Nomination and Prioritization Workgroup Report: Mucopolysaccharidosis II (Hunter Syndrome, MPS II)

Advisory Committee on Heritable Disorders in Newborns and Children

Presented by: Scott Shone, PhD, HCLD(ABB)

May 13, 2021

N&P WG: Jeffrey Brosco, Carla Cuthbert, Shawn McCandless, Cynthia Powell, Scott Shone

Nomination of Mucopolysaccharidosis II (Hunter Syndrome, MPS II)

Nominator

- Terri L. Klein, NPGC, President, National MPS Society
- N. Matthew Ellinwood, DVM, PhD, Chief Scientific Officer, National MPS Society

Co-Sponsors

- Barbara K. Burton, MD, Department of Pediatrics, Northwestern U
- Michael H. Gelb, PhD, Department of Chemistry, University of Washington
- Priya Kishnani, MD, Department of Pediatrics, Duke University
- Joseph Muenzer, MD, PhD, University of North Carolina at Chapel Hill
- C. Ronald Scott, MD, Departments of Pediatrics, University of Washington
- Bradford Therrell, PhD, Departments of Pediatrics, University of Texas

Mucopolysaccharidosis II (MPS II) Overview[1]

- Lysosomal Storage Disorder
- Progressive, multi-organ disease
- Onset ranges from approx. 1 year of age to early adolescence
  - attenuated and severe phenotypes
  - significant somatic symptoms (both)
  - profound cognitive impairment and developmental regression (severe)
    - death in second decade of life
  - somatic symptoms without significant cognitive involvement (attenuated)
    - survival into adulthood with some premature mortality

Genetics and Epidemiology of Mucopolysaccharidosis II (MPS II)

- X-linked recessive inheritance, clinical heterogeneity with two primary phenotypes: attenuated and severe
- Deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of dermatan sulfate and heparan sulfate[1]
- Incidence in US is not known. “In reality, newborn screening will determine the incidence of MPS II in the US.”
  - Estimate 0.13 to 2.16 per 100,000[2,3]
  - Illinois pilot[4]: 1 in 113,000, Missouri pilot[5]: 1 in 73,000
- Females with MPS II are rare, but typically severe phenotype
  - Carriers are generally asymptomatic[1,2]
- More than 400 disease causing variants in *IDS* locus (Xq28) described in ClinVar
  - Variable genotype-phenotype correlation

Core Requirements for Nomination

1. Validation of the laboratory test
2. Widely available confirmatory testing with a sensitive and specific diagnostic test
3. A prospective population-based pilot study

Key Questions

- Is the nominated condition(s) ***medically serious***?
- Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
- Are ***prospective pilot data*** from population-based assessments available for this disorder?
- Does the screening test(s) have established ***analytic validity***?
- Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
- Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process?
- Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?
- Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

Is the nominated condition(s) ***medically serious***?

Yes

- Despite range of phenotypes, MPS II is a progressive multi-organ disorder.
  - All forms have somatic implications including skeleton, joints, heart, upper and lower airways, hearing, eyes
  - Severe form impacts central nervous system
- Left untreated, patients with the severe form survive until only the second decade of life. Patients with the attenuated form may survive until the fifth or sixth decade of life[6].

Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.

Unclear

- Prior to onset of symptoms, it is not always possible to predict the severity of the phenotype or cognitive involvement
- Many patients have rare or private mutations in the *IDS* gene for which no pre-existent phenotypic information is available[7,8]
- A complete gene deletion or large rearrangement results in severe phenotype[1,6]
- Routine diagnostic assays that measure the activity of I2S cannot distinguish between severe and attenuated MPS II patients.

Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

Yes

- Pilot study 1: Illinois, mandated full-population screening began December 11, 2017
  - 339,269 infants screened as of February 2020[4]
  - 3 positive diagnoses confirmed by urine GAGs and molecular analysis
  - 28 false positives (includes pseudo-deficiency)
- Pilot study 2: Missouri, mandated full-population screening began November 1, 2018
  - 146,954 infants were screened as of June 30, 2020[5]
  - 2 positive diagnosis confirmed by urine GAGs and molecular analysis
  - 27 false positives (includes pseudo-deficiency)

Does the screening test(s) have established ***analytic validity***?

Yes

- Tandem Mass Spectrometry (MS/MS: FIA or LC) and Digital Microfluidics (DMF)
  - Neither FDA-cleared
- MS/MS and DMF
  - Sufficient data provided
    - Limit of detection
    - Recovery
    - Linearity
    - Accuracy
    - Precision
    - Interferences
    - Reference ranges
- Data provided demonstrate both methods have acceptable analytic validity

Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

Yes

- Laboratory developed test
- Can multiplex with other analytes for LSD screening
- False positive rate similar to other first-tier assays for current RUSP conditions
  - Illinois (MS/MS): 339,269 screened, 31 screen positive, 3 confirmed
  - Missouri (DMF): 146,954 screened, 29 screen positive, 2 confirmed
  - Second-tier/Third-tier tests ideal
    - Sequencing *IDS*
    - DBS heparan sulfate and dermatan sulfate (insufficient data currently)
- False negative rate unknown (none identified in pilot studies)
- Other disorder detected: multiple sulfatase deficiency

Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process?

Yes

- No FDA cleared tests for MPS II
- Quantitative demonstration of deficient I2S activity in combination with a quantified elevation of urinary dermatan and heparan sulfates
  - second sulfatase is quantitatively assayed in plasma or white blood cells to rule out multiple sulfatase deficiency
- Sequencing of the *IDS* gene
  - Not diagnostic, helpful to predict phenotype
- Selected CLIA laboratories performing confirmatory tests
  - Mayo Clinic-Rochester
  - Greenwood Genetic Center
  - PerkinElmer Genetics
  - University of Illinois at Chicago Biochemical Genetics Laboratory
  - Duke University Biochemical Genetics Laboratory

Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

Yes

- Two available therapies
  - Enzyme replacement therapy (ERT) with IV recombinant human I2S
  - Hematopoietic Stem Cell Transplantation (HSCT)
- ERT
  - Standard of care
  - Weekly IV infusions with idursulfase (FDA approved in 2006)
  - Does not cross blood-brain barrier and does not alter CNS disease
- HSCT
  - Infrequently used
  - Limited data on somatic and CNS improvement

Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Unclear

- Considerable clinical heterogeneity in the onset and rate of disease progression, but early intervention is important
- Screening does not clearly predict phenotype
  - Most serious phenotypes may be identified by sequencing
- Treatment can prevent somatic disease progression, but not reverse disease
- Impact of treatment on CNS remains unclear

Key Questions - Summary

- Is the nominated condition(s) ***medically serious***? **YES**
- Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening? **UNCLEAR**
- Are ***prospective pilot data*** from population-based assessments available for this disorder? **YES**
- Does the screening test(s) have established ***analytic validity***? **YES**
- Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)? **YES**
- Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process? **YES**
- Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky? **UNCLEAR**
- Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available? **YES**

Nomination and Prioritization Workgroup Recommendation

The Advisory Committee should move the nomination of Mucopolysaccharidosis II (Hunter Syndrome, MPS II) forward for a full evidence review.

References

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