WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination
11/6/2017

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	Spinal Muscular Atrophy
Description of Disorder	Autosomal recessive neuromuscular disease
Screening Method	Newborn blood spot screening test using multiplexed real-time PCR.
Gene	Survival of Motor Neuron T (SMN1)
OMIM or other names for condition	253300 (SMA1), 253550 (SMA2), 253400 (SMA3), 271150 (SMA 4) http://www.omim.org/entry/600354#0007
Case Definition	NA

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.* There are four main clinical subtypes of SMA caused by mutations in the SMN1 gene. While the same disease with the same genetic cause, each subtype has a different timing of clinical onset.(1) Infants with the severe variant called SMA Type I, which accounts for 50 to 60% of all cases, are typically normal at birth. Weakness and respiratory or bulbar insufficiency presents within the first few months of life. A very small subset of infants present with severe weakness at birth and are born with congenital arthrogryposis (SMA Type 0). SMA Type II, comprising 30-40% of all cases, has onset of symptoms typically between 6-18 months. SMA Type III patients, comprising about 10% of cases, typically present after 18 months of age through the teen years. Another very small subgroup present in adulthood, and this is called SMA Type IV.(1)

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?* In the United States, the pan-ethnic disease incidence of SMA, calculated using the measured carrier frequency of SMA of 1/54 and a detection rate of 91.2%, is calculated to be 1/11,000.(2)

Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history.* As summarized above, according to the consensus care guidelines for SMA, four main clinical sub-types are distinguished.(1) These include the acute infantile type, or Werdnig-Hoffmann disease (SMA Type I; affected infants never sit independently), the intermediate type (SMA Type II; affected children sit but never walk), the mild type (SMA Type III; affected individuals ambulate and typically manifest weakness after 18 months of age), and the adult onset form (SMA Type IV; affected individuals ambulate and typically manifest weakness as adults). The most severe form, SMA Type I, occurs during infancy and accounts for 50-60% of all cases; these children never sit, and 100% suffer bulbar and respiratory insufficiency with early mortality.(1) Two recent natural history studies in infants with SMA Type I have shown that the median age to reach the combined endpoint of death or requiring at least 16 hours/day of ventilation support is 13.5 and 8 months, respectively.(3,5) In these natural history studies, requirements for nutritional support preceded ventilation support, and the mean rate of decline in motor function as measured by The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP INTEND) scale was 1.27 points/year.(3) SMA Type II and III are slowly progressive with little change in motor function observed in most patients over a twelve-month period. Functional declines are observed over periods exceeding one-year.(7) Survival probabilities at 2, 4, 10, and 20 years of age have been reported to be 100%, 100%, 98%, and 77% in children with SMA Type II. For patients with SMA Type III, life expectancy has not been reported to be significantly less than in the unaffected population, although a significant portion lose the ability to walk by 40 years of age.(8) A very small subgroup of individuals present in adulthood, and this is called SMA Type IV. Regardless of clinical severity, 95% of all SMA patients have the same homozygous SMN1 gene deletion, and detection of the SMN1 gene deletion is used as the primary diagnostic assay. All patients possess a low-functioning analog to the SMN1 gene called SMN2. The SMN2 copy number is predictive of clinical severity. Humans have a variable copy number of the SMN2 gene (0-8 copies), which correlates with SMA disease severity. Importantly, in the context of NBS, 80% of patients with SMA Type I carry one or two SMN2 copies, and 82% of patients with SMA Type II carry three SMN2 copies, whereas 96% of patients with Type III SMA carry three or four SMN2 copies.(9) SMN2 is a key determinant of disease phenotype and is routinely determined after initial diagnosis to help predict the clinical phenotype. Thus, it is highly likely an infant identified by NBS with subsequent testing showing 3 or fewer copies of SMN2 will present with Type I or Type II SMA, which are associated with early morbidity and/or mortality. Therefore, the identification of homozygous SMN1 deletion and determination of SMN2 copy number allows confident prediction that an infant will develop SMA.

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?* Both human natural history data and animal model data suggest that early drug intervention is required for greatest efficacy in the most common and severe form of SMA Type I. In fact, in human SMA Type I, there is strong evidence that the irreplaceable loss of motor neurons begins early in the perinatal period, with severe denervation in the first 3 months of life and loss of more than 90% of motor units within 6 months of age. Moreover, a recent multi-center natural history study conducted by the NINDS NeuroNEXT clinical trial network in infants under six months of age with genetically confirmed SMA has shown significant differences between the SMA and control infants at the baseline visit in motor function tests, ulnar compound muscle action potential, and electrical impedance myography (EIM).(5) Moreover, studies looking at the timing of drug delivery in mouse models of SMA Type I have strongly suggested that early administration of SMN-based drug therapies is more effective than post-symptomatic delivery. The results have been remarkably consistent across modalities including genetic means, gene therapy vectors, and antisense oligonucleotides to increase SMN levels. All have demonstrated the best results when the drugs are given as early as possible before significant motor weakness or loss in severe mouse models of SMA.(10, 11) In addition, supportive treatment in the first few weeks to months of life prolongs survival and improves quality of life. In fact, the increases in survival of the type I infants over the past decade have been documented to correlate specifically to proactive respiratory and nutritional care.(6) However, in the current environment in the absence of newborn screening, these interventions remain predominantly reactive to medical crises. Many SMA Type I infants' initial presentation is in crisis with acute respiratory failure or bulbar insufficiency with aspiration prior to diagnosis and often associated with common viral respiratory infections. In fact, diagnostic delay is very common in SMA. A recent systematic literature search conducted from 21 reports in PubMed and Web of Science databases for studies published between 2000 and 2014 showed that the mean ages of onset were 2.5, 8.3, and 39.0 months for SMA Types I, II, and II, respectively, while the weighted mean ages of confirmed spinal muscular atrophy genetic diagnosis were 6.3, 20.7, and 50.3 months, respectively, for Types I, II, and III.(12) Better clinical outcomes are possible simply with the use of the currently available proactive care options, such as gastrostomy tube surgery prior to an aspiration event, and proactive respiratory care including use of the cough assist device to mobilize respiratory secretions and nocturnal bi-level positive airway pressure support via mask or nasal interface.(1) A comprehensive rationale for the urgency for SMA newborn screening has been delineated in the review article, "Newborn screening for spinal muscular atrophy: Anticipating an imminent need".(10)

Efficacy (Benefits)	*Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence.* Spinraza (nusinersen) in Symptomatic Infants: The efficacy of Spinraza was demonstrated in the ENDEAR Phase III randomized, double-blinded, sham-controlled clinical trial in 121 patients with infantile-onset SMA with two copies of SMN2 who were diagnosed before 6 months of age and who were less than 7 months old at the time of their first dose. Results were reported at the 2016 International Congress of the World Muscle and at the 43rd Annual Congress of the British Paediatric Neurology Association Meeting (see both slide decks appended to the references). Patients were randomized to receive an injection of Spinraza, into the fluid surrounding the spinal cord, or undergo a mock procedure without drug injection (sham). The trial assessed two primary endpoints: 1) percentage of patients with improvement in motor milestones, such as head control, sitting, ability to kick in supine position, rolling, crawling, standing and walking by measuring the proportion of motor milestone responders with the Hammersmith Infant Neurological Examination (HINE) and 2) percentage of patients reaching the combined endpoint of death or greater than 16 hours per day of ventilatory support. At a pre-specified interim analysis, 78 of 121 patients had the opportunity to be on treatment/sham for at least 6 months and were eligible for analysis (data available in the appended slides). Forty-one percent of patients treated with Spinraza (n=51) achieved improvement in motor milestones, whereas none of the control patients did (n=27, $p<0.0001$). Spinraza met the pre-specified primary endpoint for event-free survival, demonstrating a statistically significant 47% reduction in the risk of death or permanent ventilation ($p<0.01$). In the analysis, a greater percentage of untreated infants (68%) died or required permanent ventilation compared to infants treated with Spinraza (39%). Spinraza also demonstrated a favorable safety profile. The commonly reported adverse events include respiratory events and constipation, consistent with those expected in the general population of infants with SMA. The interim analysis represents 44.89 patient years of exposure to Spinraza treatment. Open label trial results of Spinraza in both infants and children have been recently published.(13,14,15) Spinraza in Pre-symptomatic Infants: Biogen is currently conducting a Phase 2, open-label, multicenter study in 10 countries for pre-symptomatic infants with SMA termed NURTURE. The study objective is to evaluate the efficacy and safety profile of Spinraza in infants with genetically diagnosed and pre-symptomatic SMA. The planned enrollment is up to 25 infants, with key inclusion criteria of 1) less than 6 weeks of age at first dose, 2) pre-symptomatic, 3) genetic diagnosis of 5q SMA gene deletion or mutation, 4) 2 or 3 SMN2 copies, and 5) Ulnar CMAP amplitude $\geq$1 mV at baseline. The primary study endpoints are time to respiratory intervention (invasive or non-invasive ventilation for $\geq$ 16 hours/day continuously for $\geq$7 days or tracheostomy) or death. The secondary endpoints include: safety, tolerability, pharmacokinetics, motor function milestones, survival (proportion of patients alive), and growth parameters. The results of an interim analysis were presented at the 2016 International Congress of the World Muscle Society (see appended slides) and at the 43rd Annual Congress of the British Paediatric Neurology Association (BPNA) Meeting (see appended slides). In the interim analysis of the ENDEAR trial, the following age appropriate motor milestone development based on HINE Motor Milestone Achievements were met: 1) head control in 18% infants with treatment (n=51) and 0% in the sham (n=27), 2) sitting independently in 10% of infants with treatment and 0% in the sham, 3) standing in 2% of infants with treatment and 0% in the sham. See ADDENDUM.

Potential Harms	*Potential medical or other ill effects from treatment.* Spinraza is a therapy administered into the intrathecal space and in some cases, anesthesia is required for administration. Therefore, the established risks of routine lumbar puncture procedure exist, which include headache, nausea, bleeding and CSF leak. In addition, there are standard risks of anesthesia, which depend upon the anesthetic used. Specifically in the SMA population, there is the respiratory risk for general anesthesia, but for whom local anesthesia would not be sufficient. Also, SMA patients who have undergone scoliosis surgery may have complicated intrathecal access, potentially requiring fluoroscopic guidance, which would include cumulative radiation risk. Finally, children responding to therapy may have improving, but still weak motor skills, and may roll or fall resulting in respiratory compromise or injury. In regard to Spinraza, the most common side effects found in clinical trial participants were upper respiratory infection, lower respiratory infection and constipation. Warnings and precautions include low blood platelet count and toxicity to the kidneys (renal toxicity). In the randomized Phase III ENDEAR clinical trial, no patient had a platelet count less than 50,000 cells per microliter and no patient developed a sustained low platelet count despite continued drug exposure. Toxicity in the nervous system (neurotoxicity) was observed in animal studies. The FDA USPI for Spinraza can be accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf

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.* On December 23, 2016, the FDA approved the first disease-modifying therapy for SMA called Spinraza (nusinersen) for the treatment of SMA patients of all types and ages. Spinraza, marketed by Biogen, is an antisense oligonucleotide drug that alters splicing of the SMN2 pre-mRNA to increase the amount of full-length SMN2 mRNA. Full-length SMN2 mRNA is translated into mRNA to increase the amount of functional SMN protein. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534611.htm). In addition to Spinraza, a number of clinical care approaches have been shown to improve survival and quality of life in SMA Type I, including: 1) nutritional support and careful monitoring of nutritional intake and swallow function, typically resulting in additional supplementation orally at first and then placement of nasogastric, nasojejunal or gastrostomy tube as needed, and prevention of fasting/catabolic state given their severe sarcopenia, and 2) respiratory support including techniques to mobilize and clear lower airway secretions such as chest physiotherapy devices, cough assist devices and pulse oximetry monitoring, and also the use of respiratory support devices including bi-level positive airway pressure via face/nose mask or tracheostomy tube to treat sleep disordered breathing.(1,6) There are also five additional therapies in development for the treatment of SMA, including SMN1 gene replacement therapy, small molecules designed to alter SMN2 mRNA splicing, and additional small molecule approaches aimed at motor neuron protection and muscle enhancement. These include Olesoxime sponsored by F. Hoffman - La Roche, which is a small molecule designed to prevent neuronal cell death (clinical trial identifiers: NCT02628743, NCT01302600, contact: Sangeeta Jethwa Schnetzler MD at sangeeta.jethwa@roche.com). There is also AVXS-101 sponsored by AveXis, which is a gene therapy to replace the SMN1 gene (clinical trial identifier: NCT02122952, contact: Douglas M. Sproule MD MSc at dsproule@avexis.com). LMI070 is sponsored by Novartis Pharmaceutical and is a small molecule designed to alter splicing of SMN2 mRNA and increase the amount of functional SMN protein (clinical trial identifier: NCT02268552, contact: Lawrence Charnas MD PhD at lawrence.charnas@novartis.com). RO7034067 and RO6885247 are sponsored by F. Hoffmann – La Roche and are small molecules designed to alter splicing of SMN2 mRNA and increase functional SMN protein (clinical trial identifiers: NCT02633709, NCT02240355, NCT02908685, NCT02913482, contact: Sangeeta Jethwa Schnetzler MD at sangeeta.jethwa@roche.com). Finally, there is CK-2127107, which is sponsored by Cytokinetics and is a small molecule to enhance muscle contraction (clinical trial identifier: NCT02644668, contact: Stacy A. Rudnicki MD at srudnicki@cytokinetics.com).
Availability	*Describe scope of availability and note any limitations.* Spinraza, which is marketed by Biogen, is FDA approved for the treatment of SMA patients of all ages and types. The FDA approved Spinraza on December 23, 2016. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm534611.htm). In addition to Spinraza, interventions including bi-level pressure support (BIPAP), cough assist machine, and placement of a gastrostomy feeding tube are widely available at major medical centers. They are currently recommended as the standard of care options for infants with SMA Type I in the “Consensus Statement for Standard of Care in Spinal Muscular Atrophy.”

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.* Consistent with existing Wisconsin NBS practices, the NBS laboratory at WSLH will communicate the presumed SMA positive results to the primary care provider and one of two neuromuscular physicians in Wisconsin, Dr. Schultz at UW Health American Family Children's Hospital and Dr. Harmelink at Children's Hospital of Wisconsin (CHW)/Medical College of Wisconsin (MCW). Both are pediatric neurologists with considerable experience in treating children with neuromuscular disorders. They will contact the primary care provider to provide further consultation and make connection with the family. If the infant is clinically well (feeding well, alert), arrangements will be made for the infant to be seen by neurology and genetic counseling within 7 days. If the infant is not feeding well or has increased respiratory symptoms, arrangements will be made to transport the infant to one of the two treatment centers for neuromuscular management. In addition, samples for confirmatory testing will be drawn to confirm the SMN1 and SMN2 copy numbers in a CAP/CLIA certified clinical diagnosis testing laboratory. A follow up clinical visit will be arranged at one of the clinical centers within 1 week to arrange for genetic counseling and review of results. Genetically confirmed SMA infants will be targeted to start treatment with Spinraza if they have 1, 2, or 3 SMN2 copies. If there are 4 or more SMN2 copies, the child will return for a neurological exam every 6 months, or sooner should symptoms occur, including delayed motor milestones, weakness, or hypotonia. Should symptoms arise suggesting SMA, then Spinraza will be offered. All patients will establish care at either UW Health AFCH in Madison or CHW/MCW. To assess the psychosocial impact on parents receiving a positive newborn screen on a child who may not present with disease until adulthood (SMA type IV) or may never present with disease (SMN1 0 copies but 5 or more SMN2 copies; in some patients the protein produced from the high number of SMN2 copies is sufficient to prevent onset of disease), all patients will be followed with regular psychosocial assessments. In addition, a control group consisting of parents of children with normal newborn screens will be included. IRB application for this study is in process.

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.* Dr. Mei Baker has recently established an SMN1 gene deletion detection assay using real-time PCR technology. The assay design involves a multiplex platform including an SMN1 gene sequence fragment to detect SMA caused by SMN1 gene deletion, a reference gene sequence fragment to monitor specimen integrity, and a T-cell excision circle sequence fragment to screen for severe conbined immunodeficiency (SCID). In 2008 the Wisconsin NBS program became the first NBS program in the world to implement routine NBS for SCID. SCID is now one of the newborn screening disorders in the recommended uniform screening panel (RUSP). The majority of state newborn screening programs in the United States currently perform NBS for SCID. A multiplex assay to simultaneously screen for SCID and SMA will lead to the most cost effective way to implement the SMA screening test because there is minimal cost to incorporate an SMN1 gene sequence fragment to detect SMA into the existing SCID screening assay. The cases with SMN1 identified as “zero” will be defined as SMA screening positive, and referred for further clinical evaluation and confirmatory testing. This approach will avoid SMA carrier identification.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other.* dried blood spot

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.* No.
Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.* As decribed earlier, a SCID/SMA multiplex real-time PCR assay development was conducted at the WSLH Newborn Screening Laboratory. From Feburary 1, 2017 to August 28, 2017, we performed the SCID/SMA assay on 20,000 de-identified residual NBS specimens. We detected four SMN1zero copy specimens in this cohort. The assay also correctly identified all seven previously diagnosed SMA cases using their dried blood specimens. SMA screening sensitivity using this assay is 95-96% because the assay only detects homozygous SMN1 exon 7 deletion SMA cases, and SMA caused by gene conversion or point mutations will not be detected by the assay. The positive predictive value of this assay can be100% for SMN1 zero copy SMA, but clinical manifestations are largely dependent on the infant's SMN2 copy number.
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.* Based on our assay development experience described above, the detection rate is 100% for SMN1 zero copy SMA. This is a qualitative assay, and results will have two categories: SMN1 present (screening negtive) and SMN1 absent (screening positve). The analytic parameter set for quantitative assays, such as numerical reference range, are not applicable here. The NBS laboratory at WSLH is a CAP/CLIA ceritied clinical testing laboratory, and will follow CAP/CLIA regulations including all QC and PT requirements. The confirmatory testing will also be done at a CAP/CLIA certified clinical diagnosis testing laboratory.
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?* NA • *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	
Number of Newborns Screened	
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.*
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.*
Number of Infants Confirmed with Diagnosis	*How is diagnosis confirmed [clinical, biochemical, molecular]?*

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.* s No new sample collection or new sample punch is needed. The same sample used for current routine SCID sceening will be used simultaneouslyfor SMA screening.

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.* It is unlikely that this assay will have screening false positive results based on the nature of the assay design described in Criterion #6 and our assay development and validation experence, but on rare occations, the sample quality may cause an inconclusive result that requires either retesting the sample or a new sample collection. This assay report method (SMN1 present or absent) is intended to avoid carrier identification. The diagnosis testing to confirm SMN1 absence and assess SMN2 copy numbers needs only a simple blood draw.
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* The screening test is a laboratory developed test.
List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests and Genetic Test Reference if applicable.* A comprehensive list can be found at: https://www.genetests.org/search/tests.php?locations[]=USA&user_submitted=1&search=SPINAL+MUSCULAR+ATROPHY&filter_status=1 All Children's Hospital, Johns Hopkins Medicine, Clinical Molecular Genetics Laboratory - St. Petersburg, FL, USA Greenwood Genetic Center Diagnostic Laboratories - Greenwood, SC, USA Invitae - San Francisco, CA, USA MNG Laboratories (Medical Neurogenetics, LLC.) - Atlanta, GA, USA□□
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.* In addition to the clinical follow up procedure described in Criterion #5, the NBS lab will follow the existing procedure of short-term follow-up for NBS: communicate with the clinics regularly for updates on confirmatory testing and clinical assessment results for all reported SMA screening positive cases, including final diagnosis and treatment/management plans. There will be a database for all presumed SMA screening positive cases to capture data from NBS testing, confirmatory testing, clinical assessment, treatment plans, and clinical outcomes. The education materials for primary care providers and parents will be sent out and posted on the WSLH website.

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	aditional $1.00 when using SCID/SMA multiplex screening assay
Confirmatory testing	
Treatment	
Counseling	
False positives	
Mechanism of funding	

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
1	Consensus statement for standard of care in spinal muscular atrophy. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A; Participants of the International Conference on SMA Standard of Care. J Child Neurol. 2007 Aug;22(8):1027-49.
	Criterion 2
2	Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, Flynn K, Hendrickson BC, Scholl T, Sirko-Osadsa DA, Allitto BA. Eur J Hum Genet. 2012 Jan;20(1):27-32. doi: 10.1038/ejhg.2011.134.
3	Observational study of spinal muscular atrophy type I and implications for clinical trials. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, Kang PB, Foley AR, Yang ML, Martens WB, Oskoui M, Glanzman AM, Flickinger J, Montes J, Dunaway S, O'Hagen J, Quigley J, Riley S, Benton M, Ryan PA, Montgomery M, Marra J, Gooch C, De Vivo DC. Neurology. 2014 Aug 26;83(9):810-7. doi: 10.1212/WNL.0000000000000741
	Criterion 3
4	Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. Taylor JL, Lee FK, Yazdanpanah GK, Staropoli JF, Liu M, Carulli JP, Sun C, Dobrowolski SF, Hannon WH, Vogt RF. Clin Chem. 2015 Feb;61(2):412-9. doi: 10.1373/clinchem.2014.231019.
5	Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, Swoboda KJ, Reyna SP, Sakonju A, Darras BT, Shell R, Kuntz N, Castro D, Iannaccone ST, Parsons J, Connolly AM, Chiriboga CA, McDonald C, Burnette WB, Werner K, Thangarajh M, Shieh PB, Finanger E, Cudkowicz ME, McGovern MM, McNeil DE, Finkel R, Kaye E, Kingsley A, Renusch SR, McGovern VL, Wang X, Zaworski PG, Prior TW, Burghes AH, Bartlett A, Kissel JT; NeuroNEXT Clinical Trial Network and on behalf of the NN101 SMA Biomarker Investigators.Ann Clin Transl Neurol. 2016 Jan 21;3(2):132-45. doi: 10.1002/acn3.283
	Criterion 4
6	The changing natural history of spinal muscular atrophy type 1. Oskoui M, Levy G, Garland CJ, Gray JM, O'Hagen J, De Vivo DC, Kaufmann P. Neurology. 2007 Nov 13;69(20):1931-6.
7	Observational study of spinal muscular atrophy types 2 and 3. Functional outcomes over 1 year. Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, Oskoui M, Constantinescu A, Gooch CL, Foley AR, Yang ML, Tawil R, Chung WK, Martens WB, Montes J, Battista V, O'Hagen J, Dunaway S, Flickinger J, Quigley J, Riley S, Glanzman AM, Benton M, Ryan PA, Punyanitya M, Montgomery MJ, Marra J, Koo B, De Vivo DC; Muscle Study Group (MSG); Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCR). Arch Neurol. 2011 68(6):779-786. doi: 10.1001/archneurol.2010.373.
	Criterion 5
8	A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. J Neurol Sci. 1997 Feb 27;146(1):67-72.
9	Quantitative analyses of SMN1 and SMN2 based on real-time LightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Am J Hum Genet. 2002 Feb;70(2):358-68.
	Criterion 6
10	Newborn screening for spinal muscular atrophy: Anticipating an imminent need. Phan HC, Taylor JL, Hannon H, Howell R. Semin Perinatol. 2015 Apr;39(3):217-29. doi: 10.1053/j.semperi.2015.03.006.
11	Emerging therapies and challenges in Spinal Muscular Atrophy. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, Swoboda KJ, Kiernan MC. Ann Neurol. 2016 Dec 27. doi: 10.1002/ana.24864.
	Criterion 7
12	Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. Lin CW, Kalb SJ, Yeh WS. Pediatr Neurol. 2015 Oct;53(4):293-300. doi: 10.1016/j.pediatrneurol.2015.06.002.

13	Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, Norris DA, Bennett CF, Bishop KM. Neurology. 2016 Mar 8;86(10):890-7.
	Criterion 8
14	Intrathecal Injections in Children With Spinal Muscular Atrophy: Nusinersen Clinical Trial Experience. Haché M, Swoboda KJ, Sethna N, Farrow-Gillespie A, Khandji A, Xia S, Bishop KM. J Child Neurol. 2016 Jun 31(7):899-906.
15	Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, Yamashita M, Rigo F, Hung G, Schneider E, Norris DA, Xia S, Bennett CF, Bishop KM. Lancet. 2017 Dec 17;388(10063):3017-3026. doi: 10.1016/S0140-6736(16)31408-8
	Criterion 9
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Additional Co-sponsoring Organizations

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Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Phone 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: Meredith Schultz, MD - see above.

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

Addendum:
Criterion 3 (continued)
Benefits (continued):

Table 1. Summary of HINE motor milestone achievements of infants receiving Spinraza in NURTURE[a] versus infants receiving Spinraza in ENDEAR.[b, c]

MILESTONE	Total no. of infants achieving milestone (%)	
	NUTURE (open-label, n=9)	**ENDEAR (treated infants, n=51)**
Head control (Full)	5/9 (55%)	9/51 (18%)
Sitting (Independent: stable, pivot)	4/9 (44%)	5/51 (10%)
Standing (Stands with support, unaided)	2/9 (22%)	1/51 (2%)
Walking (Cruising, walking)	1/9 (11%)	0/51 (0%)

[a]Only infants with 2 copies of SMN2 were included in this table (no 3 copy SMN2 patients were included from the NUTURE trial). All infants who enrolled in ENDEAR had 2 copies of SMN2.

[b]The ENDEAR interim was performed when 51 subjects who received Spinraza had the opportunity to be treated and observed for at least 183 days and up to 394 days.

[c]The data included in this chart are taken from a June 8, 2016 interim analysis of NUTURE and a June 15, 2016 interim analysis of ENDEAR. An updated data set for NUTURE is expected to be presented at the American Academy of Neurology Annual Meeting April 22-28, 2017.

The greater attainment of motor milestones in NUTURE versus ENDEAR is also demonstrated by the mean total HINE score. This data can be seen in the BPNA meeting appended slide deck slide 11. The following was observed around 300 days of treatment: ~12 point total mean improvement in NURTURE (n=5), ~4 point mean total improvement in the treatment group of ENDEAR (n=51), and less than a 2 point total mean improvement in the ENDEAR sham group (n=27). This data can be seen in BPNA meeting appended slide deck slide 12. **Thus, the total mean HINE score improvement was substantially higher in the pre-symptomatically-treated infants.**

Spinraza in Children and Teens:
In addition, a placebo controlled Phase III trial in children called CHERISH has been ongoing at over 30 sites worldwide. CHERISH was a fifteen-month study investigating Spinraza in 126 non-ambulatory patients with later-onset SMA (consistent with Type 2), including patients with the onset of signs and symptoms at greater than 6 months and an age of 2 to 12 years at screening. The trial was stopped due to positive results from an interim analysis. Results from the primary endpoint of the pre-specified interim analysis demonstrated a difference of 5.9 points (p= 0.0000002) at 15 months between the treatment (n=84) and sham-controlled (n=42) study arms, as measured by the Hammersmith Functional Motor Scale Expanded (HFMSE). From baseline to 15 months of treatment, patients who received Spinraza achieved a mean improvement of 4.0 points in the HFMSE, while patients who were not on treatment declined by a mean of 1.9 points.

Phase 1 Gene Therapy Trial of AVXS-101 in Symptomatic Infants: The open-label study is designed to evaluate safety and efficacy of AVXS-101 in infants with two copies of SMN2 less than nine months of age. The primary outcome in the study is safety and tolerability. The

secondary outcome measure is an efficacy measure as defined by the time from birth to an "event." Exploratory outcome measures include the CHOP-INTEND score, a motor function scale used in infants with SMA. There were two dosing cohorts, consisting of three patients in a low-dose cohort (6.7 $X10^{13}$ vg/kg) and six patients in a mid-dose cohort (2.0 $X10^{14}$ vg/kg).

As of August 7, 2017, AVXS-101 appeared to have a favorable safety profile and to be generally well tolerated. 15 patients were alive and event-free at 20 months of age, as compared with a rate of survival of 8% in a historical cohort. In the high-dose cohort, a rapid increase from baseline in the score on the CHOP INTEND scale followed gene delivery, with an increase of 9.8 points at 1 month and 15.4 points at 3 months, as compared with a decline in this score in a historical cohort. Of the 12 patients who had received the high dose, 11 sat unassisted, 9 rolled over, 11 fed orally and could speak, and 2 walked independently. Elevated serum aminotransferase levels occurred in 4 patients and were attenuated by prednisolone.(17)

In contrast, data from a recently reported natural history study in 33 Type I SMA infants, shows that none achieved a major milestone such as rolling over, or sitting independently.

AveXis announced plans for a pivotal study of AVXS-101 in SMA Type I infants starting in the third quarter of 2017 using a single-arm design with natural history of the disease as a comparator and is expected to enroll 15 patients.