Recommendation to ACHDNC regarding Newborn Screening for Spinal Muscular Atrophy

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Committee Representatives to the Condition Review Workgroup

ACHDNC Meeting
February 8, 2018

Decision Matrix

- Magnitude and certainty of the net benefit of screening for SMA to the population of affected newborns.
- Feasibility of newborn screening for SMA.
- Readiness of states to implement population-wide screening for SMA.

Secretary's Discretionary Advisory Committee Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (Approved January 31, 2013)

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared	Feasibility	HIGH or MODERATE / LOW
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.		
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			----	
Small to ZERO Benefit		MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			----	
NEG Benefit		MOD/HIGH	**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			----	
---	Certainty	LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.			----	

NET BENEFIT/ CERTAINTY

Spinal Muscular Atrophy (SMA)

- Autosomal recessive inheritance.
- Majority of SMA patients are homozygous for a deletion of exon 7 of *SMN1* independent of severity (5% of cases are compound heterozygotes).
- Incidence estimated at 1 in 10,000 live births.
- Carrier frequency of 1 in 40 – 80 live births.
- *SMN2* copy number modifies the severity of disease.

NET BENEFIT/ CERTAINTY

Spinal Muscular Atrophy (SMA)

	Alternate name	Age at onset	Max. muscular activity achieved	Life expectancy (palliative care)	*SMN2* copies	% of all SMA cases
SMA type 0	Congenital	Prenatal	None	< 6 months	1	Rare
SMA type I	Severe infantile acute; Werdnig-Hoffmann disease	< 6 months	Never sit without support, problems sucking and swallowing	Median: 24 months	1 – 3	40 – 60%
SMA type II	Infantile chronic; Intermediate; Dubowitz disease	6 – 12 months	Sit independently, lose this ability by mid-teens	70% alive at 25 years	2 – 4	30 – 40%
SMA type III	Juvenile; Wohlfart-Kugelberg-Welander disease	> 18 months	Walk independently, lose this ability with time	Normal	3 – 4	~10%
SMA type IV	Adult onset	20 - 30 years	Mild to moderate muscle weakness; typically only proximal muscles affected	Normal	4 – 5	Possibly often undetected
SMA other	variable	variable	variable	n/a	n/a	variable

NET BENEFIT/ CERTAINTY

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NET BENEFIT/ CERTAINTY

Spinal Muscular Atrophy (SMA)

	Age at onset	Max. muscular activity achieved	Life expectancy (palliative care)	*SMN2* copies	% of all SMA cases	Delay of Diagnosis
SMA type 0	Prenatal	None	< 6 months	1	Rare	
SMA type I	< 6 months	Never sit without support, problems sucking and swallowing	Median: 24 months	1 – 3	40 – 60%	3.6 months
SMA type II	6 – 12 months	Sit independently, lose this ability by mid-teens	70% alive at 25 years	2 – 4	30 – 40%	14.3 months
SMA type III	> 18 months	Walk independently, lose this ability with time	Normal	3 – 4	~10%	43.6 months
SMA type IV	20-30 years	Mild to moderate muscle weakness; typically only proximal muscles affected	Normal	4 – 5	Possibly often undetected	
SMA other	variable	variable	variable	n/a	n/a	variable

NET BENEFIT/ CERTAINTY

Spinal Muscular Atrophy (SMA)

	Age at onset	Max. muscular activity achieved	Life expectancy (palliative care)	*SMN2* copies	% of all SMA cases	Delay of Diagnosis
Focus of Evidence Review						
SMA type I	< 6 months	Never sit without support, problems sucking and swallowing	Median: 24 months	1 – 3	40 – 60%	3.6 months
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SMA type IV	20-30 years	Mild to moderate muscle weakness; typically only proximal muscles affected	Normal	4 – 5	Possibly often undetected	
SMA other	variable	variable	variable	n/a	n/a	variable

NET BENEFIT/
CERTAINTY

Treatment

- **Palliative/symptomatic (ventilator, gastrostomy feeding, physical therapy).**
- **Nusinersen (only FDA approved SMA-specific treatment).**
- **Gene therapy (ongoing trial).**

NET BENEFIT/ CERTAINTY

Treatment

Nusinersen (Spinraza™):

- The only FDA approved SMA-specific treatment.
- Intrathecal administration (6 doses in 1st year, then 1 dose every 4 months).
- Expensive (reported cost: $125,000 per vial/dose).
- Limited data available suggest that treatment effect is greater when:
  - initiated before symptoms develop,
  - *more SMN2* copies are present (likely because later onset and milder phenotype).

NET BENEFIT/ CERTAINTY

Treatment

Nusinersen (Spinraza™):

Limitations of treatment studies:

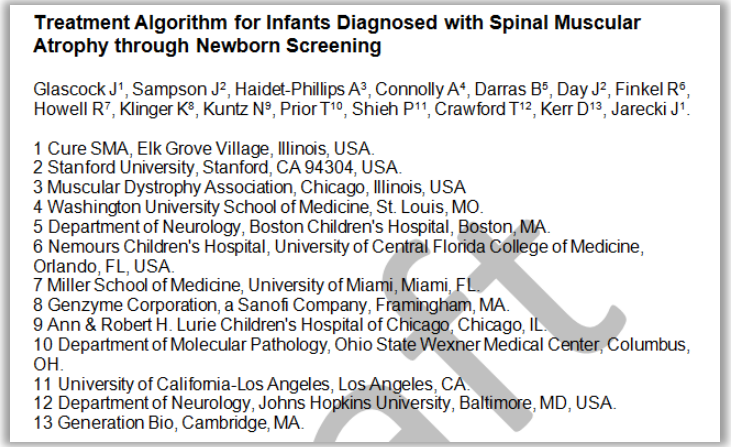
- No data on long term outcomes (follow up limited to ≤2 years).
- Small study populations (20 presymptomatically treated infants).
- Anecdotally, 1 patient with two *SMN2* copies had normal development at 12 months old (treatment started at 13 days old following positive NBS in NY; Kraszewski JN et al. *Genet Med*. doi:10.1038/gim.2017.152).
- No peer reviewed publications available on presymptomatically treated patients.

NET BENEFIT/
CERTAINTY

Treatment

Nusinersen (Spinraza™):

- Peer reviewed treatment guideline not (yet) published.
- Draft guideline has been developed by an "SMA NBS Multidisciplinary Working Group" using a modified version of the Delphi technique to reach consensus



Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening

Glascock J[1], Sampson J[2], Haidet-Phillips A[3], Connolly A[4], Darras B[5], Day J[2], Finkel R[6], Howell R[7], Klinger K[8], Kuntz N[9], Prior T[10], Shieh P[11], Crawford T[12], Kerr D[13], Jarecki J[1].

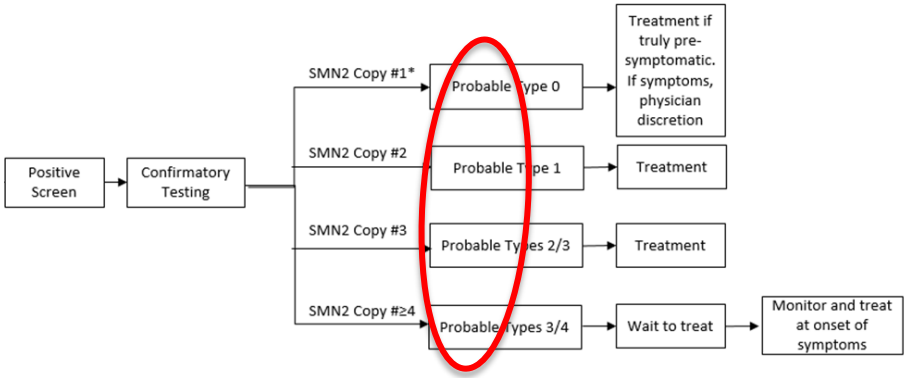
1 Cure SMA, Elk Grove Village, Illinois, USA.
2 Stanford University, Stanford, CA 94304, USA.
3 Muscular Dystrophy Association, Chicago, Illinois, USA
4 Washington University School of Medicine, St. Louis, MO.
5 Department of Neurology, Boston Children's Hospital, Boston, MA.
6 Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, FL, USA.
7 Miller School of Medicine, University of Miami, Miami, FL.
8 Genzyme Corporation, a Sanofi Company, Framingham, MA.
9 Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.
10 Department of Molecular Pathology, Ohio State Wexner Medical Center, Columbus, OH.
11 University of California-Los Angeles, Los Angeles, CA.
12 Department of Neurology, Johns Hopkins University, Baltimore, MD, USA.
13 Generation Bio, Cambridge, MA.

NET BENEFIT/ CERTAINTY

Treatment

Nusinersen (Spinraza™):

- Peer reviewed treatment guideline not (yet) published.
- Summary of draft guideline by Glascock J et al.:



"Probable" because SMA types cannot be reliably differentiated by *SMN2* copy number. Presymptomatic treatment outcomes can therefore not be reliably assigned to SMA type.

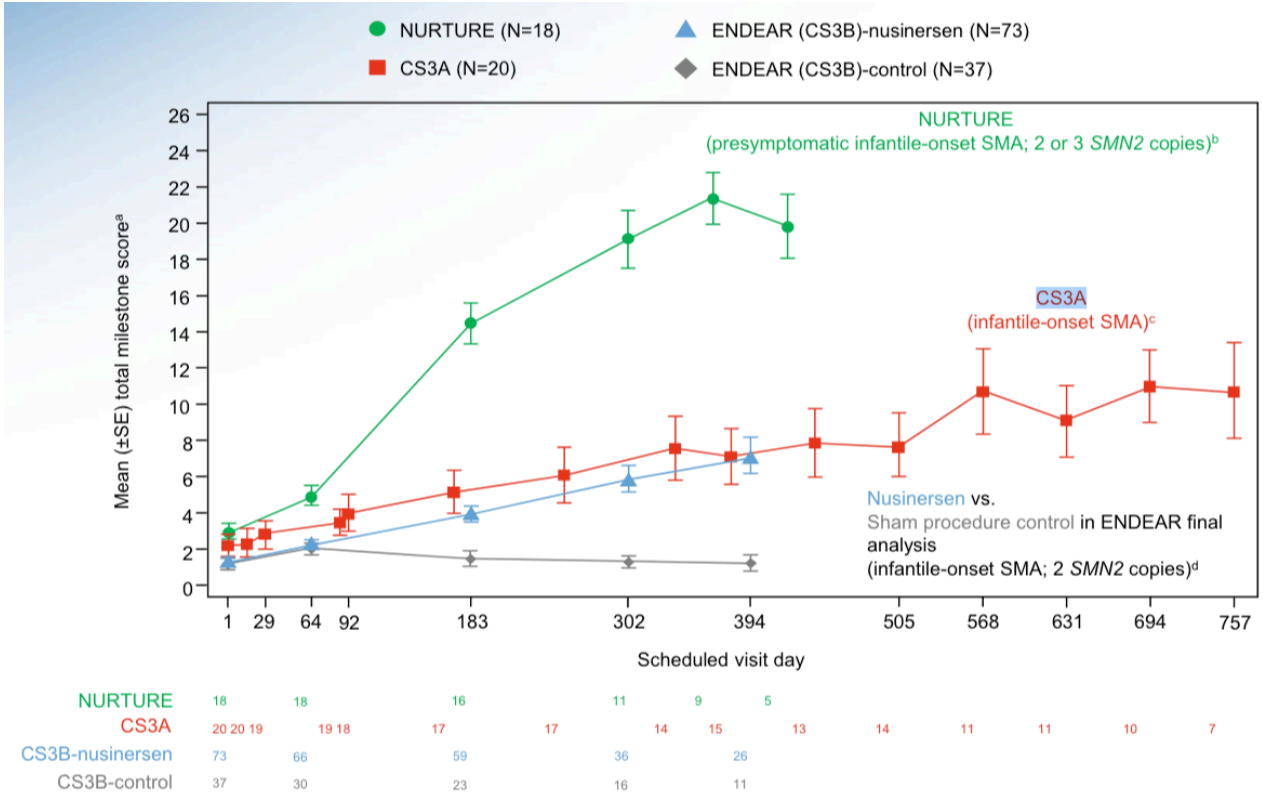
NET BENEFIT/ CERTAINTY

Spinal Muscular Atrophy (SMA)

	Age at onset	Max. muscular activity achieved	Life expectancy (palliative care)	*SMN2* copies	% of all SMA cases	Life Expectancy & Outcome (Nusinersen)
Focus of Evidence Review						
SMA type I	< 6 months	Never sit without support, problems sucking and swallowing	Median: 24 months	1 – 3	40 – 60%	**>12 months, improved development**
SMA type II	6 – 12 months	Sit independently, lose this ability by mid-teens	70% alive at 25 years old	2 – 4	30 – 40%	**>12 months, improved development**
SMA type III	> 18 months	Walk independently, lose this ability with time	Normal	3 – 4	~10%	**>12 months, better vs. untreated**
SMA type IV	20-30 years	Mild to moderate muscle weakness; typically only proximal muscles affected	Normal	4 – 5	Possibly often undetected	**No data**
SMA other	variable	variable	variable	n/a	n/a	n/a

NET BENEFIT/
CERTAINTY

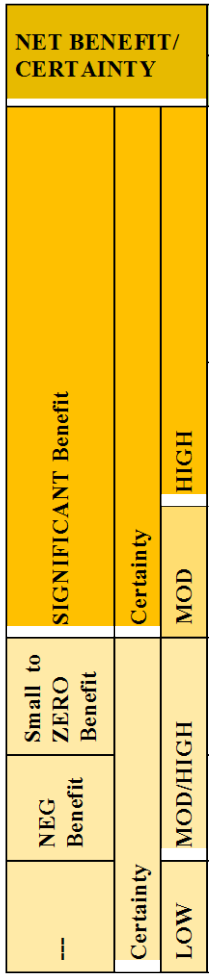
SMA Treatment with Nusinersen



- **Suggests early treatment allows for more normal development.**
- **Does not allow comparison to normal development**

from page 40 of Evidence Review report

Spinal Muscular Atrophy
(SMA)



What is SIGNIFICANT Benefit?

- if ***improved*** neuromuscular development and survival, then there appears to be MODERATE certainty of SIGNIFICANT long-term benefit of NBS for SMA;
- if ***normal*** neuromuscular development and survival, then there is LOW certainty of SIGNIFICANT long-term benefit of NBS for SMA given the limited available data, in particular of ***peer reviewed data on presymptomatic treatment*** with Nusinersen which is the only treatment available outside of clinical trials.

Secretary's Discretionary Advisory Committee Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (Approved January 31, 2013)

NET BENEFIT/ CERTAINTY			READINESS: Ready	READINESS: Developmental	READINESS: Unprepared	FEASIBILITY: Feasibility	FEASIBILITY: HIGH or MODERATE	FEASIBILITY: LOW
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.			
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.					
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			----		
Small to ZERO Benefit		MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			----		
NEG Benefit		MOD/HIGH	**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			----		
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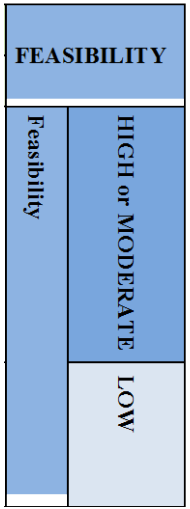
Newborn Screening for SMA



Newborn screening test is available:

- real-time PCR assay specific for exon 7 deletion in *SMN1*,
- expected to identify at least 95% of SMA cases,
- will miss ca. 5% of SMA cases that are not homozygous for exon 7 deletion unless:
  - carriers for the deletion will be reported (most will not harbor a 2nd mutation),
  - a 2nd tier test is performed to rule out a 2nd pathogenic (!) mutation.

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	Ready	Developmental	Unprepared	Feasibility
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MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			----

Newborn Screening for SMA

READINESS		
Ready	Developmental	Unprepared
most NBS programs could implement screening within 1 year after the state makes the decision to include the condition and funding is made available.	most NBS programs face barriers that would require 1–3 years to address.	most NBS programs would take longer than 3 years to implement, even with the decision to add the condition and the availability of funding to begin comprehensive screening.

Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Alex R. Kemper, MD, MPH[1], Nancy S. Green, MD[2], Ned Calonge, MD, MPH[3], Wendy K.K. Lam, PhD[1], Anne M. Comeau, PhD[4], Aaron J. Goldenberg, PhD, MPH[5], Jelili Ojodu, MPH[6], Lisa A. Prosser, PhD[7], Susan Tanksley, PhD[8] and Joseph A. Bocchini Jr, MD[9]

Newborn Screening for SMA

READINESS		
Ready	Developmental	Unprepared

Newborn screening test is available

- test can be multiplexed with SCID screening test;
- CDC's Newborn Screening Quality Assurance Program (NSQAP) can provide training, quality control and reference materials;
- incremental cost is small when multiplexed with SCID screening assay;
- higher incremental cost if 100% sensitivity is expected because:
  - 2nd tier test needed on ca. 1 in 60 newborns heterozygous for exon 7 deletion, or
  - ca. 1 in 60 newborns will require follow up but are only carriers.

Newborn Screening for SMA

READINESS		
Ready	Developmental	Unprepared

Newborn screening tests are available and used already:

- pilot study with consent in 3 hospitals in New York City (1:72 carriers);
- MA began in January 2018 (consent; no carriers identified; not multiplexed);
- Utah began 1/29/2018 (no consent; no carriers identified; multiplexed with SCID);
- Minnesota to begin in March 2018 (no consent; no carriers will be identified; multiplexed with SCID);
- WI to begin in 2018; MO to begin in 2019; NC to begin pilot study in April 2018;
- APHL's PHSI Assessment found:
  - majority of states can implement within 1-3 years;
  - addition of SMA to RUSP would "bolster implementation activities."

NBS Programs with Mandates/Pilots

State	SMA added to NBS panel	Start	Select or Whole Population	Funds	Carriers	Costs
MA	12/5/2015 (Adv. Cmte.)	1/29/2018	Whole, consent, PILOT	N/A	Not identified	n/a
MN	12/27/2018	3/5/2018	Whole	NBS fee	Not identified	< $1.00
MO	7/11/2017 (Senate Bill 50)	Must start by 1/1/2019	Whole, likely no reporting initially	NBS fee	Decision expected 4/2018	~$1.00
NC	-	Apr 2018	Select, consent, PILOT	NICHD contract	Not reported or identified	n/a
NY	-	Jan 2016	3 hospitals, consent, PILOT	Biogen	Reporting for pilot; undecided future	0.15-$1.00
UT	August 2017 (Rule R438-15)	1/29/2018	Whole	NBS fee	Not identified	TBD
WI	Expected for July 2018	TBD (likely before 7/2019)	Whole	Cure SMA as bridge funding	Not identified	$1.00

modified from APHL PHSI report

NBS Programs with Mandates/Pilots

State	SMA added to NBS panel	Start	Funds	Time from decision to add to NBS panel to start
MA	12/5/2015 (Adv. Cmte.)	1/29/2018	N/A	**Could have been < 1 year if not for a physical lab move**
MN	12/27/2018	3/5/2018	NBS fee	**< 1 year**
MO	7/11/2017 (Senate Bill 50)	Must start by 1/1/2019	NBS fee	**1.5 years**
NC	-	Apr 2018	NICHD contract	**No decision made**
NY	-	Jan 2016	Biogen	**No decision made**
UT	August 2017 (Rule R438-15)	1/29/2018	NBS fee	**< 1 year**
WI	Expected for July 2018	TBD (likely before 7/2019)	Cure SMA as bridge funding	**< 1 year**

modified from APHL PHSI report

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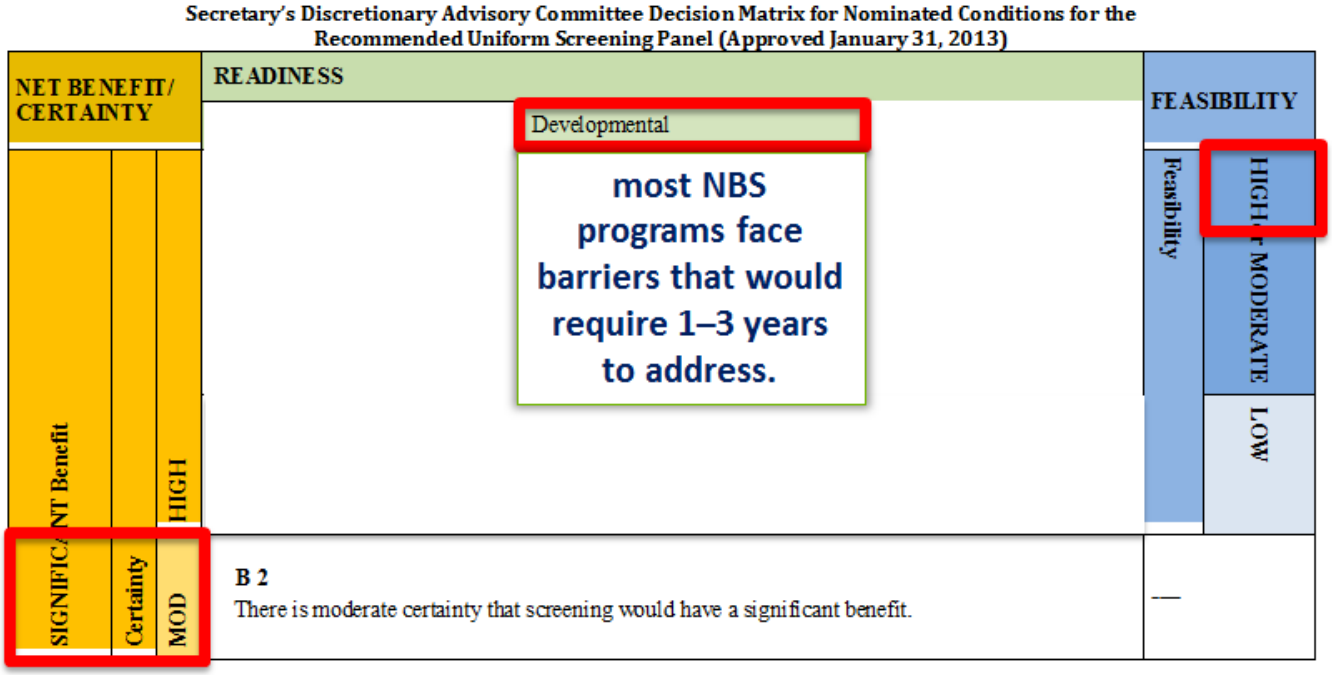
		MOD	**B 2** There is moderate certainty that screening would have a significant benefit.	—	

most NBS programs face barriers that would require 1–3 years to address.



- **Do we need to wait for peer reviewed guidelines for the management of specific SMA types?**

- **What role do disclosure (or not) of carriers and cost of treatment play in the decision?**

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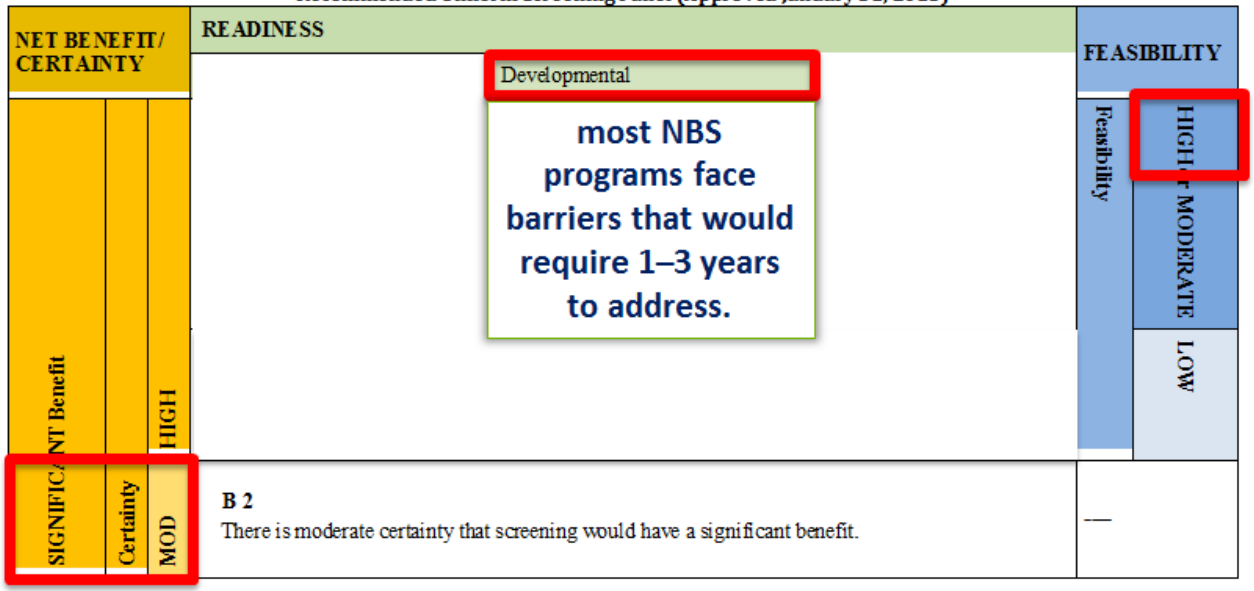

- **Do we need to wait for peer reviewed guidelines for the management of specific SMA types?** **NO**

- **What role do disclosure (or not) of carriers and cost of treatment play in the decision?** **NONE**

Newborn Screening for SMA Considerations

- **NBS for SMA is possible at low cost and with high positive predictive value when not disclosing carriers and accepting that ca. 5% of SMA cases will go undetected.**
- **To achieve 100% sensitivity the resources needed for NBS for SMA will increase either by frequent need for 2nd tier test or follow up of carriers (example: state with birth rate of 100,000 per year will have 32 carriers per week assuming carrier frequency of 1:60).**
- **If on RUSP:**
  - **"Core Condition": SMA due to homozygous deletion of *SMN1* exon 7 *or* all of SMA?**
  - **"Secondary Target(s)": None *or* SMA not due homozygous deletion of *SMN1* exon 7 (needs 2nd tier test or reporting of carriers!)**

Newborn Screening for SMA Considerations

- **NBS would likely show that the majority of SMA cases have SMA type II, III or IV**
- **SMA types II and III are likely to benefit the most from early treatment**

most patients with SMA will benefit from early treatment!

Newborn Screening for SMA

Recommendation to ACHDNC

Newborn Screening for SMA due to homozygous deletion of exon 7 *in SMN1* should be added to the RUSP as a Core Condition under matrix category B2 to the benefit of most patients with SMA.