Interim Update: Mucopolysaccharidosis Type II Evidence-Based Review

November 9, 2021

NATIONWIDE CHILDREN'S
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Objective

- Update the Advisory Committee on the status of the evidence-based review
  - Highlighting key findings
  - Identifying gaps and proposing solutions
  - Describing next steps

MPS II: Overview

- X-linked lysosomal inborn error of metabolism caused by deficiency of the enzyme iduronate 2-sulfatase, leading to the accumulation of specific glycosaminoglycans (GAGs)
- >500 mutations in the *IDS* gene (Xq28)
  - Many private mutations
- Clinical-detected prevalence: 0.2-2.5 per 100,000 live births
  - Attenuated: ~1/3 of cases
  - Severe: ~2/3 of cases
- Some who screen positive will have pseudodeficiency

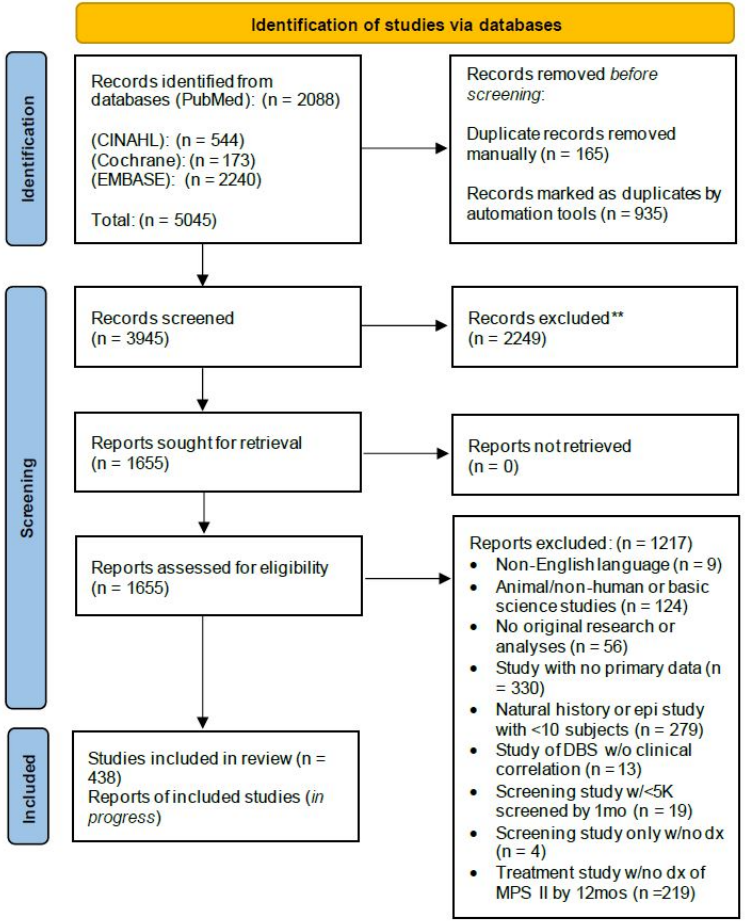
MPS II: Overview (1 of 2)

- Severe
  - Progressive multiorgan and joint involvement
  - Cognitive impairment and regression
  - Diagnosis typical in early childhood (18-36 months)
  - Death in the teens or 20s if untreated
- Attenuated
  - Later diagnosis – how much later?
  - Progressive multiorgan involvement but no CNS impairment
  - Can live well into adulthood – life expectancy is unknown

MPS II: Overview (2 of 2)

- Phenotype is not typically predictable at the time of diagnosis
  - Severe form can be predicted based on complete deletion or complex rearrangement
  - Phenotypic prediction typically is not possible for the private mutations
- Screening and diagnosis
  - MS/MS or fluorometry
  - Diagnosis: confirm low enzyme activity, measure GAGs (serum) to rule out pseudodeficiency, genotype, rule-out other conditions
- Targeted treatment
  - Enzyme replacement therapy (idursulfase) and hematopoietic stem cell transplantation (HSCT)

Published Articles



Survival in Idursulfase-Treated and Untreated Patients: Hunter Outcome Survey

Patient Characteristics	**Treated (n=800)** **median in yrs (P10, P90)**	**Untreated (n=95)** **median in yrs (P10, P90)**
Age at symptom onset	1.6 (0.3, 4.3)	1.5 (0.2, 4.2)
Age at diagnosis	3.3 (1.0, 7.1)	3.2 (0.9, 10.8)
Delay in Diagnosis	1.0 (0.0, 4.3)	1.0 (0.0, 5.8)
Age at first treatment	6.9 (2.1, 19.8)	NA
Length of time on treatment in months	57.8 (10.6, 106.2)	NA
% with Cognitive impairment	58.0%	57.9%
% died	15.5% (124/800)	29.5% (28/95)
Follow-up time, birth to death or last visit	13.0	15.1
Survival age at follow up	33.0 (30.4, 38.4)	21.2 (16.1, 31.5)

Burton, B. K.,Jego, V.,Mikl, J.,Jones, S. A.. Survival in idursulfase-treated and untreated patients with mucopolysaccharidosis type II: data from the Hunter Outcome Survey (HOS). *J Inherit Metab Dis*. 2017. 40:867-874.

MPS II – Disease Progression

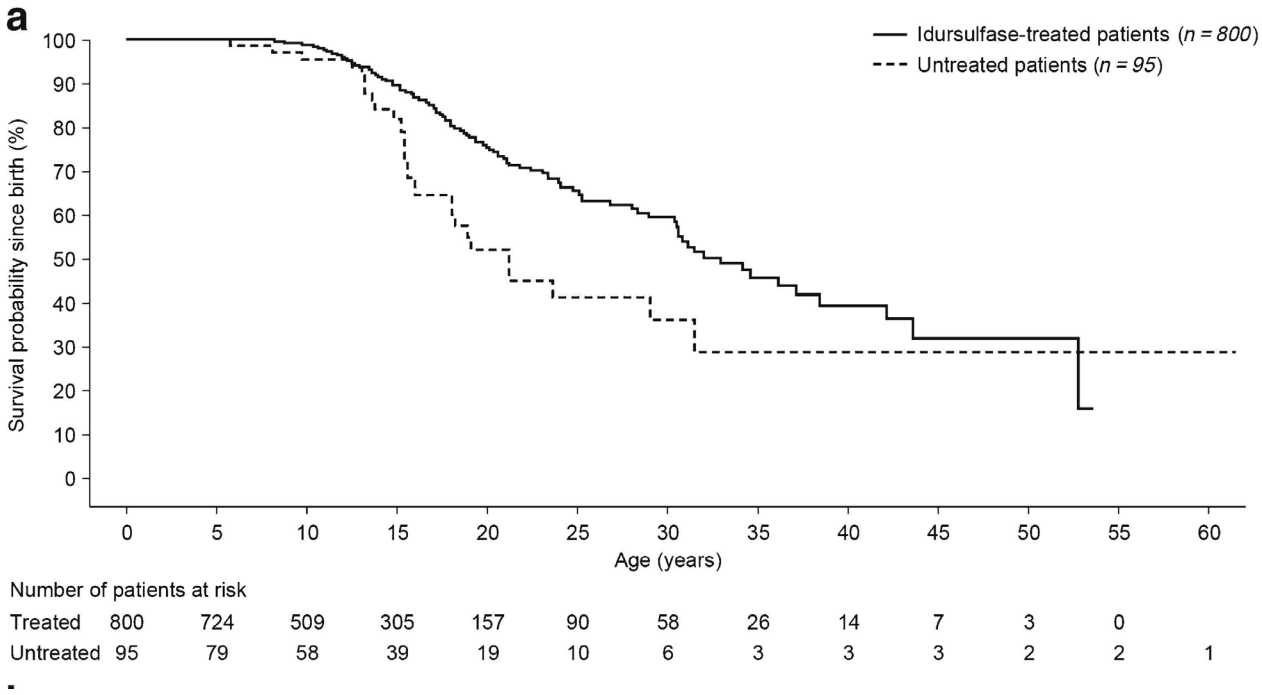
System affected	Sign or symptom	Median age at onset (10th, 90th percentile) in years	N patients (%)
Pulmonary	upper respiratory tract infections, obstructive airway disease, otitis media, sleep apnea, mechanical ventilation or oxygen dependency	2.7 (0.1, 13.4)	86 (70.0)
Central Nervous System	cognitive and developmental delay, behavior problems, hyperactivity, frequent chewing, hydrocephalus, seizure disorder (severe MPS II)	3.3 (0.1, 11.5)	58 (46.8)
Skeletal/muscular	hip dysplasia, joint disorders, kyphosis/scoliosis, restricted range of motion	3.5 (0.9, 8.6)	98 (79.0)
Cardiovascular	valve disease, heart murmur, bradycardia, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure, hypertension, angina, infarction, peripheral vascular disease, abnormal heartbeat frequency	5.6 (1.7, 14.2)	108 (87.1)
Peripheral Nervous System	Carpal tunnel syndrome, fine motor skill impairment, abnormal reflexes	5.7 (1.7, 14.2)	60 (48.4)

Link et al. 2010. Orthopedic *manifestations in patients with mucopolysaccharidosis type II (Hunter syndrome) enrolled in the Hunter Outcome Survey. Orthopedic reviews.*

Wide Range of Treatment Outcome Measures

- Mortality
- **Respiratory failure**
- **Cardiac involvement (e.g., ventricular wall hypertrophy, cardiac function)**
- **Liver volume**
- **Spleen volume**
- **Development** (cognitive, gross motor, fine motor)
- **Ability to ambulate and endurance**
- Joint mobility
- Sleep apnea
- Growth (height, weight, head circumference)
- Quality of life/*toileting abilities*
- **Physical features**
- **Urinary GAG level**

Unadjusted Risk of Survival



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3-Year Follow-up of twins, one with MPS II treated presymptomatically

- ERT at 3 months of age
- Normal ranges of movement for most joints
- Normal cardiac valves
- Normal facial appearance
- IQ: 98 (MPS II) vs. 118
- Mild deformity of one vertebrae
- Older sister
  - IQ 24 at age 7.5 years (down from 50 at 3 years), other findings consistent with MPS II

Tylki-Szymanska et al. Acta Paediatr. 2012;101:e42-47.

At 9 years…..(abstract only)

- No evident findings of MPS II
- Minor restriction of movement at the hip
- IQ: 104 (MPS II) vs.121

Tylki-Szymanska et al. *Journal of Inherited Metabolic Disease*. 2016;39:S275.

Muenzer et al. Evaluation of the long-term treatment effects of intravenous idursulfase in patients with MPS II using statistical modeling: data from the Hunter Outcome Study (HOS). *Orphanet J Rare Dis*. 2021;16:456.

- Inclusion criteria
  - Male patients with MPS II
  - IV idursulfase for ≥5 years
  - Data from at least two time points (1 after ERT)
  - No transplant and no previous clinical trial for ERT
- Categorized by age at ERT:
  - 0-<18 months
  - 18 months-<5 years
  - ≥5 years
- Evaluated out to 8 years
- Outcome measures:
  - Urine GAG levels
  - Left ventricular mass index (LVMI)
  - Palpable liver size
  - FVC/FEV_1 for subjects at least 5 years of age and no cognitive impairment at any time
  - 6MWT for subjects at least 5 years of age and no cognitive impairment any time

Study Population

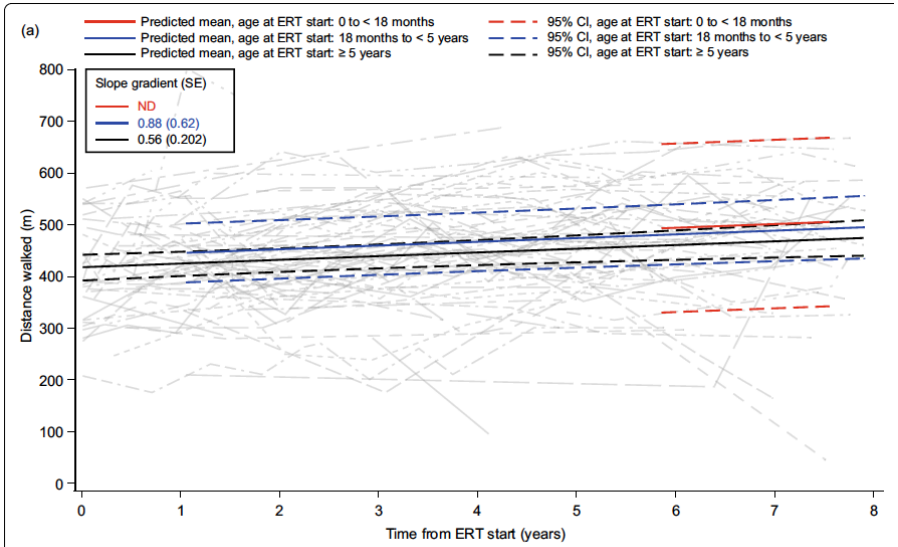
- 481 subjects
  - Symptom onset: Median - 1.5 years
  - ERT: Median – 5 years
  - Cognitive Impairment at any time: 67%

Results

- Urine GAG levels (n=180) and palpable liver size (n=413) decreased within a similar range regardless of age category at which ERT began
- FVC/FEV_1 (n=84/n=83) decreased slightly after 5 years for those without cognitive impairment with “trends…similar across all ages at treatment start”
- LVMI (n=250) “remained stable for up to 8 years post-ERT start in all age groups, with decreases of approximately 1 g/m^2 at 8 years post-ERT compared with baseline across all ages at treatment start…”

6-Minute Walk Test

(a)



(b)

	Predicted mean value (95% CI), m			
	Pre-ERT		8 years post-treatment start	
Age at ERT start	Main analysis (n = 76)	Internal validation (n = 42)	Main analysis (n = 76)	Internal validation (n = 42)
0 to < 18 months	NA	NA	507.3 (344.5, 670.1)	ND
18 months to < 5 years	NA	NA	494.7 (434.1, 555.2)	519.2 (451.5, 586.9)
≥ 5 years	416.1 (391.2, 440.9)	409.5 (381.7, 437.4)	473.9 (439.4, 508.4)	485.3 (446.0, 524.6)

- n=76; Not cognitively impaired
- Values not modeled until subjects were 5 years of age if ERT began <5 years
- Point estimates for the mean walking distance at 8 years post-ERT start was greater for patients 0 to <18 months at ERT start, with substantial overlap in the confidence intervals
  - 12.6m greater than 18 months-<5 years
  - 33.1m compared to ≥5 years

Limitations

- Findings do not demonstrate a statistically significant difference by age at ERT initiation
- Limited ability to conduct statistical inference testing
- Variability in the timing and number of measures per subject
- Incomplete data
- Risk of confounding
- Serial cross-sectional analysis
- Outcomes based on time since ERT initiation, not absolute age
- Unclear what led to the diagnosis

Gray Literature: 3 Siblings

	Oldest brother	Middle brother	Youngest brother
Age at DX	6 years	2 ½ years	0 (prenatally)
Age at Treatment	ERT "for" 4 years	ERT at 2 ½ years	ERT at 4 months Cord blood transplant at 10 months
Current Age	13	11	2 ½
Clinical history	- Significant disease progression	- Milder non-CNS involvement. - Significant cognitive impairment - Slower disease progression	- Developmental milestone gains - Significantly slower disease progression

Bivina & Boyadjiev (2014). *Molecular Gen and Metabolism*, 111, 2: S27

Grey Literature: GAGs

- GAG markers for pseudodeficiency are lower than those associated with MPS II (60 random dried-blood spots, 6 with pseudodeficiency, 18 with MPS II, 19 with MPS I (report submitted for peer review by Michael Gelb, PhD, University of Washington)

Novel Therapies

- Pabinafsup alfa (Izcargo): ERT that uses the transferrin receptor to cross the blood-brain barrier; approved in Japan with clinical trials underway in the US
- ETV:IDS (DNL310): Similar product to above, phase 1-2 clinical trials underway and has been granted FDA fast-track designation
- RGX-121: AAV gene therapy delivered intracisternally, phase 1-2 clinical trials underway and has been granted FDA fast-track designation
- Intrathecal idursulfase

Illinois Experience

- From December 2017-May 2021
  - ~559K specimens from ~473K newborns
    - Screen Positives: 63
      - Severe/Classical: 2
      - Affected: 6
      - Variants of Unknown Significance: 8
    - Pseudodeficiency: 30
    - Normal: 9
    - Lost to follow-up: 1
    - Parent Refused Further Testing: 1
    - Pending Final Close-Out: 6

Missouri Experience

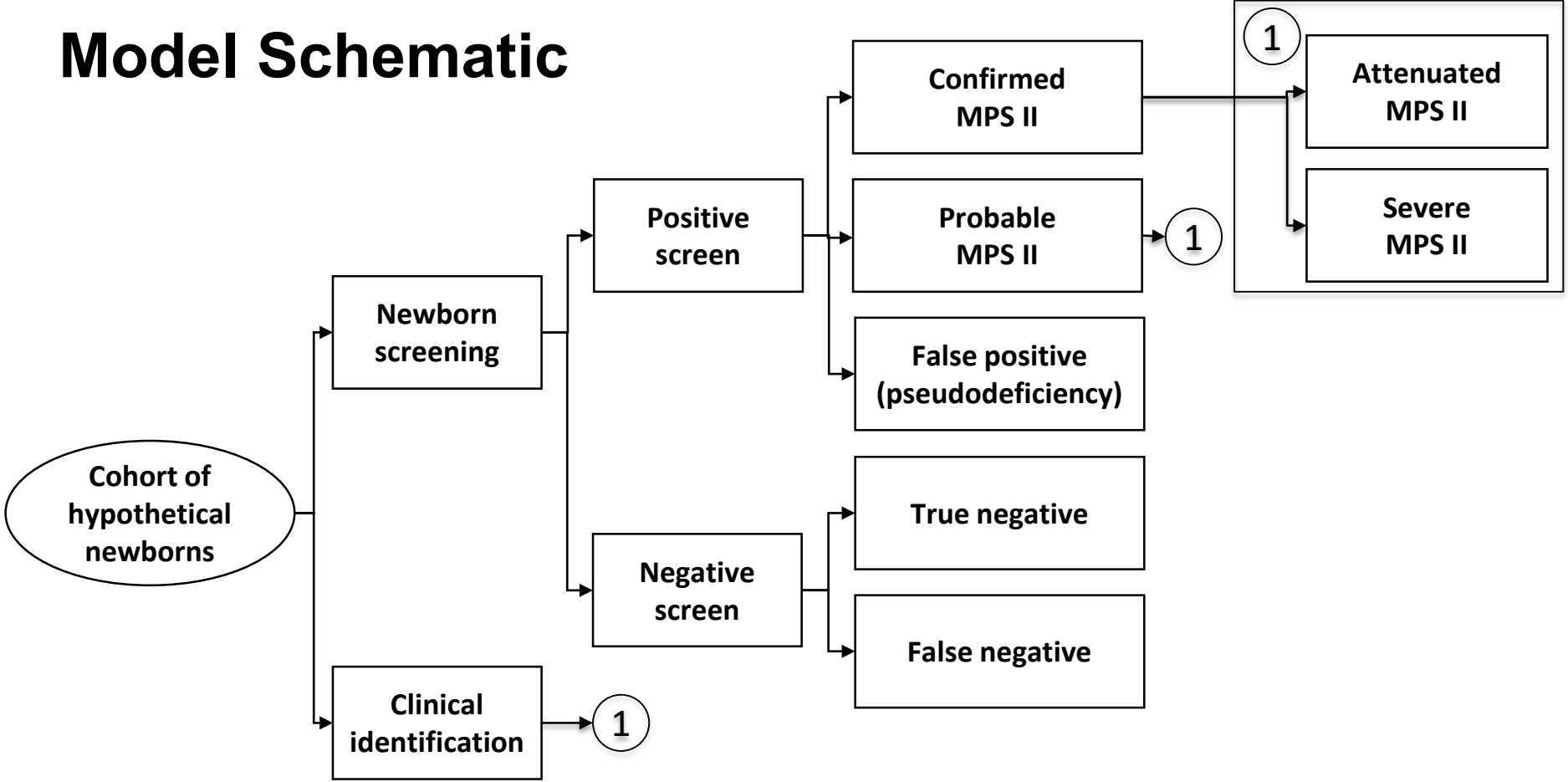
- From November 2018 – June 2021
  - ~233K specimens and ~200,000 newborns
    - Screen Positives: 28
      - Severe: 3
      - Variants of Unknown Significance: 9
    - Pseudodeficiency: 3
    - Normal: 7
    - Loss to follow-up: 1
    - Parent refused further testing: 1
    - Pending Final Close-Out: 4

Summary of Screening Results

- Referral Rates
  - Illinois: ~13/100,000 live births
  - Missouri: ~14/100,000 live births
- MPS II Cases Identified
  - Illinois: ~1.7/100,000 live births
  - Missouri: ~1.5/100,000 live births

Update on Decision-Analytic Modeling

Model Schematic



Population health outcomes

- Screening outcomes
  - Positive screens
  - Cases identified
- Insufficient evidence to model longer-term outcomes
  - Heterogeneity of outcome measures
  - Continuous progression of disease
  - Absence of key markers of progression

Next Steps

- Systematic review of clinical trials
- Review of study designs from previous condition reviews
- Discussion with TEP
- Anticipated findings
  - Proposed health outcomes for future modeling
  - Potential study designs (HOS)

Update on Public Health System Impact

- Survey: September 20-October 25
  - Following webinar and fact sheet distribution
- Newborn Screening Program Interviews
  - Illinois
  - Missouri
  - New York (pending)
  - Other states that might be doing a pilot and 2-4 additional

Update on Cost Assessment

- Start-up costs
  - Planning, hiring staff, LIMS, training space, equipment, etc.
- Operating costs
  - Lab staff, reagents, equipment rental or depreciation, supplies, utilities, follow-up staff, second tier testing, etc.
- Costs will vary by program, platform and assay, number of annual births
- Estimated range $1-6

Next Steps

- Complete evidence synthesis
  - Will close the literature search 30 days before the report deadline
  - Focus on treatment impact following earlier identification.
    - This will be a key consideration
    - At least one additional abstract has been submitted to a national meeting with sibling data
  - Model screening outcomes based on the available evidence
- Complete the PHSI assessment and cost evaluation