Duke Clinical Research Institute

Newborn Screening for MPS 1: Interim Report from the Condition Review Workgroup

Alex R. Kemper, MD, MPH, MS

September 11, 2014

Condition Review Workgroup (CRW)

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

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

	SEVERE	*ATTENUATED*	
Est Prev, Clin Det	***~72 – 84%***	***(~15 – 28%)***	
Alt. Classification	**Hurler**	**Hurler/Scheie**	**Scheie**
Onset and Progression	Onset by 1 year Rapidly Progressive	Onset by 3 to 4 years	Onset variable, 2 to 12 years Less progressive problems
Cardiac System	Cardio-respiratory failure	Cardiovascular disease	Valvular heart disease
Respiratory System	Severe respiratory, obstructive airway disease	Respiratory disease	Upper airway infections
Brain & CNS **Cognition & Development**	Progressive developmental delay	Little or no developmental delay	Normal intelligence
Vision & Hearing	Hearing loss	Decreased vision	Corneal clouding
Muscle & Skeletal Systems	Coarse facial features Spinal deformity Skeletal Dysplasia	Skeletal abnormalities Joint stiffness, contractures	Joint stiffness Carpel tunnel syndrome
Life Expectancy ***(if untreated)***	Death < 10 years of age	Death in teens or 20s	Death in later life; most have normal life span

MPS I: Life Course

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

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

†*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.*

D'Aco et al. (2012). Diagnosis and treatment trends in mucopolysaccharidosis I: Findings from the MPS I Registry. Eur J Pediatr, 171, 911-919.

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

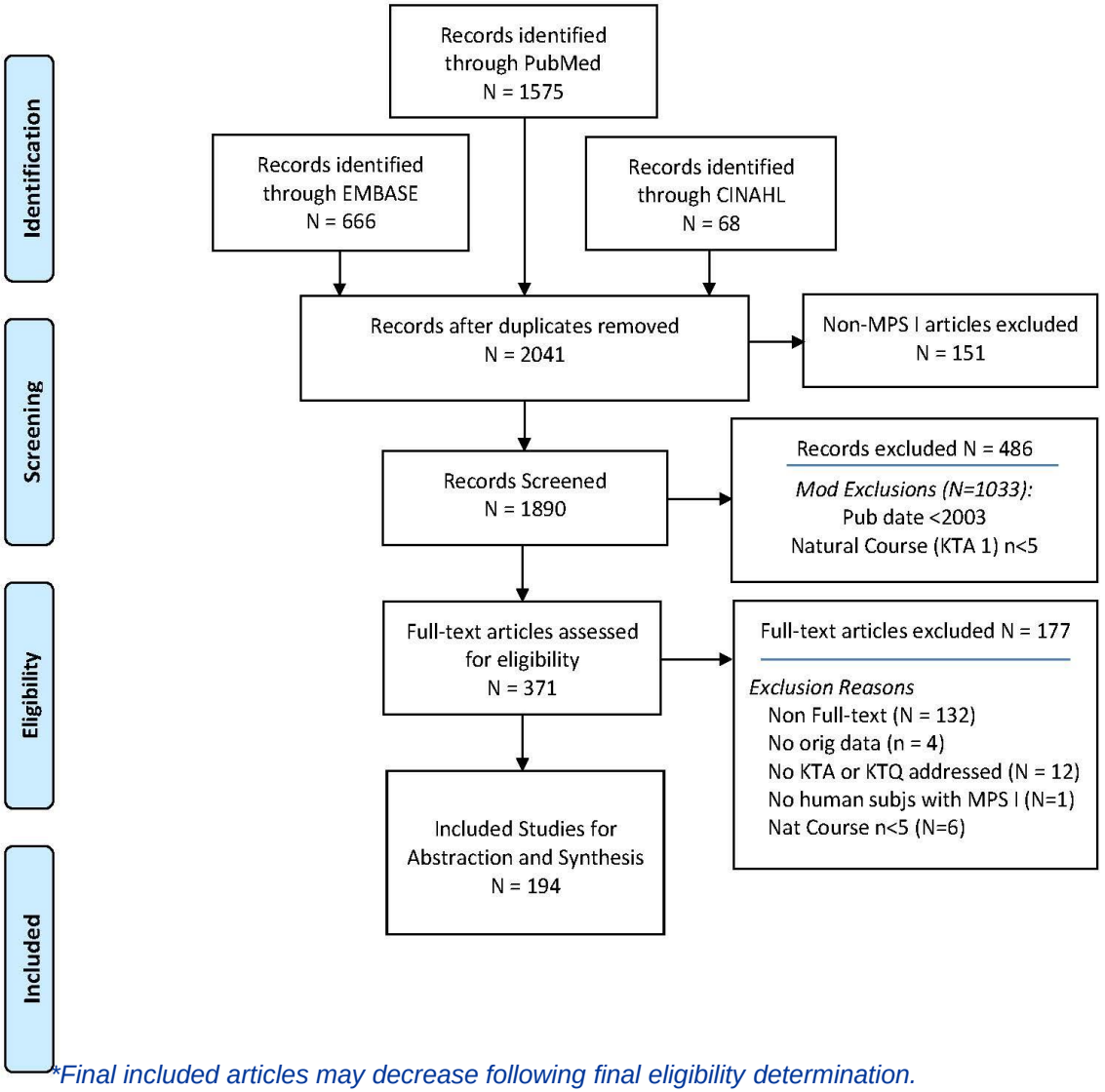
Treatment Strategies

- 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

Figure 1. PRISMA Search Flow Diagram



*Final included articles may decrease following final eligibility determination.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Distribution of Key Topic Areas for Included Articles through ~Aug 2013 (n=194):

Key Topic Area		# articles
NATURAL HISTORY	Natural Clinical Course	27
	Prevalence	**15**
SCREENING	Methods Validation	**17**
	Population-based Pilots	**3**
TREATMENT	Major Health Outcomes	**30**
	Intermediate Outcomes or Biomarkers	64
	Clinical Guidelines *[expert opin, consensus]*	4
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)

Overall Prevalence	~1 / 20,000
Types of ALD	**Period of Onset**
Childhood Cerebral	*Ages 4-10 years, survival few years after symptom onset*
Adrenomyeloneuropathy	*Early- to mid-adulthood*
Addison Disease Only	*Variable, may proceed adrenomyeloneuropathy type*

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