Newborn Screening for Mucopolysaccharidosis Type II: First Interim Report from the Evidence Review Group

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Timeline

- Nomination Approved for Evidence Review
  - May 2021
- Interim Presentations
  - August 2021
  - November 2021
- Final Presentation
  - January 2022

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) – dermatan sulfate and heparan sulfate
- >500 mutations in the *IDS* gene (Xq28)
  - Many private mutations
- Clinical-detected prevalence: 0.2-2.5 per 100,000 live births
- Screening ranges
  - Illinois: ~0.88/100,000 live births
  - Missouri: ~1.37/100,000 live births

MPS II: Overview

- Classification
  - Severe vs. Attenuated
  - Neuronopathic vs. Non-Neuronopathic
- Affected individuals can have variable phenotypic expression across these dimensions
- Key Points
  - Attenuated ≠ Benign
  - Non-Neuronopathic ≠ No Neurologic Involvement

MPS II: Overview

- Severe
  - Progressive multiorgan and joint involvement
  - Cognitive impairment and regression
  - Diagnosis typical in early childhood (18-36 months)
  - Death in the teens or 20s
  - Most (2/3) cases estimated to be “Severe” based on clinically detected cases
- Attenuated
  - Later diagnosis
  - Progressive multiorgan involvement
  - Can live into early adulthood; later death because there is not the CNS comorbidity
- Key point: Wide spectrum is possible
- Pseudodeficiency
  - Not associated with morbidity or mortality
  - Can be identified early to avoid the risk of unnecessary treatment
- Phenotype is not typically predictable at the time of diagnosis
  - Affected siblings have similar phenotype
  - 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

- Two approaches for assays to measure enzyme activity
  - MS/MS assay multiplexed with other non-MPS II markers (e.g., for other lysosomal storage disorders)
    - UPLC with MS/MS (Scott CR et al. Newborn screening for mucopolysaccharidoses: results of a pilot study with 100 000 dried blood spots. *J Pediatr*. 2020;216:204-207)
  - Microplate fluorometric assay, not multiplexed
  - Seems to be clear separation between positive and negative screens
- After a positive screen
  - Confirm enzyme activity, GAG measurement, sequencing of *IDS* gene can be helpful
  - Rule out Multiple Sulfatase Deficiency by measuring another sulfatase

MPS II: Treatment

- Enzyme Replacement Therapy – Idursulfase
  - FDA approved: 2006
  - Standard therapy - administered weekly (IV)
  - Infusion can take hours
  - Does not cross the blood-brain barrier
  - Risk of developing anti-idursulfase antibodies
  - Infusion-related side effects (rash, angioedema, bronchoconstriction, etc.)
  - Evaluation of intrathecal administration is underway
  - Cost of ERT and administration is hundreds of thousands of dollars per year
- Hematopoietic Stem Cell Transplantation (HSCT)
  - After ERT was approved, this approach fell out of favor due to risk of mortality and lack of clear neurodevelopmental benefit (in contrast to HSCT for MPS I)
  - However, some families might be interested in this approach. For example, HSCT could avoid the need for weekly infusions of ERT
- New therapies being investigated, including gene therapy

Idursulfase

- Clinical experts recommend beginning therapy as soon as possible after diagnosis
- Idursulfase was approved ~15 years ago, based on studies of primarily clinically detected subjects.
- Because of the limited data at the time of approval, the drug label states: “In patients 16 months to 5 year old, ELAPRASE did not show improvement in disease-related symptoms or long term clinical result; however, treatment with ELAPRASE has reduced spleen size similarly to patients 5 years and older. It is not known if ELAPRASE is safe and effective in children under 16 months old.”
- Since then, post-marketing studies, additional observational studies, and significant clinical experience has accumulated

Idursulfase

- The Technical Expert Panel pointed out that there is a lack of equipoise for randomized, placebo-controlled trials of idursulfase
  - Treatment after GAGs have accumulated will not reverse tissue damage
  - Development of meaningful outcomes takes longer than the duration of typical clinical trials
  - Post-marketing studies support the safety of pre-symptomatic treatment
- Beyond the concern about equipoise, enrolling subjects for early treatment with idursulfase or other novel therapies in the absence of screening is a significant barrier

Safety of Idursulfase in Younger Subjects

- 28 subjects, 1.4-7.4 years (mean age 4), in a phase IV open-label study over 1 year
- Adverse Events
  - 1 was discontinued to to “lack of compliance”
  - 19 (68%) anti-idursulfase IgG antibodies, which could impact the efficacy of therapy
  - 16 (46%) with infusion-related adverse events

- Citation: Giugliani R et al. A multicenter, open-label study evaluating safety and clinical outcomes in children (1.4-7.5 years) with Hunter syndrome receiving idursulfase enzyme replacement therapy. *Genet Med*. 2014;16:435-441.

Idursulfase Treatment

- Sibling studies
  - ERT at 3 years vs. 4 months of age
  - After ~30 months, differences in facial appearance, joint stiffness and hepatosplenomegaly; both with intellectual disability but differentially impacted (DQ: 42 vs. 74)

Treatment at 3 years

Treatment at 4 months

  - Citation: Tajima G, et al. Effects of idursulfase enzyme replacement therapy for Mucopolysaccharidosis type II when started in early infancy: comparison in two siblings. *Mol Gen Metab.* 2013;108:172-177.

Important Sources of Data

- Hunter Outcome Survey
  - Natural history and treatment study
  - >1000 patients
  - Includes a parent or patient-reported functional outcomes survey
  - Supported by Shire Human Genetic Therapies, Inc.
- State screening data – only two states screen for MPS II
  - Missouri (2018)
  - Illinois (2017)
- Other US newborn screening
  - ScreenPlus – Research study with consent in New York
- Screening outside of the US
  - Taiwan (2015)
- Open-label and other uncontrolled trials of idursulfase

Missouri

- Full population screening since 2018
- Benchtop fluorometric test
- In the first-tier assay, positive screens seem to be clearly separated from negative
- About 2 hours to prepare the samples and read the plates, with 3-4 hours to run the assay
- Unit screening cost for MPS II is ~$5, including staff time, equipment and overhead (working now to better understand cost assessment)
- GAG testing (send-out) prior to specialty referral
- Molecular second-tier testing was not particularly helpful

Missouri

- Not multiplexed
- First-Tier: IDS Activity
- Second-Tier: GAGs (Mayo)
- Then referral

Missouri

- In 2020, 86,072 screened, 20 with pseudodeficiency prior to referral and another 12 referred (potential 14/100,000 cases): MORE TO COME
- No affected females have been identified

Illinois

- Screening began in 2017
- Screening is multiplexed using UPLC and MS/MS with testing for other lysosomal storage disorders (MPS I, Fabry, Gaucher, Krabbe, Pompe, Niemann-Pick)
  - Incubation separate for MPS II
- GAG testing not done by the NBS program

Illinois

- Separate punch and extraction, with an incubation time of 17 hours
- Analysis is multiplexed with other lysosomal storage disorders
- Referral (prior to GAG testing)

Illinois

- By end of May 2021, 558,498 specimens, 72 positive, 23 of which were due to pseudodeficiency (32%) – leaving 8.8/100,000 potential cases. MORE TO COME
- No affected females have been identified

Systematic Evidence Review

- >4000 articles identified

1. What is the natural history and epidemiology of MPS II?
2. What is the analytic or clinical validity of newborn screening for MPS II?
3. What are the harms associated with screening for MPS II?
4. What are the benefits and harms of MPS II presymptomatic or early treatment compared to when MPS II is usually identified? How often do individuals or families decide to stop ERT? What is the interest in HSCT?

- There are likely to be important questions around benefits and harms of early identification. We are working with the TEP to identify relevant grey literature.

Treatment Outcomes of Interest

- 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
- Physical features
- Urinary GAG level

*Standard Outcomes

Next Steps

- Complete the evidence review
- Planning underway for the Public Health System Impact Assessment and modeling of the population health impact of screening
  - PHSI webinar planned for mid-September
- Complete the cost assessment, with a focus on ranges

Questions