Duke Clinical Research Institute

Newborn Screening for MPS I: Final Report from the Condition Review Workgroup

Alex R. Kemper, MD, MPH, MS

February 13, 2015

Outline

- Highlight key findings from the systematic evidence review
- Describe the bounds of benefit and harm based on findings from the systematic evidence review
- Summarize the capability of state newborn screening programs to offer comprehensive screening for MPS I

Review: Mucopolysaccaridosis Type I (MPS I)

- Autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IDUA) enzyme.
- Progressive, multisystem disorder
- Variable clinical symptoms; continuum of disease severity
- Traditional classification - two or three syndromes, though heterogeneous and overlapping
- Estimated MPS I incidence based on clinical prevalence:

0.54 to 1.15 per 100,000

MPS I: Classification Scheme

	SEVERE	ATTENUATED	
Est Prev, Clin Det	***61%***	***36%***	
Alt. Classification	**Hurler**	**Hurler/Scheie**	**Scheie**
Onset and Progression	Onset by 1 year Rapidly Progressive	Onset by 3 to 4 years	Onset variable, 2 to 12 years Less progressive problems
Cardiac System	Cardio-respiratory failure	Cardiovascular disease	Valvular heart disease
Respiratory System	Severe respiratory, obstructive airway disease	Respiratory disease	Upper airway infections
Brain & CNS **Cognition & Development**	Progressive developmental delay	Little or no developmental delay	Normal intelligence
Vision & Hearing	Hearing loss	Decreased vision	Corneal clouding
Muscle & Skeletal Systems	Coarse facial features Spinal deformity Skeletal Dysplasia	Skeletal abnormalities Joint stiffness, contractures	Joint stiffness Carpel tunnel syndrome
Life Expectancy ***(if untreated)***	Death < 10 years of age	Death in teens or 20s	Death in later life; most have normal life span

MPS I: Life Course

Median Age of Onset, Diagnosis, Treatment, and Death for MPS I Registry patients (N=891).†

Disease Classification‡	N [%]	Onset (years)	Diagnosis (years)	Treatment Reported‡ [n]	Treatment Initiation (years)	Death Reported [n]	Death (years)
Severe (Hurler)	**508** [57]	**0.5** (0-6.5)	**0.8** (0-23.8)	**438**	**1.4** (0.1-31.2)	**156**	**3.8** (0.4-27.2)
Attenuated (Hurler-Scheie)	**209** [23.5]	**1.9** (0-12.2)	**3.8** (0-38.7)	**197**	**8.6** (0.3-47.2)	**16**	**17.4** (7.5-30.3)
(Scheie)	**97** [10.9]	**5.4** (0-33.8)	**9.4** (0-54.1)	**85**	**17.1** (3.1-62.9)	**4**	**29** (17.4-46.6)

†*MPS I Registry (from inception in 2003 through March 2010). Patients from 33 countries (47% Eur/Mid East; 35% No Amer; 15% Latin Amer, 3% Asia Pacific).*

‡*13% reported as untreated with ERT or HSCT.*

‡*8.6% undetermined (3.1%) or missing (5.5%) form classification.*

D'Aco et al. (2012). Diagnosis and treatment trends in mucopolysaccharidosis I: Findings from the MPS I Registry. Eur J Pediatr, 171, 911-919.

MPS I: Life Course – *2014 Update*

Median Age of Onset, Diagnosis, Treatment, and Death for MPS I Registry patients (N=987).[†]

Disease Classification[‡]	N [%]	Onset (years)	Diagnosis (years)	Treatment Reported[‡] [n]	Treatment Initiation (years)	Death Reported [n]	Death (years)
Severe (Hurler)	**601** [60.9]	**0.5** (0-6.5)	**1.0** (0-23.8)	438	1.5 (0.1-31.2)	156	3.8 (0.4-27.2)
Attenuated:							
Hurler-Scheie	**227** [23.0]	**1.8** (0-12.2)	**4.0** (0-38.7)	197	8.0 (0.3-47.2)	16	17.4 (7.5-30.3)
Scheie	**127** [12.9]	**5.3** (0-33.8)	**9.4** (0-54.1)	85	16.9 (3.1-62.9)	4	29 (17.4-46.6)

[†]*MPS I Registry (from inception in 2003 through Aug 2013). Regional distribution: Europe, 45.5%; North America (34.8%), Latin America (17.3%), Asia Pacific (2.4%).*

[‡]*n=32 [3.2%] undetermined (3.1%).*

AGE OF DEATH NOT REPORT IN 2014 UPDATE.

Beck et al. (2014). The natural history of MPS I: Global perspectives from the MPS I Registry. Genet Med, 16, 759-765.

MPS I Newborn Screening

- **Low IDUA enzyme activity**
- **Detected in dried-blood spots (DBS)**
- **Key Screening Methods:**
  - *Tandem mass spectrometry (MS/MS)*
    - Different protocols used
    - FDA LSD multiplex kit under review
  - *Fluorometry by digital microfluidics*
    - Baebies

Establishing the MPS I Diagnosis

- **Definitive MPS I diagnosis: IDUA enzyme activity assay**
  - *Measured in the following: leukocytes or skin fibroblasts*
  - *IDUA activity less than 1% of normal*
  - *Enzyme activity alone does not predict phenotype*
- **Increased glycosaminoglycan (GAG) levels in urine is supportive of the diagnosis**
- **Genotyping can help if it reveals a known, recurrent mutation**
  - *Most mutations are "private"*
- **Clinical assessment required to confirm diagnosis and begin treatment**

Genotyping

- >100 known MPS I-specific IDUA mutations, many unique to specific individuals
- About 7 to 9 commonly recurring mutations, some associated with specific phenotype, most severe, some attenuated -- frequency ~ 80%
- Known IDUA-pseudodeficiency mutations
  - *Considered rare in literature, though NBS may indicate otherwise, esp. among African Americans*
- Genotype-phenotype correlation is generally unknown, but an active area of research

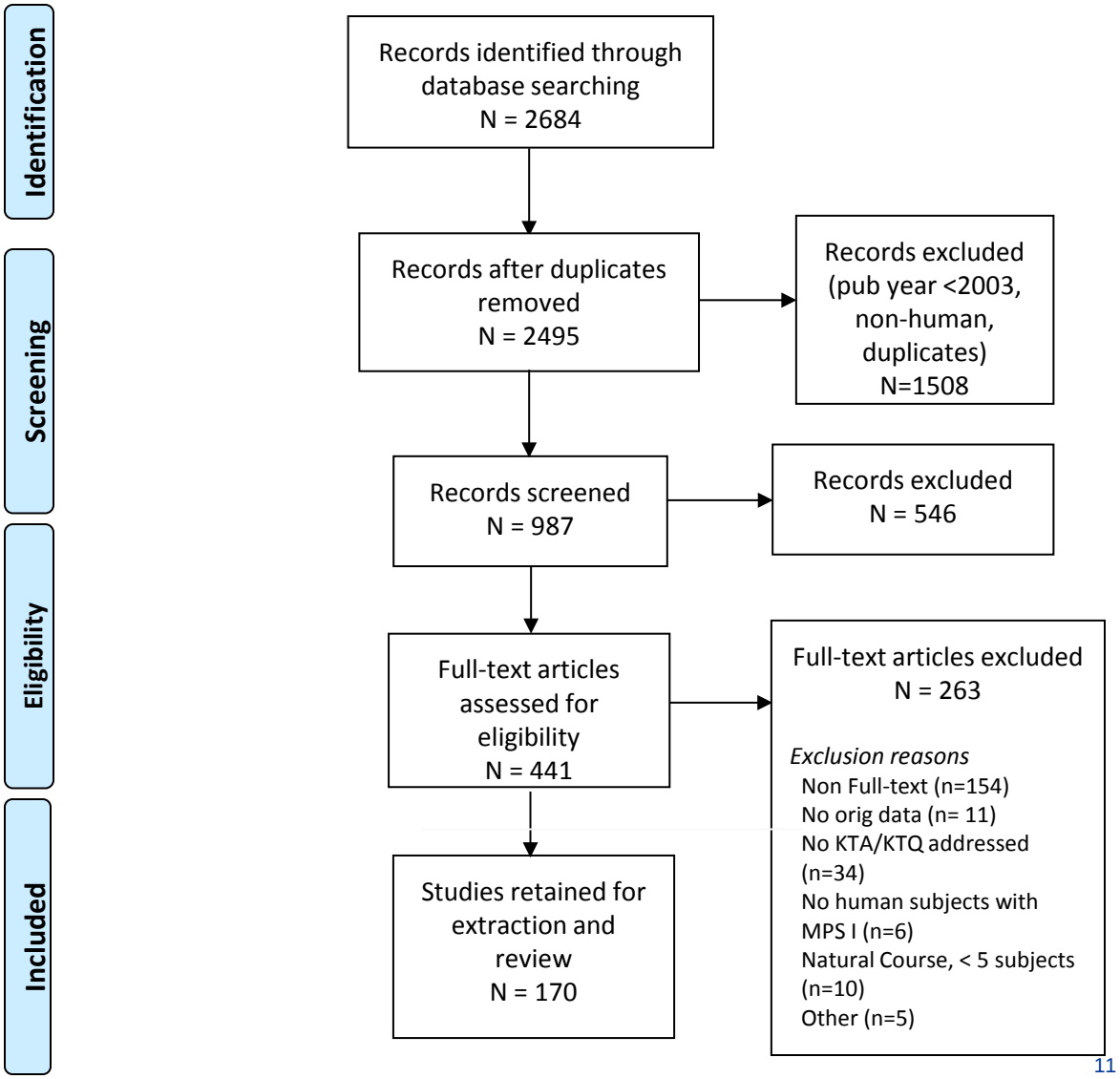
Treatment Strategies

- **Hematopoietic Stem Cell Transplantation (HSCT)**
  - *Allows individuals to produce endogenous enzyme*
  - *Established International Guidelines – HSCT recommended for MPS I (H, H/S) <age 2 or 2.5 years, with normal to moderate cognition (MPS I H, H/S)*
- **HSCT + Enzyme Replacement Therapy (ERT)**
  - *Proposed as a bridge pre- HSCT*
  - *May augment enzyme availability after HSCT*
- **ERT**
  - *May benefit patients with all forms of disease*
  - *Does not cross blood-brain barrier (standard IV)*
  - *Case report of intrathecal ERT administration suggests improved motor control and stability, normal CSF GAG levels*

Systematic Evidence Review: Published Literature – Through ~January 2015

- Keywords: *Mucopolysaccharidosis type I (MPS I); Hurler syndrome/disease; Hurler-Scheie syndrome/disease; Scheie syndrome/disease; severe MPS 1; attenuated MPS 1; gargoylism; alpha-L-iduronidase enzyme assay*
- Articles through PubMed, EMBASE, & CINAHL (2684)
- Published in 2003 or later, n>5 for natural history, other "standard" exclusions
- Articles screened for eligibility & relevance (441)
- Articles retained for data extraction & synthesis (170)
- Screening by two independent reviewers

Figure 1. PRISMA Diagram of Published Literature Search



Technical Expert Panel

EXPERT PANEL MEMBERS
Barbara K. Burton, MD Professor of Pediatrics Northwestern University Feinberg School of Medicine
Lorne A. Clarke, MD Scientific Advisory Board, National MPS Society Professor & Medical Director Provincial Medical Genetics Program University of British Columbia
Patricia Dickson, MD Chief, Division of Medical Genetics Los Angeles County - Harbor - UCLA Medical Center
Joseph Muenzer, MD, PhD Professor, Department of Pediatrics & Genetics, Metabolism Clinic University of North Carolina School of Medicine
Barbara Wedehase,[±] MSW, CGC Executive Director National MPS Society
[±]Nominator of MPS I disease for consideration to be added to the RUSP.

TEP Meetings

- *September 9, 2013*
- *November 4, 2014*
- *January 6, 2015*
- *January 23, 2015*

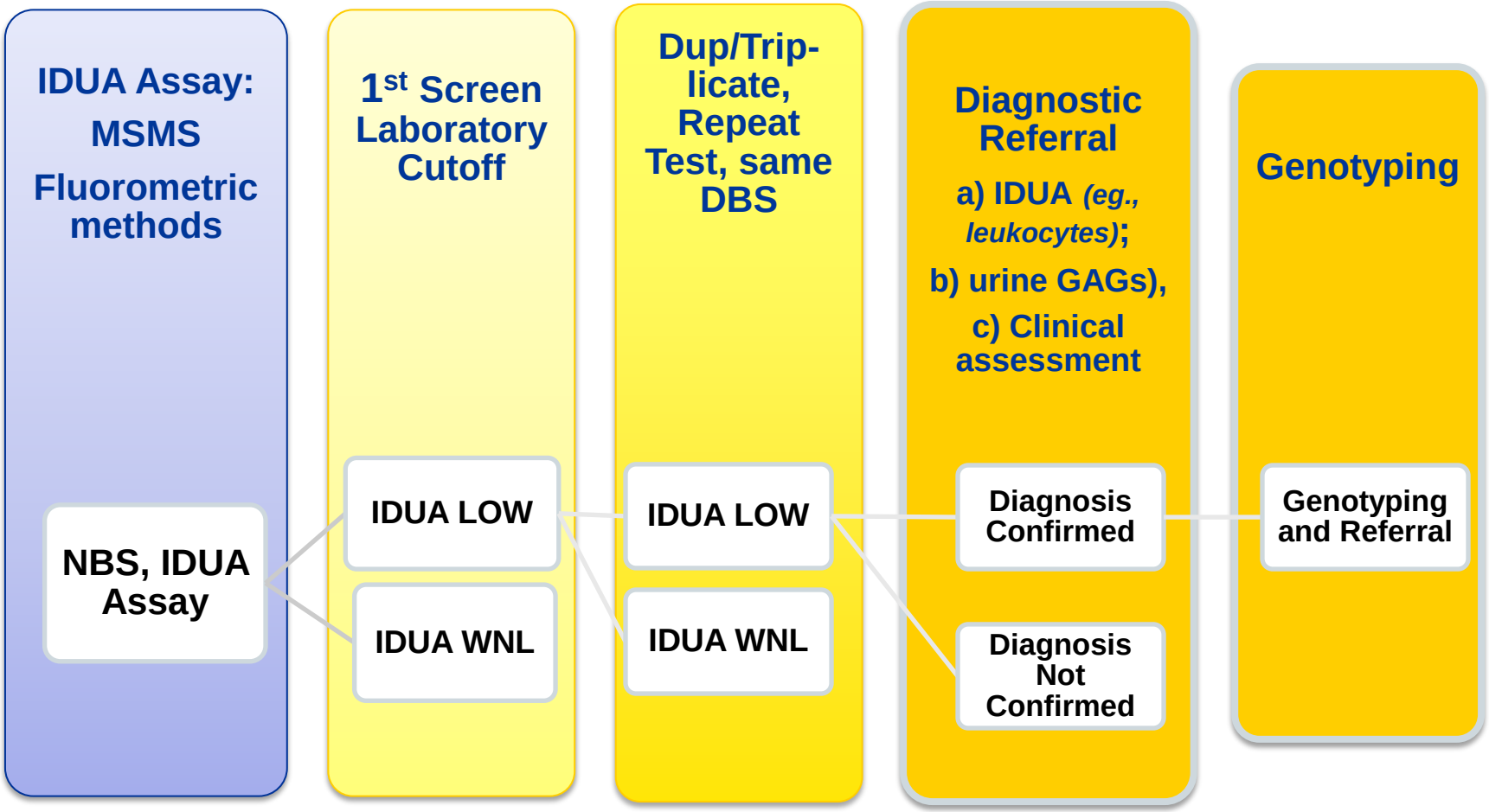
Topics

- Case Definition
- Natural History
- Screening & Diagnosis
- Treatment Initiation
- Outcomes
- Issues in Practice
- Unpublished data

INDIVIDUAL EXPERT INTERVIEWS	AFFILIATION
Michael Gelb, PhD	University of Washington
Joan Keutzer, PhD††	Genzyme
Sharmini Rogers, MD/Patrick Hopkins	Missouri NBS Program
Khaja Basheeruddin, PhD	Illinois NBS Program
Dietrich Matern, MD, PhD††	Mayo Clinic – Newborn Screening Research, Rochester, MN

†† *(Participated by written responses to questions)*

MPS I Newborn Screening Algorithm



Missouri Newborn Screening Pilot - Update

- Full population pilot screening (*no live reports*), Jan 2013 to Dec 2014
- Screening method: Digital microfluidics, LSD multiplex
- Newborns screened: ~149,500 (174,636 samples)
- IDUA cut off rate lowering ⇨ decrease in pseudodeficiency rate

Screening Results	Actual	With Current Cut Offs
Positive Screens	70	*42*
Confirmed MPS I	1 (Severe)	*1 (Severe)*
Carriers	3	*2*
False Positives	30	*11*
Pseudodeficiency	25	*21*
Pending	9	*7*
Lost to Follow Up	2	*1*
In-house repeats (p/149,500)	0.047% (p=70)	0.028% (p=42)
False Positives (n/149,500)	0.046% (n=69)	*0.027% (n=41)*
Positive Predictive Value	1.6%	*2.4%*

Hopkins et al., 2015; P. Hopkins & S. Rogers, Personal communication. Update on MO screening results. Presented with permission. Not for distribution without permission from the MO DHHS NBS Program.

Illinois Newborn Screening

- Targeted pilot screening, reporting (4 birthing hospitals)
- Screening method: UPLC-MS/MS (6plex LSDs), CDC Assay
- Newborns screened: ~17,300 (Nov 2014 – Dec 18, 2014)

Screening Results	Actual
Positive Screens	17
Confirmed MPS I	0
Carriers	0
False Positives	10
Pseudodeficiency	5
Pending	2
Lost to Follow Up	0
In-house repeats (p/17,300)	0.1% (p=17)
FP (n/17,300)	0.1% (n=17)
Positive Predictive Value	0%

MS/MS LSD Multiplex Screening Study

- Screening with 106,526 anonymous dried-blood spots (WA NBS)
- Screening method: MSMS (3plex LSDs), Gelb/UW/PE protocol

Screening Study Results	
Positive Screens	9
"Mutations consistent with MPS I"	3 (1 of which might be pseudodeficiency)
Carriers	1
Poor dried-blood spot punch	2
No identified nucleotide change	3
In-house repeats (p/106,526)	0.008% (p=9)
FP (n/106,536)	0.006% (n=6).
Positive Predictive Value*	*33%**
**PPV assumes MPS I consistent mutations would be confirmed cases*	

Scott et al. 2013. **Identification of Infants at Risk for Developing Fabry, Pompe, or MPS-I from Newborn Blood Spots by MS/MS. *J Pediatrics*.**

Summary
U.S. Population-based Newborn Screening - MPS I

	United States			Taiwan	Italy
	Missouri NBS Pilot *(ongoing)*	IL NBS Pilot *(4 hospitals)*	Univ of WA Study*	NBS Pilot	NBS Pilot
Screening method	Fluorometry Digital MFP	MS/MS UPLC	MS/MS Gelb/Uwa/PE	Fluorescence Assay	
Total screened	149,500	17,300	106,526*	35,285	3,403
Confirmed MPS I	1	0	3*	2	0
Est Incidence per 100,000	*1.5*	*0*	*3.196**	*5.67*	*0*
Positive Predictive Value	2.4%	--	33%*	10.5%	--

**anonymous DBS only with genotyping; no follow up or diagnostic confirmation with clinical examination.*

MPS I NEWBORN SCREENING - Summary

- MS/MS - multiple protocols
- Fluorometry – Digital Microfluidics
- Screening algorithm refinements are helping to balance case detection vs. false positives and pseudodeficiency
- Screening appears to identify a similar number of cases compared to usual case detection
- Some challenges exist related to predicting form at the time of initial diagnosis

Treatment Outcomes - Survival

- 17 case series treatment reports (n>5, Severe MPS I)
- *16 HSCT, +/- with ERT, 1 ERT only*

Clinically Detected Cases		Survival Rates	
Summary:	Rg of Med Ages of 1st Treatment	1-year	5-year
Ranges for All Treatment Reports (n=17)	9.5–34.8 mos *(rg 2–228 mos)*	63 to 100% *(74 to 100% without hi - low)*	53 to 100% *(65 to 100% without hi - low)*
Reports (2) with ALL subjects <=31 mos at 1st treatment	4 mos – 31 mos	83% to 100%	

MPS I Survival by Treatment Age <8 mos v ≥8mos (N=907)

Age of Treatment Initiation								
	Severe		Attenuated		Severe		Attenuated	
HSCT Only Patients (n=199)								
Years Survival	Age* < 8 months (n=10, median age =6.81)				Age* ≥ 8 months (n=189, median age = 17.07)			
1	8/10	80%	0	-	178/178	100%	11/11	100%
3	7/10	70%	0	-	135/178	76%	11/11	100%
5	7/10	70%	0	-	131/178	74%	11/11	100%
ERT + HSCT (n=192)								
	Age† < 8 months (n=30, median age = 5.20)				Age† ≥ 8 months (n=162, median age = 14.74)			
1	27/28	96%	2/2	100%	154/154	100%	8/8	100%
3	25/28	89%	2/2	100%	139/154	90%	8/8	100%
5	24/28	86%	2/2	100%	137/154	89%	8/8	100%
ERT Only (n=516)								
	Age* < 8 months (n=16, median age = 4.75)				Age* ≥ 8 months (n=500, median age = 89.16)			
1	10/11	91%	5/5	100%	186/186	100%	314/314	100%
3	9/11	82%	5/5	100%	183/186	98%	314/314	100%
5	8/11	73%	5/5	100%	180/186	97%	314/314	100%

Factors that Affect Survival and Outcomes Summary from Multivariate Analyses

Increases Chances of Event Free Survival

- Transplant age <16.7 mos (p<0.03) [N=128 vs. N=130]
- Use of pre-transplant conditioning regimen (Cy/Bus) (p=0.011)
- Shorter interval to transplant, <4.6 months interval (p=0.046)

Decreases Chances of Event Free Survival

- Unmatched cord blood (p<0.031)
- Mismatched donor grafts (p<0.007)
- History of lower airway disease or pneumonia

➲ ***These factors confound the interpretation of the association between age at the time of treatment and mortality***

Cognitive Outcomes, ERT + HSCT v. HSCT only

ELIGIBILITY:

- Severe MPS I patients
- HCT+conditioning regimen 2002-2005; HCT + ERT + conditioning regiment 2005 onward

ASSESSMENT PROTOCOL:

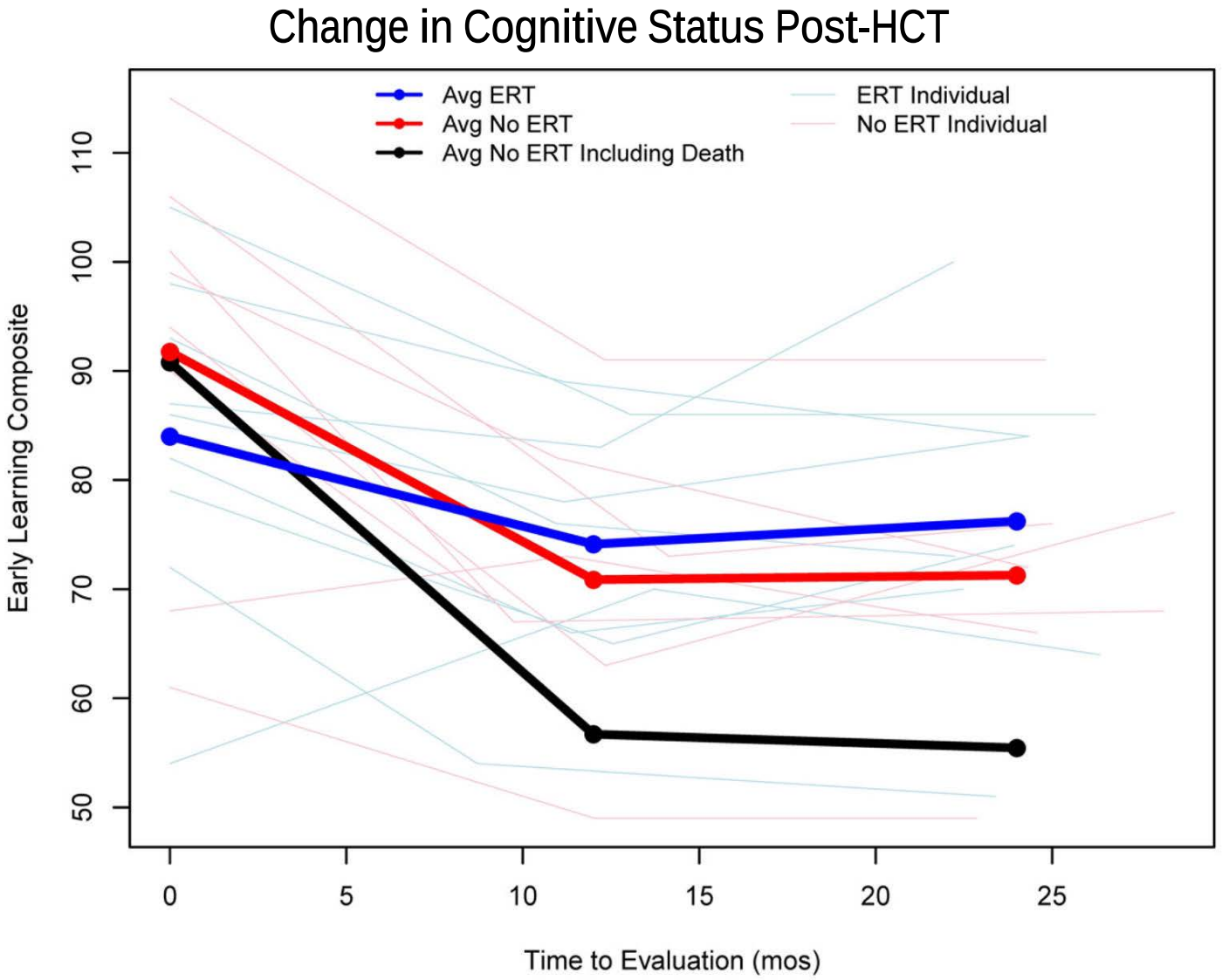
- Standard Neurodevelopmental Battery
- Baseline, 12, 24 mos post HCT
  - Cognitive – Mullen Scales Early Learning/Diff Abilities Scales

SAMPLE:	Overall (n=19)	ERT + HCT (n=9)	HCT only (n=10)
Transplant Age (mos)	17.5 (7.9)	18.0 (6.8)	17.1 (9.1)
Time since eval (days)	54.6 (72.2)	17.1 (2.2)	88.3 (88.0)
Baseline ELC	87.6 (16.4)	84.0 (15.0)	90.8 (17.7)

Eisengart et al. 2013. Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediatr. 162: 375–380.

Cognitive Outcomes, ERT + HSCT v. HSCT only

Evidence suggests ERT + HSCT may improve cognitive outcomes – though some decline



Eisengart et al. 2013. Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediatr. 162: 375–380.

Unadjusted Early Learning Composite and domain T-Scores across visits.

Score	Baseline (prior to HCT)	One Year Post-HCT	Two Years Post-HCT
Early Learning Composite*			
- ERT	84.0 (15.0)	74.1 (11.3)	76.2 (14.2)
- No ERT	91.8 (18.5)	70.9 (12.5)	71.3 (12.8)
Visual Reception Domain†			
- ERT	40.6 (10.0)	38.0 (10.4)	46.0 (12.9)
- No ERT	48.4 (10.9)	35.2 (8.89)	33.5 (6.95)
Fine Motor Domain†			
- ERT	39.9 (9.75)	34.6 (7.63)	30.6 (9.44)
- No ERT	46.1 (11.6)	33.1 (7.03)	29.0 (11.6)
Receptive Language Domain†			
- ERT	39.7 (9.64)	39.7 (12.5)	38.9 (8.98)
- No ERT	39.0 (13.4)	36.1 (10.1)	35.3 (9.05)
Expressive Language Domain†			
- ERT	40.0 (8.66)	35.3 (10.1)	33.6 (9.19)
- No ERT	44.5 (10.9)	32.5 (10.4)	37.6 (8.85)

*Mean=100, SD=15

†Mean=50, SD=10

Eisengart et al. 2013. Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome. J Pediatr. 162: 375–380.

Predictors of Long-Term Outcomes of HCT for MPSIH

ELIGIBILITY:

- Severe MPS I patients
- Successful HCT engraftment (1985 – 2011)
- Europe and U.S. centers

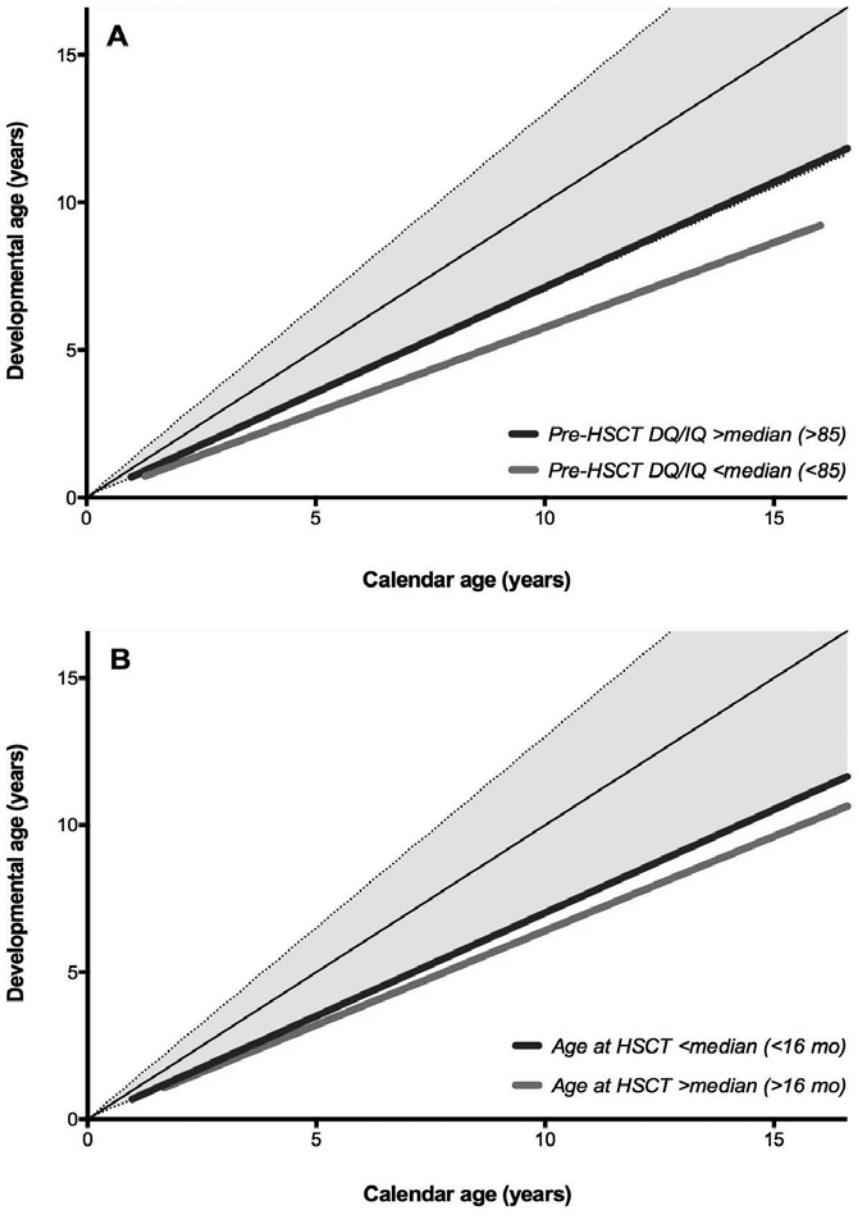
SAMPLE:

- n=217
- Med transplant age: 16 mos (rg 2 - 47)
- Med age at last follow-up: 9.2 yrs (rg 3 - 23)

RESULTS:

- Considerable residual disease burden in majority of patients
- Pre-HSCT cognitive function DQ/IQ >85 AND transplant age <16 months ⇨ superior cognitive development post-HCT
- Post-HCT normal IDUA levels, non-carrier donors ⇨ superior LT organ system outcomes

Figure 1



Aldenhoven et al. 2015. Long-term Outcome of Hurler Syndrome Patients after Hematopoietic Cell Transplantation. *Blood* *in press*..

Treatment Age and Developmental Outcomes of UBCT

ELIGIBILITY:

- Severe MPS I patients
- UCBT (1997-2013)
- Conditioning: busulfan, cyclophosphamide, GVHD Prophylaxis
- UNC-CH, U Pitt Med Ctrs

SAMPLE:

- n=31
- Med transplant age: 13.8 mos (rg 2 – 34)
- Med age at last follow-up: 7.26 yrs (rg 2 - 22)

ASSESSMENT PROTOCOL:

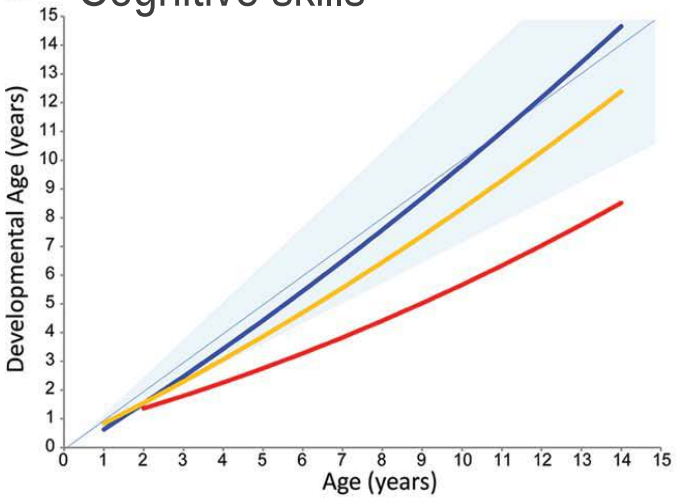
- Standard Neurodevelopmental Battery
- BL, every 6 to 12 mos post UBCT
  - Cognitive – Mullen Scales Early Learning/Diff Abilities Scales
  - Adaptive – Scales of Independent Behavior-Rev
  - Language (Exp/Rec) – Preschool Language Scale, Clin Eval of Lang Fundamentals
  - Motor - Peabody Dev Motor Scales

Poe et al. Early Treatment is Associated with Improved Cognition in Hurler Syndrome. *ANN NEUROL* 2014;76:747–753.

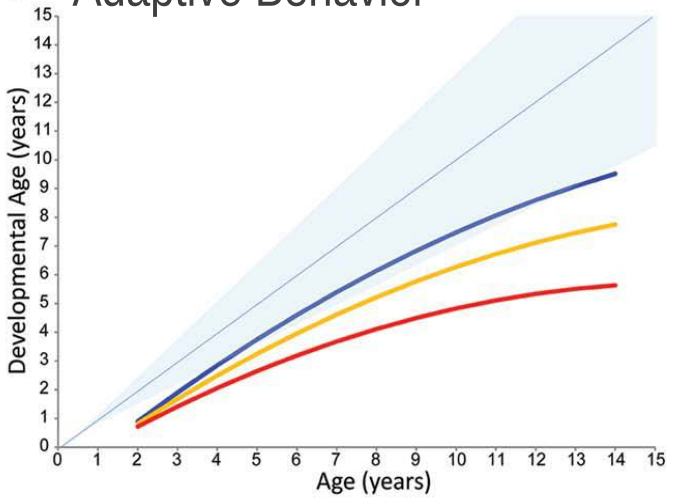
Treatment age – Cognitive Development

- 2–8 mos/med 4m (N=6)
- 9-17 mos/med 12m (N=17)
- **≥18** mos/med 26m (N=8)

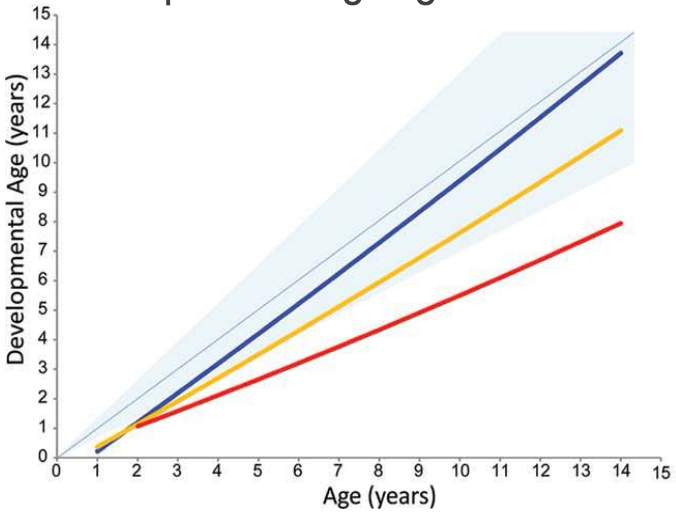
A Cognitive skills



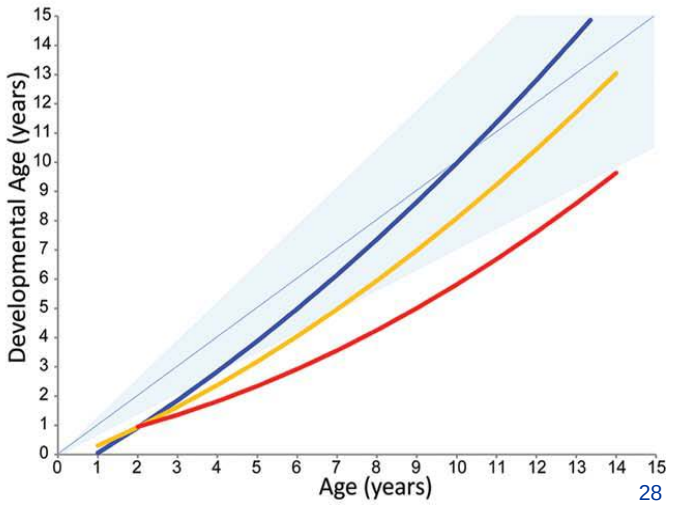
B Adaptive Behavior



C Receptive Language

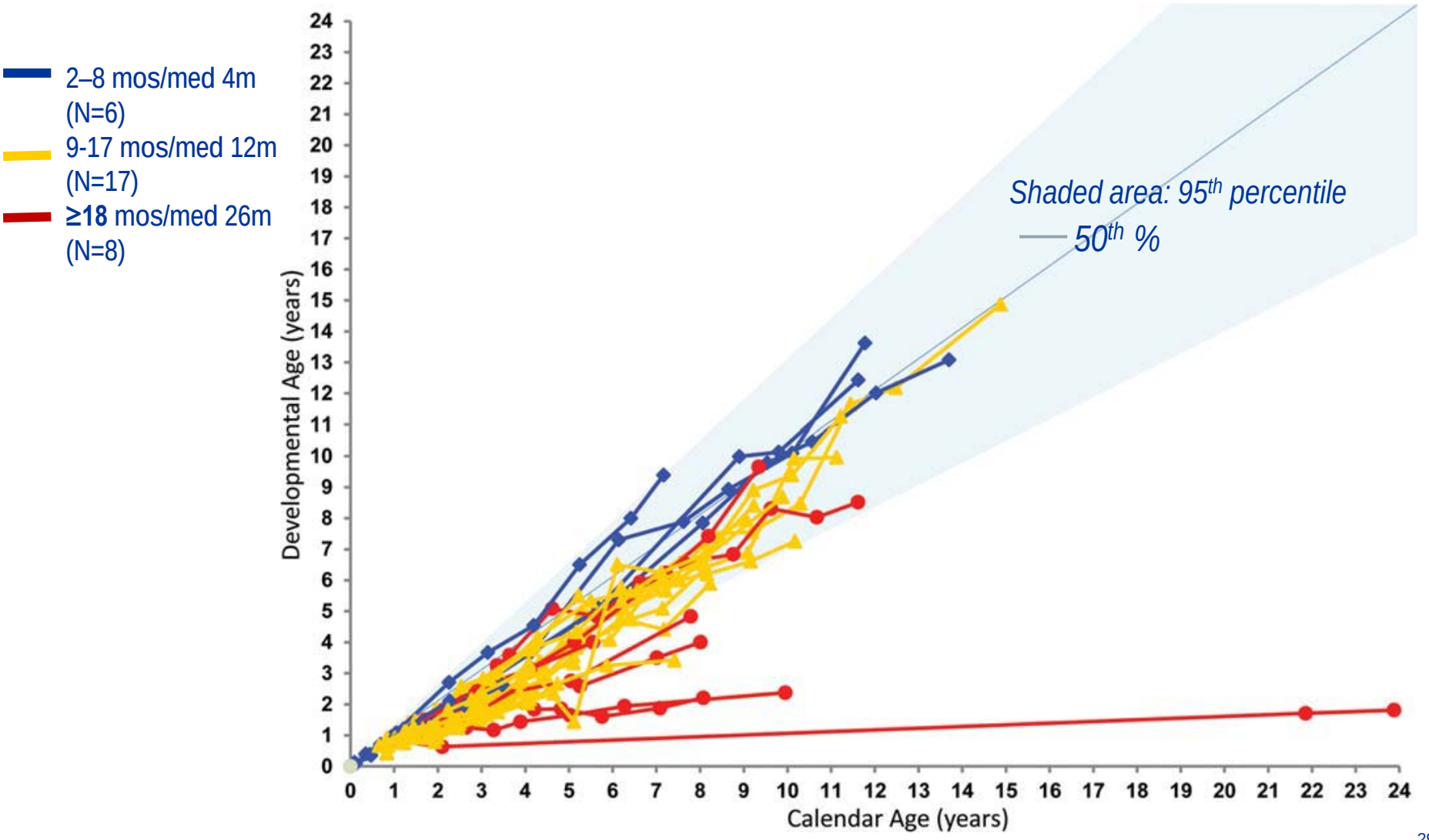


D Expressive Language



Poe et al., 2014. Early Treatment is Associated with Improved Cognition in Hurler Syndrome. *ANN NEUROL* 2014;76:747–753.

Treatment – Cognitive Development



Poe et al., 2014. Early Treatment is Associated with Improved Cognition in Hurler Syndrome. *ANN NEUROL* 2014;76:747–753.

Treatment – Summary – Severe MPS 1

- Recent advances in transplant regimens appear to improve survival
- Evidence suggests that mortality will be similar in cases detected through screening compared to clinical detection
- No evidence regarding HSCT in “asymptomatic” infants

Treatment – Summary – Severe MPS 1 (cont)

- Cognitive Outcomes –
  - *Evidence suggests ERT + HSCT may improve cognitive outcomes/reduce declines compared to HSCT only*
  - *Evidence suggests that earlier age of HSCT (<9 months) is more likely than HSCT >9 months to lead to normal developmental trajectories*

Treatment – Summary – Attenuated MPS 1

- ERT leads to improved outcomes in symptomatic individuals (RCT with follow-up)
  - *Mobility improvements (6-Minute Walk Test)*
  - *Disability Index*
- 2 case reports of sibling sets suggest early ERT (<5 months) in asymptomatic halts or limits disease progression, no other published evidence
- Harms of treatment
  - *ERT: Need for chronic infusions, antibody development*

Population-Level Outcomes for Newborn Screening of MPS I

Lisa A. Prosser, Ph.D.

February 13, 2015

UNIVERSITY OF MICHIGAN

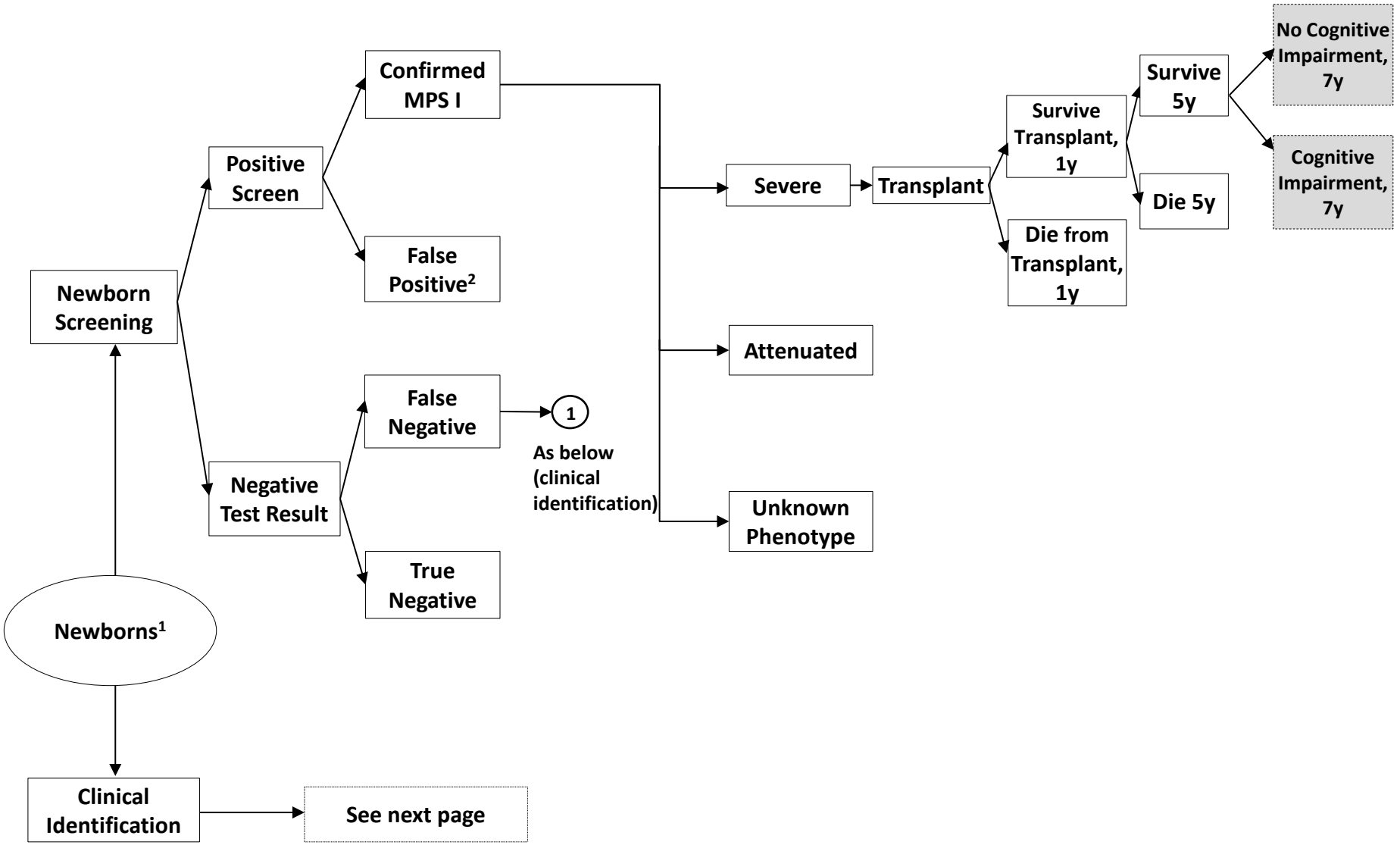
Background: Decision analysis

- Validated approach for evidence synthesis
- Using simulation modeling, ranges can be estimated for population-level health benefits
- Explicitly identify assumptions and key areas of uncertainty

Analytic Approach

- Computer simulation model to evaluate outcomes for:
  - universal newborn screening for MPS I [NBS]
  - clinical identification of MPS I [CI]
- 3 expert panels: Nov 2014, 2 in Jan 2015
- Key health endpoints:
  - # cases identified
  - [# deaths averted by 5 years of age]
  - [# cases with improvement in cognitive outcomes]

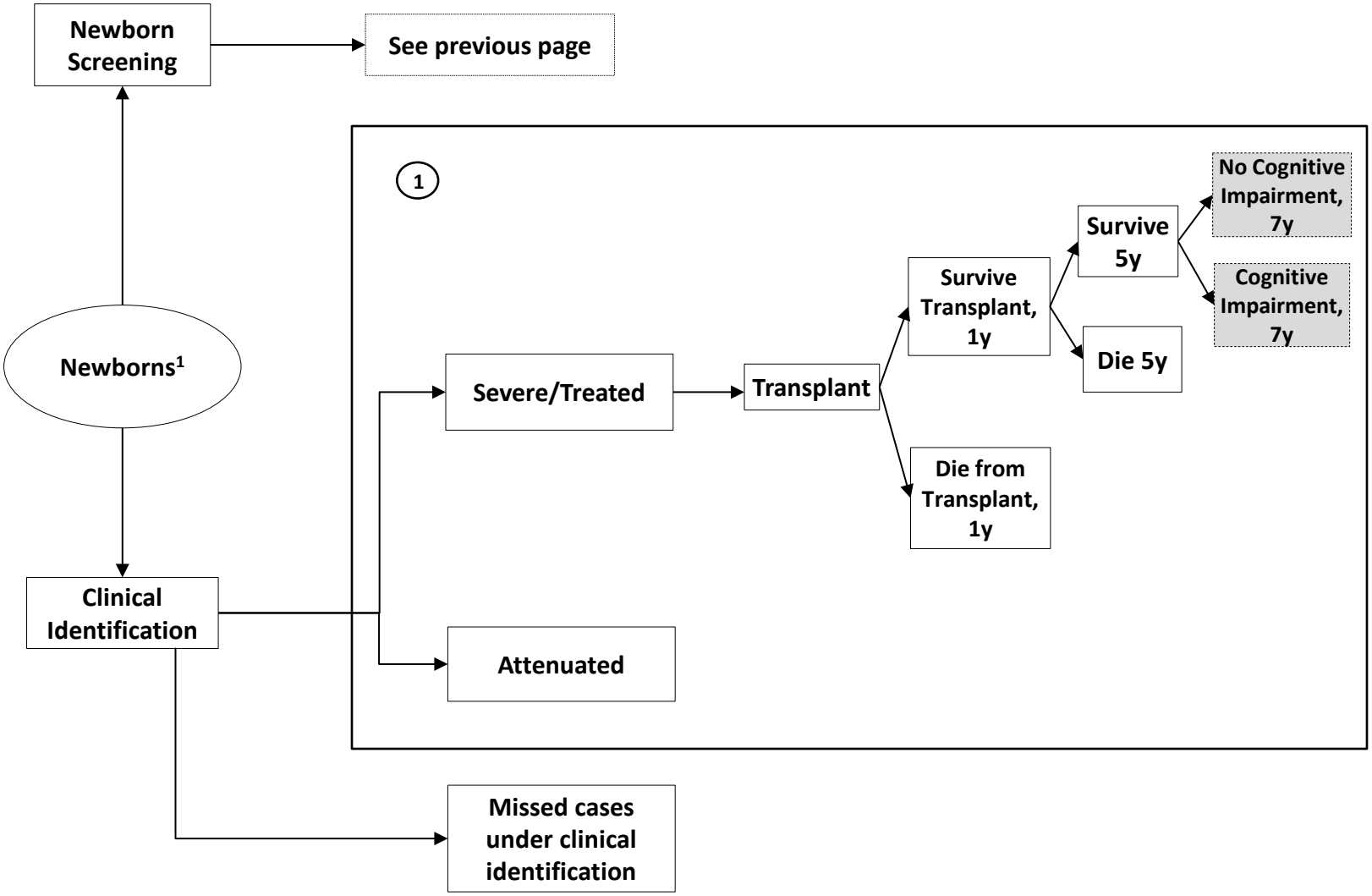
Model Schematic: NBS Submodel



[1]Not at high risk

[2]Includes True false positives, carriers, and pseudo deficiencies

Model Schematic: CI Submodel



Modeling Assumptions

- No. of Severe cases identified by 36 months assumed to be same under NBS or CI; difference will be in timing of diagnosis and initiation of treatment
- All severe cases of MPS I identified through NBS are eligible for HSCT
- Potential benefits of earlier ERT/HSCT are uncertain but may include:
  - Improved survival
  - Improved cognitive outcomes (not modeled)

Results:
Annual Cases of MPS I identified via NBS*

	NBS	Clinical Identification
Severe	29 (13-62)	29 (13-56)
Attenuated	2 (1-7)	11 (8-18)
Unknown Phenotype	13 (8-20)	—
Total MPS I (Confirmed and Possible)	**44 (22-89)**	**40 (22-74)**

*Assuming annual newborn cohort of 4 million not at higher risk of MPS I; incidence of possible & confirmed MPS I with NBS: 0.54-2.22 per 100,000

Summary

- Potential benefits of newborn screening:
  - Earlier identification and initiation of treatment (HSCT) for **severe** cases of MPS I
  - Earlier identification and initiation of treatment (ERT) for **attenuated** cases of MPS I
- Projected outcomes for NBS of MPS I reflect uncertainty in the evidence base currently available
  - Severe cases: 13-62 cases
  - Attenuated/unknown phenotype: 9-27 cases
- Decision analysis process highlighted lack of evidence to reliably model:
  - Cognitive outcomes and other morbidity for severe cases
  - Outcomes for attenuated cases and those of unknown phenotype

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES™

Analysis. Answers. Action.

www.aphl.org

Public Health System Impact Assessment for MPS I

Jelili Ojodu, MPH

February 13, 2015

PUBLIC HEALTH SYSTEM IMPACT ASSESSMENT

Overview

- PHSI Background
- APHL's Role
- Methods
- Results
- Summary

PHSI Background

- The Secretary of HHS Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) makes recommendations to the Secretary, HHS, about what conditions should be included in the RUSP

- These recommendations are based on
  - Certainty of net benefit
  - Feasibility and readiness of implementing comprehensive screening
- Feasibility and readiness is based on an assessment of the public health system impact

SACHDNC Decision Matrix

PHSI

NET BENEFIT		FEASIBILITY	READINESS		
			Ready	Developmental	Unprepared
Significant Benefit	High Certainty	High or Moderate Feasibility	A1	A2	A3
		Low Feasibility	A4		
	Moderate Certainty		B		
Zero to Small Benefit	High or Moderate Certainty		C		
Negative Benefit			D		
	Low Certainty		L		

APHL's Role

- 2013-present: APHL worked with the DACHDNC condition review workgroup (CRW) to improve the process for assessing PHSI
- Sept 2014 - Jan 2015: APHL conducted a PHSI assessment to evaluate NBS programs' capability to implement screening for MPS I

Why is this Assessment Important?

- Inform the DACHDNC
- Opportunity to
  - Understand the “real world” barriers and facilitators related to screening
  - Identify research gaps
  - Conduct a needs assessment
  - Evaluate opportunity costs
  - Share practices that can ultimately improve implementation

Methods

- Survey to 53 U.S. states and territories
- Informant interviews for 3 state NBS programs
- MPS I factsheet
- Webinar and outreach

Feasibility

- An established and available screening test
- A clear approach to diagnostic confirmation
- Acceptable treatment plan, and
- Established approach to long-term follow-up plans

Readiness

- Ready: most NBS programs could implement within 1 year
- Developmental Readiness: most NBS programs could implement within 1–3 years
- Unprepared: most NBS programs would take more than 3 years to implement

Results: Interviews

	Legislative Mandate	Statewide Pilot	Other Pilot
Illinois	X		X
Missouri	X	X	
New Jersey	X		

Results: Interviews

Considerations during the implementation process included:

- Meeting with state Advisory boards
- Obtaining equipment
- Choosing and validating a screening method
- Developing clinical protocols
- Resolving database/LIMS issues
- Collaborating with medical specialists
- Conducting pre-pilots

Results: Interviews

Barriers to implementation:

- Cost/time involved with obtaining new equipment and making laboratory upgrades
- Hiring staff for testing
- Dealing with a high number of false positives and cases of pseudodeficiency
- Low incidence of the disorder

Results: Interviews

Barriers to implementation:

- Difficulty creating treatment algorithms
- Uncertainty regarding age of onset and how to handle cases of unknown phenotypes
- Broad burden on the medical system
- Method validation process

Results: Interviews

Factors that have/will aid in implementation:

- Multiplexing MPS I with other LSDs
- Conducting a pilot
- Having infrastructure in place
- Developing well-defined protocols
- Strong relationships, communication and expertise from staff, medical professionals and partners

Results: Interviews

Challenges with implementing method:

- Time required to validate it
- Adjusting cutoffs to reduce false positives
- Not having quality control or proficiency testing materials available by CDC
- Not having an FDA approved kit

Results: Interviews

NBS program directors interviewed believed it would take 2-3 years or more than 3 years to complete the entire implementation process from obtaining equipment to conducting statewide screening

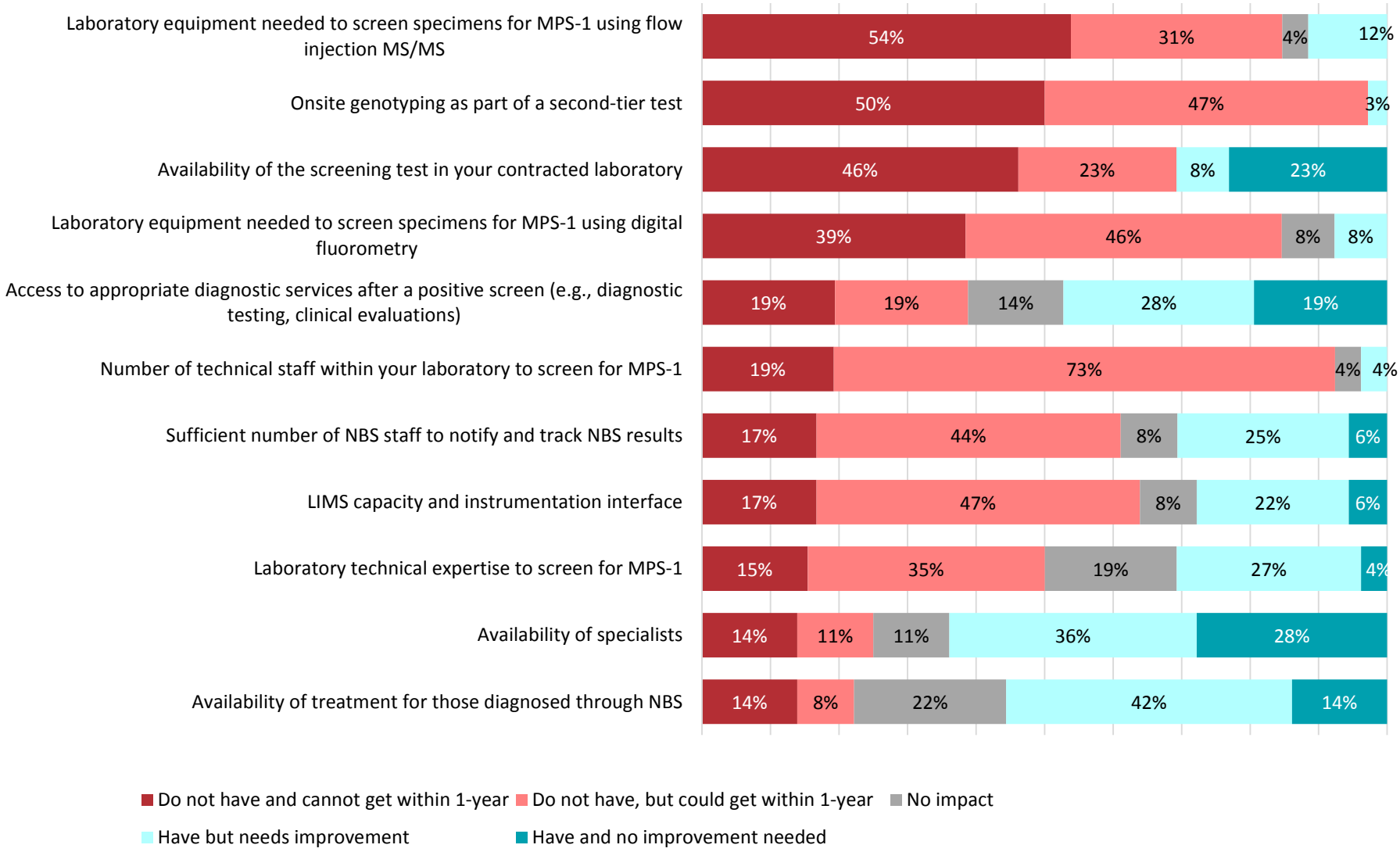
Results: Survey

- Response rate of 74%
- Three states NBS programs were excluded from the analysis because they participated in the interview

Results: Funding Challenges

Activity	Major Challenge		Minor Challenge		Not a challenge	
	N	%	N	%	n	%
Providing the screening test	29	81%	5	14%	2	6%
Long-term follow-up for those with late-onset disease or who are carriers*	26	74%	7	20%	2	6%
Increasing your NBS fee	20	56%	14	39%	2	6%
Support to treatment for MPS-1*	18	51%	13	37%	4	11%
Support to specialists in MPS-1	17	47%	15	42%	4	11%
Short-term follow-up of abnormal screening tests, including tracking and follow-up testing	14	39%	17	47%	5	14%

Results: Factors Impeding or Facilitating Screening



Results: Factors Impeding or Facilitating Screening

	Will hinder implement-ation		May hinder implement-ation		No impact		May aid in implement-ation		Will aid in implement-ation	
	N	%	N	%	n	%	N	%	N	%
Cost per specimen to conduct screening (personnel, equipment, reagents)	13	36%	19	53%	1	3%	3	8%	0	0%
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)	11	31%	18	50%	0	0%	5	14%	2	6%
Predicted run time to screen for MPS-1 as it relates to other workload	8	22%	14	39%	0	0%	14	39%	0	0%
Extent to which screening protocol for MPS-1 has been demonstrated in other NBS programs	7	19%	7	19%	5	14%	4	11%	13	36%
Cost of treatment for newborns diagnosed with NBS	4	11%	21	58%	1	3%	9	25%	1	3%
Other non-NBS public health priorities within your state	4	11%	14	39%	0	0%	17	47%	1	3%
Expected clinical outcomes of newborns identified by screening	3	8%	14	39%	4	11%	6	17%	9	25%
Expected cost-benefit of screening in your state	3	8%	10	28%	3	8%	8	22%	12	33%
Advocacy for screening for this condition	0	0%	3	8%	4	11%	9	25%	20	56%

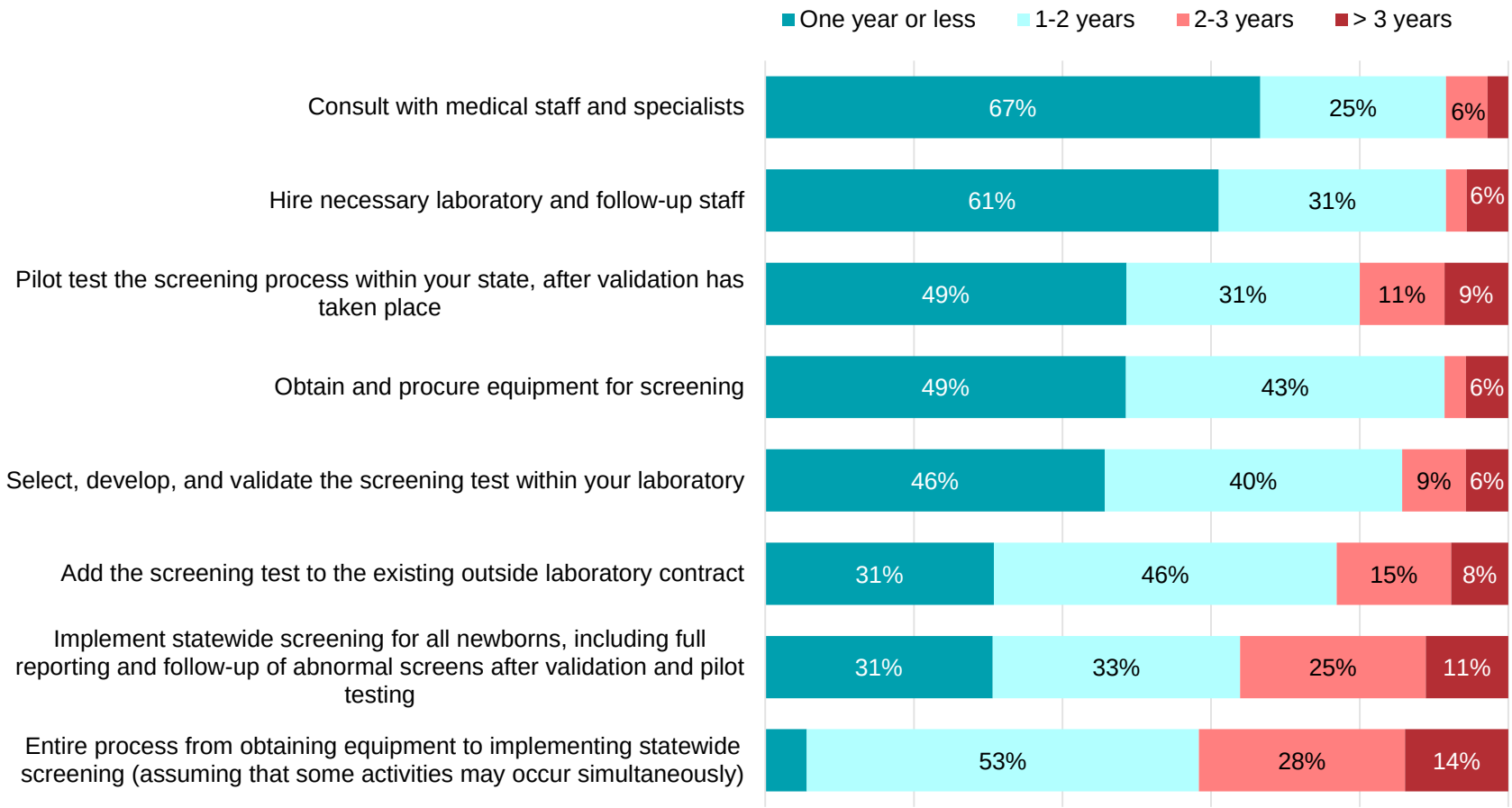
Results: Most Significant Barrier

- 50% of programs: funding and costs associated with implementation
- Other barriers:
  - Not having MPS I on the RUSP
  - Condition not meeting criteria for screening
  - Limited ERT capabilities
  - High number of false positives
  - Uncertainty with mild cases of the disorder

Results: Greatest Facilitator

- 25% of programs: Having treatment, clinical and outcome evidence showing the utility of screening
- 22% of programs: Funding associated with implementation
- Others facilitators:
  - FDA approved kit
  - Addition to the RUSP

Results: Timing for Implementation Activities



Strengths of PHSI Assessment

- Survey response rate of 74%
- Webinar and factsheet for survey responders
- Survey assessed perceptions about implementation based on experiences with other disorders
- Interviews assessed real world experiences

Limitations of PHSI Assessment

- Assumption that approval had occurred and funds were allocated
- Hypothetical survey questions and subjective responses
- Limited data on screening for MPS I in NBS setting

Conclusions

- 79% of programs believed it would take between 1 and 3 years to implement screening for MPS I after approval and allocation of funds

- Developmentally ready

Conclusions

- Funding and cost related challenges
- Other important barriers:
  - ➢ Uncertainty about pseudodeficiency, mutations of unknown significance, and long-term follow-up

Conclusions

- The two states that have begun screening provide important lessons
- Detecting a large number of false positives and cases of pseudodeficiency remain an important challenge

Summary

- Birth prevalence about 1/100,000; most cases are severe
- Screening can identify newborns with MPS I and has been implemented in Missouri and Illinois.
- It is unclear which screening method is best, and all require adoption of new methods for states not screening for lysosomal storage disorders.
- The expected number of false-positives related to pseudodeficiency is greater than anticipated.
- Early identification of MPS I compared to clinical detection may not improve survival in young children.
- Early treatment (<9-16 months) may lead to improved developmental trajectories for cognitive outcomes
- Attenuated MPS I
  - *Age at which symptoms develop cannot be predicted.*
  - *No direct evidence that pre-symptomatic treatment leads to better outcome*

Thank You!

Questions?

Presentation Contact:

Alex R. Kemper, MD, MPH, MS
alex.kemper@duke.edu