Newborn Screening for MPS I Disease: Condition Review Update

Alex R. Kemper, MD, MPH, MS
September 20, 2013
## Condition Review Workgroup (CRW)

<table>
<thead>
<tr>
<th>CRW Members</th>
<th>Role</th>
<th>Institution</th>
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<tbody>
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Condition Review Workgroup Updates

• Revised Conceptual Framework of NBS Impact

• MPS I Condition Review
  – Technical Expert Panel
  – Teleconference 1 to Refine Scope of Review
    • Case Definition
    • Newborn Screening & Diagnosis Procedures
    • Key Questions
    • Key Sources of Information
  – Developed Evidence Review Protocol
  – Conducted Initial Systematic Literature Search
The Model Formerly Known As…

Figure 1. Analytic Framework for the Systematic Evidence Review

- KQ 1
- KQ 2
- KQ 3
- KQ 4
- KQ 5
- KQ 6
- KQ 7
- KQ 8

Early Detection of the Targeted Condition → KQ 4 → Intermediate Outcome → KQ 6 → Health Outcomes

Adverse Effects of Screening → KQ 7

Adverse Effects of Treatment → KQ 8
(Old) Key Questions

KQ1: What is the life course and spectrum of disease related to the condition?

KQ2: What is the direct evidence that screening for the condition improves health outcomes?

KQ3: What is the analytic validity and clinical validity of the screening test or algorithm and the diagnostic test?

KQ4: Are treatments available that make a difference in intermediate outcomes when the condition is caught early?

KQ5: Are treatments available that make a difference in health outcomes when the condition is caught early?

KQ6: How strong is the association between intermediate outcomes and health outcomes?

KQ7: What are the harms associated with screening?

KQ8: What are the harms associated with treatment?
Conceptual Framework of NBS Impact-\textit{Revised}

- Goal to ensure comprehensive consideration of all key aspects of benefits and harms
- Key topic questions (KTQs) are groupings of relevant questions
- Integrates across the three report types (evidence review, modeling of expected benefit and harm, assessment of public health system)
Conceptual Framework: Effects of NBS for MPS I

1. Usual Care
   - Undiagnosed

2. Newborn Screening
   - Positive Screen
   - Negative Screen

3. Diagnosis
   - Short-term Follow-up

4. Screening & Short-term Follow-up: Net Benefits & Harms

5. Treatment & Long-term Follow-up
   - Diagnosed

6. Intermediate Measures
7. Primary Health Outcomes
8. Secondary Outcomes
   - Population
   - Healthcare Service System -- Public and Private

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PUBLIC HEALTH – NEWBORN SCREENING PROGRAMS & LABORATORIES

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Key Topic Questions

1. Usual Care and Course
2. Screening and Short-Term Follow-Up
3. Diagnosis
4. Benefits & Harms - Screening & Diagnosis (*unrelated to treatment*)
5. Treatment and Long-Term Follow-up
6. Intermediate Outcome Measures
7. Primary Health Outcomes (Patient)
8. Secondary Outcomes (Patient, Caregivers)
9. Benefits & Harms - Treatment & Long-Term Follow-up
10. Health Care System
KTQ 1: Usual Care and Course

- What is the incidence of clinically detected MPS I in the United States?
- What is the distribution of MPS I forms?
- What is the incidence of pseudodeficiency?
- What is the average age of symptom onset, diagnosis, and treatment initiation for each form of MPS 1?
KTQ 2: Screening and Short-Term Follow Up

- What analytic markers are associated with MPS I that can be used in population-based screening?
- What screening tests can be used to find these markers?
- What is the analytic validity of the screening tests for MPS I? If the marker is present in dried-blood spots, will it be found?
- What is the clinical validity of available screening test algorithms in dried-blood spots?
- If a screening test is positive, how likely is it the child has MPS I (e.g., what is the expected “positive predictive value” [PPV] in newborn screening)?
- Are those most likely to benefit from early treatment identified by screening?
- Can screening predict the form of MPS 1, carrier status, or pseudodeficiency?
- Has the screening test algorithm been evaluated prospectively to generate an understanding of the likely numbers and types of screening results?
- Is there a method of MPS I screening quality assurance and proficiency testing available for screening laboratories?
KTQ 3: Diagnosis

- What is the case definition?
- What approaches are available to diagnose MPS I in newborns? What approaches are available to diagnose MPS I in older children?
- How are each of the forms of MPS I identified? How is carrier status identified? How is pseudodeficiency identified? Is there agreement on the diagnostic approaches? Are there quality assurance programs available for, for example, proficiency testing of diagnostic laboratories?
- How long does it take to establish the diagnosis? How long does it take to rule out the diagnosis?
- What other specific factors that may affect treatment plans or outcomes must be evaluated during the diagnostic period?
KTQ 4: Benefits & Harms of Screening and Diagnosis *(unrelated to treatment)*

- What benefits to the child or the family are associated with presymptomatic identification of MPS I independent of the timing of treatment?
- To what extent does newborn screening change the observed incidence or spectrum of MPS I compared to clinical detection?
- What physical and psychosocial harms are associated with other screening outcomes?
  - false-negative newborn screen for MPS I?
  - false-positive newborn screen for MPS I (i.e., unaffected with MPS I and has a positive screen)?
  - MPS I carrier status?
  - Pseudodeficiency?
- Does screening for MPS I detect other conditions?
- What harms are associated with diagnosis and diagnostic process of each form of MPS I when detected through newborn screening (i.e., severe and attenuated forms)?
- What strategies can minimize these harms?
KTQ 5: Treatment and Long-Term Follow-up

– What are the standard of care treatment strategies for each form of MPS I?
– What clinical guidelines are available for long-term follow-up of each form of MPS I?
KTQ 6: Intermediate Outcome Measures

- What intermediate or proximal outcome measures, biomarkers (e.g., urine GAGs) or functional tests (e.g., echocardiograms, neurodevelopmental tests), can be used to monitor and evaluate the status of MPS I?

- Do interventions for MPS I detected through newborn screening lead to improvement in intermediate measures compared to clinical detection?

- Other than age of initiation, what other factors modify the effect of treatment on intermediate measures?
KTQ 7: Primary Health Outcomes

– What are the most important primary health outcomes related to treatment of each form of MPS I identified by
  • usual care?
  • newborn screening?

– Other than age of initiation, what factors modify the effect of treatment on primary health outcomes?

– How strongly are the intermediate measures associated with primary outcomes? Do the intermediate measures predict the time course of primary health outcomes?

– What influences the association between intermediate measures and primary outcomes?
KTQ 8: Secondary Outcomes

– What is the quality of life over time associated with the different forms of MPS I when identified through
  • usual care?
  • newborn screening?

– What are the family or caregiver impacts over time associated with different forms of MPS I when identified through
  • usual care?
  • newborn screening?
KTQ 9: Benefits & Harms—Treatment & Long-Term Follow-up

– Do interventions for MPS I detected through newborn screening lead to
  • improvements in primary or secondary outcomes compared to clinical detection (benefits) [e.g., delay or prevent]?
  • worsening of primary or secondary outcomes compared to clinical detection (harms) [e.g., hasten or precipitate]?

– Are there strategies that can improve these benefits or decrease or delay these harms?

– To what degree does improvement in a primary or secondary outcome for MPS I lead to another outcome that may be considered a harm?
KTQ 10: Health Care System

How many newborns are projected to be affected by newborn screening for MPS I (and may require short- or long-term follow-up services for any MPS I form)?

- True and false positive cases?
- True and false negative cases?

What resources are required to ensure readiness and feasibility of states’ NBS programs to adopt screening and follow-up services for MPS I?

What resources are required to ensure capacity of health service delivery system for short- or long-term follow-up resulting from expanded newborn screening (diagnosis, treatment, follow up)?

What is the availability and accessibility of these required screening, diagnostic and treatment resources?
Conceptual Framework: Effects of NBS for MPS I

1. Usual Care

2. Newborn Screening
   - Positive Screen
   - Negative Screen

3. Diagnosis
4. Screening & Short-Term Follow-Up: Net Benefits & Harms

5. Treatment & Long-Term Follow-Up
   - Intermediate Measures
   - Primary Health Outcomes
   - Secondary Outcomes

6. Undiagnosed
7. Diagnosed
8. Short-Term Follow-Up
9. Long-Term Follow-Up
10. Health Care System

Public Health – Newborn Screening Programs & Laboratories
Population
Health Care Service System -- Public and Private
# MPS I Technical Expert Panel (TEP)

<table>
<thead>
<tr>
<th>TEP Members</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Barbara K. Burton, MD</td>
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<td>Joseph Muenzer, MD, PhD</td>
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<td>Barbara Wedehase, MSW, CGC</td>
<td>National MPS Society</td>
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(MPS I lead nominator)
Technical Expert Panel Teleconference 1
Sept 9, 2013

Aims

• Refine case definition
• Delineate usual care screening, diagnosis process
• Review current standard-of-care treatments and clinical management guidelines -- major benefits, limits, harms
• Identify key informants, sources of information, and emerging clinical research areas
MPS I: Case Definition

- Autosomal recessive lysosomal storage disorder (LSD) caused by deficiency of enzyme $\alpha$-L-iduronidase (IDUA)
- Progressive, multisystem disorder
- Traditionally classified into three syndromes
  - Hurler; Hurler-Scheie; Scheie
  - However, symptoms suggest spectrum of disease severity
- Current characterizations reflect presentation, severity, and treatment options:
  - Severe (Hurler)
  - Attenuated Forms (Hurler-Scheie; Scheie)
Severe MPS I

- Infants appear normal at birth, onset in first year.
- Rapidly progressing
- Central nervous system (CNS) involvement
- Severe cognitive deficits
- Progressive skeletal dysplasia involving all bones

### Typical Natural Course

<table>
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<tr>
<th>Age</th>
<th>Symptom Presentation</th>
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<tr>
<td>&lt; 1 year</td>
<td>Non-specific manifestations (hernia, respiratory infections)</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>Facial features coarsen&lt;br&gt;Lower spine deformity</td>
</tr>
<tr>
<td>&gt; 3 years</td>
<td>Linear growth stops&lt;br&gt;Progressive and profound intellectual disability&lt;br&gt;Hearing loss</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>Death due to cardiorespiratory failure, neurodegeneration</td>
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</table>
Attenuated MPS I

- Heterogeneous disease presentation, onset, and severity
- Symptom onset usually before age 5 years.
- Slower and more variable progression than Severe MPS I
- Multisystem disease manifestations similar to Severe MPS I, though more variable presentation.
  - Variable CNS/neurologic involvement
  - Cognitive deficits/learning disabilities
  - Hearing loss, cardiac valvular disease, joint manifestations
    ➢ Difficult to diagnose
- Life span ranges from 20 – 30s to normal life span
Estimated Birth Prevalence

- Sample: 106,526 anonymous DBS from CA
- Cannot distinguish form (i.e., severe vs. attenuated)
- Not the same as population epidemiology

<table>
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<tr>
<th>MPS I Screening Results</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
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<tbody>
<tr>
<td>Estimated Prevalence</td>
<td>1 in 35,700</td>
<td>1/11,100 – 1/143,000</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.33</td>
<td>0.08 – 0.65</td>
</tr>
<tr>
<td>3 MPS I “True Positives”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Positives</td>
<td>1 in 17,750</td>
<td>1/7,250 – 1/31,900</td>
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<tr>
<td>6 “False-Positives”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1 carrier</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 2 poor punch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 3 low IDUA, normal alleles</td>
<td></td>
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Scott et al., 2013
Table 1. Median years of age (range) of onset, diagnosis, and death for MPS I Registry patients [N=891].

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<thead>
<tr>
<th></th>
<th>Total number [#] (%)</th>
<th>Onset</th>
<th>Diagnosis</th>
<th>Treatment Initiation</th>
<th>Death [# (%)]</th>
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<tbody>
<tr>
<td>Severe MPS I</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(Hurler)</td>
<td>[508] (57)</td>
<td>0.5</td>
<td>0.8</td>
<td>1.4</td>
<td>3.8</td>
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<td></td>
<td></td>
<td>(0-6.5)</td>
<td>(0-23.8)</td>
<td>(0.1-31.2)</td>
<td>(0.4-27.2)</td>
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<tr>
<td></td>
<td></td>
<td>[485]</td>
<td>[508]</td>
<td>[438]</td>
<td>[156 (30.7)]</td>
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<tr>
<td>Attenuated MPS I</td>
<td></td>
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<tr>
<td>(Hurler-Scheie)</td>
<td>[209] (23.5)</td>
<td>1.9</td>
<td>3.8</td>
<td>8.6</td>
<td>17.4</td>
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<td></td>
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<td>(0-12.4)</td>
<td>(0-38.7)</td>
<td>(0.3-47.2)</td>
<td>(7.5-30.3)</td>
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<td></td>
<td></td>
<td>[187]</td>
<td>[209]</td>
<td>[197]</td>
<td>[16 (7.7)]</td>
</tr>
<tr>
<td>(Scheie)</td>
<td>[97] (10.9)</td>
<td>5.4</td>
<td>9.4</td>
<td>17.1</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-33.8)</td>
<td>(0-54.1)</td>
<td>(3.1-62.9)</td>
<td>(17.4-46.6)</td>
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<td></td>
<td>[87]</td>
<td>[97]</td>
<td>[85]</td>
<td>[4 (4.1)]</td>
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<tr>
<td>Undetermined</td>
<td>[28] (3.1)</td>
<td>0.8</td>
<td>1.3</td>
<td>2.9</td>
<td>5.1</td>
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<td>(0.1-7.2)</td>
<td>(0-43.9)</td>
<td>(0.3-44)</td>
<td>(1.8-9.7)</td>
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<td>[28]</td>
<td>[23]</td>
<td>[4 (14.3)]</td>
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D'Aco et al., 2012
MPS I Screening and Diagnosis

1. NEWBORN SCREENING - DBS
   a. Enzyme Assay for IDUA activity level (MS/MS, Lumina, Digital Microfluidics)
      - Normal IDUA (>5%) → Negative Screen
      - Low IDUA activity (<5%) → Positive Screen → Short-Term Follow Up

2. SHORT-TERM FOLLOW UP (2nd sample - blood, fibroblasts)
   a. Confirm low IDUA
   b. Glycosaminoglycan (GAG) test (urine or serum) –
      - Non-elevated GAG → pseudodeficiency or false-positive screen →
      - Elevated GAG → MPS I → Referral
   c. Mutation Analysis

3. MPS I – confirmation:
   a. IDUA < 5%, and
   b. Elevated GAG levels
   c. Mutation analysis (can, but does not always, inform MPS I phenotype)

⇒ Refer for multisystem clinical evaluation.
⇒ Treatment initiation and follow up - based on evaluation results and phenotype information from mutation analysis, if available.
MPS I Treatment Options

Hematopoietic stem cell transplantation (HSCT)

- **Standard of Care for Severe MPS I**
- *Early in disease course is considered to be better]*
- *Mortality from HSCT ~10%*
- *Morbidity includes acute or chronic GVHD*
- *ERT may be used prior to HSCT to stabilize; studies still underway to fully evaluate this approach*
- *The critical window for HSCT may be up to 2 or 3 months of age.*
MPS I Treatment Options

Enzyme replacement therapy (ERT)

- Recombinant human IDUA (Laronidase; Genzyme) FDA-approved in 2003
- Indicated for Attenuated MPS I; and Severe MPS I when HSCT declined or contraindicated
- Treatment = lifelong; weekly IV infusions, generally well-tolerated. Infusion associated reactions mild and common in first 6 months; do not require intervention
- Limitation: ERT does NOT cross the blood-brain barrier (BBB), cannot treat CNS involvement.
MPS I Treatment: Moderating Factors

• Disease symptoms and progression at time of HSCT and ERT initiation is main factor influencing outcomes.
• Earlier initiation (e.g., <1 year, ERT and HSCT) recommended to arrest/prevent CNS involvement
• Supplemental interventions for specific disease complications (e.g., corneal transplant, joint replacement, spinal fusion, BiPAP)
• Experimental studies for Intrathecal ERT to cross BBB
• CRIM status is not a concern
Expert Opinion, MPS I TEP

If MPS I detected earlier through newborn screening…

• Hypothesized that earlier initiation of treatment (both HSCT and ERT) will improve outcomes.
• May allow later decreases in ERT dosage.
• Timing of treatment for pre-symptomatic patients. Currently, treatment initiation indicated by presentation of clinical signs/symptoms. How to determine which symptom criteria/clinical signs to indicate treatment initiation is unclear and varies by providers.
Initial Literature Search

- *PubMed, EMBASE, CINAHL (1966 – August 2013)*
  - PubMed: 1575 abstracts
  - EMBASE: 666
  - CINAHL: 68 abstracts

- *MeSH Terms/Associated key words:*
  - Mucopolysaccharidosis type I (MPS I)
  - Hurler syndrome/disease
  - Hurler-Scheie syndrome/disease
  - Scheie syndrome/disease
  - Severe MPS 1
  - Attenuated MPS 1
  - Glycosaminoglycan (GAG)
  - Alpha-L-iduronidase enzyme
Initial Abstract and Title Screening (August 2013)

• Screening Criteria
  Inclusions: Relevant to key questions
  All study designs (n ≥ 1)
  English language abstracts
  Exclusions: Non-human studies
  Non-English or no abstract available
  No new empirical data/analyses

• Two independent reviewers
• Discussion and/or 3rd reviewer to resolve conflicts
Grey Literature Search

**MPS/LSD Specific**
- National MPS Society
- MPS Research Lab (UCLA-Harbor; PI: Dickson)
- MPS I Registry/(Genzyme) Lysosomal Disease Network
- NIH Rare Diseases Clinical Research Network (RDCRN)

**Newborn Screening – Research, Laboratory Methods**
- Newborn Screening Translation Research Initiative (NSTRI)
- CDC Newborn Screening Quality Assurance Program
- The Newborn Screening Technical Assistance & Evaluation Program
- The National Newborn Screening & Global Resource Center
- The American College of Medical Genetics
- The American Academy of Pediatrics

**Other**
- Clinicaltrials.gov
- The FDA
Other Relevant Sources of Information

- The MPS I Registry (Genzyme)
- Pilot screening programs and research
  - MO, IL NBS Programs
  - Washington State, Mayo Clinic
- Follow up TEP and Key Informant calls
Next Steps

• Posting protocol
• Completing abstract/literature review
• TEP and Key informant interviews
• Grey literature review
• KTQ 10 – Health Care System Impact Assessment Planning:
  – Population Impact Modeling – (Dr. Prosser)
  – Public Health System – Assessment of Resources for Readiness and Feasibility assessment (APHL)
Discussion