WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

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Condition	**STATEMENT**
Nominated Condition	Acid sphingomyelinase deficiency (ASMD), aka Niemann Pick types A, A/B, B
Description of Disorder	Acid sphingomyelinase deficiency (ASMD) is an ultra-rare autosomal recessive lysosomal disorder caused by biallelic pathogenic variants in the sphingomyelin phosphodiesterase 1 gene (SMPD1) resulting in impaired lysosomal hydrolysis of sphingomyelin into ceramide and phosphocholine. Sphingomyelin is a major component of the cell membrane in addition to being the primary phospholipid of the myelin sheath. ASMD is a progressive multisystemic disease characterized by accumulation of sphingomyelin within tissues that are rich in reticuloendothelial cells including the spleen, liver, lung, bone marrow and lymph nodes with more severe disease impacting neurons. At the severe end of the spectrum, ASMD is rapidly progressive and results in premature death (type A or infantile neurovisceral). At the less severe end, type B or chronic viceral ASMD is characterized by primary visceral disease with minimal or absent neurologic symptoms. An intermediate phenotype (A/B or chronic neurovisceral) is characterized by both viceral and neurologic disease (ataxia, pheripheral neuropathy and developmental delay) resulting in earlier mortality than type B, often in childhood [McGovern 2016 and Cassiman 2016].
Screening Method	enzyme measured as % of daily median from dried blood spot via tandem mass spectrometry
Gene	sphingomyeline phosphodiesterase 1 gene-SMPD1
OMIM or other names for condition	(607608 (SPHINGOMYELIN PHOSPHODIESTERASE 1, ACID LYSOSOMAL;SMPD1)

	https://www.omim.org/entry/607608 #607616 (Niemann Pick Disease Type B-NPB) https://www.omim.org/entry/607616 #257200 (Niemann Pick Disease Type A-NPA) https://www.omim.org/entry/257200 acid sphingomyelinase, ASM,ASM_HUMAN sphingomyelin phosphodiesterase 1, acid lysosomal sphingomyelin phosphodiesterase 1, acid lysosomal (acid sphingomyelinase)
Case Definition	A diagnosis of ASMD is established based on detection of biallelic pathogenic variants in SMPD1 or deficient ASM activity in peripheral blood and can be confirmed through gene sequencing and/or biomarker data.

NOTE: Please reference each statement/answer with the corresponding reference number listed in **Key References**.

CRITERION	
Criterion 1: Mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.	
Timing of Clinical Onset	*Relevance of the timing of newborn screening to onset of clinical manifestations. Must cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.* Multiple studies report the first symptoms of ASMD appear as early as the first few months of life, and pathologic evidence of visceral disease is present before birth. Pathologic evaluation was performed on 3 fetuses that were in the second trimester of pregnancies that all had a family history of ASMD and lacked sphingomyelinase activity in the amniotic fluid. The autopsy results demonstrated significant sphingomyelin deposition in all organs except the brain [Higami 1978 and Schoenfeld 1982]. In a study of 10 patients with Niemann-Pick type A (the most severe phenotype of the disease), the median age at diagnosis was 6 months. The first symptom detected in all patients was organomegaly which was first noted at a median age of 3 months [McGovern 2006]. In a study of 59 type A/B and B patients, the mean age at first symptom onset occurred earlier in patients that were currently <18 years of age (N=30) than the adult group (N=29): 2.5 years ± 2.8 (range 0.1–14.0) years versus 7.9 years ± 8.8 (range 0.9–30) years [McGovern 2021]. In a cross-sectional qualitative study that included 12 adult and 17 ASMD patients without severe neurologic symptoms (type B and A/B), the medain age of onset of symptoms for adults was 2 (0-24) and 1.5(0-3) for the pediatric patients [Pokrzywinski 2021]. A mixed methods study involving chart review and qualitative interviews of 25 type B and 2 A/B patients in Europe, Latin America and the United States found the average age of symptom onset to be 2 years. This study found that diagnosis took an average of 3 years to obtain after first seeking medical care, and the average age at diagnosis was 5 years. Time to diagnosis ranged 0–10 years for patients with ASMD type A/B or type B, and most patients (85%) received an incorrect initial diagnosis [Doerr 2024].
Criterion 2: For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.	

Incidence	*Determined by what method(s): pilot screening or clinical identification?* The incidence of ASMD is low like other rare diseases which is compounded by the fact that it is likely underdiagnosed and misdiagnosed. A study of lysosomal storage disorders conducted across six different countries during 1999-2013 reported a live birth prevalence of 0.25-0.6/100,000 [Kingma 2015]. Orphanet estimates the prevalence of ASMD to be .4/100,000 in Europe [Orphanet Prevalence of rare diseases 2023]. Disease incidence calculated in a state-wide NBS pilot in Illinois were similar to the reported incidence above at 0.79/100,000 [Hickey 2024].

Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history*. Clinical features of type A include irritability, sleep disturbance, failure to thrive, hypotonia, and severe gastrointestinal symptoms, including frequent vomiting and progressive respiratory symptoms. All 10 infants in one natural history study developed progressive respiratory symptoms with frequent respiratory infections secondary to aspiration, and 9 of 10 infants eventually died of respiratory failure. The infants also had abnormal laboratory values including elevated liver enzymes, low HDL cholesterol, progressive decrease in hemoglobin values and platelet counts; one patient died of complications from bleeding. The median time from diagnosis to death was 21 months with all patients succumbing at or before the age of 3 years [McGovern 2006]. Clinical features of type B were reported in an international cross-sectional study of 59 patients and included splenomegaly (78%) and hepatomegaly (73%) at presentation. Pre-existing complaints in these patients included bleeding (49%), shortness of breath (42%), pulmonary infections (42%), joint and/or limb pain (39%), bruising (27%), headaches (24%), diarrhea (20%) and bone fractures (19%). In addition, most patients with type B had below-average height and weight which was most pronounced in adolescence but appeared to approach normal values in early adulthood. [McGovern 2021]. In a prospective US study of 64 patients with NPD B who underwent detailed neurologic and ophthalmologic examinations, 19 (30%) were found to have neurologic abnormalities suggesting that patients with a phenotype that includes neurologic manifestations constitute a significant proportion of ASMD patients [Wasserstein 2006]. Cassiman and colleagues evaluated the records of 85 type B and A/B patients who had either died or received a liver transplant. In this population, the average age of first symptom was 0.8 years. The average age of death in the A/B cohort was 8 years of age with an average age of death of 23 years in the type B cohort. Common disease-related morbidities included splenomegaly (96.6%), hepatomegaly (91.4%), liver dysunction (82.6%), and pulmonary disease (75.0%). The overall leading causes of death were respiratory failure and liver failure (27.7% each) irrespective of age [Cassiman 2016]. A U.S. oberservatinal study at 29 medical centers reviewed a study population (N = 110) that included 69 patients with ASMD type B, nine with type A/B, and 32 with ASMD “non-type A" (ASMD subtype was unknown, but patients were confirmed as not having ASMD type A). The majority of patients were male with a median age at diagnosis of 3.8 years. Thirty-eight patients died during the study observation period, at a median age of 6.8 years. The median (95% confidence interval) survival age from birth was 21.3 (10.2; 60.4) years. At diagnosis or first presentation, 42.7% patients had ≥1 ASMD-related complication; splenic (30.0%) and hepatobiliary (20.9%) being the most common, and 40.9% required ≥1 medical visit due to complications [Pulikottil-Jacob, 2023]. A German study showing the following: observational, multicentre, retrospective cohort study was conducted using medical records from four German medical sites 33 chart records of patients with ASMD type B (n = 24) and type A/B (n = 9), with a median (interquartile range [IQR]) age of 8.0 [3.0–20.0] years and 1.0 [1.0–2.0] years, respectively, at diagnosis. The commonly reported manifestations were related to spleen (100.0%), liver (93.9%), and respiratory (77.4%) abnormalities. Nine deaths were reported at a median [IQR] age of 17.0 [5.0–25.0] years, with 66.7% of overall patients deceased at less than 18 years of age; the median [IQR] age at death for patients with ASMD type B (n = 4) and type A/B (n = 5) was 31.0 [11.0–55.0] and 9.0 [4.0–18.0] years, respectively. All deaths were ASMD-related and primarily caused by liver or respiratory failures or severe progressive neurodegeneration (two patients with ASMD type A/B). The median (95% confidence

	interval [CI]) overall survival age since birth was 45.4 (17.5–65.0) years. Additionally, an SMR [95% CI] analysis (21.6 [9.8–38.0]) showed that age-specific deaths in the ASMD population were 21.6 times more frequent than that in the general German population [Mengal 2024]. One single center observational study of over 100 patients ASMD patients without neurologic symptoms (type B) found 2/3 of all deaths occurred before the age of 21, and the overall disease mortality for the pediatric population in this study was 19%. The most common cause of death in this study was pneumonia/respiratory failure (n = 5). Three patients died from liver failure and three died from complications following bone marrow transplant. The following were the causes of death in one patient each: postoperative bleeding, splenic vein tear, liver cancer, low-output heart failure, multiorgan failure, and subdural bleed [McGovern 2013]. A study involving 17 adult patients (mean age 38.7 years, 12 female), three caregivers of adults with ASMD, 12 pediatric/adolescent patients with ASMD (mean age 10.5 years, six female), and 12 caregivers of pediatric/adolescent patients with ASMD described the morbidity associated with the disease. The most commonly reported disease manifestations were respiratory (n = 26, 89.7%), abdominal (n = 25, 86.2%), and musculoskeletal symptoms (n = 23, 79.3%); excessive bleeding or bruising (n = 20, 69%); fatigue (n = 20, 69%); gastrointestinal symptoms (n = 18, 62.1%); and headache (n = 15, 51.7%). ASMD was reported to negatively impact patients' physical function (n = 23, 79.3%), self-esteem (n = 18, 62.1%), emotions (n = 16, 55.2%), social function and relationships (n = 16, 55.2%), and personal care (n = 9, 31%). Providing care for individuals with ASMD negatively affected caregivers' emotional well-being (n = 12, 80%), social function (n = 4, 26.7%), relationships (n = 6, 40%), and financial security (n = 7, 46.7%). The physical toll of providing care, the need for lifestyle changes and the responsibility for making medical decisions added to the burden for caregivers. This study showed that ASMD is a substantial burden for patients and caregivers with long-term physical, emotional, social, and financial impacts [Pokrzywinski 2021].

Criterion 3: Conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences.	
Urgency	How soon after birth must treatment be initiated to be effective? NBS is needed to better understand this RWD suggests that treatment at the onset of symptoms can help prevent visceral damage that may not be reversible.

Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence. Screening for ASMD will limit the number of missed diagnoses and avoid misdiagnoses with little increased cost as many NBS programs already perform the newborn screening test for ASMD but currently blind the results as part of the NeoLSD test kit from Revvity used for Pompe disease, Krabbe, Gaucher disease, and MPS I. Multiple case reports in the literature highlight ASMD patients that were misdiagnosed with Gaucher disease, some for years. Expert opinion advises testing for ASMD whenever testing for Gaucher disease [McGovern 2017]. ERT is approved for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) based on three clinical trials outlined below: NCT02004691 was a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial in adult patients with ASMD. Treatment was administered in both groups as an intravenous infusion once every 2 weeks. Olipudase alfa was dosed as follows: 0.1 mg/kg (Day 1, Week 0), 0.3 mg/kg (Weeks 2 and 4), 0.6 mg/kg (Weeks 6 and 8), 1 mg/kg (Week 10), 2 mg/kg (Week 12), and then a maintenance dose of 3 mg/kg (Week 14 onwards). The trial was divided into 2 consecutive periods: a randomized placebo-controlled, double-blinded primary analysis period (PAP) which lasted to Week 52, followed by an extension treatment period (ETP) for up to 4 years. Patients randomized to the placebo arm in the PAP crossed over to receive olipudase alfa treatment in the ETP to reach the targeted dose of 3 mg/kg, while patients in the original olipudase alfa arm continued treatment. Patients enrolled in the trial had a diffusion capacity of the lungs for carbon monoxide (DLco) ≤70% of the predicted normal value and a spleen volume ≥6 multiples of normal (MN). Five males and 13 females with a median age of 34 years (range: 18 to 66) were included in the placebo arm and 8 males and 5 females with a median age of 34 years (range: 20 to 59) were included in the olipudase alfa arm. Key efficacy endpoints included assessment of % predicted DLco, spleen volume, liver volume and platelet count. At week 52 during the PAP, an increase of 21% in the mean percent change in % predicted DLco was observed in the olipudase alfa-treated patients compared to the placebo-treated patients. A reduction in spleen volume of 39% was observed in the olipudase alfa-treated patients compared to the placebo-treated patients. A decrease in mean liver volume of 24% and an increase in mean platelet count of 15.6 were noted in the olipudase alfa-treated patients compared to the placebo-treated patients at week 52. Seventeen of 18 patients previously receiving placebo and 13 of 13 patients previously treated with olipudase alfa for 52 weeks (in the PAP) started or continued treatment with olipudase alfa, respectively, for up to 4 years. At week 104, patients initially randomized to placebo had received olipudase alfa for 52 weeks and demonstrated the following LS mean (SE) percent changes in clinical parameters from baseline (before first administration of olipudase alfa): increase in % predicted DLco was 26.8% (6.2); reduction in spleen volume (MN) was 36.5% (2.5); reduction in liver volume (MN) was 29.5 (2.6); and increase in platelet count was 19.5 (6.7). Patients in the previous olipudase alfa group demonstrated improvement from baseline to week 104 in the following parameters: LS mean (SE) percent increase in % predicted DLco was 34.1% (7.9); reduction in spleen volume (MN) was 48.3 (2.9); reduction in liver volume (MN) was 31.7 (2.9); increase in platelet count was 24.0 (8.2). NCT02292654 was a multi-center, open-label, repeated-dose trial of olipudase alfa administered intravenously once every 2 weeks (via infusion) for 64 weeks in pediatric patients aged <18 years with a clinical diagnosis consistent with ASMD type B and A/B.

Exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at Week 52. Olipudase alfa was dosed as follows: 0.03 mg/kg (Day 1, Week 0), 0.1 mg/kg (Weeks 2), 0.3 mg/kg (Weeks 4 and 6), 0.6 mg/kg (Week 8 and 10), 1 mg/kg (Week 12), 2 mg/kg (Week 14) and then a maintenance dose of 3 mg/kg (Week 16 onwards). In this trial, 8 patients (7 patients from 2 to <12 years old, and 1 patient <2 years old) received an initial dose of 0.03 mg/kg olipudase alfa and all but one completed the dose escalation up to the maintenance dose of 3 mg/kg within 22 weeks. All patients were white and of non-Hispanic/Latino ethnicity. Patients enrolled in the trial had a spleen volume ≥5 MN measured by MRI. Age of patients treated with olipudase alfa ranged from 1 to 10 years old, with both sexes equally represented. Treatment with olipudase alfa resulted in improvement in mean percent change in % predicted DLco by 46%, spleen volume reduction by 47%, liver volume reduction by 44%, increase in platelet count by 14%, and improvement in linear growth progression (as measured by height Z-scores) at week 52 as compared to baseline with LS mean change of 0.5 and SE of .1.

The 8 pediatric patients 2 to <12 years of age from NCT02292654 continued treatment in an open label long term trial (NCT02004704) and were treated with olipudase alfa for 2.5 to 3.2 years. Efficacy analyses showed continued improvements in the 3 patients evaluated for % predicted DLco, 6 patients evaluated for platelet counts, and all 8 patients evaluated for spleen and liver volumes, compared to baseline, during the additional 6 months extension. In addition, the height Z-score increased by 1.3 from baseline when evaluated through 24 months of olipudase alfa treatment. Bone age, as assessed by hand x-ray, was delayed by a mean of 26.4 months at baseline in the 7 pediatric patients enrolled in NCT02292654 with a bone age measured at month 24 in NCT02004704. The bone age improved to within a mean of 12 months of the chronological age when assessed at month 24 in these 7 patients [FDA label].

While this cohort continued to demonstrate sustained benefit years into treatment, splenomegaly persisted [Diaz 2022]. Development of splenomegaly is considered a trigger to start therapy by some experts in the field.

Two recent meta-analyses detailed the real world experience of treating 20 pediatric patients with ERT for 4-8 years that demonstrated persistent splenomegaly that was much improved from baseliner [Scarpa 2025]. Antonello et al has abstract available ahead of print detailing the experience of 46 pediatric patients in the Am J Med Gen.

One study of sibling pairs showed the younger sibling who had started earlier on treatment did not experience any deceleration in growth parameters and has normal height and weight for age, while the older sibling showed a decline in growth velocity that improved once treatment was initiated. Similarly, the older sibling showed similar-to-worse ILD and more persistent organomegaly compared to the younger sibling [Sinha 2025].

In addition to the long term study that followed 20 pediatric patients out more than 4 years, publications on ERT use in Taiwan [Pan 2023] and Egypt [Youssef 2025] highlight the further success in treating patients with neurologic disease. Youssef et al treated 10 patients, 6 starting at age 3 or under with 5 identified as having type A/B. They noted success in treating clinical disease with no evidence of neurologic progression in any of the patients at 1 year.

A 2024 publication highlighted the patient and caregiver experience for 10 pediatric ASMD patients who received olipudase alfa for more than 6 months. In this study that included 4 patients with neurologic symptoms, all patients reported a positive impact on all non-neurologic symptoms and improved quality of life for both the patient and caregiver.

	Caregivers reported universal satisfaction with olipudase alfa as an effective treatment for ASMD. They noted it to be safe and effective in treating all the non-neurologic symptoms associated with ASMD. Improvement in the caregivers' physical and mental health was also noteworthy [Raebel 2024]. A poster presented at SSIEM in 2024 highlights the safety and efficacy of ERT in 3 patients with severe neurologic disease (classic type A). All 3 patients suffered from seizures and developmental delay. All three were also treated with an experimental oral therapy (FAAH inibitor). All 3 remain alive and clincially stable today almost 2 years after this data was abstracted [SSIEM poster 2024].
Potential Harms	Potential medical or other ill effects from treatment. ERT requires intravenous administration. In clinical trials, olipudase alfa was generally well-tolerated. The adverse event profile is similar to that which is expected for ERT. Most common adverse reactions in adult patients (incidence ≥10%) are headache, cough, diarrhea, hypotension and ocular hyperemia. Most common adverse reactions in pediatric patients (incidence ≥20%) are pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue and pharyngitis. Hypersensitivity related reactions that were mild to moderate in severity occurred in 10 (33%) olipudase alfa-treated adult patients and 4 (50%) olipudase alfa-treated pediatric patients in clinical trials. Hypersensitivity reactions in adults included urticaria, pruritus, erythema, rash, rash erythematous, eczema, angioedema and erythema nodosum. Hypersensitivity reactions in pediatric patients included urticaria, pruritus, rash, erythema and localized edema. Hypersensitivity related reactions that were mild to moderate in severity occurred in 10 (33%) of the olipudase alfa-treated adult patients and 4 (50%) olipudase alfa-treated pediatric patients in clinical trials. Following 0.4 to 3.7 years of olipudase alfa treatment in the adult trial, 9 out of 30 (30%) olipudase alfa-treated adult patients with ASMD developed anti-olipudase alfa-rpcp IgG antibodies (referred to as IgG ADA). The median time to seroconversion from first olipudase alfa infusion was approximately 8 weeks. One out of these 9 (11%) adult patients had neutralizing antibodies (NAb) that inhibited the olipudase alfa-rpcp enzyme activity. None of these 9 patients had NAb that inhibit the cellular uptake of olipudase alfa-rpcp. Following 2.5 to 3.2 years of olipudase alfa treatment in the two pediatric studies, 6 out of 8 (75%) olipudase alfa-treated pediatric patients with ASMD developed IgG ADA. The median time to seroconversion from first olipudase alfa infusion was 10 weeks. One out of the 6 (17%) pediatric patients developed NAb that inhibited olipudase alfa-rpcp enzyme activity. None of these 6 patients had NAb that inhibited the cellular uptake of olipudase alfa-rpcp. There was no identified clinically significant effect of ADA on pharmacokinetics of olipudase alfa. Hypersensitivity reactions, including anaphylaxis, have been reported in olipudase alfa-treatedpatients. One 18-month-old olipudase alfa-treated patient experienced an anaphylactic reaction during the sixth infusion in the dose escalation period. After treatment discontinuation,olipudase alfa was resumed four months later using a diluted drug solution and a desensitization procedure. Additionally, a 16-month-old patient with ASMD type A, treated with a version of olipudase alfa manufactured from a different process, experienced two anaphylactic reactions during the fifth and sixth infusions in the dose escalation period; the patient received an immune tolerance induction therapy prior to treatment. In both of these pediatric patients who had anaphylaxis, anti-olipudase alfa-rpcp IgE (IgE ADA) and IgG (IgG ADA) antibodies were detected [FDA label].

Criterion 4: The interventions should be reasonably available to affected newborns.	
Modality	*Drug(s), diet, replacement therapy, transplant, surgery, other. Include information regarding regulatory status of treatment.* FDA-approved enzyme replacement therapy Xenpozyme (olipudase alfa) every 2 weeks is recommended for the treatment of the non-CNS manifestations of the disease [Geberhiwot 2023].
Availability	*Describe scope of availability and note any limitations.* Olipudase alfa is widely available throughout the United States. The National Niemann Pick Disease Foundation (NNPDF), in partnership with Sanofi's Care Connect team, supports all patients who desire access to olipudase alfa by identifying local infusions sites and supporting local providers. Many patients transition to home infusions over time. Coverage by payers has been consistently reported across the community.
Criterion 5: Appropriate follow-up should be available for newborns that have a false positive newborn screen.	
Follow-up for False Positives	*Define the follow-up process.* There were no false positives in the Illinois pilot that did not include biomarker testing as a secondary/confirmatory test, so one would hope the superior performance of the test to date combined with biomarker testing and genetic sequencing could result in a false positive rate that should approach zero. Sphingosylphosphorylcholine (also known as lysosphingomyelin/lyso-SM) is the most specific plasma biomarker in ASMD. A marked increase in lyso-SM is only seen in ASMD compared to a small and inconsistent 2-3x increase in NPC [Kuchar 2017]. A positive correlation between lyso-SM levels and clinical severity has been noted [Margo-Sheck 2021], and lyso-SM levels improved with ERT in pediatric and adults patients [FDA label]. A large retrospective study on 271 patients diagnosed in France demonstrated a strong correlation between elevated lysoS-M levels and the more severe phenotype [Froissart 2025]. In summary, lyso-SM can serve as a diagnostic and prognostic biomarker. In the rare circumstance when diagnostic uncertainty persists after 1)plasma enzyme activity measurement, 2)genetic sequencing and 3)measurement of lysoSM, N-palmitoly-O-phosphocholine-serince (PPCS) measurement is helpful. PPCS (initially named lysosphingomyelin-509) is another sensitive biomarker for ASMD that is also elevated in NPC. The advantage of measuring PPCS can be found in simultaneously measuring lyso-SM, PPS, lyso-Gb3 and lyso-Gb1 to differentiate ASMD, Fabry, Gaucher and NPC. Striking elevations of lyso-Gb1 allow quick differention of Gaucher and lyso-Gb3 for Fabry. The elevations of both PPCS and lyso-SM are the signature of ASMD while PPCS is disproportionately elevated compared to lyso-SM in NPC [Kuchar 2017, Polo 2016, Geberhiwot 2023, Froissart 2025].
Criterion 6: The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.	

Screening test(s) to be used	*Description of the high volume method, instrumentation and if available as part of multi-analyte platform.* Newborn screening for ASMD can be performed by measuring ASM enzyme activity in dried blood spots on filter paper (DBS) using a tandem mass spectrometry enzyme assay [Elliott 2016 and Burton 2017]. The activity of the ASM enzyme can be quantitated using flow-injection-tandem mass spectrometry or liquid chromatography-tandem mass spectrometry. Hong and colleagues included lysosphingomyelin (lyso-SM) in their multiplex panel along with multiple other enzymatic assays with the intent that lyso-SM could be used a potiential disease indicator/biomarker [Hong 2020]. This method of measuring enzymatic activity is generally aligned with the high throughput workflow of newborn screening laboratories. The approach of measuring enzyme activity is like that of other LSDs (MPS I and Pompe disease). Measuring ASM activity using tandem mass spectrometry (MS/MS) is considered the method of choice for assaying ASM activity rather than fluorometric enzyme assay. The fluorometric enzyme assay comes with a significant false negative problem due to use of the artificial substrate [Ghomashchi 2015].
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other* ASM enzyme activity is measured in DBS using MS/MS. A 3 mm punch of the DBS is incubated with an ASM substrate. After incubation and extraction, samples are injected into the MS/MS to quantify ASM enzyme activity [Elliott 2016 and Burton 2017].
Does the screening algorithm include a second tier test? If so, what type of test and availability?	*Dried blood spot, physical or physiologic assessment, other* Demonstration of missing or significantly diminished enzyme activity remains the diagnostic gold standard. Based on the performance of the ASM enzyme assay in DBS, this assay is currently being used as a diagnostic assay [Mechtler 2012]. Illinois does not used a second tier test; all patients enzyme levels <12% of the daily median are considered positive and referred for plamsa enzyme testing and SMPD1 gene sequencing with 12-15% considered borderline. Although it is not required to confirm a diagnosis, sequencing of the SMPD1 gene is recommended as standard of care since genotype can be helpful in predicting phenotype and support the confirmed diagnosis [Geberhiwot 2023].
Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.* A pilot program was conducted in the Washington State Newborn Screening Laboratory using liquid chromatography-MS/MS. Following a pilot study, Illinois became the first state to implement statewide NBS for ASMD on 6/1/2015 and remains one of two states to include ASMD on their NBS panel with New Jersey being the other. In Illinois, a positive screen is defined as ASM activity less than 11% of the daily mean. Samples at 12% - 15% of the daily mean are considered borderline and repeat testing is done. Ten infants were referred for diagnostic evaluationat Lurie, and all 10 infants were classified as confirmed ASMD or at risk for ASMD through a combination of molecular and biochemical testing. Six infants had confirmed diagnosis due to identification of biallelic pathogenic or likely pathogenic variants. The other four infants are considered at risk for ASMD, due to either the presence of variants of uncertain significance (VUS) or incomplete variant phasing [Hickey 2024].

Analytic Validation	*Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., QC and PT for both screening and confirmatory tests.* The MS/MS method to measure ASM enzyme activity is accepted by the FDA and used by many state labs to test for other LSDs (MPS1, Pompe, and Krabbe). In March 2022, Khaja Basheeruddin, the Public Service Administrator at the Illinois State Department of Health described his state's experience with in NBS of ASMD. Illinois uses tandem mass spectrometry as part of a multiplex assay to screen a total of 7 LSDs including ASMD, MPS I, MPS II, Fabry, Pompe, Gaucher, and Krabbe. The lab uses 2 punches: one for MPS II, the other for all other testing. The test for ASMD is enzyme based, and enzyme activity is expressed as % daily median. Repeat analysis is done for samples that are borderline. For samples that are retested, if the average of the three replicates is below the referral cutoff of 11%, ASM is suspected. If the percent of enzyme activity is 12-15% of the daily median, this is considered a borderline result and a repeat specimen submission is requested. By 2022, Illinois had tested 675,000 newborns for ASMD with no false positive results and five true positive results. No false negative tests have been reported.
Potential Secondary Findings	*May other disorders be identified by the screening test for the nominated condition?* ☐ Yes ☒ No ***If yes:*** • *How should that identification be handled—should those screening results be disclosed to the physicians or parents?* • *Would that disorder(s) meet the outlined criteria?* ☐ Yes ☐ No o *If yes, please prepare a separate nomination form for the secondary disorder(s)* o *If no, what criteria does it not meet?*

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	Illinois
Number of Newborns Screened	675,000 reported in 2023
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* 10
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* 0
Number of Infants Confirmed with Diagnosis	*How are diagnosis confirmed [clinical, biochemical, molecular]?* 10

Criterion 7: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.	
Is this a new sample collection system?	*If yes, demonstrate reliability and timeliness of sample collection process, including data collection, analysis, and reporting of new results.* This test can be completed using existing testing platforms that currently utilize MS/MS on DBS samples.
Criterion 8: Before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.	

Considerations of Screening and Diagnostic Testing	*False positives, carrier detection, invasiveness of method, other* There were no false positives in the Illinois pilot, so one would hope the superior performance of the test to date combined with biomarker testing (lysosphingomyelin alone or combined with PPCS) and genetic sequencing could result in a false positive rate that should approach zero. This test appears unlikely to detect carriers. The test is not invasive. .
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* It is FDA cleared and is used for multiple other disorders.
List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests, and Genetic Test Reference if applicable.* The following laboratories measure ASM enzyme activity or sequence the entire SMPD1 gene. Some were identified in Genetic Test Reference. Others are known to ASMD experts but not listed in the Genetic Test Reference Database. ASM enzyme assay Thomas Jefferson University Lysosomal Diseases Testing Laboratory, Philadelphia, PA, CLIA number 39D0948425 Mayo Clinic Laboratories, Rochester, MN, CLIA number 24D0404292 Greenwood Genetic Center, Greenwood, SC, CLIA number 42D0689473 PerkinElmer Genomics, Pittsburgh, PA, CLIA number 39D0673919 Biochemical Genetics Laboratory, University of Illinois Medical Center, Chicago, IL; CLIA number 14D0664392 SMPD1 Sequencing Tests Blueprint Genetics, Seattle, WA, CLIA number 99D2092375 Center for Human Genetics, Inc., Cambridge, MA, CLIA number 22D0650242 Fulgent Genetics, Temple City, CA, CLIA number 05D2043189 Gene by Gene, Houston, TX, CLIA number 45D1102202 GeneDx , Gaithersberg, MD, CLIA number 21D0969951 Greenwood Genetic Center, Greenwood, SC, CLIA number 42D0689473 PreventionGenetics, Marshfield, WI, CLIA number 52D2065132 PerkinElmer Genomics, Pittsburgh, PA, CLIA number 39D0673919 Johns Hopkins Medical Institutions Pathology Laboratory, Baltimore, MD, CLIA number 21D0709511 Invitae Corporation, San Francisco, CA, CLIA number 06D2084040
Follow-up and management process	*Development of standard instructions, identification of consultants, identification of appropriate referral centers throughout the state/region, follow-up for results, management of ongoing care, education, and outreach.* As a member of the NIH-funded Screen-Plus project, the NNPDF created an intake process for all newly diagnosed patients to provide them timely access to resources through our Family Services Coordinator and patient/family volunteers. [NNPDF] The NNPDF has identified Comprehensive Care Centers across the country that have the resources and experience to provide the comprehensive care recommended by the international consensus guidelines [Geberhiwot 2023]. In addition, NNPDF and Care Connect/Sanofi have resources and people dedicated to the education of families and providers so patients can receive the best possible care close to home. They NNPDF remains active in providing support to patients and families throughout their patient journey including financial assistance when needed through their Financial Assstance and Support Program (FASP).

Criterion 9: Recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.

Screening test	There will be minimal additional cost for the Wisconsin state lab if they are already using either the GelbChem or Revvity platforms to screen for Pompe and MPS I. ASM is part of that platform.
Confirmatory testing	With the precision of the screening test demonstrated at Illinois, the cost of confirmatory screening with serum enzyme measurement and DNA sequencing should be low compared to other disorders that are currently screened for.
Treatment	Fortunately the ASMD community has been well supported by NNPDF and the Care Connect team. Payor coverage of olipudase alfa has not been a barrier for the vast majority of patients.
Counseling	The NNPDF provides support through to assist families with accessing local services like counseling. NNPDF annual meetings include in-person counseling services for siblings and caregivers. NNPDF schedules multiple virtual "Community Chats" throughout the year that allow families to connect in real time. NNPDF also hosts a number of regional in-person meetings and social media platforms that allow patients and families the opportunity to communicate and connect.
False positives	One could reasonably hope to approach zero with the testing process outlined above.
Mechanism of funding	Testing through the current infrastructure can be implemented without significant financial burden on the system because of the excellent performance of the test. For each patient, an earlier diagnosis will result in significant cost savings for the patient and the system.

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
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	Criterion 7
	Criterion 8
	Criterion 9

Additional Co-sponsoring Organizations

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Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number
CO-SPONSORING ORGANIZATION #5	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

Submission Checklist	
☒	Nomination form
☒	Conflict of Interest Forms completed by Nominator and all Co-Sponsoring Organizations
☒	PDF(s) or hard copies of references

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