WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

2/25/24

NOMINATOR	
Name Jill Beirl	Organization National Niemann-Pick Disease Foundation
Affiliation (i.e., health professional, researcher, clinician, advocate) Advocate	
Address 525 Madison Avenue, Sullivan WI, 53178	
Email Address jbeirl@nnpdf.org	Telephone Number 262-617-4203

CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
Name Dr. Robert D. Steiner	Organization University of Wisconson
Affiliation (i.e., health professional, researcher, clinician, advocate) clinician, researcher	
Address 11 Babcock Drive Rochester NY 14610	
Email Address RDSteiner111@gmail.com	Telephone Number (608) 265-4806

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 storage disorder that is caused by mutations 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.
Screening Method	enzyme based on 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.* In one study of 10 patients with Niemann-Pick type A, 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]. Pathologic evaluation was performed on 3 fetuses in the 2nd trimester of pregnancies that all had no sphingomyelinase activity in the amniotic fluid and a family history of Niemann-Pick. The autopsy results demonstrated significant sphingomyelin deposition in all organs except the brain [Higami 1978 and Schoenfeld 1982]. In another study of 59 type A/B and B patients, the mean age at first symptom onset occurred earlier in patients <18 years of age (N=30) than the adult group (N=29): 2.5 ± 2.8 (range 0.1–14.0) years versus 7.9 ± 8.8 (range 0.9–30) years [McGovern 2021]. In a cross-sectional qualitative study that included 12 adult and 17 ASMD patients without significant 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 onsest of this cohort to be 2 years [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].

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]. 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 identified 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]. A study exploring the lived experience of patients with ASMD in Latin America, Europe and America 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 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? For those with the most severe form of the disease, symptom onset begins at 3 months. Respiratory and gastrointestinal symptoms are among those that are most impactful to patients at this stage of life, and utilizing ERT to ameriolate these symptoms improves oxygenation, work of breathing, nausea, vomiting, and sleep for both parents and caregivers. ERT is associated with marked improvement in the quality of life of patients and caregivers [Raebel 2024]. Lysosphingomyelin (LSM) is a plasma biomarker that has was evaluated as a prognostic biomarker in a recent student involving 28 ASMD patients. LSM elevations in patients with infantile ASMD were greater than those with chronic ASMD. Among patients with chronic ASMD, a positive relationship was observed between LSM levels and clinical severity [Marg-Scheck 2021]. As noted above, the diagnostic delay is associated with significant morbidity in ASMD. A recent paper published by the EveryLife Foundation quantified the financial impact of the diagnostic delay of similar disorders. On average, a 3 year delay in the diagnosis of Pompe resulted in a cumulative cost per patient of $168,000. Other diseases like SCID resulted in a cost per patient of over $500,000 for a delayed diagnosis [Parker 2023].

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, Gaucher disease, and MPS I. Multiple case reports in the literature highlight patients with ASMD 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. A recent 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 quality of life for both the patient and caregiver. Families reported olipudase alfa 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 noteworth (Raebel 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.
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, in partnership with Sanofi's Care Connect team, support all patients in obtaining access to olipudase alfa through local infusions sites and local provider with many transitioning to home infusions. 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, 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.
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 ASM products of the enzyme can be quantitated using flow-injection-tandem mass spectrometry or liquid chromatography-tandem mass spectrometry [Hong 2020]. This method 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]. 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. Infants with low ASM activity (<11% of daily median) are referred to metabolic centers as positive screens. As of 2022, 5 patients had positive screens through the NBS program in Illinois and all 5 were evaluated at Lurie Children's hospital. All 5 patients were diagnosed with ASMD or suspected ASMD based on deficient ASMD enzyme levels. The cohort was notable for 1 sibling pair and 3 other unrelated patients. The sibling pair was compound heterozygous for known pathogenic variants previously described in the literature. The other genotypes identified were novel. Patients 3 and 4 are presumed type B given the normal development and absence of clinical manifestations within the first year of life (now 4 and 3 years old respectively). Given this, pseudodeficiency can't be ruled out though it has not yet been reported for this condition. Patient 5's type is yet to be determined due to age (less than 1 year of age). This information was shared in poster presentation at the WORLD conference in 2023 and is attached as a reference. Since 2022, the team at Lurie Children's Hospital has evaluated 4 more ASMD patients that were diagnosed through NBS, and all had deficient ASMD enzyme levels. This yields a total of 9 patients diagnosed through the Illinois NBS program. A manuscript of these results is pending publication.

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 ASMD enzyme activity is FDA approved 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 disease, Pompe disease, Gaucher disease, and Krabbe disease. 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 report at less than 20% daily median activity. For samples that were retesting, if the average of the three replicates was below the referral cutoff of 11%, ASM is suspected. If the percent of enzyme activity is 11-15% of the daily median, this is considered a borderline result and a repeat specimen submission is requested. In 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.* 5
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]?* 5
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 through existing testing platforms already being done on DBS through MS/MS.
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 has an inatke process for all newly diagnosed patients to provide them timely access to resources that are newly diagnosed through our Family Services Coordinator and volunteers. The NNPDF has also 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, these two groups have resources and people dedicated to the education of families and providers so they 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 as this test 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 relatively low compared to other screened disorders
Treatment	Fortunately the ASMD community has been well supported by NNPDF and the Care Connect team. Payor coverage of olipudase alfa has really not been an issue for the vast majority of patients.
Counseling	The NNPDF provides support through our Family Services Manager to assist families with accessing local services like counseling. NNPDF annual meetings have included services with a counselor 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 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**
1,2	Higami et al. Prenatal Diagnosis and Fetal Pathology of Niemann-Pick Disease. Tohoku J. exp. Med., 1978, 125, 11-17. Schoenfeld Chemical and biochemical studies in fetuses affected with Niemann-Pick Disease Type A. Prenatal Diagnosis. Vol. 2, 177-1 83 (1982)
3-5	McGovern et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet Journal of Rare Diseases. 10 May 2021 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;11(1):20972. doi: 10.1038/s41598-021-99921-6. PMID: 34697402; PMCID: PMC8546120. Andrew Doerr, Maliha Farooq, Chad Faulkner, Rebecca Gould, Krista Perry, Ruth Pulikottil-Jacob, Pamela Rajasekhar. Diagnostic odyssey for patients with acid sphingomyelinase deficiency (ASMD): Exploring the potential indicators of diagnosis using quantitative and qualitative data. Molecular Genetics and Metabolism Reports, Volume 38, 2024, 101052, ISSN 2214-4269. https://doi.org/10.1016/j.ymgmr.2024.101052.
	Criterion 2
67	Kingma SD, Bodamer OA, Wijburg FA. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. Best Practice & Research Clinical Endocrinology & Metabolism. 2015;29(2):145-57. Orphanet Report Series November 2023. Prevalence and incidence of rare diseases: Bibliographic data Diseases listed by decreasing prevalence, incidence or number of published cases McGovern M, Aaron A, Brodie S, Desnick R, Wasserstein M. Natural history of type A Niemann Pick disease. Neurology. Jan 24 2006. 66 (2) 228-232.
8,9	McGovern, M.M., Wasserstein, M.P., Bembi, B. et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis 16, 212 (2021). https://doi.org/10.1186/s13023-021-01842-0 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. doi: 10.1016/j.jpeds.2006.06.034. PMID: 17011332.
	Criterion 3
10	Raebel EM, Wiseman S, Donnelly C, Mathieson T, Pountney J, Crowe J, Hopkin J. Real-life impacts of olipudase alfa: The experience of patients and families taking an enzyme replacement therapy for acid sphingomyelinase deficiency. Orphanet J Rare Dis. 2024 Feb 1;19(1):36. doi: 10.1186/s13023-024-03020-4. PMID: 38303068; PMCID: PMC10835881. Margo-Sheck B, Wenyue Zhang, Chunli Yu, Melissa P. Wasserstein. Plasma lyso-sphingomyelin levels are positively associated with clinical severity in acid sphingomyelinase deficiency. Molecular Genetics and Metabolism Reports,Volume 28, 2021, 100780, ISSN 2214-4269, https://doi.org/10.1016/j.ymgmr.2021.100780.

12	Parker E et al. The Lewin Group, expert stakeholders and the rared disease community sponsored by Everylife Foundation. The cost of a delayed diagnosis in rare disease: a health economics study. https://everylifefoundation.org/wp-content/uploads/2023/09/EveryLife-Cost-of-Delayed-Diagnosis-in-Rare-Disease_Final-Full-Study-Report_0914223.pdf. September 2023 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):967-974. doi: 10.1038/gim.2017.7. Epub 2017 Apr 13. PMID: 28406489; PMCID: PMC5589980. FDA label for olipudase alfa: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761261s000lbl.pdf
	Criterion 4
15	Geberhiwot T, Wasserstein M, Wanninayake S, Bolton SC, Dardis A, Lehman A, Lidove O, Dawson C, Giugliani R, Imrie J, Hopkin J, Green J, de Vicente Corbeira D, Madathil S, Mengel E, Ezgü F, Pettazzoni M, Sjouke B, Hollak C, Vanier MT, McGovern M, Schuchman E. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis. 2023 Apr 17;18(1):85. doi: 10.1186/s13023-023-02686-6. PMID: 37069638; PMCID: PMC10108815.
	Criterion 5
	Criterion 6
16	Elliott S, Norman Buroker, Jason J. Cournoyer, Anna M. Potier, Joseph D. Trometer, Carole Elbin, Mack J. Schermer, Jaana Kantola, Aaron Boyce, Frantisek Turecek, Michael H. Gelb, C. Ronald Scott. Pilot study of newborn screening for six lysosomal storage diseases using Tandem Mass Spectrometry, Molecular Genetics and Metabolism, Volume 118, Issue 4, 2016, pages 304-309. ISSN 1096-7192, https://doi.org/10.1016/j.ymgme.2016.05.015. Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, Schneider M, Grange DK, Nash C, Shryock H, Barnett R, Shao R, Basheeruddin K, Dizikes G. Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience. J Pediatr. 2017 Nov;190:130-135. doi: 10.1016/j.jpeds.2017.06.048. Epub 2017 Jul 17. PMID: 28728811.
18	Hong, X., Sadilek, M. & Gelb, M.H. A highly multiplexed biochemical assay for analytes in dried blood spots: application to newborn screening and diagnosis of lysosomal storage disorders and other inborn errors of metabolism. Genet Med 22, 1262–1268 (2020). https://doi.org/10.1038/s41436-020-0790-9 Ghomashchi, Farideh & Barcenas, Mariana & Turecek, Frantisek & Scott, Cynthia & Gelb, Michael. (2015). Reliable Assay of Acid Sphingomyelinase Deficiency with the Mutation Q292K by Tandem Mass Spectrometry. Clinical chemistry. 61. 10.1373/clinchem.2014.236448. Mechtler TP, Stary S, Metz TF, De Jesús VR, Greber-Platzer S, Pollak A, Herkner KR, Streubel B, Kasper DC. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. Lancet. 2012 Jan 28;379(9813):335-41. doi: 10.1016/S0140-6736(11)61266-X. Epub 2011 Nov 29. PMID: 22133539. photo of poster presentation from Genetics team at Laurie Children's Hospital in Illinois
	Criterion 7
	Criterion 8
	Criterion 9

Additional Co-sponsoring Organizations

CO-SPONSORING ORGANIZATION #2	
Name Justin Hopkin	Organization National Niemann Pick Disease Foundation
Affiliation (i.e., health professional, researcher, clinician, advocate) parent, advocate, healthcare provider	
Address 11 Babock Drive Rochester NY 14610	
Email Address jhopkin@nnpdf.org	Telephone Number 307 438-0233
CO-SPONSORING ORGANIZATION #3	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number
CO-SPONSORING ORGANIZATION #4	
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

Contact information of Nominator:

Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov

Or mail to:

WI Division of Public Health
Newborn Screening Program
1 West Wilson Street – Room 233
Madison, WI 53703