WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination
8/26/2019

NOMINATOR	
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CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
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Condition	**STATEMENT**
Nominated Condition	Pompe Disease
Description of Disorder	Pompe disease is an autosomal recessive disorder that is caused by a lack of function of the enzyme acid alpha-1, 4-glugosidase (GAA) or acid maltase. Pompe disease is also a lysosomal storage disorder. Without the proper function of GAA, glycogen that enters into the lysosome is not broken down, but continues to build up and disrupt the function of the lysosome. Since there is no (or little) enzyme to break down the glycogen, muscles accumulate large deposits of glycogen. The large deposits of glycogen cause lysosomes to grow larger until they will eventually breakdown and disrupt the function of the cell and the organs that the cell makes up-including the heart and skeletal muscles.
Screening Method	Dried blood spot test with deficiency of acid alpha-glucosidase enzyme activity, and confirmed through molecular genetic testing (DNA analysis)
Gene	Acid Alpha-Glucosidase (GAA)
OMIM or other names for condition	Glycogen Strorage Disease II, GSD2, Acid Alpha-Glucosidase deficiency, GAA deficiency, Acid Maltase deficiency, AMD
Case Definition	Abnormal GAA enzyme and 2 pathogenic or likely pathogenic DNA variants

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.* Infantile-onset Pompe disease (individuals with onset before the age of twelve months with cardiomyopathy) typically onset is at the median age of four months with hypotonia, generalized muscle weakness, feeding difficulties, failure to thrive, respiratory distress, and hypertrophic cardiomyopathy. Without the treatment of enzyme replacement therapy (ERT), IOPD commonly results in death by the age of two from progressive left ventricular outflow obstruction and respiratory insufficiency. With treatment of ERT as soon as diagnosis is established infants show improved survival, ventilator-independent survival, improved acquisition of motor skills, and reduced cardiac mass. In mamy cases, in the absence of NBS, the diagnosis of IOPD will be made after the recognition of cardiomyopathy. The federal advisory committee recommend adding Pompe Disease to the Recommended Uniform Screening Panel (RUSP) in 2013, and as of 2015, the RUSP recommends that state newborn screening programs include Pompe Disease. (RUSP Executive Summary, 2015) Late-onset Pompe disease (individuals with onset before age twelve months without cardiomyopathy, and all individuals with onset after age twelve months) is characterized by proximal muscle weakness and respiratory insufficiency. ERT may stabilize the functions most likely to be lost; respiratory and motor ability The following statement is taken from the HRSA RUSP Document " Imaging and histologic studies suggest that there is muscle damage by the time that cases of late-onset Pompe disease are clinically detected. The argument in favor of screening is that treatment does not reverse muscle damage but that treatment begun before the onset of muscle damage may prevent it from occurring. However, the benefit of pre-symptomatic treatment in the prevention of progressive muscle damage has not yet been clearly established." (Kemper, 2013) https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/pompe-external-evidence-review-report-2013.pdf)
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?* From July 14, 2017 to March 31, 2019, total 108,862 infants were screened for Pompe, and 13 infants were identified with late-onset Pompe disease. The incidence based on the pilot project is 1 in 8,374. Detirmined by Wisconsin Pompe Pilot Program: Pome Screening positive cases 13 Confirmed positive cases 13 Infants screened 108,862 False Negatives 0 False Positives 0 Incidence 1 in 8374 Infantile onset Pompe 0 Late onset Pompe 13

Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history*. Pompe disease is divided into infantile (classic or nonclassic) and late-onset disease. The differences between these conditions are described below. 1. Infantile-onset Pompe Disease Pompe disease generally exhibit poor feeding and failure to thrive, gross motor delay with muscle weakness, early respiratory insufficiency, and significant cardiac issues with the most severe concern being cardiomyopathy. (van den Hout et al. 2003, Kishnani et al. 2006) Without treatment, the median age of death is six to nine months due to cardiac dysfunction. (van den Hout et al 2003, Kishnani et al. 2006) Fewer than 10% survive past 24 months of age. (Kishnani et al. 2006) Some with infantile-onset Pompe disease may have longer survival. (Slonim et al. 2000). ERT has been shown to reduce hypertrophic cardiomyopathy improve motor function and prolong ventilator-free survival. (Hahn, 2019) Despite the lifesaving benefits of ERT, IOPD remains a complex phenotype with significant morbidity, recent but limited evidence suggests that some IOPD survivors who are treated with ERT may develop CNS manifestations of the disorder including sensorineural hearing loss, white matter changes and/or cognitive decline. The frequency of CNS involvement in survivors is unknown. (Korlimarla, 2017, Hahn 2019, Ebbink 2018) 2. Late-onset Pompe Disease Over half of all Pompe patients with late onset disease will have disease onset in childhood (Laforet, Nicolino et al. 2000; Hagemans, Winkel et al. 2005). Prior to NBS, over 1/3 of late onset patients initially had the wrong diagnosis, providing the wrong prognosis and potentially alternate harmful therapies. Furthermore there is on average a 10 (Muller-Felber, Horvath et al. 2007) or 12.5 year (Kishnani, Amartino et al. 2013) year lag from the time of first symptoms to making a diagnosis in two large published series. Aside from the potential psychosocial harms of being mislabeled, studies have demonstrated that such patients are subjects to many expensive tests and multiple invasive tests including muscle biopsy and repeated EMGs (Hagemans, Winkel et al. 2005; Muller-Felber, Horvath et al. 2007) Untreated adult onset disease has a severe effect on quality of life (Hagemans, van Schie et al. 2007; Gungor, de Vries et al. 2011; Kanters, Hagemans et al. 2011) However, unlike infantile-onset Pompe disease, cardiomegaly is not typically present. Late-onset Pompe disease is characterized by muscle weakness and respiratory insufficiency. A review of 225 published case reports found a wide range of death in 36 patients (median 25 years, range 0.9-66 years), primarily due to respiratory failure, onset ranged from 0 to 71 years. (Winkel et al. 2005). ERT has been shown to increase survival "considerably" (Kanters 2017) in patients LOPD patients and has beneficial effects on muscle strength scores and ambulation in the first 2 years of treatment and has a positive effect on quality of life. (Kanters 2017, Schoser 2016, Anderson 2014)

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 IOPD treatment with ERT should begin as soon as possible after a diagnosis is confirmed and CRIM status determined. ERT should be started as early as possible before irreversible damage has occurred. (Kronn 2017) The majority of patients diagnosed with LOPD on NBS have not been treated with the ERT. The correct time to initiate ERT in LOPD is the subject of debate, some evidence suggests that treatment should begin when clinical signs (decreased PFTs) are present but the patient is still largely asymptomatic (Kronn 2017) before irreversible muscle damage (Van der Beek, Hagemans et al. 2009) or at the commencement of symptoms (Cupler 2012). This may be as soon as 1 year of age with over half of all late onset patients being symptomatic before adulthood.
Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence. FDA registered studies of enzyme replacement therapy have demonstrated that this is immediately life saving for infantile onset Pompe disease. Furthermore it is associated with a significant delay in need for invasive ventilation in CRIM negative patients and with avoidance for the need for invasive ventilation in CRIM positive infantile onset disease. Specifically from the original trial, follow up published on 16 patients in 2009 followed for, for up to a total of 3 y. These children continued to exhibit the benefits of alglucosidase alpha at the age of 36 mo. Cox regression analyses showed that over the entire study period, alglucosidase alpha treatment reduced the risk of death by 95%, reduced the risk of invasive ventilation or death by 91%, and reduced the risk of any type of ventilation or death by 87%, compared with an untreated historical control group. Cardiomyopathy continued to improve and 11 patients learned and sustained substantial motor skills (Kishnani P.S. 2009). The non-responsive children were CRIM negative (Kishnani P.S. 2010). Long-term outcomes (up to 12 years) demonstrate normal IQ and when sufficiently mobile participation in mainstream schools (Ebbink 2012, Spiridigliozzi 2012a Spiridigliozzi 2012b) In CRIM negative patients, who will invariably develop neutralizing anti-bodies, immunomodulation therapy is recommended by consensus but has not been systematically studied. (Poelman 2019) Recent reports have shown progressive white matter lesions and cognitive delays in some LOPD survivors treated with ERT. (Ebbink 2018) Treatment provides health benefits in late onset Pompe disease (Toscano and Schoser 2013) It is recommended to start before irreversible muscle damage (Van der Beek, Hagemans et al. 2009) or at the commencement of symptoms (AANEM Consensus statement: Cupler 2012) ERT may improve or stabilize motor performance and respiratory function in at least 2/3 of treated patients (van Capelle, van der Beek et al. 2010; van der Ploeg, Clemens et al. 2010; de Vries, van der Beek et al. 2012) van der Meijden (2018) looked at long term follow up in 17 patients with childhood onset Pompe (82% carried the c-32-13T variant) and found 56-69% of patients improved in lung function and 71-93% for muscle strength on ERT.

Potential Harms	Potential medical or other ill effects from treatment. Enzyme replacement therapy may be associated with potentially life threatening infusion related reactions, including anaphylaxis. In addition weekly or every other week, infusion do have a modest negative impact on quality of life. CRIM negative and some CRIM positive babies will develop anti rhGAA antibodies and require immune modulation therapy, which carries the risk of infections. There is concern about the identification of late onset disorders in newborn screening even in disorders with high benefit to risk ratio (Fost, 2016). The potential harms include emotional and financial stress, the fear of living with uncertainty, labeling a healthy child as "sick" or "unwell" and unnecessary or harmful medical interventions (Kwon JM, Steiner RD. "I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients. Neurology. 2011;77:522-3.PMID: 21753177, Grosse, 2019). The Wisconsin pilot program parental questionnaire found differences in views of newborn screening for Pompe, with 3/5 families noting financial and/or emotional stress associated with the diagnosis of late onset Pompe disease and lack of clarity surrounding prognosis. Other families noted very a positive experience and were grateful for the knowledge. We are hopeful that the negative responses can be mitigated with genetic counseling and improved understanding of phenotype genotype correlations (Reuser 2019) making a more genotype tailored approach to follow up possible. Prunski (2018) surveyed 9 families with children with Pompe disease (6 LOPD and 3 IOPD) and despite fear and anxiety expressed similar to Wisconsin families all the families viewed newborn screening Pompe positively and were grateful to avoid a long diagnostic odyssey and for possible for early recognition and treatment. Additionally, recent evidence suggest that screening may offer some benefit even to young children even with the mildest form of LOPD. Herbert (2019) reported that 4/84 LOPD patients with the common c.-32-13T>G variant had symptoms prior to 2 years of age, including proximal muscle weakness, swallowing and feeding problems, sleep apnea and developmental delay. The identification of these children by newborn screening can allow for treatment and prevent unnecessary medical evaluations and tests. Furthermore, many of the conditions currently screened for by NBS have mild or late onset variants (including PKU, VLCADD, CF, CUD, MCADD, IVA, Citrullinemia type 1, Galactosemia, among others). Over time, through improved understanding of the natural history of these conditions, metabolic clinicians have been able to adjust their counseling to help families cope with uncertainties surrounding the spectrum of disease and have been able to make better predictions about what families can expect. While the concerns about identification of individuals with LOPD are valid, they should be put in the context of life saving benefit in the identification of IOPD and benefits of treatment for LOPD as individuals become symptomatic later in life.
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.* There are currently two FDA approved enzyme replacement therapies for Pompe disease Myozyme and Lumizyme both manufactured by Genzyme.
Availability	*Describe scope of availability and note any limitations.* Myozyme has limited availability, Lumizyme is freely available. Both are standard care and in our experience to date have been routinely reimbursed by payers. Ongoing monitoring of late onset Pompe patients is akin to that provided to pre-symptomatic VLCADD patients. In both instances this is driven by approved standards of care and is routinely covered by payers.
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.* All presumed Pompe screening positive cases will undergo echocardiogram evaluation. If the result is unremarkable, parents will be telephoned to explain that the child may have Pompe disease without early infantile onset, or that this may be a false positive screen and the child does not have Pompe disease. A follow-up clinical visit will be arranged at one of the clinical centers within one to two weeks to arrange for genetic counseling and return of results. The metabolic physicians and advanced practice providers, with assistance from metabolic nurses and the genetic counselors, will provide genetic counseling to the families whose children are identified as affected by Pompe disease, including both infantile onset and late onset forms. They will also discuss the possibility of false positive results with families in the context of general NBS principle and unique situations with Pompe screening test, such as pseudo-deficiency. Additional educational materials will be supplied to parents.
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.* In the Wisconsin Pompe NBS pilot project, GAA enzyme activity in dried blood spots is used as a primary screening tool, using a 6 enzyme mutliplex assay. The assay involves incubating a 3.2-mm dried blood spot punch with substrate and internal standard for GAA at 37°C for 18 or 3 hours. The products are purified, dried, suspended, and then analyzed using flow injection tandem mass spectrometry. The enzyme activities are calculated as the function of product per hour compared to the internal standard for the sample analysis. The current Pompe screening assay is in a multiplex format. Besides GAA activity for Pompe, the assay also includes ASM for Niemann–Pick disease, GLA for Fabry disease, IDUA for MPS I, ABG for Gaucher disease, and GALC for Krabbe disease. When GAA activity is less than the cutoff value, the lab will review the other five enzyme activities. With one or more additional enzyme activity lower than 15% of the daily median, the specimen will be deemed as unsatisfactory. The multiplexing assay was chosen for specimen quality assessment, and to thereby reduce false positive results. Therefore, except for the targeted GAA, the other five enzyme activities are not reportable regardless of their values and no cutoffs have been developed.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other* DBS
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* YES, specimens with GAA enzyme lower than 10% of the daily median or "likely Pompe" per CLIR undergo GAA gene variant analysis and biochemical second tier testing. Specimens with GAA enzyme between 10-15% of the daily median were reported as possible screening positive with a recommendation to repeat NBS.
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 set of blinded samples provided by the MO newborn screening program. The results presented in the table below indicate that our assay and established cutoffs can correctly identify Pompe cases and normal sample, with the possibility of fewer false positive results.

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 dried blood spot samples with two known levels of enzyme activities were prepared and supplied by PerkinElmer. PE-low samples were with reduced enzyme activities, and PE-high samples were with normal enzyme activities. Analytic Accuracy: In total 50 tested samples, 45 samples (90%) were within the expected range, five PE-low samples had a value lower than the expected range, which will have no negative effect on the clinical sensitivity. The assay accuracy assessment is satisfactory. Assay within-run Precision: GAA enzyme activities of five replicates of low and high PE samples were assessed for five days. The coefficient of variation (CV) for all measured samples was less than 15%. The assay within-run precision assessment is satisfactory. Assay between-run Precision: The coefficient of variation (CV) for the daily mean of the PE samples measured was less than 6%. The assay between-run precision assessment is satisfactory. Assay linearity (reportable range): The obtained means (triplecates) and expected means of six levels of PE samples were used to assess the linearity. The coefficient of determination (R2) was 0.9999 as shown in the graph below. The assay's measurement range was determined to be 0.03-18.45 µM/L/h. Analytical Sensitivity (Limit of Quantification): Based on the assay linearity study, the assay's limit of quantification was determined to be 0.03µM/L/h. Analytical Specificity (interferences): The GAA assay design includes an internal standard for each sample throughout the whole process, so any potential interference can be normalized by the process. Assay Cutoff Establishment: To take into consideration of the variability nature of enzymatic assays, and the experience of other newborn screening program, we have planned to use lower 10% of the daily median as screening abnormal cutoff, and 10-15% of the daily median as screening possible abnormal cutoff. The data from 6,634 residual routine NBS specimens over 21 days indicated that the cutoffs were consistent and stable. The potential screening positives are acceptable.

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?* A 6 enzyme multiplex panel will be used. In addition to GAA for Pompe the assay also includes activity for Niemann–Pick disease, GLA for Fabry disease, IDUA for MPS I, ABG for Gaucher disease, and GALC for Krabbe disease. When GAA activity is less than the cutoff value, the lab will review the other five enzyme activities for specimen quality. The multiplexing assay was chosen for specimen quality assessment, and to thereby reduce false positive results. Therefore, except for the targeted GAA, the other five enzyme activities are not reportable regardless of their values and no cutoffs have been developed. • *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?* Only MPS I has been accepted on the RUSP, but this condition has not been nominated for review in Wiscosnin.

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	Wisconsin
Number of Newborns Screened	Infants screened 108,862
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* 13
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* None, 0/108,862
Number of Infants Confirmed with Diagnosis	*How are diagnosis confirmed [clinical, biochemical, molecular]?* 13 screening positive cases were confirmed to have Pompe disease by low GAA enzyme activity in whole blood, and two disease causing mutations in GAA gene.
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.* NO
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* Pompe testing will be integrated into our ongoing routine NBS workflow, and the testing will follow the general principles established for other disorders. Clinical geneticist physicians who and are clinical consultants for the Wisconsin Newborn Screening Program appointed by the State Chief Medical Officer of Community Health Promotion, and available to the NBS laboratory 24/7 for NBS presumed positive results related matters. Consistent with existing Wisconsin NBS practices, upon receiving a phone call on presumed Pompe positives from the NBS laboratory, the metabolic consultants will contact the primary care provider. From this, the clinical status and location of the infant will be established, and contact details for the parents will be obtained. The primary care provider will be provided information on the newborn screen results and the natural history of the conditions. The consultant will provide the primary doctor with a list of studies and tests that should be performed (Echocardiogram and GAA enzyme, CK level). The primary doctor will then call the parents and discuss the status of the child. If clinically well (feeding well, alert, no reduced tone) the child will be transported by the parents to the nearest echocardiographic facility for an echocardiogram. In addition, samples for confirmatory testing will be drawn to establish the GAA enzymatic activity on a dried blood spot and to facilitate molecular confirmation of Pompe disease and a CK level. All children with evidence of cardiomyopathy and/or impaired cardiac function on echocardiogram will immediately be transferred to one of the three treatment centers (Marshfield Clinics, Medical College of Wisconsin, and University of Wisconsin American Family Children's Hospital) for cardiomyopathy management, and prepared to receive enzyme replacement therapy. If the echocardiogram is performed at a remote location and is unremarkable, parents will be telephoned by the primary doctor to explain that the child may have Pompe disease without early infantile onset, or that this may be a false positive screen and the child does not have Pompe disease. A follow-up clinical visit will be arranged at one of the clinical centers within one to two week to arrange for genetic counseling and return of results. Additional educational materials will be supplied to parents. Presumed Pompe screening positive cases will be collected whole blood, and undergo both GAA enzymatic activity confirmation testing. Mutation analysis by full gene sequencing through the State Laboratory of Hygiene on the DBS. The GAA gene sequencing will allow us to identify all known GAA mutations that are associated with infantile onset, late onset, and pseudo deficiency. The combination of GAA enzyme activity level and mutation information will enable us to timely determine Pompe disease status. .
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* No
List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests, and Genetic Test Reference if applicable.* http://www.genetests.org/search/tests.php?search=POMPE DISEASE TEST&submit=Search&start=120

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.* Clinical follow up for Pompe disease screening positive cases will utilize the existing network of metabolic referral centers in Wisconsin used for metabolic disorders. All three centers have metabolic geneticists with considerable experience in treating children with lysosomal storage diseases. Enzymatically confirmed Pompe infants with any one of following will be targeted to start enzyme replacement therapy within 2 weeks if they have any of the following: • Clinical signs/symptoms of Pompe disease • Elevated CK consistent with muscle disease • Echocardiogram revealing cardiomyopathy • Genotype consistent with infantile onset disease Although ERT has been shown to improve quality and quantity of life, the benefit is not as great in CRIM negative children (Kishnani P.S. 2010). Therefore, children with a CRIM negative status will be offered immunomodulatory therapy in line with current clinical practice (Messinger YH 2012, Banugaria SG, 2013). Late onset individuals will be followed at least annually with a measurement of CK and clinical assessment of neuromuscular function including respiratory status per current consensus care guidelines (Cupler 2012). They will be offered ERT if they are demonstrating signs or symptoms of Pompe disease. Those who are found to be unaffected carriers, pseudo-deficiency carriers and false positives will receive genetic counseling and discharged from clinical follow-up.
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	GAA enzyme and DNA from DBS
Confirmatory testing	Confirmatory testing by GAA enzyme is available at several CLIA/CAP certified laboratories including Mayo Laboratories and Duke
Treatment	ERT is a standard care for Pompe disease and is covered by insurance
Counseling	Counseling can be performed at any of the 3 regional centers
False positives	No false positives from the Wisconsin Pompe NBS pilot project
Mechanism of funding	NBS for Pompe would need to be funded through the NBS fee.

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 2

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Criterion 4

Criterion 5

Criterion 6

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Criterion 7

Criterion 8

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Criterion 9

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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:

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