50%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Growth delay is most pronounced in adolescents, who also may have delayed bone age that corresponds with delayed onset of puberty. However, most adults (≥ 18 years of age) have heights in the low normal range, suggesting that a period of catch-up growth occurs in late adolescence and/or early adulthood (41). Thus, although short stature is a cause of concern for adolescent patients with ASMD type B, final adult heights appear to approach normal values in most patients.

viii. What are the impacts of ASMD on Quality of Life?

Statement 11

Few studies have collected information about the impact of ASMD on health-related quality of life (QoL) and the psychosocial burden of ASMD. ASMD type A is devastating for the patient and the family.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

ASMD type A has a devastating physical and emotional impact for the affected children and their families (48). Frequently, infants with ASMD type A have irritability, sleep disturbances and insomnia, prolonged periods of crying and frequent vomiting (28). The need for constant care for these infants has a profound negative effect on caregivers' QoL. A single study (41) that assessed QoL in a small number of patients with NPD type B using generic QoL instruments (i.e., the Child Health Questionnaire – Parental Form 50 for pediatric patients [CHQ-PF50] and the Short-Form 36 [SF-36] for adults) suggested diminished QoL associated with physical functioning, mental health, general health perceptions and/or emotional well-being in a subset of patients. The psychosocial impact of the disease has been evaluated in a small number of patients with ASMD type B and identified psychosocial problems due to limited physical activity and social isolation (49) (50). Overall, there is a paucity of quantitative and qualitative data on QoL and the impact of the disease on patients and families (50).

3. DIAGNOSTIC INVESTIGATIONS

Being a rare disease and having variable phenotypic manifestations may lead to misdiagnosis of ASMD, especially in the later onset group (type B or A/B). ASMD has several laboratory/imaging manifestations; some of them are non-specific but may be detected by routine tests before a specific suspicion is raised. A close look on the combination of results of these tests may lead to the suspicion of ASMD and consequently to the request of a specific diagnostic test. (Fig. 1)

i. General laboratory tests

BLOOD COUNTS: Patients with ASMD usually present with mild thrombocytopenia, which can be detected in a routine blood count. Anemia may be present as well; also, leucopenia/neutropenia can be present (30).

LIPID PROFILE: An abnormal lipid profile is common in patients with ASMD, the most frequent abnormalities include increased levels of triglycerides and total cholesterol, with low HDL-cholesterol levels (30).

IMAGING: The increased sizes of liver and spleen can be observed incidentally on physical examination or plain radiography, but to measure the volume and to evaluate echogenity it is recommended to perform ultrasonography. More accurate measurements can be obtained with tomography or preferably with MRI. Interstitial lung disease can be suspected from chest X-ray or CT.

ii. Bone marrow and tissue biopsies

Although not needed nor recommended for the diagnosis of ASMD, adult patients may be often subjected to a bone marrow biopsy due to the suspicion of malignancy in a subject with unexplained splenomegaly. In the bone marrow, ASMD patients will display foamy macrophages (“Niemann-Pick” cells) and/or typical “sea blue histiocytes”. These storage cells are not specific for ASMD. Both types can also be present in bone marrow aspirates from patients with NPC and similar foamy macrophages can also be found in other lysosomal storage disorders, such as acid lipase deficiency or GM1 gangliosidosis.

iii. Laboratory tests essential to confirm the diagnosis of ASMD

(**a**) Significant increase of 3β,5α,6β-cholestane-triol (C-triol), 7-ketocholesterol (7-KC), 3β,5α,6β-trihydroxy-cholanoyl-glycine (TCG), lysosphingomyelin (lyso-SM), *N*-palmitoyl-*O*-phosphocholine-serine (PPCS). A difference with an NPC profile is the normal or slightly elevated lyso-SM level in the latter. Other causes of elevated C-triol levels include cerebrotendinous xanthomatosis (CTX) and acid lipase deficiency. (**b**) LC-MS/MS (or radioisotopic) preferred methods (see Statement 13). (**c**) Recommendation for ASM in DBS to be confirmed on leukocytes or by genetic testing. (**d**) Importance of parental study. **(e)** MLPA/RNA analysis. Abbreviation: VUS: variant of uncertain significance

Statement 12

Whenever ASMD is suspected, an enzyme assay for ASM activity should be performed. The diagnosis is established by demonstration of deficient or very significantly diminished ASM activity in leucocytes or fibroblasts. Biomarkers could be helpful in combination with enzyme activity measurement to establish the diagnosis especially if enzyme activity measurement is performed in dried blood spots.

- Strength of recommendation: 1
- Level of evidence: A
- Experts’ opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

1. Biological sources for assay of acid sphingomyelinase activity

Peripheral blood leukocytes/lymphocytes or dried blood spots (DBS) are the usual biological sources; isolated lymphocytes/monocytes have a specific activity 2-3-fold higher than total leukocytes. Cultured skin fibroblasts have a much higher level of specific activity than leukocytes (x40-50) and may be useful in equivocal cases. The use of DBS facilitates sample shipping, but has limitations, including influence of anemia, leucopenia, and recent transfusions on the results (14). Sampling temperature and storage

conditions are important since enzyme activities in DBS are highly sensitive to heat and humidity (51). A diagnosis made by DBS should be confirmed in leucocytes or fibroblasts. Vice versa, a strong clinical suspicion with a normal DBS result should prompt further investigation of ASM activity in leucocytes or fibroblasts.

2. Is there an optimal method for determination of acid sphingomyelinase activity?

Statement 13

For determination of acid sphingomyelinase activity, the choice of a specific substrate is critical. Use of a short-chain fatty acid sphingomyelin analogue with detection by tandem mass spectrometry (MS/MS) is considered the method of choice.

- Strength of recommendation : 1
- Level of evidence : B
- Experts' opinion: completely agree (67%), mostly agree (33%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

3. Evaluation of different methods for assay of ASM activity

Accurate and sensitive methods using natural sphingomyelin radioactively labeled on the choline moiety, historically developed and validated by expert laboratories (52) (53) (54) (55) (56), are still excellent. However, due to the need of periodical purification of the substrate and of licensing for use of radiochemicals, this methodological approach is currently on the wane.

A synthetic fluorogenic substrate, 6-hexadecanoylamino-4MU-phosphorylcholine, was proposed as a simpler replacement for radiolabeled sphingomyelin (57). Patients with some pathogenic *SMPD1* variants such as the recurrent p.Q294K (34) were not detected by the original method. This problem could be solved by assessing the extent of inhibition of enzymatic hydrolysis of the artificial substrate by an unlabeled natural substrate, in particular lysosphingomyelin (57). This substrate, however, has a low sensitivity and provides a lesser discrimination between unaffected and affected subjects than that used in tandem mass spectrometric (MS/MS) assays (58) (59).

Radioisotopic and fluorimetric assays have been superseded by highly sensitive techniques using a short-chain fatty acid sphingomyelin analogue and detection by MS/MS, now considered the method of choice (14), with a good specificity (59) and adaptability to DBS with a high throughput (60). Multiplex enzyme assays kits using this principle for simultaneous diagnosis of six lysosomal storage diseases are commercialized (61). They allow, among others, simultaneous testing for ASMD and Gaucher disease, as has recently been recommended (14). They can also be used for neonatal screening (58) (61) (62) (63).

4. Evaluation of different methods for assay of ASM activity

Statement 14

Although type B patients often show a slightly higher level of residual activity, the in vitro assay does not reliably distinguish neuronopathic from non-neuronopathic phenotypes.

- Strength of recommendation : 1
- Level of evidence : B
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Whatever substrate is used, *in vitro* assays of ASM activity have primarily been designed to optimally demonstrate a deficiency. They do not reflect the true *in vivo* activity and will not allow a reliable distinction between clinical phenotypes. The *in situ* loading tests in living fibroblasts (64) (65) (66) (13) were more informative, but they are no longer offered by diagnostic laboratories.

iv. Are there useful plasma biomarkers for screening or diagnosis of ASMD?

Statement 15

Several plasma biomarkers show abnormally high levels in ASMD. Despite a lack of specificity for some of them, they can constitute a good first line test before measuring ASM enzyme activity or in combination with enzyme activity measurement. To date, the most specific one is sphingosylphosphorylcholine (SPC) also called lysosphingomyelin (lyso-SM). Its measurement can optimally be combined with that of N-palmitoyl-O-phosphocholine-serine (PPCS), previously named lysosphingomyelin-509 (lyso-SM509).

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

1. Chitotriosidase activity

The activity of chitotriosidase, a human chitinase secreted by macrophages, is strikingly elevated in Gaucher disease (67), and increased to varying degrees in many lysosomal storage diseases (LSDs), as well as in some other disorders in which macrophages are activated. Its assay which only requires simple equipment is widely available. It is therefore still proposed by many laboratories as a first screening test whenever LSD is suspected, in spite of its lack of specificity, and the fact that a number of individuals show a partial or complete deficiency of activity due to common 24-bp duplication in exon 10 of the *CHIT1* gene (68). In ASMD, elevation is generally modest (69), not constant, and it does not differentiate ASMD from Niemann-Pick type C (NPC), nor from several other diseases with (hepato)splenomegaly.

2. Oxysterol and bile acid derivatives

The oxysterols cholestane-3β,5α,6β-triol (C-triol) and 7-ketocholesterol (7KC), first identified in the search for plasma biomarkers of NPC (70), were found to be also elevated in ASMD (71) (72) (73). But they also show increases in a number of other diseases, including differential diagnoses of ASMD such as acid lipase deficiency or some causes of neonatal cholestasis (74). The more stable bile acid derivative of C-triol, N-(3β,5α,6β-trihydroxycholan-24-oyl) glycine (TCG), is also increased in both NPC and ASMD (75) (76).

3. Lysosphingomyelin and PPC/lyso-SM509

The most specific plasma biomarker in ASMD to date is sphingosylphosphorylcholine (or lysosphingomyelin, lyso-SM), corresponding to the deacylated form of sphingomyelin, the primary accumulated lipid (77) (78) (79) (80) (81) (31). A marked increase is only observed in ASMD, compared to a small and inconsistent 2-3-fold increase in NPC (82) (77), and in some metabolic syndrome patients (83). A pilot study suggests that lyso-SM levels are positively associated to the degree of clinical severity of the patients (84). Of note, plasma lyso-SM levels have been used and proven useful in follow-up of a recent enzyme replacement therapy trials (85) (86).

N-palmitoyl-*O*-phosphocholine-serine (PPCS) initially named lysosphingomyelin-509 (72) is a sensitive biomarker corresponding to a novel class of lipids (87) (88). It is strikingly elevated in both ASMD and NPC; a modest increase may occur in some other conditions (78) (79). In ASMD, nominal concentrations of PPCS are much higher than those of Lyso-SM. Until 2019 only the molecular mass (509Da) of this compound was known (hence its initial name) (72), and not its exact structure. Therefore, in currently published work, lyso-SM509 semi-quantitative measurements have been made with external calibration using a lyso-SM standard for both molecules, with quantification of lyso-SM509 expressed in multiple of median of controls (MoM). Thus far, exact quantifications of PPCS in ASMD patients using homemade standards (in genuine nmol/L) have only been reported from Ory's and Maekawa's groups, respectively (89) (90). Determination of lyso-SM and PPCS is also possible in DBS although less discriminative than in plasma (77) (91).

4. What is the advantage of a multiplex lysosphingolipids and PPC/lyso-SM509 measurement?

Statement 16

Simultaneous measurement of lyso-SM, PPCS and lyso-Gb1 (glucosylsphingosine) can provide good indication for differential diagnosis of ASMD, Gaucher disease, or NPC.

- Strength of recommendation: 1
- Level of evidence: B

- Experts' opinion: completely agree (50%), mostly agree (50%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

MS/MS multiplex methods have been developed (79) (78) (91) (80), allowing the simultaneous measurement in the same assay of lyso-SM, PPCS, lyso-Gb1 (the best biomarker for Gaucher disease), lyso-Gb3 (biomarker for Fabry disease) and other lyso-glycosphingolipids. Such panels have proven useful in screening of sphingolipidoses and NPC. Striking elevation of lyso-Gb1 allows quick differential diagnosis of Gaucher disease, while a marked elevation of both lyso-SM and PPCS is the signature of ASMD, but not that of NPC.

v. Genetic testing

Statement 17

Genetic testing of SMPD1 gene should be performed to confirm diagnosis in subjects with ASM activity below normal reference intervals and allow genetic counselling. In case SMPD1 sequencing is done before assessing ASM activity and the identified variant for 1 or 2 alleles is not known as pathogenic, demonstration of a deficient ASM activity is mandatory to confirm the diagnosis. Measurement of biomarkers can also be helpful.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

ASMD is caused by biallelic pathogenetic variants in the *SMPD1* gene (1) (92). Molecular analysis of *SMPD1* is highly recommended to support the diagnosis of ASMD; it is the only reliable method for carrier identification within family members, and it is the preferred method for prenatal diagnosis. In addition, it might be useful to establish genotype/phenotype correlations.

The *SMPD1* gene (GenBank#NC_000011.10) spans ~ 5 kb of chromosome 11 (11p15.1–11p15.4) and consists of six exons (92) (93) (1) (94). Although two in-frame translation initiation ATG codons located 32 codons apart from each other have been described, *SMPD1* variants are described according to current mutation nomenclature guidelines (http://www.hgvs.org/mutnomen) (95), ascribing the A of the first ATG translational initiation codon as nucleotide + 1 (GeneBank accession number, NM_000543.4). However, two different cDNA reference sequences have been used to number the *SMPD1* variants (GeneBank accession number, NM_000543.4 and M81780.1) that differed in the length of a highly polymorphic hexanucleotide sequence, hexanucleotide GCTGGC (p.L37_A38), located in exon 1 within the region encoding the signal peptide. Therefore, reports of genetic tests should always include the transcript reference number considered to numbered variants. In this manuscript sequence reference NM_000543.4 is used.

To date, more than 346 variants have been described throughout the whole *SMPD1* gene; among them 295 have been classified as disease associated variants in HGMD Professional 2022.1. All variety of point mutations have been reported in ASMD patients, including missense, nonsense, frameshift, indels and intronic variants, while only 3 large alterations (gross deletions, deletions/duplications, repeat variations) have been identified so far.

Considering this mutational spectrum, sequencing analysis of the *SMPD1* exons and the intronic flanking regions should be performed as a primary genetic test to confirm/support the diagnosis of ASMD. Sanger or parallel next generation sequencing (NGS) could be used to analyze *SMPD1* as a single gene or as part of a gene panel, respectively (96) (97). Segregation of alleles by identifying variants in parents should be determined.

The presence of homozygous pathogenic variants not confirmed in parents, as well as the absence of pathogenic variants (in one or both allele) after sequencing should always be questioned and the presence of possible undetected copy number variations (CNV) or deep intronic pathogenic variants should be investigated.

Newly identified variants should be classified following current ACMG/AMP criteria and in case of identification of variants of uncertain significance (VUS), pathogenicity should be tested by functional analysis (98).

1. Are there specific phenotypes that occur in specific regions or ethnicities?

Patients with *SMPD1* variants have been described in many regions of the world. However, there are some regions where specific phenotypes are more frequently identified. Although the frequency and distribution of *SMPD1* pathogenic variants vary among different populations and ethnic groups (31) (99) (29) (13) (100) (101) (102) (103) (104) (105) (106) (107), the most frequently reported mutation worldwide is a 3-base deletion, p.R610del, first described by Levran et al (108).

Some mutations are more frequently represented among individuals of a particular ethnic group. Three pathogenetic variants, the frame shift mutation p.F333SfsX52 and the missense mutations p.L304P and p.R498L (109) (110) (111) account for 90% of the alleles found in ASMD patients affected by the infantile neurovisceral phenotype in Ashkenazi Jewish populations. The p.R610del variant is highly prevalent (> 90% of alleles) in patients originating from Maghreb (Tunisia, Algeria, Morocco) and also frequent in patients of Spanish and French descent (107) (102) (112), rarer in Italy (101) or Poland (31). Of note, this variant has not been reported in patients from the Czech Republic (13) or from China, where mutations p.R602H, p.R3AfsX76 and p.H284SfsX7 are frequent (105) (106).

The missense variant p.W393G is present in 100% of the alleles in the Sinti and Romanies population and frequent in patients from the Western Balkan region (35). Even though the p.Q294K variant has been

found in patients from different populations it is highly frequent in patients from Czech and Slovak heritage (13).

Finally, the missense variant p.A359D is highly prevalent in Chile, where it has been originated by a founder effect (42).

2. Genotype/phenotype correlation

The spectrum of reported ASMD associated *SMPD1* variants is extremely heterogeneous. Most mutations have been found in single families and in compound heterozygosity. Therefore, it is quite difficult to correlate the genotype with the phenotype. However, some assumptions can be made based on functional analysis of single mutants and for recurrent mutations found in homozygosity (113).

While the presence of nonsense variants, large deletions or variants leading to a reading frameshift in both alleles is associated with the severe neurovisceral phenotype, a correlation with a specific clinical phenotype is more difficult to establish for pathogenetic missense variants. However, the current evidence indicates that patients carrying at least one *SMPD1* pathogenic allele leading to the synthesis of a partially active ASM protein present with the visceral non-neurological phenotype.

Some exemptions applied to this general consideration. Indeed, although the p.W32X mutation, commonly found in Italian patients, would be expected to lead to complete absence of expression of an active protein, it has been nonetheless associated with the non-neurological phenotype. This data suggests that in vivo, when the first ATG is present but unable to produce a canonical transcript, the second initiation codon (ATG33) may be used resulting in the synthesis of a protein missing the first 32 residues of the predicted signal peptide but still partially active (114).

A similar hypothesis can be proposed for the p.R3AfsX76 mutation predicted to introduce a premature stop codon. In fact, even in the absence of *in vitro* evidence, this mutation is frequently found among ASMD type B Chinese patients even in homozygous status (105).

Regarding recurrent variants, the deletion of arginine at position 610 of the protein (p.R610del) is associated with high residual ASM activity (107) (102) (103) (101) (115) and has been always identified in patients with the non-neuronopathic phenotype (107) (102) (112). However, a wide range of disease severity has been observed in homozygous patients.

The most frequent missense variants identified in Ashkenazi Jewish, p.L304P and p.R498L, have been associated to the severe neuronopathic phenotype in this population (110) (109). The presence of the p.Q294K variant both in homozygosity or compound heterozygosity has been associated with the intermediate phenotype (13).

Particularly significant is the occurrence of p.W393G mutation, first described by Ferlinz et al. in a family from Serbian origin (33). The patients were classified as affected by an intermediate clinical phenotype due to the presence of a macular halo and a low in situ ASM activity. However, they were all

neurologically normal and we now know that macular halo can occur in typical non-neurological type B patients. Nevertheless, a variable neural phenotype was described in a genetically homogeneous group of 20 Gypsy patients with this mutation (35).

4. MANAGEMENT

ASMD is not yet curable, but it is a treatable condition. Optimal disease management requires a multi-disciplinary, multi-professional team (116) based in a specialist centre, closely liaising with community care providers. The mainstay of therapy is addressing the existing/impending complications and symptom management (117). Once available on the market, disease modifying agents are anticipated to slow the progression of non-CNS manifestations of disease (117) (118).

i. How is optimal care delivered for a patient with ASMD?

Statement 18: *Patients with ASMD exhibit variably progressive multisystem disease and benefit from multidisciplinary and multi-professional follow up from physicians and allied health care professionals with experience in this condition. Wherever possible, patients identified with ASMD should be referred to a centre with expertise in the care of this condition.*

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (75%), mostly agree (19%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Experience from other ultra-rare, multisystemic diseases showed that patients who have access to a highly specialised clinical service reported high levels of satisfaction in their care. Patient treatment compliance and clinic attendance was better in a multi-disciplinary clinic compared to the usual standard of care (119). Depending on the country's health care service setup, level of expertise and patient needs, a multi-disciplinary team (MDT) can be formed to enable ASMD patients to receive a collaborative management plan from a wide range of experts in an integrated manner. Specialists in the different disciplines (Table 3) have to work together to integrate information and care as much as possible.

International expert guidelines have been established to monitor ASMD given the multi-systemic involvement and progressive nature of the disorder. Monitoring goals should be established at diagnosis and reviewed regularly, aimed at identifying and managing disease complications, and enhancing quality of life (118).

ii. How should burden of illness be assessed?

The clinical phenotype and life expectancy of patients with ASMD vary widely depending on the spectrum/type of the disease, age of onset, extents of target organ involvements and pre-existing/impending complications (47). ASMD type A is the most severe form with a relatively homogenous natural history of rapid progression and short life expectancy (47) (37). On the other hand,

individuals with ASMD type B have a wide range of disease manifestations, variable rate of disease progression, severity level and life expectancy (30) (29) (31). Individuals with ASMD type A/B have a phenotype intermediate between types A and B that typically includes a more slowly progressive neurodegenerative course. Recommendations for clinical monitoring of patients with ASMD have been published (118). The following assessments should take place at the time of diagnosis or symptom onset and at regular intervals for optimal symptom control and maintain functional capacity (Table 4).

1. Growth and nutrition

Statement 19

The growth of children with ASMD (height, weight and head circumference) should be assessed at regular intervals as part of routine health assessments. In addition, adult patients should undergo a careful assessment of their anthropometric measurements.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (25%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Faltered growth is common in children with all types of ASMD and is frequently associated with significant bone age delay. Degree of growth restriction appears to correlate inversely with organomegaly (120). Children with ASMD A/B and B often have delayed onset of puberty (47) (121).

2. Developmental assessments

Statement 20

Children with ASMD should have assessments of their age-appropriate acquisition of developmental milestones. Developmental screens can be performed by primary health care providers, and more formal age-appropriate developmental assessments should be performed as part of MDT assessments. Those with developmental milestones concern should have accesses to early intervention and development support.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (87%), mostly agree (13%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Delayed acquisition of developmental milestones is seen in patients with ASMD type A and common in children with type A/B. Regular evaluation of their motor and cognitive function, speech and language is indicated. Consideration should be given to changes in these abilities that may impact on daily living activities. Testing should be age and functionally appropriate, using standardised assessment tools.

Strategies to ensure the safety of the patient's environment and the availability of support mechanisms are essential to improve the quality of life of the patient/families. Appropriate ongoing education and developmental support into adulthood and beyond is required.

3. Physical examination

Statement 21

Individuals with ASMD should undergo a comprehensive physical examination including detailed neurological assessment at the time of diagnosis and thereafter on regular interval.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (81%), mostly agree (6%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Detailed neurologic examination is particularly important for newly diagnosed children, especially when the ASMD type has not yet been established. The presence or absence of neurologic findings may help determine the phenotype and enable more accurate prognostics.

4. Routine monitoring laboratory tests

Statement 22

Biochemical and haematological abnormalities are common in patients with ASMD and hence they need blood tests at baseline and regular interval. These include but are not limited to, full blood cell count, liver enzymes, vitamin D, lipid profile, clotting markers, enhanced liver fibrosis test, lysosphingomyelin and PPCS.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (44%), mostly agree (44%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Haematological abnormalities such as thrombocytopenia, leukopenia and anaemia are common ranging from 21–53% study population (41). Mixed dyslipidaemia with atherogenic lipoprotein profile is highly suggestive of ASMD. Liver function test abnormalities such as raised transaminases can occur in up to 75% of patients with ASMD(37) (30). Lysosphingomyelin appears to be a valuable biomarker for overall ASMD disease severity (84).

5. Evaluation of liver and spleen

Statement 23

Hepatosplenomegaly is present in most ASMD patients at the time of diagnosis. We recommend liver and spleen MRI including volumetric assessment, although ultrasounds can be performed in younger patients.

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

The most common observation at presentation is splenomegaly (78%) and hepatomegaly (73%) (41). The sphingomyelin deposition in the liver poses an increased risk of progression to fibrosis, cirrhosis and eventually liver failure and its related complications. Liver failure is the second common cause of death in patients with ASMD of type B (43). Non-invasive evaluation of liver fibrosis by ultrasound/MRI and elastographic techniques at regular interval is warranted (118).

6. Evaluation of pulmonary disease

Statement 24

Interstitial lung disease occurs in the majority of ASMD patients at some time in their lives, especially in the younger ones. Chest X ray and high resolution chest CT scan should be performed at baseline and regular interval as required. Impaired O_2/CO_2 exchange is reflected by compromised diffusion capacity. This may be associated with shortness of breath and greater disease severity. Chest tomography is the most useful imaging modality to evaluate the interstitial lung disease, with typical ground glass appearance. Pulmonary function tests (especially DLCO – diffusion capacity for carbon monoxide) - are important to detect impaired diffusion capacity.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Pulmonary pathology in ASMD typically manifests as "interstitial lung disease" (ILD) caused by sphingomyelin accumulation in alveolar macrophages within the alveolar septum. This results in distortion and thickening of the alveolar septum, and impaired O_2/CO_2 exchange (122).

Pulmonary dysfunction is a key clinical characteristic of all ASMD phenotypes. Pulmonary involvement affects many patients with ASMD to some degree, with some patients experiencing progressive lung deterioration and respiratory failure (123) (118) (37). However, several attenuated adult patients may have no evidence of lung disease (29).

For patients with ASMD type A, pulmonary manifestations can include frequent infections (e.g., pneumonia) and respiratory arrest (28). For patients with ASMD type B and A/B, pulmonary manifestations can include: frequent infections, shortness of breath, and exercise dyspnea and reduced exercise tolerance (123) (37) (47) (41). Diffusing capacity of carbon monoxide (DLCO) is a clinically meaningful measure of disease burden for patients with ASMD (127). However, due to the rarity of ASMD and often inadequate diagnostic screening initiatives, available evidence remains limited, especially on mortality/survival, frequency, and timing of significant clinical events (127).

7. Evaluation of cardiovascular disease

Statement 25

Adult patients with ASMD usually have an atherogenic lipid profile and hence may be at an increased risk of premature cardiovascular events. Appropriate assessments including echocardiogram and EKG should be performed as clinically indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (56%), mostly agree (31%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Dyslipidemia with low high-density lipoprotein cholesterol, increased low density lipoprotein cholesterol, and hypertriglyceridemia appears to be associated with early atherosclerotic heart disease (46) in line with the general population. To date, increased risk of premature CV events is not proven despite atherogenic lipid profile as well as coronary artery status. Therefore, the use of lipid lowering therapy (e.g. statins) in ASMD patients as a primary prevention needs careful consideration in the context of the overall cardiovascular risk of the individual.

8. Evaluation of skeletal disease

Statement 26

Individuals with ASMD may be at risk of osteopenia and osteoporosis. Bone density studies could be performed in individuals as clinically indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (63%), mostly agree (31%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Adults with ASMD type B may have some degree of osteopenia or osteoporosis. Children with ASMD may also have low Z scores for bone mineral content and density (45). Pathologic fractures have been

reported in some ASMD individuals with severe disease (124) However, treatment with of bisphosphonates may carry a risk as they have been shown to be strong inhibitors of ASM (125).

iii. Symptoms management

i. What optimal symptomatic therapy should be considered for a patient with ASMD deficiency?

1. Liver disease and splenomegaly

Statement 27

Liver enlargement with elevated transaminases is common in ASMD, which may progress to fibrosis and cirrhosis in the third to fourth decade. In some severely affected individuals, liver failure may occur resulting in portal hypertension with associated oesophageal varices, ascites, and hepatic encephalopathy. Close monitoring of liver function and early consultation with a hepatologist is recommended as needed.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Advanced cases of chronic liver disease (CLD) with fulminant liver failure were reported in a few adults with ASMD (37) (42). The rate of progression of liver disease is extremely variable (30) (41) (43). More research is needed to determine the cause and rate of progression of advanced CLD in ASMD patients. Liver failure is one of a leading cause of mortality in ASMD patients (37) and adult patients with evidence of transaminitis/fibrosis should be followed by hepatologists. Liver biopsy in persons with evidence of deteriorating liver function may be indicated if non-invasive means to ascertain fibrosis are not available (119). If patients are known to have advanced CLD then they should be monitored and treated for risk of gastrointestinal bleeding and surveillance for hepatocellular cancer. The outcomes of liver transplantation have been reported in several individuals with ASMD type B who had progressive liver dysfunction. In addition to improvements in hepatic function and dyslipidemia, significant improvements in lung disease and paediatric growth parameters were observed (119) (41) (126) (127).

Splenectomy on the other hand is not recommended as it may lead to exacerbation of liver disease and increased sphingomyelin accumulation in the lungs causing progressive respiratory insufficiency. If splenectomy is required due to massive splenomegaly, pressure symptoms, and severe unsustainable hypersplenism, then partial splenectomy or partial splenic arterial embolization are options. If partial or total splenectomy should be performed according to surgical indications, standard post-surgical antibiotic prophylaxis and vaccinations should be used.

2. Respiratory system

Statement 28

ASMD patients with pulmonary and/or neurological disease are at an increased risk of frequent respiratory infection including aspiration pneumonia and care givers should be vigilant in preventing and/or promptly managing respiratory infection. Older individuals with ASMD should have their history reviewed for respiratory symptoms and lung function test along the need for non-invasive ventilation. Vaccination against influenza, COVID-19 and Streptococcus pneumoniae should be encouraged.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (63%), mostly agree (25%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Respiratory disease is a primary and independent contributor to mortality in ASMD type A (27.7% of cases) (43), and disease burden and morbidity for patients with chronic forms of ASMD (47) (42) (30) (41) (32). Progressive interstitial lung disease is a prevalent clinical feature of ASMD contributing to decreased QoL and increased disease burden.

Patients with progressive pulmonary disease may require long-term oxygen therapy. Other treatment for interstitial lung disease (e.g., steroids) and therapeutic lung lavage may be indicated. Endoscopic treatment of bronchial casts may be urgently required. Lung transplantation does not have proven extra benefit. Supporting measures such as smoking cessation should be encouraged. Other treatments for interstitial lung disease (e.g., steroids) have not been well studied (128) (129). Therapeutic bronchopulmonary lavage for some patients with ASMD-B has been associated with temporary clinical improvement, but with variable results (128) (129) (116). Four cases of lung transplantation in ASMD-B with variable results have been reported (130) (131) (132) (133). However, lung transplantation involves two important issues: 1) the disease may reappear; and 2) debulking of ceramide after cleavage of the sphingomyelin substrate by transplanted lung cells may cause a pro-inflammatory cascade, by releasing ceramide similar to enzyme replacement therapy (ERT) (134).

3. Haematology

Statement 29

Bleeding tendency is common but the type and severity of bleeding is highly variable. Consultation with a haematologist in case of severe thrombocytopenia is recommended for evaluation and management.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

The most common bleeding event is epistaxis and mostly self-limiting. However, significant bleeding event such as post-surgical and trauma-related haemorrhages and life-threatening, liver-disease associated oesophageal variceal disease can occur (43) (37). Although thrombocytopenia is a common manifestation of ASMD, the platelets are rarely low enough to cause significant bleeding suggesting the presence of additional factors that impact clotting.

4. Swallowing and diet

Statement 30

Children with neuronopathic ASMD (types A and A/B) should undergo a comprehensive swallowing assessment by a speech and language therapist. Instruction in dietary modification and compensatory postures may be beneficial for individuals with dysphagia. The family should be educated regarding the progressive worsening of swallowing skills and increased risk of aspiration as part of an ongoing care. Nasogastric tube feeding or surgical placement of feeding tube can be considered to enhance caloric intake and possibly reduce the risk of aspiration, although the family should be counselled that this is optional given that ASMD type A is, at present, uniformly fatal.

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

5. Irritability and sleep disturbance

Statement 31

Clinicians and caregivers of individuals with Type A ASMD should be aware that there is an increased prevalence of irritability and sleep disturbance affecting quality of life for entire family. Management plans for irritability and sleep disturbance should be considered as indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

6. Chronic pain and fatigue

Statement 32

Chronic pain and fatigue may occur in the majority of ASMD patients at some time in their lives. Optimising pain management and assessment for fatigue should be performed as indicated according to the local standards.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (50%), mostly agree (44%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

7. Psychosocial wellbeing

Statement 33

Clinicians, caregivers and individuals with ASMD should be aware that there is an increased prevalence of behavioural problems and other psychiatric disorders such as anxiety and depression in ASMD. There should be a low threshold for referral to a clinical psychology/psychiatric team as appropriate, and for the use of both non-pharmacological and/or pharmacological treatments.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (62.5%), mostly agree (18.75%), partially agree (0%), mostly disagree (18.75%) and completely disagree (0%).

As with most ultra-rare diseases, there is a limited robust data regarding the disease burden and the impact on the psychosocial wellbeing of an individual with ASMD and their immediate family members (50). In a small study based on interviews with patients and caregivers, numerous psychosocial stressors such as social isolation, peer rejection, chronic pain, fatigue and living with a life-threatening disease were associated with high level of stress, anxiety and depression (49). In addition, children with ASMD type A show increased signs of irritability, prolonged crying and sleep disturbance (28). Similarly, depression and psychosis requiring anti-depressant/psychotic therapies may occur in adult patients with ASMD (47).

iv. Disease modifying therapy

Olipudase alfa

Statement 34

Olipudase alfa, an enzyme replacement therapy (ERT) using human recombinant acid sphingomyelinase, is indicated as a disease-modifying enzyme replacement therapy for the long-term treatment of non-central nervous system (CNS) manifestations of ASMD. At the time of writing, olipudase alfa has received regulatory approval in Brazil, Japan, Europe and the United States of America and is awaiting approval in other countries.

- Strength of recommendation: 1
- Level of evidence: B

- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Four studies have been completed, two in phase 1 (NCT00410566; NCT01722526), one in phase 1/2 (NCT02292654) and the other in phase 2/3 (NCT02004691). A phase 1 single ascending dose study of olipudase alfa, aiming to address the safety of ASM ERT in adult patients identified 0.6 mg/kg as the starting dose of olipudase alfa and supported a dose escalation strategy to gradually clear accumulated sphingomyelin (NCT00410566; (135). This study reported that the regimen was generally well tolerated, showing reduced liver and spleen volumes, improved lung diffusing capacity, and improved haematological markers and plasma lipid profile (136) (137).

ASCEND (adult) (NCT02004691/Sanofi Genzyme), is a Phase 2/3, international multicentre, randomized, 52-week, double-blind, placebo-controlled trial in 36 adults with chronic ASMD randomized 1:1 to receive olipudase alfa or placebo. One-year results have been published (86). A Phase 1/2, international, multicentre, open label single-arm ASCEND-Peds study (NCT02292654/Sanofi Genzyme) was conducted in 20 paediatric patients (aged between 1.5 and 17.5 years) to evaluate the safety, tolerability and efficacy outcomes at 52 weeks, by measuring pharmacokinetics, spleen and liver volumes, lung diffusing capacity (DL_{CO}), lipid profiles, platelet count, biomarkers and height Z-score, of olipudase alfa with ascending doses to reach the maintenance dose of 3 mg/kg at least by week 64 (85). In summary, olipudase alfa was well-tolerated in children and adults and, after 1 year of treatment, resulted in improved lung function, reductions in spleen and liver volumes, improved platelet counts and lipid profiles, reductions in disease biomarkers, and (in children) improved growth (85) (138) (139) (86).

Haematopoietic stem cell transplantation

Statement 35

Variable results have been reported with Haematopoietic stem cell transplantation (HSCT) and morbidity and mortality associated with HSCT limits its use. HSCT may be useful to correct the metabolic defect, improve blood counts, and reduce increased liver and spleen volumes, but does not address neurologic disease. Therefore, any attempts to perform HSCT in individuals with clinically evident neurologic disease should be considered experimental as it does not correct or stabilize neurologic disease.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (56%), mostly agree (31%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

v. Transition, family and reproductive care and advanced care planning

1. Transition

Statement 36

Most children with chronic visceral ASMD are expected to reach adulthood with complex medical and psychosocial needs. The process of transition from paediatric to adult services should begin early and must include appropriate services in the community to provide a seamless transition from childhood to adult life. Individuals with ASMD may benefit from a detailed assessment identifying barriers to independence.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

2. Family and reproductive care

Statement 37

Once the SMPD1 pathogenic variants have been identified in an affected family member, diagnostic testing of all at-risk family members is warranted to allow for early diagnosis and treatment of ASMD. All patients identified pre-symptomatically should be referred to specialist centres for surveillance and early detection of disease progression.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (75%), mostly agree (25%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *SMPD1* pathogenic variant and to allow testing for at risk relatives. Either test for the familial *SMPD1* pathogenic variants or measure residual acid sphingomyelinase enzyme activity is appropriate to detect affected individuals.

Individuals at risk will require careful genetic counselling by genetics professionals to inform affected persons and their families regarding nature and implications of ASMD to facilitate medical and personal decision making.

Statement 38

Prenatal ASMD testing for a pregnancy at increased risk should be offered to all at risk couples, subject to local protocols and laws. Molecular testing for the familial SMPD1 variants using chorionic villus sampling (CVS) or amniotic fluid sampling is the most common means of testing at risk pregnancies. Biochemical prenatal diagnosis by testing of ASM enzyme activity in CVS or cultured amniocytes may also be used for at risk pregnancies.

- Strength of recommendation: 2

- Level of evidence: B
- Experts' opinion: completely agree (63%), mostly agree (31%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

The determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing should be carried out before pregnancy. Genetic counselling (including discussion of potential risks to offspring and reproductive options) should be offered to young adults who are affected, are carriers, or are at risk of being carriers.

3. Advance care planning

Statement 39: *Specialist centre care providers, family physician/ paediatrician, health care decision makers, local palliative care services and patient advocates should develop close working links to select treatments and develop disease management plans that address patients' holistic needs in order to support individuals, caregivers and families with ASMD through the lifespan, including: a) advance care planning with regular updating, b) proper flow of communication and information for patients and their families, and c) a designated point of contact for each stage in their care pathway. An individual identified as being near the end of life may benefit from ongoing access to palliative care services including for symptom control, respite, psychological and spiritual support.*

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Table 3
Multidisciplinary assessment of patients with ASMD

Discipline	Features of ASMD for which this discipline may be of assistance	Recommended for all ASMD or as needed
Primary care physician	Assist with general medical care; Coordinate specialists; Provide support for family	All
Metabolic diseases specialist	Diagnosis of ASMD and exclusion of other disorders in the differential diagnosis; Ongoing patient assessment for disease progression and response to therapy. Coordinate the overall care working with primary care physician	All
Neurologist	Assess the possible neurological manifestation of the disease and manage accordingly	All
Hepatologist	Periodic assessments of liver derangements; Manage the impending/existing liver failure	As needed
Haematologist	Assess the risk of bleeding disorder and long term complications	As needed
Pulmonologist	Assess the baseline respiratory functions and periodic assessment for deterioration; Manage the pulmonary disease and its complications	As needed
Genetic counsellor	To inform affected persons and their families regarding nature and implications of ASMD to facilitate medical and personal decision making; Provide counselling for families as to recurrence risk and options for prenatal diagnosis if desired	All
Lipidologist/ Cardiologist	Manage the mixed dyslipidemia, and perform cardiovascular risk assessment for indicated primary or secondary prevention interventions	As needed
Psychiatrist/clinical psychologist	Assess for behavioural disturbances, depression and manage accordingly	As needed
Speech and language therapist	Assess for dysphagia and aspiration risk; Speech and feeding therapy for children with neuronopathic phenotypes	As needed
Occupational and physical therapists/Rehabilitation physician	Assess and develop aids and home adjustments as needed for patients with communication and physical challenges	As needed
Nutritionist	Periodic assessments of nutritional status in patients who may be losing weight due to dysphagia or side effects of therapy; Gastrostomy tube insertion as indicated	As needed
Social worker	Support of patients and families living with disabilities who require enhanced resources in the community	As needed

Discipline	Features of ASMD for which this discipline may be of assistance	Recommended for all ASMD or as needed
Developmental and Behavioral Paediatrician	Assess for the presence or absence of developmental delays in children; recommend appropriate therapies and educational interventions	As needed

Table 4
Recommended assessments

Recommended assessment	Rationale	Frequency	Recommended for all ASMD or as needed
Baseline history	Establish natural history, systemic involvement, current level of disease severity and estimate rate of progression	At diagnosis	All
Interval history	Establish rate of disease progression; Monitor for compliance with and side effects from therapy.	3–12 monthly / Each visit	As needed
Physical examination	Document growth parameters, assess for neurological features and organomegaly, assess for fatigue, abdominal pain, and/or bleeding tendency at least annually.	At diagnosis then 6–12 monthly / Each visit	As needed
Nutrition	Evaluation of nutritional status and safety of oral intake	At diagnosis then at each visit	As needed
Pulmonary assessment	Assess recurrent chest infections Assess for shortness of breath	At diagnosis then at each visit	All
	Pulmonary function testing including assessment of diffusing capacity in persons old enough to cooperate	At diagnosis then annually	As needed
	Chest radiograph and high resolution chest CT to assess extent of interstitial lung disease	At diagnosis regardless of age then every 2 to 4 years	All
Musculoskeletal assessment	Assess for fractures and/or extremity pain	At diagnosis then each visit	All
Neurologic assessment	Comprehensive neurologic evaluation, assess neurologic function and frequency of headaches	At diagnosis then annually	As needed
Ophthalmology evaluation	Presence of cherry-red spots at baseline and document	At diagnosis	All
Cardiac assessment (Adult only)	EKG, echocardiogram,	At diagnosis Every 3 to 5years	As needed

Recommended assessment	Rationale	Frequency	Recommended for all ASMD or as needed
Blood investigations	Serum chemistries including liver transaminases (ALT, AST), albumin, and clotting factors to evaluate for progression of hepatic dysfunction Complete blood count to evaluate for thrombocytopenia, leukopenia, anaemia, and increased bleeding Measurement of lipid profile	At diagnosis then at least annually.	As needed
Imaging studies	Radiologic measurements of liver and spleen size as needed. Liver elastography or FibroScan to evaluate for hepatic fibrosis and cirrhosis	At diagnosis then as needed	As needed
Swallowing assessment	Swallowing assessment in all patients at risk; Document presence of dysphagia and aspiration and response to therapy	At diagnosis and then 6 monthly in children; in adults, frequency could be reduced to every 12 months if asymptomatic and disease is stable	As needed
Developmental or cognitive assessment	Developmental assessment, monitor developmental progress and educational needs (Evaluation for early intervention / special education)	At diagnosis then at each visit	As needed
	Document baseline degree of cognitive impairment including motor, adaptive, cognitive and speech/language and monitor response to therapy	At diagnosis; 6 monthly in children;12 monthly in adults	As needed
Neuropsychiatric evaluation	Document psychiatric manifestations and response to therapy	At diagnosis then 6–12 monthly	As needed
Family support and resources	Assess need for family support and resources at each visit. Assess need for community or online resources such as Parent to Parent; Social work involvement for parental support; Home nursing referral. Assess for any change in social, domestic, or school or work related activities.	At diagnosis then each visit	As needed

Conclusion

These guidelines are the result of an international collaboration of experts in the care of ASMD and the evidence gathered to write the guidelines are the best evidence available to the experts. The guidelines address the management of patients affected by subtypes of ASMD and are intended to facilitate optimal care to all ASMD patients regardless of their demography and access to health care. In addition, it defines the standard of care against which practice can be audited and best practices can be disseminated. The Guidelines Development Group commits itself to revise this work in 3–5 years' time to reflect new data pertaining to future research findings and new therapies.

Methods

This guideline was developed by expert physicians, geneticists, allied healthcare professionals and patient support groups involved in the International Niemann-Pick Disease Registry (INPDR) project (www.inpdr.org). The INPDR is a subsidiary of the International Niemann-Pick Disease Alliance (INPDA), a global network of not-for-profit organisations, supporting individuals affected by Niemann-Pick diseases. One of the goals of the INPDR is to support patients and care givers to provide equitable care of Niemann-Pick disease patients by standardizing the quality of care all patients receive.

The Guidelines Development Group (GDG) consisted of expert representatives from a range of professional groups including paediatric and adult metabolic specialists, geneticists, neurologists, hepatologists, pulmonologists, epidemiologists, clinical biochemists, specialist nurses and patient support group representatives. The GDG committee at their first meeting agreed upon the remit of the guidelines and selected a list of guidelines topics for development.

A systematic literature review on ASMD in the last 20 years until December 2021 was carried out using Medline, Embase and the Cochrane Library. The following search-string was used for PubMed, with appropriate modifications for the other two databases: (Acid Sphingomyelinase Deficiency[Text Word]) OR (Niemann-Pick B[Text Word]) OR (Niemann-Pick A[Text Word]). Relevant papers which were previously published and considered by the GDG members as important were included. Searches were limited to English language publications only. The initial search identified 720 reference abstracts, of which 195 were accepted as relevant after the first screen. References related to a single topic (i.e., Epidemiology, Genetics, Pathophysiology, Clinical Diagnosis, Laboratory, Imaging, Therapy, Recommendations) were pulled together and the GDG was divided into subgroups aimed to critically appraise references devoted to a specific topic. The committee met virtually twice (February 2022 and June 2022), face to face once (August 2022) and corresponded by email on a regular basis throughout the duration of the guideline development process. Additionally, an in-person meeting to consult with patients regarding guideline contents took place (August 2022). During the first meeting, the GDG adopted the second version of the Appraisal of Guidelines for Research & Evaluation (AGREE II) system as methodological approach in order to meet the guideline development standards outlined in the AGREE II system: however, our

guidelines didn't completely meet 5 of the 23 items outlined in the AGREE II system, and we haven't calculated quality scores for all appraisal items (140).

Relevant papers were evaluated by members of the GDG before the evidence was considered. Sub-group leaders individually assessed the selected literature and wrote a short document containing key questions to be addressed in the topic and drafted key statements and further explanation describing the study findings and related recommendations. All GDG members discussed the draft documents at the virtual and face to face meetings. Evidence levels were classified in accordance with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology and recommendations were graded from A to C (Table 5). In addition, for the adoption of recommendations, we structured a panel of experts that represented a group of specialists caring for ASMD patients and used the Delphi method for the development of the guidelines. In total, 24 international experts participated, and after the first round of Delphi consensus 5 statements required substantial revision and the expert opinion expressed in the guidelines were based on the revised statements.

Table 5
Evidence levels and strength of recommendations

Item	Definition
Level of evidence	
II. High-quality evidence	Further research is unlikely to change our confidence in the estimate of effect. Consistent evidence from Randomised Controlled Trials (RCTs) without important limitations or exceptionally strong evidence from observational studies.
III. Moderate-quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies.
IV. Low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws, or indirect evidence, or expert's consensus.
Strength of recommendation	
1. Strong recommendation	Recommendation can apply to most patients in most circumstances.
2. Weak recommendation	The best course of action may differ depending on circumstances or patient or society values. Other alternatives may be equally reasonable.

The guidelines will be published in an open access journal and will be promoted through the INPDR and the International Niemann-Pick Disease Alliance (INPDA) websites. These guidelines will be reviewed every 3–5 years to reflect new data pertaining to future research findings, new therapies and the

development of diagnostic methods. The development of these guidelines was made without external financial support from industries involved in the manufacturing of therapies for ASMD. Competing interests of members of the guideline development group have been recorded in writing and addressed.

Developing treatment guidelines in an objective and scientific manner for a rare disease is challenging owing to the relative lack of randomized controlled trials (RCT). We have attempted to apply all the AGREE II domains in our guidelines development. However, the AGREE II methodology was developed for common disorders, where there is wealth of evidence in a form of RCTs. Despite our best effort, we found it difficult to apply AGREE II in full for an ultra-rare disorder. We have therefore created guidelines using the best available data and expert opinion.

Abbreviations

7KC: 7-ketocholesterol;

AGREE II: Appraisal of Guidelines for Research & Evaluation;

ASMD: Acid sphingomyelinase deficiency;

BMC: Bone mineral content;

BMD: Bone mineral density;

C-triol: cholestane-3β,5α,6β-triol;

CHQ-PF50: Child Health Questionnaire – Parental Form 50 for pediatric patients;

CLD: chronic liver disease;

CNV: copy number variations;

DBS: Dried blood spots;

DLCO: Diffusing capacity of carbon monoxide;

ERT: enzyme replacement therapy;

GDG: Guidelines Development Group;

GRADE: Grading of Recommendations, Assessment, Development and Evaluations;

HSCT: Haematopoietic stem cell transplantation;

INPDA: International Niemann-Pick Disease Alliance;

INPDR: International Niemann-Pick Disease Registry;

LAL-D: Lysosomal acid lipase deficiency;

LSD: Lysosomal storage diseases;

lyso-Gb1: Glucosylsphingosine;

lyso-SM: Lysosphingomyelin;

lyso-SM509: Lysosphingomyelin-509;

MDT: multidisciplinary team;

MoM: median of controls;

NPC: Niemann-Pick disease type C;

NPD: Niemann-Pick disease;

PPCS: N-palmitoyl-O-phosphocholine-serine (previously named lyso-SM509

QoL: quality of life;

RCT: randomized controlled trials;

SF-36: Short-Form 36;

SPC: Sphingosylphosphorylcholine;

TCG: N-(3β,5α,6β-trihydroxycholan-24-oyl) glycine;

VUS: variants of uncertain significance;

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests

Sanofi has provided financial support to AD, AL, ES, OL, RG, SB and TH, research grant to ES and TH, and honorarium to AD, ES, OL, MTV and RG. Honorarium has been provided by Orphazyme to AD and MTV.

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Authors' contributions

TG conceived the idea. AD, ES, TG, MM and MW, led the various section of guidelines development group in reviewing the literature and drafting their respective section of the manuscript. All authors have contributed to the guidelines development process of planning, writing and revising of the manuscript. All authors read and approved the final manuscript.

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References

1. Schuchman EH, Levran O, Pereira LV, Desnick RJ. Structural organization and complete nucleotide sequence of the gene encoding human acid sphingomyelinase (SMPD1). Genomics. 1992 Feb;12(2):197–205.
2. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Jang W, Karapetyan K, Katz K, Liu C, Maddipatla Z, Malheiro A, McDaniel K, Ovetsky M, Riley G, Zhou G, Holmes JB, Kattman BL, Maglott DR. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan;46(D1)(4):D1062–7.
3. Stenson PD, Ball EV, Mort M, Phillips AD, Shiel JA, Thomas NS, Abeysinghe S, Krawczak M, Cooper DN. Human Gene Mutation Database (HGMD): 2003 update. Hum Mutat. 2003 Jun;21(6):577–81.
4. Simonaro CM, Park JH, Eliyahu E, Shtraizent N, McGovern MM, Schuchman EH. Imprinting at the SMPD1 locus: implications for acid sphingomyelinase-deficient Niemann-Pick disease. Am J Hum Genet. 2006 May;78(5):865–70.
5. Niemann A. Ein unbekanntes Krankheitsbild. Jahrb Kinderheilkd. 1914;79(1).
6. Pick L. Über die lipoidzellige splenohepatomegalie typus Niemann-Pick als Stoffwechselerkrankung. Med Klin (Munich). 1927;23:1483–6.

7. Pfändler U. La maladie de Niemann-Pick dans le cadre des lipoidoses. Schweiz Med Wschr. 1946;76.
8. Crocker AC, Farber S. Niemann-Pick disease: a review of eighteen patients. Med (Baltim). 1958 Feb;37(1):1–95.
9. Kruth HS, Comly ME, Butler JD, Vanier MT, Fink JK, Wenger DA, Patel S, Pentchev PG. Type C Niemann-Pick disease. Abnormal metabolism of low density lipoprotein in homozygous and heterozygous fibroblasts. J Biol Chem. 1986 Dec 15;261(35):16769–74.
10. Carstea ED, Morris JA, Coleman KG, Loftus SK, Zhang D, Cummings C, Gu J, Rosenfeld MA, Pavan WJ, Krizman DB, Nagle J, Polymeropoulos MH, Sturley SL, Ioannou YA, Higgins ME, Comly M, Cooney A, Brown A, Kaneski CR, Blanchette-Mackie EJ, Dwyer NK, Neufeld EB, Chang TY, Liscum L, Strauss JF 3rd, Ohno K, Zeigler M, Carmi R, Sokol J, Markie D, O'Neill RR, van Diggelen OP, Elleder M, Patterson MC, Brady RO, Vanier MT, Pentchev PG, Tagle DA. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. Science. 1997 Jul 11;277(5323):228 – 31.
11. Naureckiene S, Sleat DE, Lackland H, Fensom A, Vanier MT, Wattiaux R, Jadot M, Lobel P. Identification of HE1 as the second gene of Niemann-Pick C disease. Science. 2000 Dec 22;290(5500):2298 – 301.
12. Brady RO, Kanfer JN, Mock MB, Fredrickson DS. The metabolism of sphingomyelin. II. Evidence of an enzymatic deficiency in Niemann-Pick diseae. Proc Natl Acad Sci U S A. 1966 Feb;55(2):366–9.
13. Pavlů-Pereira H, Asfaw B, Poupctová H, Ledvinová J, Sikora J, Vanier MT, Sandhoff K, Zeman J, Novotná Z, Chudoba D, Elleder M. Acid sphingomyelinase deficiency. Phenotype variability with prevalence of intermediate phenotype in a series of twenty-five Czech and Slovak patients. A multi-approach study. J Inherit Metab Dis. 2005;28(2):203–27.
14. McGovern MM, Dionisi-Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, Eugen Mengel K, Mistry PK, Schuchman EH, Wasserstein MP. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med. 2017 Sep;19(9):967–74.
15. Schuchman EH, Miranda SR. Niemann-Pick disease: mutation update, genotype/phenotype correlations, and prospects for genetic testing. Genet Test. 1997;1(1):13–9.
16. Schuchman EH. The pathogenesis and treatment of acid sphingomyelinase-deficient Niemann-Pick disease. J Inherit Metab Dis. 2007 Oct;30(5):654–63.
17. Pinto R, Caseiro C, Lemos M, Lopes L, Fontes A, Ribeiro H, Pinto E, Silva E, Rocha S, Marcão A, Ribeiro I, Lacerda L, Ribeiro G, Amaral O, Sá Miranda MC. Prevalence of lysosomal storage diseases in Portugal. Eur J Hum Genet. 2004 Feb;12(2):87–92.
18. Poupetová H, Ledvinová J, Berná L, Dvoráková L, Kozich V, Elleder M. The birth prevalence of lysosomal storage disorders in the Czech Republic: comparison with data in different populations. J Inherit Metab Dis. 2010 Aug;33(4):387–96.
19. Chin SJ, Fuller M. Prevalence of lysosomal storage disorders in Australia from 2009 to 2020. Lancet Reg Health West Pac. 2021 Dec 12;19:100344.
20. Hult M, Darin N, von Döbeln U, Månsson JE. Epidemiology of lysosomal storage diseases in Sweden. Acta Paediatr. 2014 Dec;103(12):1258–63.

21. Walkley SU, Vanier MT. Secondary lipid accumulation in lysosomal disease. Biochim Biophys Acta. 2009 Apr;1793(4):726–36.
22. Vanier MT. Biochemical studies in Niemann-Pick disease. I. Major sphingolipids of liver and spleen. Biochim Biophys Acta. 1983 Jan 7;750(1):178–84.
23. Breiden B, Sandhoff K. Mechanism of Secondary Ganglioside and Lipid Accumulation in Lysosomal Disease. Int J Mol Sci. 2020 Apr 7;21(7):2566.
24. Elleder M, Cihula J. Niemann-Pick disease (variation in the sphingomyelinase deficient group). Neurovisceral phenotype (A) with an abnormally protracted clinical course and variable expression of neurological symptomatology in three siblings. Eur J Pediatr. 1983 Sep;140(4):323–8.
25. Rodriguez-Lafrasse C, Vanier MT. Sphingosylphosphorylcholine in Niemann-Pick disease brain: accumulation in type A but not in type B. Neurochem Res. 1999 Feb;24(2):199–205.
26. Thurberg BL, Wasserstein MP, Schiano T, O'Brien F, Richards S, Cox GF, McGovern MM. Liver and skin histopathology in adults with acid sphingomyelinase deficiency (Niemann-Pick disease type B). Am J Surg Pathol. 2012 Aug;36(8):1234–46.
27. Schuchman EH, Wasserstein MP. Types A, Niemann-Pick B disease. Best Pract Res Clin Endocrinol Metab. 2015 Mar;29(2):237 – 47.
28. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. Neurology. 2006 Jan 24;66(2):228–32.
29. Hollak CE, de Sonnaville ES, Cassiman D, Linthorst GE, Groener JE, Morava E, Wevers RA, Mannens M, Aerts JM, Meersseman W, Akkerman E, Niezen-Koning KE, Mulder MF, Visser G, Wijburg FA, Lefeber D, Poorthuis BJ. Acid sphingomyelinase (Asm) deficiency patients in The Netherlands and Belgium: disease spectrum and natural course in attenuated patients. Mol Genet Metab. 2012 Nov;107(3):526–33.
30. Wasserstein MP, Desnick RJ, Schuchman EH, Hossain S, Wallenstein S, Lamm C, McGovern MM. The natural history of type B Niemann-Pick disease: results from a 10-year longitudinal study. Pediatrics. 2004 Dec;114(6):e672-7.
31. Lipiński P, Kuchar L, Zakharova EY, Baydakova GV, Ługowska A, Tylki-Szymańska A. Chronic visceral acid sphingomyelinase deficiency (Niemann-Pick disease type B) in 16 Polish patients: long-term follow-up. Orphanet J Rare Dis. 2019 Feb;22(1):55. 14(.
32. Cox GF, Clarke LA, Giugliani R, McGovern MM. Burden of Illness in Acid Sphingomyelinase Deficiency: A Retrospective Chart Review of 100 Patients. JIMD Reports. 2018;119–29.
33. Ferlinz K, Hurwitz R, Weiler M, Suzuki K, Sandhoff K, Vanier MT. Molecular analysis of the acid sphingomyelinase deficiency in a family with an intermediate form of Niemann-Pick disease. Am J Hum Genet. 1995 Jun;56(6):1343–9.
34. Harzer K, Rolfs A, Bauer P, Zschiesche M, Mengel E, Backes J, Kustermann-Kuhn B, Bruchelt G, van Diggelen OP, Mayrhofer H, Krägeloh-Mann I. Niemann-Pick disease type A and B are clinically but also enzymatically heterogeneous: pitfall in the laboratory diagnosis of sphingomyelinase deficiency associated with the mutation Q292 K. Neuropediatrics. 2003 Dec;34(6):301-6.

35. Mihaylova V, Hantke J, Sinigerska I, Cherninkova S, Raicheva M, Bouwer S, Tincheva R, Khuyomdziev D, Bertranpetit J, Chandler D, Angelicheva D, Kremensky I, Seeman P, Tournev I, Kalaydjieva L. Highly variable neural involvement in sphingomyelinase-deficient Niemann-Pick disease caused by an ancestral Gypsy mutation. Brain. 2007 Apr;130(Pt 4):1050–61.
36. Wasserstein MP, Aron A, Brodie SE, Simonaro C, Desnick RJ, McGovern MM. Acid sphingomyelinase deficiency: prevalence and characterization of an intermediate phenotype of Niemann-Pick disease. J Pediatr. 2006 Oct;149(4):554–9.
37. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann-Pick disease. Genet Med. 2013 Aug;15(8):618–23.
38. Sogawa H, Horino K, Nakamura F, Kudoh T, Oyanagi K, Yamanouchi T, Minami R, Nakao T, Watanabe A, Matsuura Y. Chronic Niemann-Pick disease with sphingomyelinase deficiency in two brothers with mental retardation. Eur J Pediatr. 1978 Jul;19(4):235–40. 128(.
39. Schuchman EH, Desnick RJ. Niemann-Pick disease types A and B: acid sphingomyelinase deficiencies. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson KM, Mitchell G, editors. OMMBID-The online metabolic and molecular bases of inherited disease. New York: McGraw Hill; 2013.
40. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, Zhang Q, Peterschmitt MJ. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021 May;10(1):212. 16(.
41. McGovern MM, Wasserstein MP, Giugliani R, Bembi B, Vanier MT, Mengel E, Brodie SE, Mendelson D, Skloot G, Desnick RJ, Kuriyama N, Cox GF. A prospective, cross-sectional survey study of the natural history of Niemann-Pick disease type B. Pediatrics. 2008 Aug;122(2):e341-9.
42. Acuña M, Martínez P, Moraga C, He X, Moraga M, Hunter B, Nuernberg P, Gutiérrez RA, González M, Schuchman EH, Santos JL, Miquel JF, Mabe P, Zanlungo S. Epidemiological, clinical and biochemical characterization of the p.(Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. Eur J Hum Genet. 2016 Feb;24(2):208–13.
43. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, Imrie J, Mabe P, Takahashi T, Mengel KE, Giugliani R, Cox GF. 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 Jul;118(3):206–13.
44. Mendelson DS, Wasserstein MP, Desnick RJ, Glass R, Simpson W, Skloot G, Vanier M, Bembi B, Giugliani R, Mengel E, Cox GF, McGovern MM. Type B Niemann-Pick disease: findings at chest radiography, thin-section CT, and pulmonary function testing. Radiology. 2006 Jan;238(1):339–45.
45. Wasserstein M, Godbold J, McGovern MM. Skeletal manifestations in pediatric and adult patients with Niemann Pick disease type B. J Inherit Metab Dis. 2013 Jan;36(1):123–7.
46. McGovern MM, Pohl-Worgall T, Deckelbaum RJ, Simpson W, Mendelson D, Desnick RJ, Schuchman EH, Wasserstein MP. Lipid abnormalities in children with types A and B Niemann Pick disease. J Pediatr. 2004 Jul;145(1):77–81.

47. 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 Feb 23;12(1):41.
48. National Niemann-Pick Disease Foundation. Niemann-Pick disease overview — types A, B and C. 2015.
49. Henderson SL, Packman W, Packman S. Psychosocial aspects of patients with Niemann-Pick disease, type B. Am J Med Genet A. 2009 Nov;149A(11):2430–6.
50. Pokrzywinski R, Hareendran A, Nalysnyk L, Cowie S, Crowe J, Hopkin J, Joshi D, Pulikottil-Jacob R. Impact and burden of acid sphingomyelinase deficiency from a patient and caregiver perspective. Sci Rep. 2021 Oct;25(1):20972. 11(.
51. Elbin CS, Olivova P, Marashio CA, Cooper SK, Cullen E, Keutzer JM, Zhang XK. The effect of preparation, storage and shipping of dried blood spots on the activity of five lysosomal enzymes. Clin Chim Acta. 2011 Jun 11;412(13–14):1207–12.
52. Kampine JP, Brady RO, Kanfer JN, Feld M, Shapiro D. Diagnosis of gaucher's disease and niemann-pick disease with small samples of venous blood. Science. 1967 Jan 6;155(3758):86–8.
53. Wenger DA. Assay of beta-glucosidase and sphingomyelinase for identification of patients and carriers of Gaucher's and Niemann-Pick diseases. Adv Exp Med Biol. 1978;101:707–17.
54. Besley GT. Studies on sphingomyelinase activity in cultured cells and leucocytes. J Inherit Metab Dis. 1978;1(1):29–33.
55. Svennerholm L, Håkansson G, Månsson JE, Vanier MT. The assay of sphingolipid hydrolases in white blood cells with labelled natural substrates. Clin Chim Acta. 1979 Feb;15(1):53–64. 92(.
56. Vanier MT, Revol A, Fichet M. Sphingomyelinase activities of various human tissues in control subjects and in Niemann-Pick disease - development and evaluation of a microprocedure. Clin Chim Acta. 1980 Oct 9;106(3):257 – 67.
57. van Diggelen OP, Voznyi YV, Keulemans JL, Schoonderwoerd K, Ledvinova J, Mengel E, Zschiesche M, Santer R, Harzer K. A new fluorimetric enzyme assay for the diagnosis of Niemann-Pick A/B, with specificity of natural sphingomyelinase substrate. J Inherit Metab Dis. 2005;28(5):733–41.
58. Gelb MH, Scott CR, Turecek F. Newborn screening for lysosomal storage diseases. Clin Chem. 2015 Feb;61(2):335–46.
59. Ghomashchi F, Barcenas M, Turecek F, Scott CR, Gelb MH. Reliable Assay of Acid Sphingomyelinase Deficiency with the Mutation Q292K by Tandem Mass Spectrometry. Clin Chem. 2015 May;61(5):771–2.
60. Piraud M, Pettazzoni M, Lavoie P, Ruet S, Pagan C, Cheillan D, Latour P, Vianey-Saban C, Auray-Blais C, Froissart R. Contribution of tandem mass spectrometry to the diagnosis of lysosomal storage disorders. J Inherit Metab Dis. 2018 May;41(3):457–77.
61. Elliott S, Buroker N, Cournoyer JJ, Potier AM, Trometer JD, Elbin C, Schermer MJ, Kantola J, Boyce A, Turecek F, Gelb MH, Scott CR. Dataset and standard operating procedure for newborn screening of six lysosomal storage diseases: By tandem mass spectrometry. Data Brief. 2016 Jul;5:8:915–24.

62. Elliott S, Buroker N, Cournoyer JJ, Potier AM, Trometer JD, Elbin C, Schermer MJ, Kantola J, Boyce A, Turecek F, Gelb MH, Scott CR. Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry. Mol Genet Metab. 2016 Aug;118(4):304–9.
63. Wasserstein MP, Caggana M, Bailey SM, Desnick RJ, Edelmann L, Estrella L, Holzman I, Kelly NR, Kornreich R, Kupchik SG, Martin M, Nafday SM, Wasserman R, Yang A, Yu C, Orsini JJ. The New York pilot newborn screening program for lysosomal storage diseases: Report of the First 65,000 Infants. Genet Med. 2019 Mar;21(3):631–40.
64. Kudoh T, Velkoff MA, Wenger DA. Uptake and metabolism of radioactively labeled sphingomyelin in cultured skin fibroblasts from controls and patients with Niemann-Pick disease and other lysosomal storage diseases. Biochim Biophys Acta. 1983 Nov;754(1)(1):82–92.
65. Vanier MT, Rousson R, Garcia I, Bailloud G, Juge MC, Revol A, Louisot P. Biochemical studies in Niemann-Pick disease. III. In vitro and in vivo assays of sphingomyelin degradation in cultured skin fibroblasts and amniotic fluid cells for the diagnosis of the various forms of the disease. Clin Genet. 1985 Jan;27(1):20–32.
66. Graber D, Salvayre R, Levade T. Accurate differentiation of neuronopathic and nonneuronopathic forms of Niemann-Pick disease by evaluation of the effective residual lysosomal sphingomyelinase activity in intact cells. J Neurochem. 1994 Sep;63(3):1060–8.
67. Hollak CE, van Weely S, van Oers MH, Aerts JM. Marked elevation of plasma chitotriosidase activity. A novel hallmark of Gaucher disease. J Clin Invest. 1994 Mar;93(3):1288–92.
68. Boot RG, Renkema GH, Verhoek M, Strijland A, Bliek J, de Meulemeester TM, Mannens MM, Aerts JM. The human chitotriosidase gene. Nature of inherited enzyme deficiency. J Biol Chem. 1998 Oct 2;273(40):25680-5.
69. Ries M, Schaefer E, Lührs T, Mani L, Kuhn J, Vanier MT, Krummenauer F, Gal A, Beck M, Mengel E. Critical assessment of chitotriosidase analysis in the rational laboratory diagnosis of children with Gaucher disease and Niemann-Pick disease type A/B and C. J Inherit Metab Dis. 2006 Oct;29(5):647–52.
70. Porter FD, Scherrer DE, Lanier MH, Langmade SJ, Molugu V, Gale SE, Olzeski D, Sidhu R, Dietzen DJ, Fu R, Wassif CA, Yanjanin NM, Marso SP, House J, Vite C, Schaffer JE, Ory DS. Cholesterol oxidation products are sensitive and specific blood-based biomarkers for Niemann-Pick C1 disease. Sci Transl Med. 2010 Nov;2(56)(3):56ra81.
71. Klinke G, Rohrbach M, Giugliani R, Burda P, Baumgartner MR, Tran C, Gautschi M, Mathis D, Hersberger M. LC-MS/MS based assay and reference intervals in children and adolescents for oxysterols elevated in Niemann-Pick diseases. Clin Biochem. 2015 Jun;48(9):596–602.
72. Giese AK, Mascher H, Grittner U, Eichler S, Kramp G, Lukas J, te Vruchte D, Al Eisa N, Cortina-Borja M, Porter FD, Platt FM, Rolfs A. A novel, highly sensitive and specific biomarker for Niemann-Pick type C1 disease. Orphanet J Rare Dis. 2015 Jun 17;10:78.
73. Romanello M, Zampieri S, Bortolotti N, Deroma L, Sechi A, Fiumara A, Parini R, Borroni B, Brancati F, Bruni A, Russo CV, Bordugo A, Bembi B, Dardis A. Comprehensive Evaluation of Plasma 7-

Ketocholesterol and Cholestan-3β,5α,6β-Triol in an Italian Cohort of Patients Affected by Niemann-Pick Disease due to NPC1 and SMPD1 Mutations. Clin Chim Acta. 2016 Apr 1;455:39–45.

74. Vanier MT, Gissen P, Bauer P, Coll MJ, Burlina A, Hendriksz CJ, Latour P, Goizet C, Welford RW, Marquardt T, Kolb SA. Diagnostic tests for Niemann-Pick disease type C (NP-C): A critical review. Mol Genet Metab. 2016 Aug;118(4):244–54.
75. Jiang X, Sidhu R, Dietzen DJ, Yanjanin Farhat N, Porter FD, Schaffer JE, et al. Improved diagnostics for Niemann-Pick disease type C based on a novel bile acid biomarker. Mol Genet Metab. 2016;117(2):62.
76. Sidhu R, Kell P, Dietzen DJ, Farhat NY, Do AND, Porter FD, Berry-Kravis E, Reunert J, Marquardt T, Giugliani R, Lourenço CM, Wang RY, Movsesyan N, Plummer E, Schaffer JE, Ory DS, Jiang X. Application of a glycinated bile acid biomarker for diagnosis and assessment of response to treatment in Niemann-pick disease type C1. Mol Genet Metab. 2020 Dec;131(4):405–17.
77. Kuchar L, Sikora J, Gulinello ME, Poupetova H, Lugowska A, Malinova V, Jahnova H, Asfaw B, Ledvinova J. Quantitation of plasmatic lysosphingomyelin and lysosphingomyelin-509 for differential screening of Niemann-Pick A/B and C diseases. Anal Biochem. 2017 May 15;525:73–77.
78. Polo G, Burlina AP, Kolamunnage TB, Zampieri M, Dionisi-Vici C, Strisciuglio P, Zaninotto M, Plebani M, Burlina AB. Diagnosis of sphingolipidoses: a new simultaneous measurement of lysosphingolipids by LC-MS/MS. Clin Chem Lab Med. 2017 Mar 1;55(3):403–414.
79. Pettazzoni M, Froissart R, Pagan C, Vanier MT, Ruet S, Latour P, Guffon N, Fouilhoux A, Germain DP, Levade T, Vianey-Saban C, Piraud M, Cheillan D. LC-MS/MS multiplex analysis of lysosphingolipids in plasma and amniotic fluid: A novel tool for the screening of sphingolipidoses and Niemann-Pick type C disease. PLoS One. 2017 Jul 27;12(7):e0181700.
80. Voorink-Moret M, Goorden SMI, van Kuilenburg ABP, Wijburg FA, Ghauharali-van der Vlugt JMM, Beers-Stet FS, Zoetekouw A, Kulik W, Hollak CEM, Vaz FM. Rapid screening for lipid storage disorders using biochemical markers. Expert center data and review of the literature. Mol Genet Metab. 2018 Feb;123(2):76–84.
81. Deodato F, Boenzi S, Taurisano R, Semeraro M, Sacchetti E, Carrozzo R, Dionisi-Vici C. The impact of biomarkers analysis in the diagnosis of Niemann-Pick C disease and acid sphingomyelinase deficiency. Clin Chim Acta. 2018 Nov;486:387–94.
82. Welford RW, Garzotti M, Marques Lourenço C, Mengel E, Marquardt T, Reunert J, Amraoui Y, Kolb SA, Morand O, Groenen P. Plasma lysosphingomyelin demonstrates great potential as a diagnostic biomarker for Niemann-Pick disease type C in a retrospective study. PLoS One. 2014 Dec 5;9(12):e114669.
83. El-Najjar N, Orsó E, Wallner S, Liebisch G, Schmitz G. Increased Levels of Sphingosylphosphorylcholine (SPC) in Plasma of Metabolic Syndrome Patients. PLoS One. 2015 Oct 14;10(10):e0140683.
84. Breilyn MS, Zhang W, Yu C, Wasserstein MP. Plasma lyso-sphingomyelin levels are positively associated with clinical severity in acid sphingomyelinase deficiency. Mol Genet Metab Rep. 2021

Jul 7;28:100780.

85. Diaz GA, Jones SA, Scarpa M, Mengel KE, Giugliani R, Guffon N, Batsu I, Fraser PA, Li J, Zhang Q, Ortemann-Renon C. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genet Med. 2021 Aug;23(8):1543–50.
86. Wasserstein M, Lachmann R, Hollak C, Arash-Kaps L, Barbato A, Gallagher RC, Giugliani R, Guelbert NB, Ikezoe T, Lidove O, Mabe P, Mengel E, Scarpa M, Senates E, Tchan M, Villarrubia J, Chen Y, Furey S, Thurberg BL, Zaher A, Kumar M. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genet Med. 2022 Apr 26:S1098-3600(22)00716-X.
87. Sidhu R, Mondjinou Y, Qian M, Song H, Kumar AB, Hong X, Hsu FF, Dietzen DJ, Yanjanin NM, Porter FD, Berry-Kravis E, Vite CH, Gelb MH, Schaffer JE, Ory DS, Jiang X. N-acyl-O-phosphocholineserines: structures of a novel class of lipids that are biomarkers for Niemann-Pick C1 disease. J Lipid Res. 2019 Aug;60(8):1410–24.
88. Maekawa M, Jinnoh I, Matsumoto Y, Narita A, Mashima R, Takahashi H, Iwahori A, Saigusa D, Fujii K, Abe A, Higaki K, Yamauchi S, Ozeki Y, Shimoda K, Tomioka Y, Okuyama T, Eto Y, Ohno K, Clayton T, Yamaguchi P, Mano H N. Structural Determination of Lysosphingomyelin-509 and Discovery of Novel Class Lipids from Patients with Niemann-Pick Disease Type C. Int J Mol Sci. 2019 Oct 10;20(20):5018.
89. Sidhu R, Kell P, Dietzen DJ, Farhat NY, Do AND, Porter FD, Berry-Kravis E, Vite CH, Reunert J, Marquardt T, Giugliani R, Lourenço CM, Bodamer O, Wang RY, Plummer E, Schaffer JE, Ory DS, Jiang X. Application of N-palmitoyl-O-phosphocholineserine for diagnosis and assessment of response to treatment in Niemann-Pick type C disease. Mol Genet Metab. 2020 Apr;129(4):292–302.
90. Iwahori A, Maekawa M, Narita A, Kato A, Sato T, Ogura J, Sato Y, Kikuchi M, Noguchi A, Higaki K, Okuyama T, Takahashi T, Eto Y, Mano N. Development of a Diagnostic Screening Strategy for Niemann-Pick Diseases Based on Simultaneous Liquid Chromatography-Tandem Mass Spectrometry Analyses of N-Palmitoyl-O-phosphocholine-serine and Sphingosylphosphorylcholine. Biol Pharm Bull. 2020 Sep 1;43(9):1398–1406.
91. Polo G, Burlina AP, Ranieri E, Colucci F, Rubert L, Pascarella A, Duro G, Tummolo A, Padoan A, Plebani M, Burlina AB. Plasma and dried blood spot lysosphingolipids for the diagnosis of different sphingolipidoses: a comparative study. Clin Chem Lab Med. 2019 Nov;26(12):1863–74. 57(.
92. da Veiga Pereira L, Desnick RJ, Adler DA, Disteche CM, Schuchman EH. Regional assignment of the human acid sphingomyelinase gene (SMPD1) by PCR analysis of somatic cell hybrids and in situ hybridization to 11p15.1—p15.4. Genomics. 1991 Feb;9(2):229–34.
93. Quintern LE, Schuchman EH, Levran O, Suchi M, Ferlinz K, Reinke H, Sandhoff K, Desnick RJ. Isolation of cDNA clones encoding human acid sphingomyelinase: occurrence of alternatively processed transcripts. EMBO J. 1989 Sep;8(9):2469–73.
94. Schuchman EH, Suchi M, Takahashi T, Sandhoff K, Desnick RJ. Human acid sphingomyelinase. Isolation, nucleotide sequence and expression of the full-length and alternatively spliced cDNAs. J

Biol Chem. 1991 May;5(13):8531–9. 266(.

95. den Dunnen JT, Antonarakis SE. Nomenclature for the description of human sequence variations. Hum Genet. 2001 Jul;109(1):121–4.
96. Zanetti A, D'Avanzo F, Bertoldi L, Zampieri G, Feltrin E, De Pascale F, Rampazzo A, Forzan M, Valle G, Tomanin R. Setup and Validation of a Targeted Next-Generation Sequencing Approach for the Diagnosis of Lysosomal Storage Disorders. J Mol Diagn. 2020 Apr;22(4):488–502.
97. La Cognata V, Guarnaccia M, Morello G, Ruggieri M, Polizzi A, Cavallaro S. Design and Validation of a Custom NGS Panel Targeting a Set of Lysosomal Storage Diseases Candidate for NBS Applications. Int J Mol Sci. 2021 Sep 17;22(18):10064.
98. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405–24.
99. Ranganath P, Matta D, Bhavani GS, Wangnekar S, Jain JM, Verma IC, Kabra M, Puri RD, Danda S, Gupta N, Girisha KM, Sankar VH, Patil SJ, Ramadevi AR, Bhat M, Gowrishankar K, Mandal K, Aggarwal S, Tamhankar PM, Tilak P, Phadke SR, Dalal A. Spectrum of SMPD1 mutations in Asian-Indian patients with acid sphingomyelinase (ASM)-deficient Niemann-Pick disease. Am J Med Genet A. 2016 Oct;170(10):2719–30.
100. Ricci V, Stroppiano M, Corsolini F, Di Rocco M, Parenti G, Regis S, Grossi S, Biancheri R, Mazzotti R, Filocamo M. Screening of 25 Italian patients with Niemann-Pick A reveals fourteen new mutations, one common and thirteen private. Hum Mutat. 2004;in SMPD1(1):105. Jul;24(.
101. Pittis MG, Ricci V, Guerci VI, Marçais C, Ciana G, Dardis A, Gerin F, Stroppiano M, Vanier MT, Filocamo M, Bembi B. Acid sphingomyelinase: identification of nine novel mutations among Italian Niemann Pick type B patients and characterization of in vivo functional in-frame start codon. Hum Mutat. 2004 Aug;24(2):186–7.
102. Rodríguez-Pascau L, Gort L, Schuchman EH, Vilageliu L, Grinberg D, Chabás A. Identification and characterization of SMPD1 mutations causing Niemann-Pick types A and B in Spanish patients. Hum Mutat. 2009 Jul;30(7):1117–22.
103. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH. The demographics and distribution of type B Niemann-Pick disease: novel mutations lead to new genotype/phenotype correlations. Am J Hum Genet. 2002 Dec;71(6):1413–9.
104. Aykut A, Karaca E, Onay H, Ucar SK, Coker M, Cogulu O, Ozkinay F. Analysis of the sphingomyelin phosphodiesterase 1 gene (SMPD1) in Turkish Niemann-Pick disease patients: mutation profile and description of a novel mutation. Gene. 2013 Sep;10(2):484–6. 526(.
105. Zhang H, Wang Y, Gong Z, Li X, Qiu W, Han L, Ye J, Gu X. Identification of a distinct mutation spectrum in the SMPD1 gene of Chinese patients with acid sphingomyelinase-deficient Niemann-Pick disease. Orphanet J Rare Dis. 2013 Jan;28:8:15.

106. Hu J, Maegawa GHB, Zhan X, Gao X, Wang Y, Xu F, Qiu W, Han L, Gu X, Zhang H. Clinical, biochemical, and genotype-phenotype correlations of 118 patients with Niemann-Pick disease Types A/B. Hum Mutat. 2021 May;42(5):614–25.
107. Vanier MT, Ferlinz K, Rousson R, Duthel S, Louisot P, Sandhoff K, Suzuki K. Deletion of arginine (608) in acid sphingomyelinase is the prevalent mutation among Niemann-Pick disease type B patients from northern Africa. Hum Genet. 1993 Oct;92(4):325–30.
108. Levran O, Desnick RJ, Schuchman EH. Niemann-Pick type B disease. Identification of a single codon deletion in the acid sphingomyelinase gene and genotype/phenotype correlations in type A and B patients. J Clin Invest. 1991 Sep;88(3):806–10.
109. Levran O, Desnick RJ, Schuchman EH. Niemann-Pick disease: a frequent missense mutation in the acid sphingomyelinase gene of Ashkenazi Jewish type A and B patients. Proc Natl Acad Sci U S A. 1991 May 1;88(9):3748-52.
110. Levran O, Desnick RJ, Schuchman EH. Identification and expression of a common missense mutation (L302P) in the acid sphingomyelinase gene of Ashkenazi Jewish type A Niemann-Pick disease patients. Blood. 1992 Oct 15;80(8):2081–7.
111. Levran O, Desnick RJ, Schuchman EH. Type A Niemann-Pick disease: a frameshift mutation in the acid sphingomyelinase gene (fsP330) occurs in Ashkenazi Jewish patients. Hum Mutat. 1993;2(4):317–9.
112. Lidove O, Belmatoug N, Froissart R, Lavigne C, Durieu I, Mazodier K, Serratrice C, Douillard C, Goizet C, Cathebras P, Besson G, Amoura Z, Tazi A, Gatfossé M, Rivière S, Sené T, Vanier MT, Ziza JM. Déficit en sphingomyélinase acide (maladie de Niemann-Pick B): une étude rétrospective multicentrique de 28 patients adultes [Acid sphingomyelinase deficiency (Niemann-Pick disease type B) in adulthood: A retrospective multicentric study of 28 adult cases]. Rev Med Interne. 2017 May;38(5):291–9.
113. Zampieri S, Filocamo M, Pianta A, Lualdi S, Gort L, Coll MJ, Sinnott R, Geberhiwot T, Bembi B, Dardis A. SMPD1 Mutation Update: Database and Comprehensive Analysis of Published and Novel Variants. Hum Mutat. 2016 Feb;37(2):139–47.
114. Dardis A, Zampieri S, Filocamo M, Burlina A, Bembi B, Pittis MG. Functional in vitro characterization of 14 SMPD1 mutations identified in Italian patients affected by Niemann Pick Type B disease. Hum Mutat. 2005 Aug;26(2):164.
115. Fernández-Burriel M, Peña L, Ramos JC, Cabrera JC, Marti M, Rodríguez-Quiñones F, Chabás A. The R608del mutation in the acid sphingomyelinase gene (SMPD1) is the most prevalent among patients from Gran Canaria Island with Niemann-Pick disease type B. Clin Genet. 2003 Mar;63(3):235–6.
116. Borie R, Crestani B, Guyard A, Lidove O. Interstitial lung disease in lysosomal storage disorders. Eur Respir Rev. 2021 Apr 29;30(160):200363.
117. Pinto C, Sousa D, Ghilas V, Dardis A, Scarpa M, Macedo MF. Acid Sphingomyelinase Deficiency: A Clinical and Immunological Perspective. Int J Mol Sci. 2021 Nov 28;22(23):12870.
118. Wasserstein M, Dionisi-Vici C, Giugliani R, Hwu WL, Lidove O, Lukacs Z, Mengel E, Mistry PK, Schuchman EH, McGovern M. Recommendations for clinical monitoring of patients with acid

sphingomyelinase deficiency (ASMD). Mol Genet Metab. 2019 Feb;126(2):98–105.

119. Van Groenendael S, Giacovazzi L, Davison F, Holtkemper O, Huang Z, Wang Q, Parkinson K, Barrett T, Geberhiwot T. High quality, patient centred and coordinated care for Alstrom syndrome: a model of care for an ultra-rare disease. Orphanet J Rare Dis. 2015 Nov;24:10:149.
120. Wasserstein MP, Larkin AE, Glass RB, Schuchman EH, Desnick RJ, McGovern MM. Growth restriction in children with type B Niemann-Pick disease. J Pediatr. 2003 Apr;142(4):424–8.
121. Naifar M, Kallel F, HadjKacem F, Boudabous H, Kallel R, Boudawara T, Messaoud O, Tbib N, Charfi N, Abid M, Froissart R, Messedi SH, Ayedi F. Homozygous pArg610del Mutation Unusually Associated With Severe Delay of Growth in 2 Acid Sphingomyelinase Deficiency-affected Sibs. J Pediatr Hematol Oncol. 2020 Aug;42(6):e499–502.
122. Jones SA, McGovern M, Lidove O, Giugliani R, Mistry PK, Dionisi-Vici C, Munoz-Rojas MV, Nalysnyk L, Schecter AD, Wasserstein M. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. Mol Genet Metab. 2020 Sep-Oct;131(1–2):116–123.
123. Faverio P, Stainer A, De Giacomi F, Gasperini S, Motta S, Canonico F, Pieruzzi F, Monzani A, Pesci A, Biondi A. Molecular Pathways and Respiratory Involvement in Lysosomal Storage Diseases. Int J Mol Sci. 2019 Jan 15;20(2):327.
124. Volders P, Van Hove J, Lories RJ, Vandekerckhove P, Matthijs G, De Vos R, Vanier MT, Vincent MF, Westhovens R, Luyten FP. Niemann-Pick disease type B: an unusual clinical presentation with multiple vertebral fractures. Am J Med Genet. 2002 Apr;15(1):42–51. 109(.
125. Arenz C. Small molecule inhibitors of acid sphingomyelinase. Cell Physiol Biochem. 2010;26(1):1–8.
126. Coelho GR, Praciano AM, Rodrigues JP, Viana CF, Brandão KP, Valenca JT Jr, Garcia JH. Liver Transplantation in Patients With Niemann-Pick Disease–Single-Center Experience. Transplant Proc. 2015 Dec;47(10):2929-31.
127. Liu Y, Luo Y, Xia L, Qiu B, Zhou T, Feng M, Xue F, Chen X, Han L, Zhang J, Xia Q. The Effects of Liver Transplantation in Children With Niemann-Pick Disease Type B. Liver Transpl. 2019 Aug;25(8):1233–40.
128. Nicholson AG, Wells AU, Hooper J, Hansell DM, Kelleher A, Morgan C. Successful treatment of endogenous lipoid pneumonia due to Niemann-Pick Type B disease with whole-lung lavage. Am J Respir Crit Care Med. 2002 Jan 1;165(1):128 – 31.
129. Uyan ZS, Karadağ B, Ersu R, Kiyan G, Kotiloğlu E, Sirvanci S, Ercan F, Dağli T, Karakoç F, Dağli E. Early pulmonary involvement in Niemann-Pick type B disease: lung lavage is not useful. Pediatr Pulmonol. 2005 Aug;40(2):169–72.
130. Mannem H, Kilbourne S, Weder M. Lung transplantation in a patient with Niemann-Pick disease. J Heart Lung Transplant. 2019 Jan;38(1):100–1.
131. O'Neill RS, Belousova N, Malouf MA. Pulmonary Type B Niemann-Pick Disease Successfully Treated with Lung Transplantation. Case Rep Transplant. 2019 Jun 16;2019:9431751.

132. Ding F, Mehta AC, Arrossi AV. Successful lung transplantation in a patient with Niemann–Pick disease. J Heart Lung Transplant. 2019 May;38(5):582–3.
133. Mora VMC, Osorio JSC, Iturbe DF, Tello SM, Guzmán YG, Sánchez LM, Gómez JJR, Cifrián JMM. Double-Lung Transplantation in a Patient with Pulmonary Type B Niemann-Pick Disease: A Valid Treatment Option. Case Rep Transplant. 2022 Apr 27;2022:5428381.
134. Lidove O, Mauhin W, London J. Acid sphingomyelinase deficiency (Niemann–Pick disease Type B) as an inflammatory disease. J Heart Lung Transplant. 2019 May;38(5):583–4.
135. McGovern MM, Wasserstein MP, Kirmse B, Duvall WL, Schiano T, Thurberg BL, Richards S, Cox GF. Novel first-dose adverse drug reactions during a phase I trial of olipudase alfa (recombinant human acid sphingomyelinase) in adults with Niemann-Pick disease type B (acid sphingomyelinase deficiency). Genet Med. 2016 Jan;18(1):34–40.
136. Wasserstein MP, Jones SA, Soran H, Diaz GA, Lippa N, Thurberg BL, Culm-Merdek K, Shamiyeh E, Inguilizian H, Cox GF, Puga AC. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol Genet Metab. 2015 Sep-Oct;116(1–2):88–97.
137. Thurberg BL, Wasserstein MP, Jones SA, Schiano TD, Cox GF, Puga AC. Clearance of Hepatic Sphingomyelin by Olipudase Alfa Is Associated With Improvement in Lipid Profiles in Acid Sphingomyelinase Deficiency. Am J Surg Pathol. 2016 Sep;40(9):1232–42.
138. Wasserstein MP, Diaz GA, Lachmann RH, Jouvin MH, Nandy I, Ji AJ, Puga AC. Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. J Inherit Metab Dis. 2018 Sep;41(5):829–38.
139. Thurberg BL, Diaz GA, Lachmann RH, Schiano T, Wasserstein MP, Ji AJ, Zaher A, Peterschmitt MJ. Long-term efficacy of olipudase alfa in adults with acid sphingomyelinase deficiency (ASMD): Further clearance of hepatic sphingomyelin is associated with additional improvements in pro- and anti-atherogenic lipid profiles after 42 months of treatment. Mol Genet Metab. 2020 Sep-Oct;131(1–2):245–252.
140. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L, AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010 Dec;14(18):E839-42. 182(.

Figures

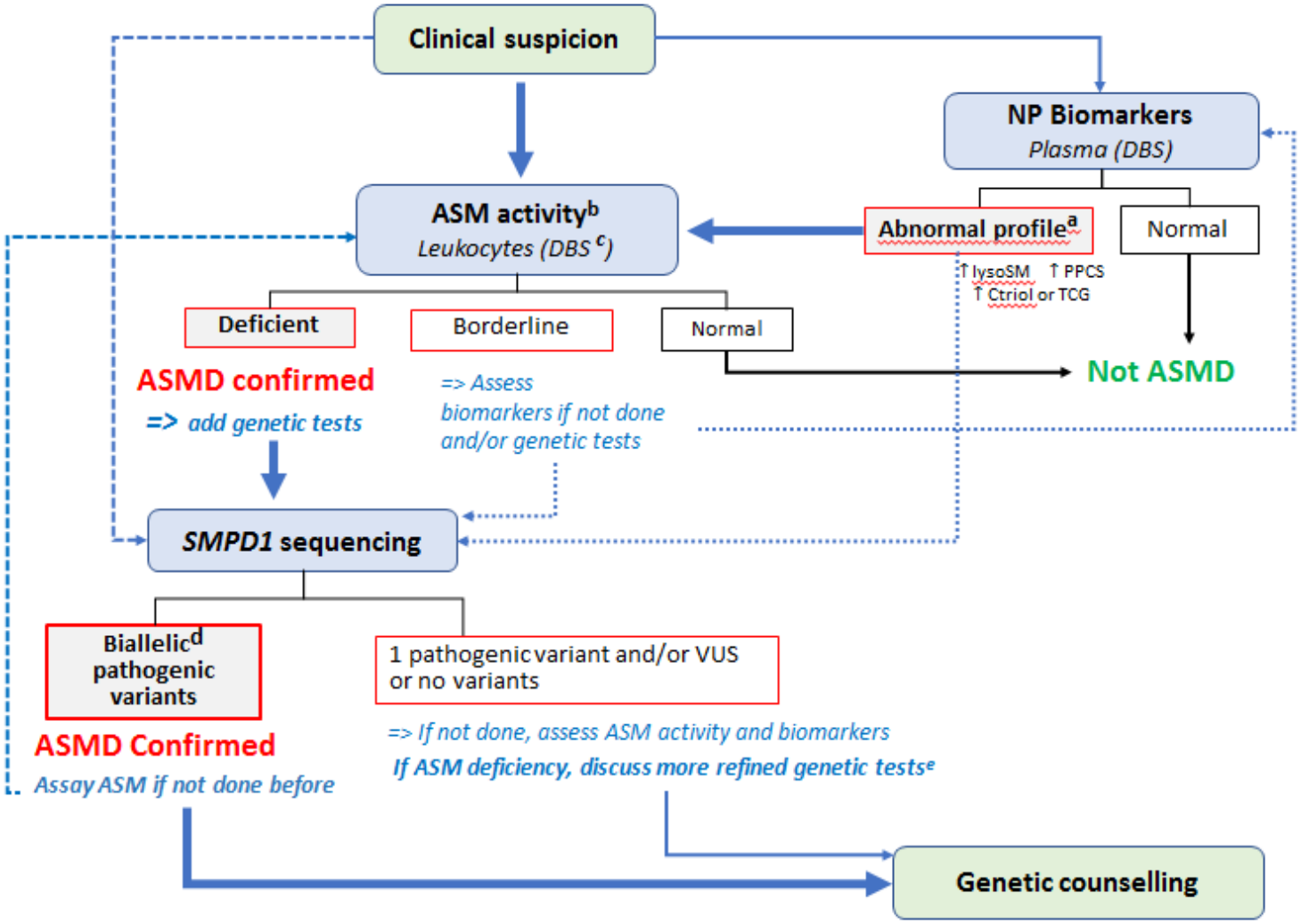

Figure 1

Algorithm for the laboratory diagnosis of ASMD