Mucopolysaccharidosis Type II Evidence-Based Review

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Joseph Muenzer, MD, PhD*	Professor of Pediatrics, University of North Carolina

*Also nominated MPS II to the Advisory Committee

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MPS II: Overview

- X-linked lysosomal storage disorder
- Dysfunction of the enzyme iduronate-2-sulfatase (I2S) caused by mutations in the *IDS* gene, leading to accumulation of two glycosaminoglycans (GAGs) - dermatan sulphate and heparan sulphate

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MPS II: Overview

- Classified as
  - Severe or attenuated
  - Neuronopathic or non-neuronopathic
- ~60% have the severe phenotype
- Variable phenotypic expression
  - MPS II presents with a spectrum of involvement

References: Vollebregt et al., 2017; Seo, 2020; Shapiro & Eisengart, 2021

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Disease Course and Epidemiology

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Hunter Outcome Study (HOS)

- Established in 2005
- Volunteer registry
- 29 countries
- Includes patients who are untreated, received idursulfase, or hematopoietic stem cell transplant (HSCT)
- Excludes patients who received other enzyme replacement therapy (ERT)
- Includes retrospective data on patients who died prior to study entry
- Many studies – with different subpopulations and analytic approaches

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Disease Course

- Common clinically important features
  - Cardiac valve thickening
  - Splenomegaly and hepatomegaly
  - Obstructive sleep apnea, associated with enlarged tonsils and adenoids
  - Reduced pulmonary function
  - Skeletal disease (dysostosis multiplex) and progressive joint stiffness
  - Behavior problems and cognitive impairment
- Severe form
  - Intellectual disability
  - More significant behavior problems

References: Wraith et al., 2008; Seo et al., 2020, Shapiro & Eisengart, 2021

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Disease Course

- Presentation of common clinical (HOS; first 263 subjects; 24% receiving enzyme replacement therapy (ERT) at enrollment, median age 12.2 years)

Clinical Finding	Prevalence (%)	Median age of onset in years
Otitis media	74	1.2
Abdominal hernia	78	1.3
Nasal obstruction	34	2.0
Facial dysmorphism	95	2.8
Enlarged liver or spleen	89	2.8
Enlarged tonsils or adenoids	68	2.9
Cognitive problems	37	3.2
Enlarged tongue	70	3.4
Hyperactivity	31	3.5
Joint stiffness/musculoskelotal	84	3.6
Behavior problems	36	3.7
Fine motor skill impairment	33	4.0
Gait problems	33	5.5
Heart murmur	62	5.8
Cardiac valve disease	57	6.1

References: Wraith et al., 2008

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Disease Course

- HOS, 800 ERT treated and 95 untreated
  - Median age of symptom onset ~1.5 years
  - Median age of diagnosis ~3.2 years

References: Burton et al., 2017

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Disease Course

- 110 pediatric patients in England, 2006-2016, median age~10 years
- Survival rate to 21 years
  - 52% - treated with ERT at any age (n=78)
  - 9% - not treated with ERT (n=18)

Reference: Broomfield et al, 2020

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Epidemiology

- Clinically Diagnosed MPS II per 100,000 children
  - Recent Review: 0.13-2.16
  - Japan and Taiwan: 0.84-1.07
  - Excluding outliers and East Asian countries: 0.26-0.64

References: Puckett et al., 2021b; B. Celik et al., 2021; Khan et al., 2017; H.Y. Lin et al., 2009

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Diagnosis

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Establishing the Diagnosis in Infants

- Low I2S enzyme activity
- Normal enzyme activity in at least one other sulfatase
- Elevated urine GAG levels
- Molecular diagnosis supportive but may not be confirmatory
  - >700 variants
  - A study from 2013 found ~60% of 218 subjects had a private mutation not clearly predictive of phenotype
- Diagnostic uncertainty can lead to follow-up every 6-12 months, for a variable duration (up to 2 years according to experts)

References: Dvorakova et al., 2014; Julien et al., 2020; Jurecka et al., 2012; Pollard et al., 2013

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Screening

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Screening

- First-tier: I2S enzyme activity in dried-blood spots
  - MS/MS
  - Fluorometric enzymatic assay
- Second-tier: GAG levels in dried-blood spots to reduce the false-positive rate

References: Herbst eta l. 2022; Kumar et al., 2015; Liu et al., 2017; Scott et al., 2020; Stapleton et al., 2020

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Screening: Illinois

Method: MS/MS, began December 2017

MPS II NBS Screen Positive Results Illinois, Dec 2017 - Dec 2021	No.
Total newborns screened	~546,000
Positive screens, clinic referrals	71
- Confirmed MPS II	9
- Biochemical pseudodeficiency	43
- Normal	9
- In follow-up	5
- Lost to Follow up	5

- No systematic information on additional family members identified after diagnosis through screening. However, screening led to the identification of
  - 2-year-old brother
  - Maternal great uncle
  - Maternal grandfather with pseudodeficiency

References: Burton et al., 2020; Personal Communication

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Screening: Missouri

Method: Fluorometric Enzyme Assay and second-tier dried-blood spot GAGs, began 2018

NBS MPS II Screen Positive Results Missouri, Jan – Dec 2020	No.
Total newborns screened	68,640
Positive screens, clinic referrals	11
- Confirmed MPS II	1
- Biochemical pseudodeficiency	2
- Normal	1
- In follow-up	5
- Death before referral	1
- Declined further testing	1

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Pilot Screening: New York

- Screen Plus
  - Pilot study in selected hospitals
  - MS/MS
- Too early to assess

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Screening: Taiwan

- MS/MS
- Screening is with consent
- Multiple programs, each reporting outcomes; details in the report

References: Liao et al., 2014; Chien et al., 2020; Chuang et al., 2021; Chan et al., 2019; Lin et al., 2020

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Screening: Summary

Location	Time Period	Newborns Screened	Diagnostic Follow-up Referral Rate per 100,000 Screened	MPS II Cases Detected per 100,000 Screened	Infants in Diagnostic Follow-up Without Diagnosis per 100,000 Screened
Illinois	2017-2021	546,000	13	1.6	0.9
Missouri	2020	68,640	16	1.5	7.3
Missouri	2018-2021	186,000	15	1.6	2.1
Taiwan	2015-2021	307,731	61	2.9	4.5
Taiwan	2018-2019	73,743	44	4.1	None

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Summary: Screening

- Illinois and Missouri have adopted screening and have identified newborns with MPS II. Some infants are followed because of diagnostic uncertainty
- Case detection rate from screening is higher than the expected clinical detection rate

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Treatment

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Enzyme Replacement Therapy: Standard Targeted Treatment in the US

- Idursulfase
  - FDA approved in 2006
  - Weekly IV infusion over several hours
  - Does not significantly cross the blood-brain barrier
  - Adverse effects
    - Infusion reactions, treated by slowing infusion, sometimes requires premedication (antihistamines, steroids)
    - Antibodies can develop, although these do not seem to interfere with the overall effectiveness of therapy

Reference: McBride, Berry, & Braverman, 2020.

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Enzyme Replacement Therapy: Standard Targeted Treatment in the US

- Idursulfase FDA drug label last updated in 2018

"ELAPRASE is a hydrolytic lysosomal glycosaminoglycan (GAG) specific enzyme indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II). ELAPRASE has been shown to improve walking capacity in patients 5 years and older. In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome; however, treatment with ELAPRASE has reduced spleen volume similarly to that of adults and children 5 years of age and older. The safety and efficacy of ELAPRASE have not been established in pediatric patients less than 16 months of age"

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Other Therapies

- HSCT – lack of clear benefit on neurologic outcomes, risk of mortality
- Investigational approaches
  - Intrathecal and intraventricular idursulfase
  - Modified ERT to enhance uptake across the blood-brain barrier
  - Gene therapy

References: Muenzer et al., 2019; Tanaka et al., 2012; Tomita et al., 2021; Seo et al., 2021; Muenzer et al., 2018; Hogan et al., 2020; Muenzer et al., 2021; Ficicioglu et al., 2021

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Early MPS II Treatment

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Timing of Initiation of ERT

- Idursulfase targets the somatic aspects of MPS II
- No cohort studies directly evaluate early treatment vs. treatment after clinical identification

Reference: Muenzer et al., 2007; Muenzer et al., 2006; Broomfield et al, 2020

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Practice Guideline

- American College of Medical Genetics and Genomics Therapeutics Committee, based on a Delphi panel (10 specialty experts, no public member)

Reference: McBride et al., 2020. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 22(11):1735-1742.

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ACMG Practice Guideline

1. "All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting ERT, prior to showing signs or symptoms.
2. Individuals with signs or symptoms with either attenuated or severe MPS II warrant ERT.
3. Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.
4. Home infusions may be considered for those with early disease, easily managed ERT infusion reactions, and a stable home environment.
5. Individuals receiving ERT who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have ERT discontinued.
6. Pressure equalizing (PE) tubes and hearing aids are useful therapies.
7. Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment, with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. Pulmonary function tests (PFTs) are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6-minute walk test (6MWT). Lab studies of GAGs are recommended, as well as antibodies to ERT to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress"

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Reference: McBride et al., 2020. Treatment of mucopolysaccharidosis type II (Hunter syndrome): a Delphi derived practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 22(11):1735-1742.

Different Perspectives

- ACMG recommendation #3 suggests not treating patients with attenuated phenotype who have not yet developed clinical signs
- Some Delphi panel participants and all TEP experts recommended offering ERT to all patients with MPS II, regardless of predicted phenotype even in the absence of clinical findings
  - GAG accumulation leads to progressive involvement, regardless of phenotype
  - ERT will not reverse damage caused by GAG accumulation
- Parents can make informed choices as to when to start treatment

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Treatment following Newborn Screening

- In Illinois, of 7 in one referral center, 5 started ERT and 2 families elected close clinical follow-up
- In Missouri, 3 with severe MPS II started on ERT, one of whom also received HSCT and died due to transplant-related complications

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Early vs. Later Treatment: Registry Study

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Early vs. Later ERT Treatment: Registry Study

- Data from the HOS
  - Subjects (n=481) stratified by age at ERT start (<18 months, 18 months-5 years, ≥5 years)
  - Variation in completeness of data and length of follow-up
  - Outcomes based on time since ERT, not absolute age

Reference: Muenzer et al., 2021

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Early vs. Later ERT Treatment: Registry Study

- Urine GAG levels decreased similarly for all subjects
- Left ventricular mass index stable
- Liver size decreased with faster resolution for those who started earlier
- Among those without cognitive impairment, following 8 years of ERT, 6MWT increased, more for those who started earlier (wide confidence intervals)
  - 0-18 months: 507.3 meters
  - 18 months-5 years: 494.7 meters
  - ≥5 years: 473.9 meters

Reference: Muenzer et al., 2021

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ERT < 1 Year:
Case Reports and Sibling Studies

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ERT <1 Year: Case Reports

- Case series of 8 infants diagnosed based on family history and treated with ERT, follow-up of six for 20 months-5.5 years
  - Normal growth
  - Minor joint impairment
  - Improved development
  - Decreased hepatosplenomegaly
  - One with mild aortic valve stenosis with insufficiency
- Report lacks standard measures across all cases and matched comparators for all

Reference: Lampe et al., 2014. Enzyme Replacement Therapy in Mucopolysaccharidosis II Patients Under 1 Year of Age. *JIMD* 14:99-113.

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ERT <1 Year: Sibling Studies

- Siblings with MPS II are expected to have a similar phenotype
- A natural comparator for early vs. later treatment
- Number of reports:
  - <7 months: 3 articles and 2 conference abstracts describing 7 sibling pairs
  - ≥7 months: 1 article and 1 conference abstract describing 2 sibling pairs

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ERT <7 months: Sibling Studies

Reference: Tajima et al., 2013	Older sibling (O)		Younger sibling (Y)	
Age at diagnosis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	2 yrs 7 mos male Yes 3y 6 years/34 months of ERT		<1mo male No 4 months 3 years/32 months of ERT	
Findings	**At initiation**	**At follow up**	**At initiation**	**At follow-up**
Head Eyes Ears Nose and Throat Findings	Coarse facies Exudative otitis	Coarse facies Exudative otitis	Normal	Normal
Skin	Coarse	Coarse/Improved	Normal	Normal
Hepatosplenomegaly	Present	Present/improved	Not present	Not present
Cardiac function	Abnormal	Abnormal/stable	Normal	Normal
Muscluoskeletal	Joint limitations Dysotosis multiplex	Joints stable Dysostosis progressive	Joint limitations Dysotosis multiplex	Joints Stable Dysotosis progressive
DQ	49	42	89	74

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ERT <7 months: Sibling Studies

Reference: Tajima et al., 2013	Older sibling (O)		Younger sibling (Y)	
Age at diagnosis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	2 yrs 7 mos male Yes 3y 6 years/34 months of ERT		<1mo male No 4 months 3 years/32 months of ERT	
Signs/symptoms	**At initiation**	**At follow up**	**At initiation**	**At follow-up**
Head Eyes Ears Nose and Throat Findings	Coarse facies Exudative otitis	Coarse facies Exudative otitis	Normal	Normal
Skin	Coarse	Coarse/Improved	Normal	Normal
Hepatosplenomegaly	Present	Present/improved	Not present	Not present
Cardiac function	Abnormal	Abnormal/stable	Normal	Normal
Muscluoskeletal	Joint limitations Dysotosis multiplex	Joints stable Dysostosis progressive	Joint limitations Dysotosis multiplex	Joints Stable Dysotosis progressive
DQ	49	42	89	74

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ERT <7 months: Sibling Studies

Reference: Tylki-Szymanska et al., 2012	Older sibling (O)	Younger sibling (Y)
Age at diagnosis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	5 years female Present 7.5 years 10 years/3 years	14 days male Not present 3 months 3 years/3 years
Symptoms at follow-up		
Head, Eyes, Ears, Nose, and Throat (HEENT)	Coarse facies	Normal
Hepatosplenomegaly	Mild, with umbilical hernia	Normal
Cardiac function	Decreased, worsened while on ERT	Normal
Musculoskeletal	Decreased ROM, contractures, short stature dystosis multiplex	Normal
IQ	At 7.5 years old (ERT initiation) = 50 At 10 years old (after 3y of ERT) = 24	At 3 years old (after 3y of ERT) = 98 Healthy twin brother 3 years old = 118

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ERT <7 months: Sibling Studies

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Reference: Tomita et al. 2021	Older sibling (O)		Younger sibling (Y)	
Age at diagnosis	2 yrs male		<1mo male	
Diagnosis of symptoms	Yes		No	
Age at ERT initiation	2 years		4 months	
Age at follow-up report/Duration of ERT	6 years old/34 months of ERT		3 years old/32 months of ERT	
Symptoms	**At initiation**	**At follow up**	**At initiation**	**At follow-up**
Head Eyes Ears Nose and Throat (HEENT)	Coarse facies Otits media	Coarse facies Otits media	Normal	Otitis media
Musculoskeletal	Joint limitations Dysostosis multiplex	Stable joints Dystosis progressive	Dystosis present	Dystosis stable
Skin	Coarse	Coarse/improved	Normal	Normal
Hepatosplenomegaly	Present	Present/improved	Not present	Not present
Cardiac function	Abnormal	Abnormal/stable	Normal	Normal
DQ	49	42	89	74
Additional findings at follow- up				
HEENT	Adenoid vegetation			
Musculoskeletal	Stiffness, skeletal deformity			
Hepatosplenomegaly	Present		Slight	
Cardiac signs			ASD	
Inguinal hernia	Present		Present	
Brain imaging	Ventriculomegaly, brain atrophy			
Motor skills	Lost ability to climb stairs			
Speech	Delayed/regressing			
Behavior	ADHD, behavioral problems			
DQ	53 at 4 years		104 at 3 years 11mo	

ERT <7 months: Sibling Studies

Reference: Quadri 2022 (WORLD Symposium, abstract)	3 Older siblings (O)	3 Younger sibling (Y)
Age at diagnosis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	21-36 mo male Yes Post ERT 2-3 years	Prenatal/newborn male (age not specified) No 1-2 months 5 years
Symptoms at follow-up		
Head Eyes Ears Nose and Throat (HEENT) symptoms	Coarse features Persistent ear effusions or PET	Normal facies
Hepatosplenomegaly	Resolved with ERT	Absent
Cardiac involvement	2 of 3	Absent
Joint problems	Generalized stiffness	Absent
Cognitive	Persistent developmental or speech delays	Mild speech delay in 2 of 3

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ERT <7 months: Sibling Studies

Reference: Vashakmadze et al., 2021 (abstract)	Older sibling (O)		Younger sibling (Y)	
Age at diagnosis **Symptoms diagnosis** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	2.9 yrs Yes 4 years 11 years of ERT		1mo Yes 5 months 5 years of ERT	
Symptoms	**At initiation**	**At follow-up**	**At initiation**	**At follow-up**
Head Eyes Ears Nose and Throat (HEENT) symptoms	Coarse facies, adenoid hypertrophy	Course/stable		Coarse facies
Hepatosplenomegaly	Present			Mild
Cardiac function	Abnormal (mitral and aortic valve)	Abnormal (mitral and aortic valve)		Mitral valve thickening
Musculoskeletal	Dysostosis multiplex present	Dysostosis present claw hand deformity carpal tunnel	Mild muscle dystony	
DQ		Normal cognitive function		

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ERT ≥7 months: Sibling Studies

Reference: Polgreen et al., 2022, WORLD Symposium (abstract)	Older sibling (O)	Younger sibling (Y)
Age at diagnosis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	Not reported Not specified 5.2 years 15 years/10 years of ERT	Not reported Not specified 1.7 years Not reported
Symptoms at follow-up		
Musculoskeletal	Scoliosis, limited joint range of motion	Scoliosis, limited joint range of motion but less severe
Adaptive function score	79	106
Cognitive function	Above average, communication skills 105	Above average

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ERT ≥7 months: Sibling Studies

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Ref: Grant et al., 2022	Older sibling (O)		Younger sibling (Y)	
Age at diagonsis **Diagnosis of symptoms** **Age at ERT initiation** **Age at follow-up report/Duration of ERT**	3 yrs 8 mo Yes 3.9 years, then IT ERT 6-10yo 11 years/6 years of ERT, discontinued due to progression		12mo No 13m; IT ERT from 5y9m to 9 years, CNS-penetrant ERT since 9 yrs old	
Symptoms	**At initiation**	**At follow-up**	**At initiation**	**At follow-up**
Head Eyes Ears Nose and Throat (HEENT) symptoms		Normal hearing at 8 years old		Mild hearing loss at 4 yrs, hearing aids
Hepatosplenomegaly	Present	Resolved	Absent	Absent
Cardiac function	Thickened mitral and aortic valves	10 y 1 mo mitral and aortic valves progressive thickening, aortic regurgitation	1 y 1 mo, Normal at diagnosis	9 y 8mo No valve thickening, mild aortic regurgitaiton
Musculoskeletal	Cleneched hands at birth. Dysostosis multiplex at diagnosis	13y upper and lower extremity contractures worsening, walking < 1 mi. Progressive skeletal deformities	Mild shoulder contracture at diagnosis	At 10 y could hike 6 miles. No functional limitations
Differential ability scale score at 5.5 years		46 at 5 years		91 (average)
Communication		Minimally verbal since 6 yo		Delayed/3yr old level
Behavior		Significant problems, aggression, ADHD		ADHD
ADLs		Requires significant family support		Independent bathing, dressing, toileting

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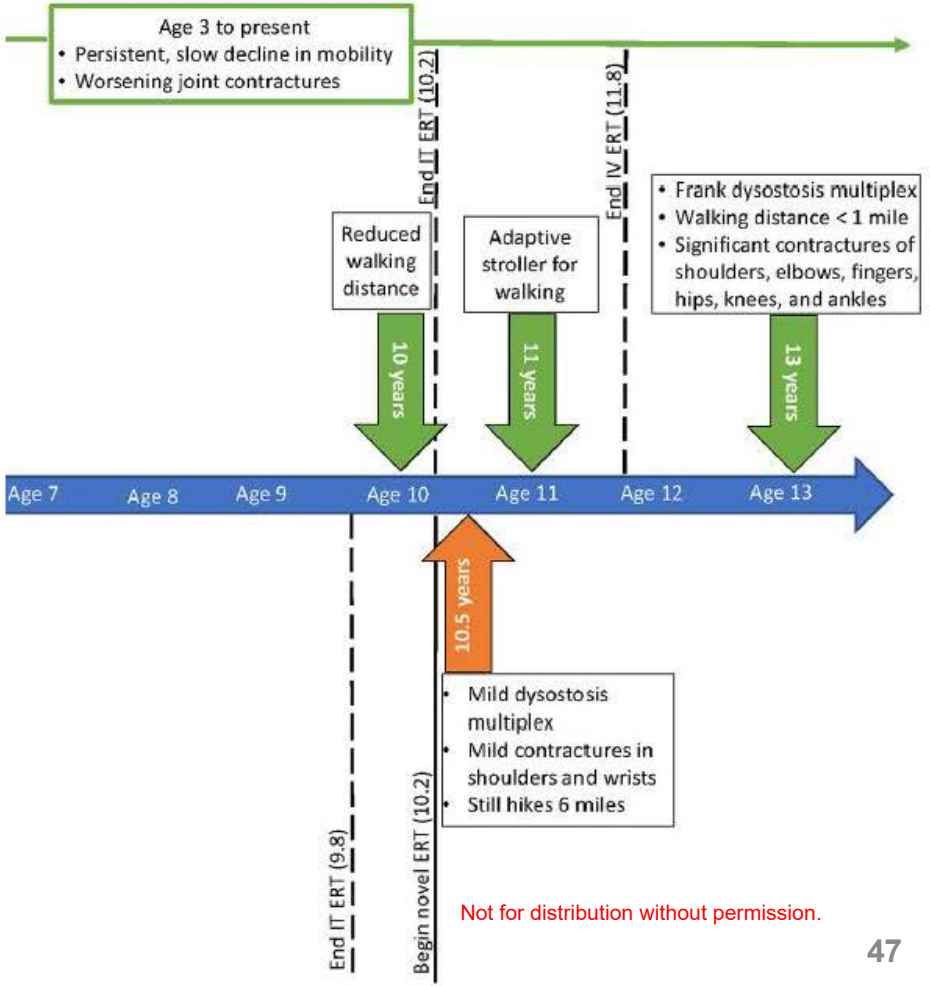
Ambulation

- Older sibling at age 11 had limited assisted ambulation
- Younger sibling diagnosed at 12 months fully ambulatory at same chronological age as older sibling
- HOS walk test findings reported less dramatic differences in ambulation



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Summary: Sibling Studies

- Earlier treatment consistently associated with improved somatic outcomes and ability to perform daily activities
- Heterogeneity
  - Phenotype
  - Timing of treatment
  - Outcome measures
- Positive impacts on families with earlier treatment

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Summary: Treatment

- Idursulfase
  - Treats the somatic component of MPS II and is associated with decreased risk of mortality by adulthood.
  - Well tolerated
  - No prospective or retrospective cohort studies comparing ERT in the first year of life to later treatment with standardized measures at specific ages
  - Sibling case reports provide indirect evidence of early treatment benefit
- Other targeted therapies are an active area of research

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Projected Population-Level Outcomes:

MPS II Newborn Screening compared with clinical case detection

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Goal

- Compare projected outcomes from MPS II newborn screening for all newborns in the U.S. with usual case detection in the absence of screening.

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Approach

- Annual U.S. newborn cohort of 3.6 million
- Newborn screening
  - Screening outcomes
  - Cases of MPS II
  - False positives
- Clinical identification
  - Confirmed cases of MPS II

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Health Outcomes

- Previous models conducted for evidence review have evaluated outcomes such as death, cognitive impairment, and need for mechanical ventilation
- Insufficient data from MPS II cohort studies to model outcomes after post-NBS diagnosis compared to clinical identification
  - Requires standardized outcome measures assessed at comparable ages stratified by age at diagnosis
- Although sibling studies are informative, they are not sufficient to inform modeling

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Decision Analysis

- Systematic approach to decision making under conditions of uncertainty
- Project ***ranges*** of short-term outcomes
- Allows decision maker to identify which alternative is expected to yield the most health benefit
- Identify key parameters and assumptions

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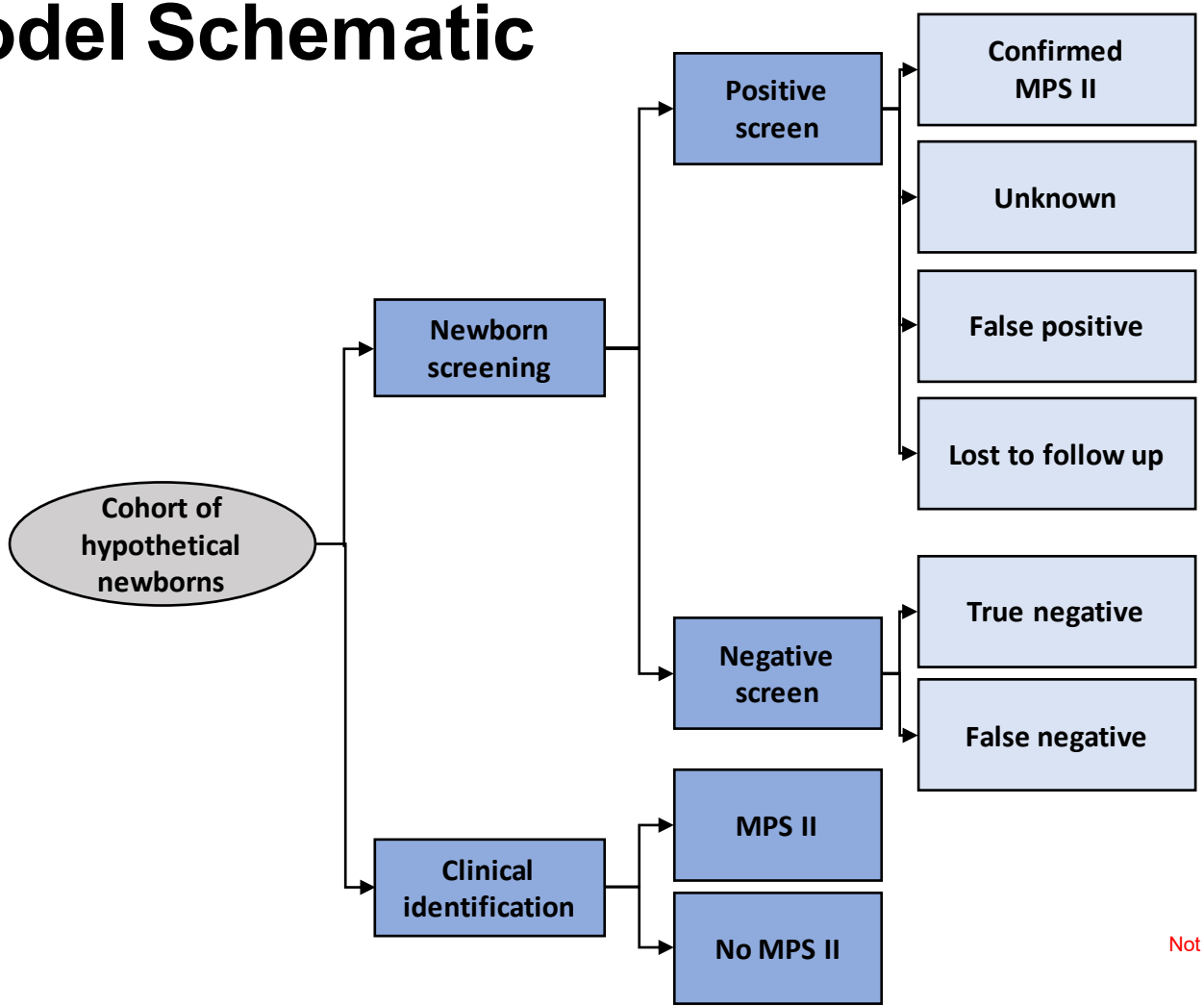
Model Schematic



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Model Inputs

Probability	Most Likely	Range (min-max)	Source
Positive screen, newborn screening	13.3 per 100,000	9.6-14.5 per 100,000*	Illinois and Missouri Newborn Screening Data
MPS II diagnosed after a positive screen	12%** (1.6 per 100,000)	9%-13%** (1.5-1.6 per 100,000)†	
Diagnostic uncertainty leading to follow-up after a positive screen	12% (1.6 per 100,000)	7%-45% (0.9-7.3 per 100,000)†	
Positive screen is false‡	67% (8.9 per 100,000)	27%-73% (4.4-9.5 per 100,000)†	
Lost to follow-up after a positive screen	9% (1.1 per 100,000)	7%-18% (0.9-2.9 per 100,000)†	
MPS II, clinical identification	0.67 per 100,000	0.13-2.16 per 100,000*	See evidence review

* 95% confidence interval derived using binomial distribution
**Conditional probability given a positive screen, ranges for conditional probability based on IL and MO experiences
† Range represents range of data from Illinois and Missouri screening programs
‡ Includes biochemical pseudodeficiency

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Projected Cases for MPS II Newborn Screening Compared with Clinical Identification, U.S. Cohort of 3.6 million Newborns

	Newborn Screening	Clinical Identification
Positive screen	480 (346 - 523)	-
MPS II diagnosed	59 (44 - 61)	24 (5-78)
Diagnostic uncertainty requiring follow-up	59 (34 - 218)	-
False positive	322 (131 - 352)	-
Lost to follow-up	41 (34 - 87)	-

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Summary

- Newborn screening would identify a greater number of cases of MPS II compared with clinical identification.
- The number of cases requiring follow-up because of diagnostic uncertainty is similar to the number of cases of MPS II diagnosed immediately following newborn screening.
- If cases lost to follow-up had further evaluation, estimates from this model could change.
- This is the first condition considered by the ACHDNC since the incorporation of decision modeling for which there has been insufficient evidence to model outcomes to quantify the potential benefits of screening.

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Newborn Screening Program Costs of MPS II Screening

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Newborn Screening Program
Costs of MPS II Screening

- Based on interviews with representatives from the Illinois and Missouri newborn screening programs
- Included in estimated costs
  - Equipment, reagents, added laboratory technician and scientist time
  - MPS II screening is incorporated into existing activities, so breaking out specific costs is challenging

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Newborn Screening Program
Costs of MPS II Screening

- Estimated cost above and beyond the fixed costs of an existing program: $2 to $6 per infant
- Influencing factors
  - Technology (MS/MS or fluorometric enzyme assay
  - Volume of specimens
  - Need for additional technician time
  - Commercial assay vs. laboratory-developed test
  - Equipment rental vs. purchase
  - Additional fixed cost: Updating the LIMS system
- Because of the low positive first-tier screening rate, factors that do not significantly increase the cost
  - Second-tier GAG testing
  - Short-term follow-up

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Public Health System Impact Assessment

Mucopolysaccharidosis Type II

Jelili Ojodu, MPH

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BACKGROUND

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Public Health System Impact

- Recommendations are based on
  - Certainty of net benefit.
  - **Feasibility** and **Readiness** of implementing comprehensive newborn screening.

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Definition of 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 longer than 3 years to implement.

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Components of Feasibility

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

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Why is this Assessment Important?

- Opportunity to
  - Understand both the “real world” barriers and the facilitators related to screening.
  - Evaluate opportunity cost.

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METHODS

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Methods

- MPS II fact sheet
- Webinar and outreach
- Survey, revised incorporating Committee and public feedback, sent to 53 US states and territories and DC
- Interviews with NBS programs that are screening for MPS II, have a mandate, or are exploring screening
- Three additional programs were interviewed to better understand how recent changes to the RUSP might impact adoption of MPS II newborn screening.

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RESULTS

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Status of MPS II Screening in the US

NBS Program	Universal Screening	Legislative Mandate	Considering/ Performing Pilot Screening	Start Date/ Anticipated Start Date	Completed APHL Interview	Method
Illinois	X			2017	X	MS/MS
Missouri	X			2018	X	Fluorometry
North Carolina			X	2022	X	N/A
New York			X	N/A	X	N/A
West Virginia		X		N/A		N/A

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Survey Results: Respondent Characteristics

- Thirty-seven NBS programs included; five interviewed instead of completing the online survey

Characteristics of NBS Program Respondents	n
State public health laboratory or NBS program	23
Regional contract for NBS laboratory services	7
State university with intra-state agency agreement for NBS laboratory services	4
Commercial contract for NBS laboratory services	3

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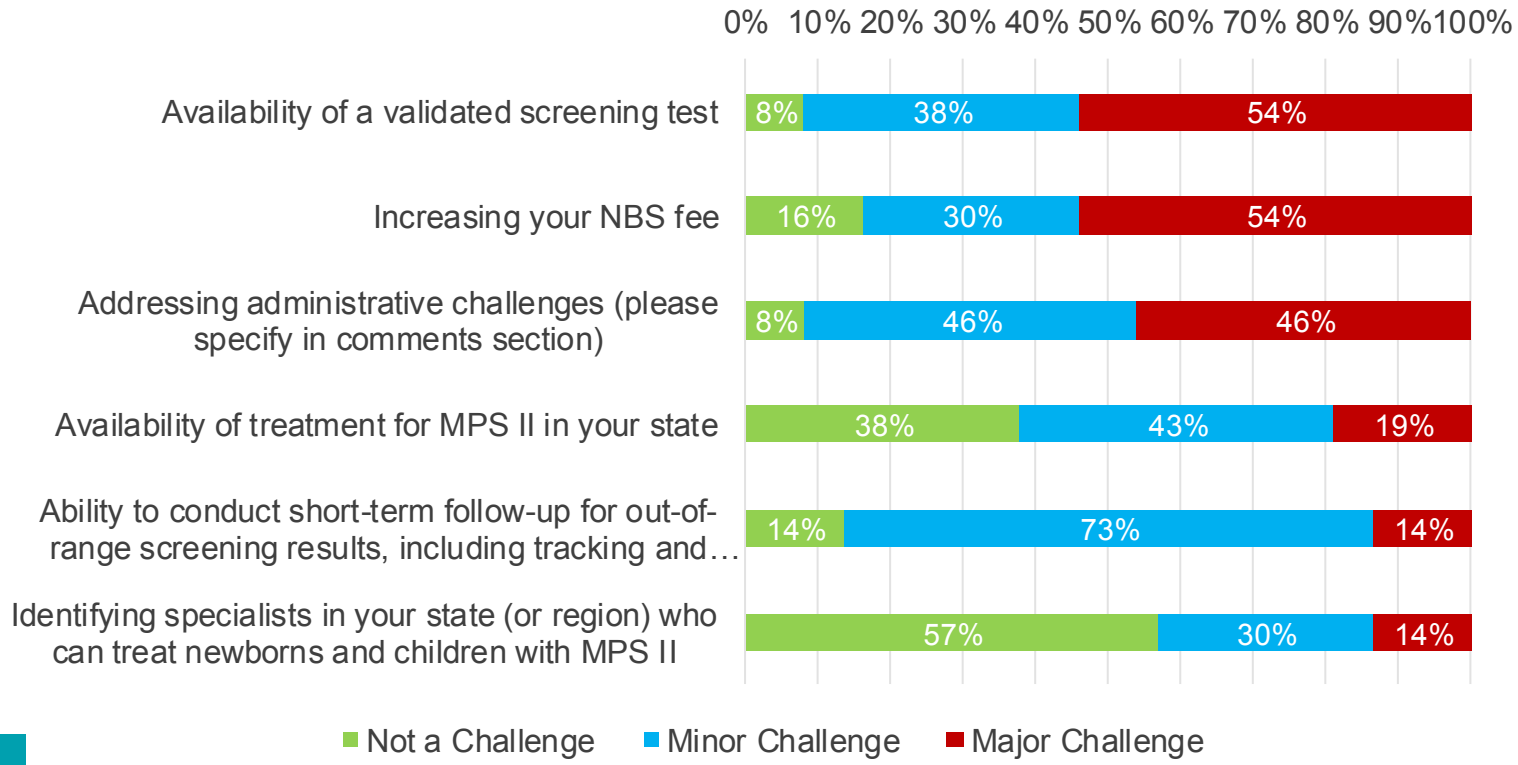
Survey Results: Implementation Challenges



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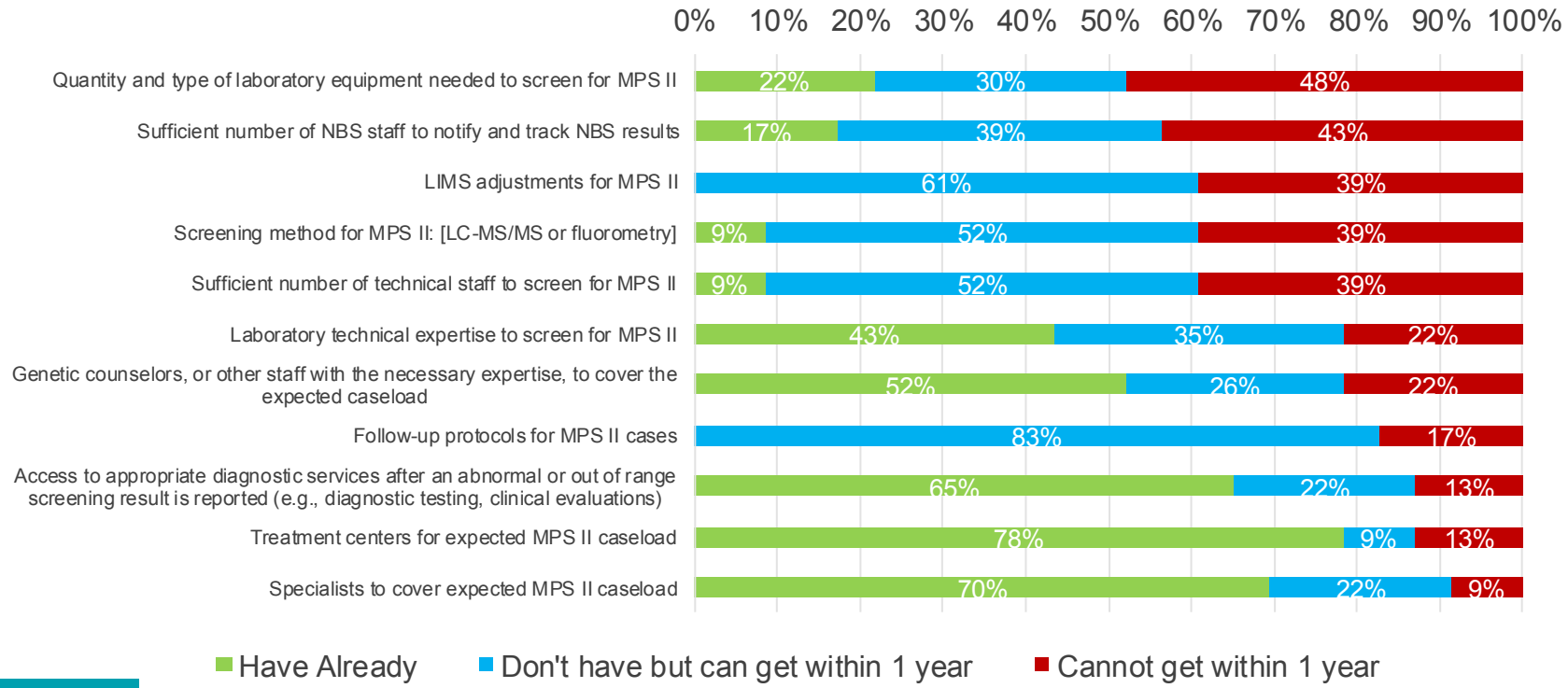
Survey Results: Resources Needed For Own State's Public Health or NBS Laboratory



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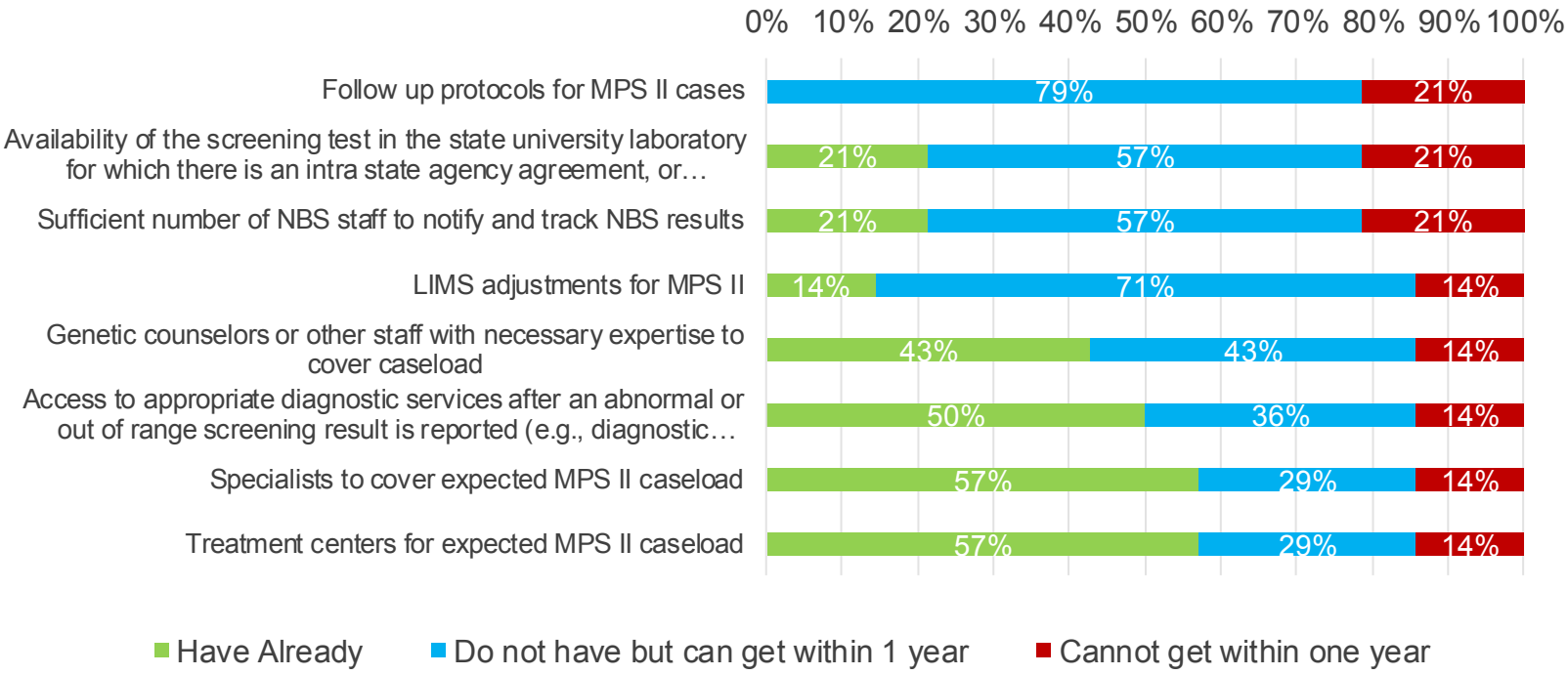
Survey Results: Resources Needed For Contracted or State University Laboratories with Intrastate Agreement



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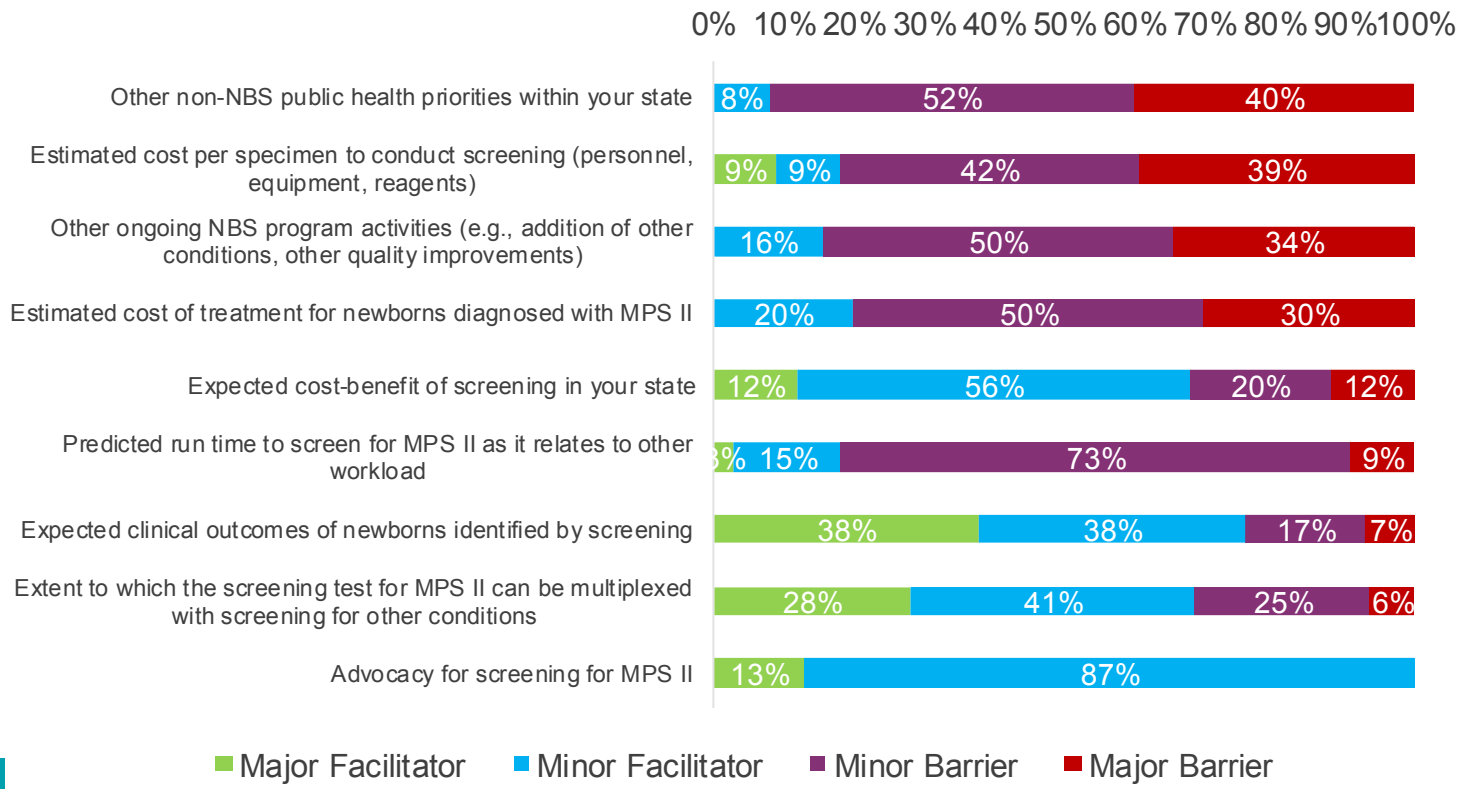
Survey Results: Barriers and Facilitators



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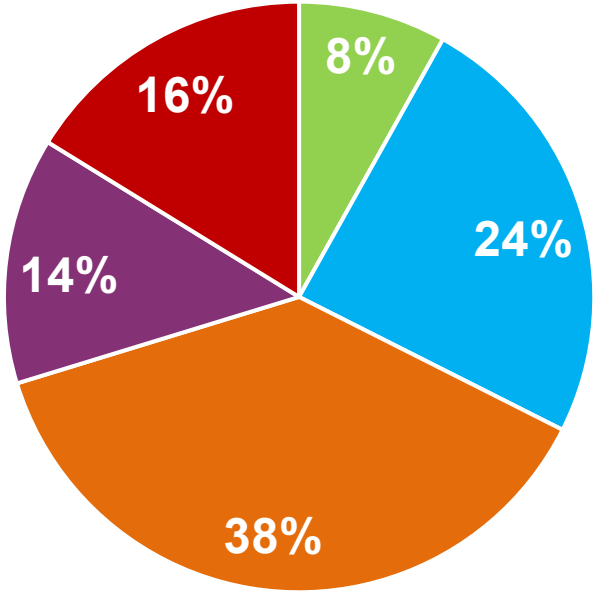
Survey Results: Estimated Time it Would Take to Implement MPS II Screening In Your State



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Interview Results: Lessons Learned from NBS Programs Screening

- Assays provided good separation between normal and affected.
- The second-tier GAG test reduced false positives.
- The ability to multiplex with other LSDs is an advantage, however there are challenges with not being able to do it in the traditional sense.
- There continue to be challenges with making LIMS revisions, figuring out how to handle variants of unknown significance, and periodic re-evaluation of screening cutoffs to reduce false positives.

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Interview Results: Lessons Learned from Additional NBS Programs

- The NBS program screening for the latest RUSP conditions has the advantage of annual fee increases, typically relies on ACHDNC recommendations, and has a readiness tool.
- These three programs highlighted challenges of funding, hiring staff, laboratory space, and updating their laboratory information management system.
- None of the programs were concerned about the challenges of short-term follow-up or access to treatment.

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Strengths of PHSI

- Survey response rate was 79%.
- Webinar and factsheet for survey responders.
- Survey assessed perceptions about implementation based on experiences with other disorders.
- Interviews assessed real world experiences.

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Limitations of PHSI

- Hypothetical survey questions and subjective responses.
- Limited data on screening for MPS II in NBS setting.
- There is great variation among NBS programs, which could limit generalizability.

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SUMMARY

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Summary

- The majority of NBS programs (62%) reported that it would take between 1 and 3 years to implement screening for MPS II.
  - 1-2 years: 24%
  - 2-3 years: 38%
- Variation among NBS programs.
- Programs that have already implemented previous RUSP conditions may be in a better position to implement MPS II.

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Summary

Most commonly reported challenges to adding MPS II newborn screening:

- Ability to increase NBS fees or obtain funding
- Administrative challenges
- Hiring/staffing issues
- Laboratory capacity for additional instrumentation
- Competing priorities (e.g., COVID, LIMS projects, adding other disorders)

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