# Condition Review Workgroup (CRW)

<table>
<thead>
<tr>
<th>CRW Members</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex R. Kemper, MD, MPH, MS</td>
<td>Chair, Clinical Pediatrician, USPSTF</td>
<td>Duke University</td>
</tr>
<tr>
<td>Jeff Brosco, MD, PhD</td>
<td>Pediatric /NBS Bioethicist, and Regional Title V Services</td>
<td>Mailman Center for Child Development&lt;br&gt;CMS South Region (Florida's Title V Agency)&lt;br&gt;Pediatrics Bioethics Committee, Jackson Health System</td>
</tr>
<tr>
<td>Anne M. Comeau, PhD</td>
<td>State NBS Public Health Program</td>
<td>New England NBS Program, University of Mass Medical School</td>
</tr>
<tr>
<td>Nancy S. Green, MD</td>
<td>Clinical Pediatric – Hematology Specialist</td>
<td>Department of Pediatrics, Columbia University Medical Center</td>
</tr>
<tr>
<td>Scott Grosse, PhD</td>
<td>Federal Advisor, Health Economist</td>
<td>Nat’l Center on Birth Defects &amp; Developmental Disabilities, CDC</td>
</tr>
<tr>
<td>Jelili Ojodu, MPH</td>
<td>Public Health Impact Task Leader</td>
<td>NBS &amp; Genetics, Association of Public Health Laboratories</td>
</tr>
<tr>
<td>Lisa Prosser, PhD</td>
<td>Decision Analysis Leader, NBS Health Economist</td>
<td>Health Management &amp; Policy/ SPH; Pediatrics/Univ of Michigan Med School</td>
</tr>
<tr>
<td>Susan Tanksley, PhD</td>
<td>State NBS Public Health Program</td>
<td>Newborn Screening Laboratory&lt;br&gt;TX Department of State Health Services</td>
</tr>
<tr>
<td>K.K. Lam, PhD</td>
<td>Project Leader</td>
<td>Duke University</td>
</tr>
<tr>
<td>Jeffrey R. Botkin, MD, MPH</td>
<td>Committee Liaison for MPS I Review</td>
<td>Professor of Pediatrics &amp; Medical Ethics&lt;br&gt;University of Utah</td>
</tr>
<tr>
<td>Stephen McDonough, M.D.</td>
<td>Committee Liaison for MPS I Review</td>
<td>Medicenter One Health Systems, Inc. Department of Pediatrics</td>
</tr>
</tbody>
</table>
Review: Mucopolysaccaridosis Type I (MPS 1)

• Autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IDUA) enzyme.
• Progressive, multisystem disorder
• Variable clinical symptoms; continuum of disease severity
• Estimated Prevalence
  – Clinical detection: ~0.54 to 1.15 per 100,000
  – Screening: ~3 to ~6 in 100,000 (Population Pilot Studies)
• Traditional classification - two or three syndromes, though heterogeneous and overlapping
# MPS I: Disease Spectrum

<table>
<thead>
<tr>
<th></th>
<th><strong>SEVERE</strong></th>
<th><strong>ATTENUATED</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Est Prev, Clin Det</strong></td>
<td>~72 – 84%</td>
<td>(~15 – 28%)</td>
</tr>
<tr>
<td><strong>Alt. Classification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Onset and Progression</strong></td>
<td>Onset by 1 year</td>
<td>Onset by 3 to 4 years</td>
</tr>
<tr>
<td><strong>Cardiac System</strong></td>
<td>Cardio-respiratory failure</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td><strong>Respiratory System</strong></td>
<td>Severe respiratory, obstructive airway disease</td>
<td>Respiratory disease</td>
</tr>
<tr>
<td><strong>Brain &amp; CNS Cognition &amp; Development</strong></td>
<td>Progressive developmental delay</td>
<td>Little or no developmental delay</td>
</tr>
<tr>
<td><strong>Vision &amp; Hearing</strong></td>
<td>Hearing loss</td>
<td>Decreased vision</td>
</tr>
<tr>
<td><strong>Muscle &amp; Skeletal Systems</strong></td>
<td>Coarse facial features, Spinal deformity, Skeletal Dysplasia</td>
<td>Skeletal abnormalities, Joint stiffness, contractures</td>
</tr>
<tr>
<td><strong>Life Expectancy (if untreated)</strong></td>
<td>Death &lt; 10 years of age</td>
<td>Death in teens or 20s</td>
</tr>
</tbody>
</table>
# MPS I: Life Course

## Median Age of Onset, Diagnosis, Treatment, and Death for MPS I Registry patients (N=891).†

<table>
<thead>
<tr>
<th>Disease Classification†‡</th>
<th>N [%]</th>
<th>Onset (years)</th>
<th>Diagnosis (years)</th>
<th>Treatment Reported† [n]</th>
<th>Treatment Initiation (years)</th>
<th>Death Reported [n]</th>
<th>Death (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (Hurler)</td>
<td>508 [57]</td>
<td>0.5 (0-6.5)</td>
<td>0.8 (0-23.8)</td>
<td>438</td>
<td>1.4 (0.1-31.2)</td>
<td>156</td>
<td>3.8 (0.4-27.2)</td>
</tr>
<tr>
<td>Attenuated (Hurler-Scheie)</td>
<td>209 [23.5]</td>
<td>1.9 (0-12.2)</td>
<td>3.8 (0-38.7)</td>
<td>197</td>
<td>8.6 (0.3-47.2)</td>
<td>16</td>
<td>17.4 (7.5-30.3)</td>
</tr>
<tr>
<td>(Scheie)</td>
<td>97 [10.9]</td>
<td>5.4 (0-33.8)</td>
<td>9.4 (0-54.1)</td>
<td>85</td>
<td>17.1 (3.1-62.9)</td>
<td>4</td>
<td>29 (17.4-46.6)</td>
</tr>
</tbody>
</table>

†MPS I Registry (from inception in 2003 through March 2010). Patients from 33 countries (47% Eur/Mid East; 35% No Amer; 15% Latin Amer, 3% Asia Pacific).
‡13% reported as untreated with ERT or HSCT.
.§8.6% undetermined (3.1%) or missing (5.5%) form classification.

MPS I Newborn Screening

• Low IDUA enzyme activity
• Detected in dried-blood spots (DBS)
• Screening Methods:
  – *Tandem mass spectrometry (MS/MS)*
  – *Fluorometry by digital microfluidics*
  – *Fluorometry on microtiter plate*
Establishing the MPS I Diagnosis

- **Definitive MPS I diagnosis: IDUA enzyme activity assay**
  - Measured in the following: leukocytes or skin fibroblasts
  - IDUA activity less than 1% of normal
  - Enzyme activity alone does not predict phenotype

- **Increased glycosaminoglycan (GAG) levels in urine is supportive of the diagnosis**

- **Genotyping can help if it reveals a known mutation**
  - Most mutations are “private”
Genotyping

• >100 known MPS I-specific IDUA mutations, many unique to specific individuals

• Known IDUA-pseudodeficiency mutation
  – Considered rare in literature, though NBS may indicate otherwise, esp. among African Americans

• Genotype-phenotype correlation is generally unknown, but an active area of research
Treatment Strategies

• Hematopoietic Stem Cell Transplantation (HSCT)
  – Allows individuals to produce endogenous enzyme
  – Recommended for MPS I (H, H/S) <age 2 or 2.5 years, with normal to moderate cognition (MPS I H, H/S) [Int’l Consensus, 2008; European Consensus, 2011]
  – Benefit of earlier treatment (i.e., within first two years) uncertain

• HSCT + Enzyme Replacement Therapy (ERT)
  – Proposed as a bridge pre- HSCT
  – May augment enzyme availability after HSCT

• ERT
  – Does not cross blood-brain barrier (intrathecal administration proposed)
  – May benefit patients with all forms of disease
Systematic Evidence Review: Published Literature – Through ~August 2013

- Keywords: Mucopolysaccharidosis type I (MPS I); Hurler syndrome/disease; Hurler-Scheie syndrome/disease; Scheie syndrome/disease; severe MPS 1; attenuated MPS 1; gargoylism; alpha-L-iduronidase enzyme assay
- Articles through PubMed, EMBASE, and CINAHL Search (2,041)
- Articles screened for eligibility & relevance (n=371)
- Articles retained for data extraction (n=194)*
- Screening by two independent reviewers

*Final included articles may decrease following final eligibility determination.
Distribution of Key Topic Areas for Included Articles through ~Aug 2013 (n=194):

<table>
<thead>
<tr>
<th>Key Topic Area</th>
<th># articles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NATURAL HISTORY</strong></td>
<td></td>
</tr>
<tr>
<td>Natural Clinical Course</td>
<td>27</td>
</tr>
<tr>
<td>Prevalence</td>
<td>15</td>
</tr>
<tr>
<td><strong>SCREENING</strong></td>
<td></td>
</tr>
<tr>
<td>Methods Validation</td>
<td>17</td>
</tr>
<tr>
<td>Population-based Pilots</td>
<td>3</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
</tr>
<tr>
<td>Major Health Outcomes</td>
<td>30</td>
</tr>
<tr>
<td>Intermediate Outcomes or Biomarkers</td>
<td>64</td>
</tr>
<tr>
<td>Clinical Guidelines [expert opin, consensus]</td>
<td>4</td>
</tr>
</tbody>
</table>

2nd Level Exclusions:
- Treatment Case Reports (n=1) 23
- Duplicate reports 11

• **Lit search update** (Aug 2013 to Aug 2014): 178 identified, ~91 to review
Missouri Newborn Screening Pilot - Update

- Full population pilot screening *(have not yet “gone live”), Jan 2013 to present*
- Screening method: Digital microfluidics
- Newborns screened to date: ~117,000 (135,476 samples)
- 57 Referrals for confirmation which resulted as follows:
  - 1 confirmed MPS-I
  - 24 pseudo-deficiencies *(2 of these were genotypes of unknown significance for several months)*
  - 3 carriers
  - 24 false positive
  - 4 pending
  - 1 lost to follow-up

- **False positive rate** = 56/135,476 X 100 = 0.04%
- **In-house sample repeat rate** = 0.49%
- **IDUA cut off rate** lowered over time, 50% decrease in pseudodeficiency rate
- **Prelim** observation: True MPS I appears to yield IDUA levels close to 0
Illinois Newborn Screening Validation

• Validation study with CDC assay
• Population Pilot Screening start date pending
• Screening method: UPLC-MSMS (6plex LSDs)

Screening validation results to date:
  – 12,404 specimens analyzed
    • 20 repeated for low IDUA
      – 7 below second cut-off
        » Follow-up results of 7:
          • 2 Pseudodeficiency
          • 1 normal
            ➢ 1 mutation
            ➢ 1 mutation+pseudodeficiency
          • 2 pending results

• 2 specimens with mutation ➢ “low risk to develop Hurler”
• More detail and follow up pending interview
MPS I NEWBORN SCREENING - Summary

• IDUA activity can be measured
• Screening algorithm still being refined to balance case detection vs. false positives and pseudodeficiency
• Challenges exist in predicting form / severity
Treatment – Summary – Severe MPS 1

• HSCT compared to historical controls leads to:
  – *Increased survival* (<5% vs. 65% at 10 years)
  – *Preserved development*
  – *Improvement in mobility*

• Little evidence regarding HSCT in asymptomatic infants
• Earlier treatment likely better, but ideal timing is unclear.
• Clinical guidelines consistently recommend HSCT for infants < 2 or 2.5 years, development and cognition not significantly affected (>70 IQ)
• Short-term ERT often given prior to HSCT
Treatment – Summary – Attenuated MPS 1

• ERT leads to improved outcomes (RCT with follow-up)
  – Mobility improvements (6-Minute Walk Test)
  – Disability Index

• ERT benefits in asymptomatic Attenuated MPS 1 unclear

• Harms of treatment
  – ERT: Need for chronic infusions, antibody development
Remaining Questions

• Expert Interviews and Expert Panel Follow Up
  – Pseudodeficiency mutations, African Americans
  – Predicting severity / form
  – “Genotypes of unknown significance” and early identification of Attenuated forms – implications and benefits unclear
  – Importance of earlier initiation of treatment for Severe MPS I (What is the critical window?)
  – Treatment approaches to address CNS involvement – Intrathecal ERT?
  – Pilot screening program experiences
  – Other info from MPS I Registry or unpublished data
Next Steps – MPS I Condition Review

- Update and Finalize Evidence Review
- Project Population Net Benefits of Screening
- Assess Public Health System Impact
- Finalize Condition Review Report
# X-linked Adrenoleukodystrophy (ALD)

<table>
<thead>
<tr>
<th>Overall Prevalence</th>
<th>~1 / 20,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Types of ALD</strong></td>
<td><strong>Period of Onset</strong></td>
</tr>
<tr>
<td>Childhood Cerebral</td>
<td><em>Ages 4-10 years, survival few years after symptom onset</em></td>
</tr>
<tr>
<td>Adrenomyeloneuropathy</td>
<td><em>Early- to mid-adulthood</em></td>
</tr>
<tr>
<td>Addison Disease Only</td>
<td><em>Variable, may proceed adrenomyeloneuropathy type</em></td>
</tr>
</tbody>
</table>

**Genetics:**
- ABCD1 gene mutations, produces adrenoleukodystrophy protein (ALDP), transports long-chain fatty acids into peroxisomes
- *Poor genotype-phenotype correlation, even within families*

**Screening:**
- Dried-blood spots – laboratory pilot conducted by Mayo Clinic

**Diagnosis:**
- Mutation analysis, measurement of very long-chain fatty acids, MRI (“Loes Score”)

**Treatment:**
- HSCT, adrenal hormone replacement therapy, N-acetyl-L-cysteine
Thank You!

Questions?

Presentation Contact:
Alex R. Kemper, MD, MPH, MS
alex.kemper@duke.edu