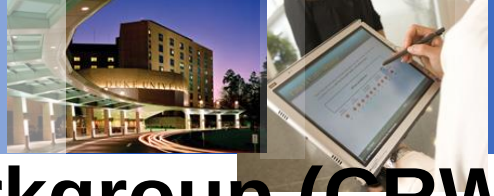
Duke Clinical Research Institute

Newborn Screening for MPS 1: Brief Update from the Condition Review Workgroup

Alex R. Kemper, MD, MPH, MS

January 17, 2014

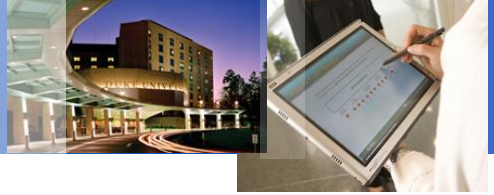


Condition Review Workgroup (CRW)

CRW Members	Role	Institution
Alex R. Kemper, MD, MPH, MS	Chair	Duke University
Anne M. Comeau, PhD	State NBS Public Health Program	New England NBS Program, University of Mass Medical School
Aaron Goldenberg, PhD, MPH	NBS Bioethicist	Center for Genetic Research Ethics & Law, Case Western University
Nancy S. Green, MD	Nomination & Prioritization Workgroup Liaison	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	*Advisory Committee Liaison for MPS I Review*	Professor of Pediatrics & Medical Ethics University of Utah
Stephen McDonough, M.D.	*Advisory Committee Liaison MPS I Review*	Medicenter One Health Systems, Inc. Department of Pediatrics

Overview: Mucopolysaccaridosis Type I (MPS 1)

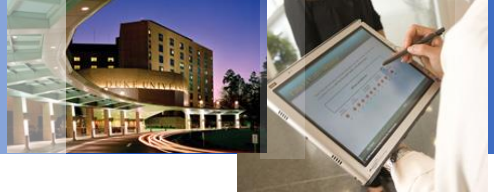
- Autosomal recessive Lysosomal Storage Disorder (LSD) caused by deficiency of α-L-iduronidase (IDUA) enzyme.
- MPS I is a progressive, multisystem disorder
- Variable clinical symptoms; continuum of disease severity.
- Traditionally classified into two or three MPS I syndromes, though classifications are heterogeneous and overlapping:
  - *SEVERE:*
    - Hurler syndrome (H)
  - *ATTENUATED:*
    - Hurler-Scheie syndrome (H/S)
    - Scheie syndrome (S)



MPS I Epidemiology: **Clinical Detection**

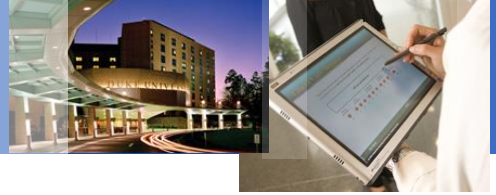
	Estimated Incidence Based on Clinically Detected Cases *(per 100,000)*	% Severe Form (MPS I H)
Europe	0.54 – 1.85	70 – 84%
Australia	0.83 – 0.93	100%
Africa *(Tunisia)*	0.63	72%
Asia *(Taiwan)*	0.11	57%
North America *(British Columbia)*	0.58 – 1.15	*NA*

- *Significant risk of bias, including under-ascertainment of Attenuated form.*



MPS I: Disease Spectrum

	Severe	*Attenuated*	
	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; obstructive airway disease	Upper airway infections
Brain & CNS **Cognition & Development**	Progressive developmental delay	Little or no developmental delay	Normal intelligence
Vision & Hearing	Hearing loss	Decreased visual acuity	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 before age 10 years	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 any of the following: leukocytes or skin fibroblasts*
  - *IDUA activity less than 1% of normal*
- **Increased glycosaminoglycan (GAG) levels in urine is supportive of the diagnosis**
- **In general, IDUA activity does not predict disease form or severity**
- **Genotyping can help if it reveals a known mutation**

Genotyping

- >100 known MPS I-specific IDUA mutations, many unique to specific individuals
- Known IDUA-pseudodeficiency mutation
- 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) [International Consensus, 2008; European Consensus, 2011]*
- 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 has been proposed)*
  - *May benefit patients with all forms of disease*

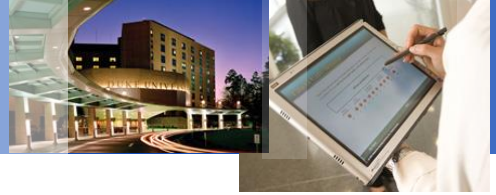
Condition Review Aims:

Relative to usual diagnostic and treatment practices, what is the net impact of newborn screening/ early detection of MPS I on the following:

1. **Patient disease course and prognosis**
   a) *age of diagnosis*
   b) *treatment initiation and outcomes*
   c) *prognosis and survival*
2. **Population health outcomes – incidence & prevalence of MPS I**
3. **Public health system impact**

Condition Review of Newborn Screening (NBS) for MPS I: Methods

1. MPS I Screening and Treatment Effects: Systematic Evidence Review
2. Population Health Outcomes of MPS I NBS: Decision Analysis
3. Public Health System Impact: Assessment of Feasibility and Readiness of the Public Health System to expand screening and follow up of MPS I



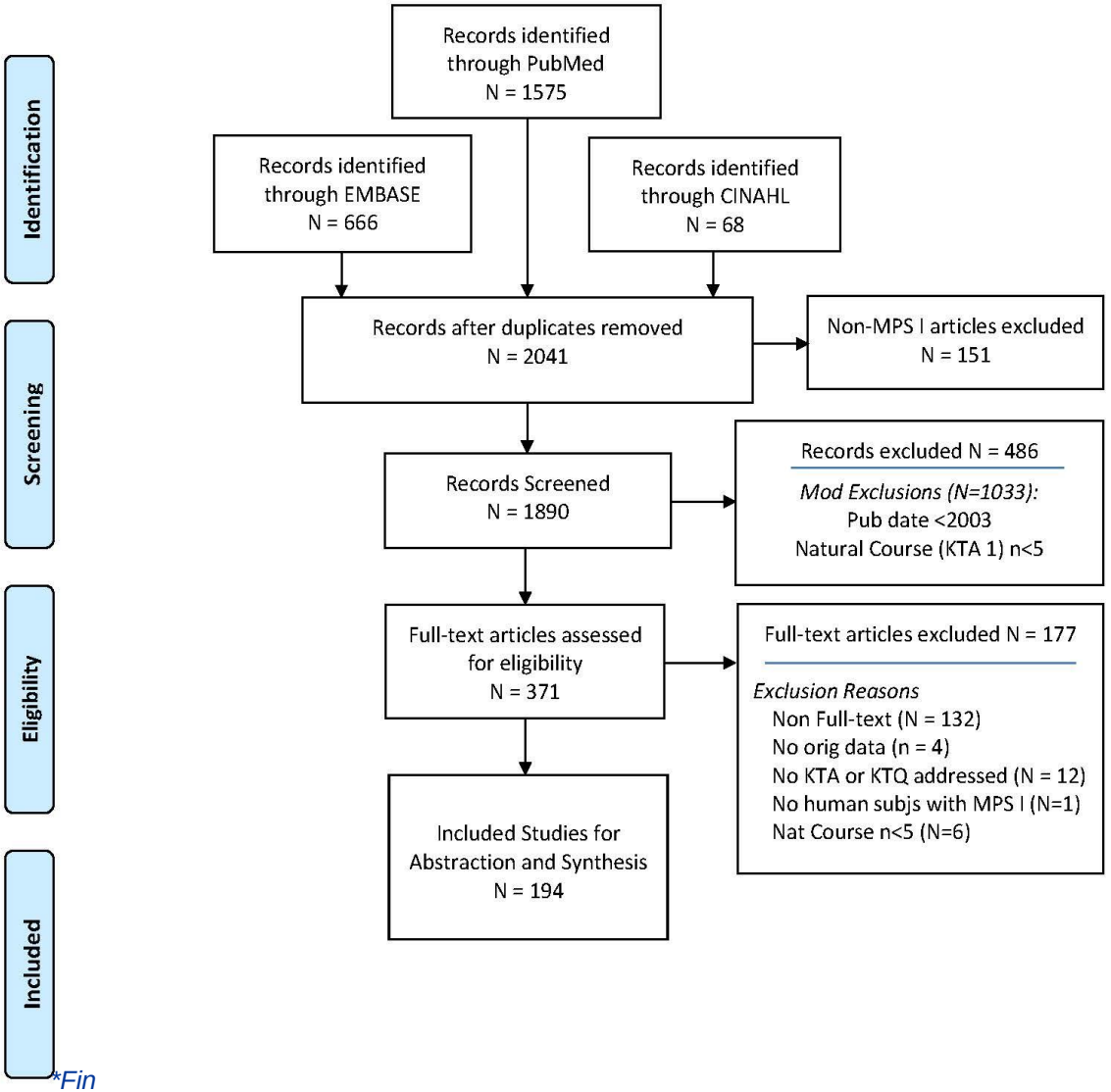
Systematic Evidence Review: Technical Expert Panel

- Case Definition
- Natural History
- Screening Methods
- Usual Care Treatments
- Outcomes
- Issues in Practice
- Unpublished data

EXPERT PANEL MEMBERS	TEP 1: Sept 9, 2013
Barbara K. Burton, MD Professor of Pediatrics Northwestern University Feinberg School of Medicine	
Lorne A. Clarke, MD Scientific Advisory Board, National MPS Society Professor & Medical Director Provincial Medical Genetics Program University of British Columbia	
Patricia Dickson, MD Chief, Division of Medical Genetics Los Angeles County - Harbor - UCLA Medical Center	
Joseph Muenzer, MD, PhD Professor, Department of Pediatrics and Genetics and Metabolism Clinic University of North Carolina School of Medicine	
Barbara Wedehase,[±] MSW, CGS Executive Director National MPS Society	
[±]Nominator of MPS I disease for consideration to be added to the RUSP.	

Systematic Evidence Review: Published Literature

- 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



*Fin

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

MPS I Newborn Screening

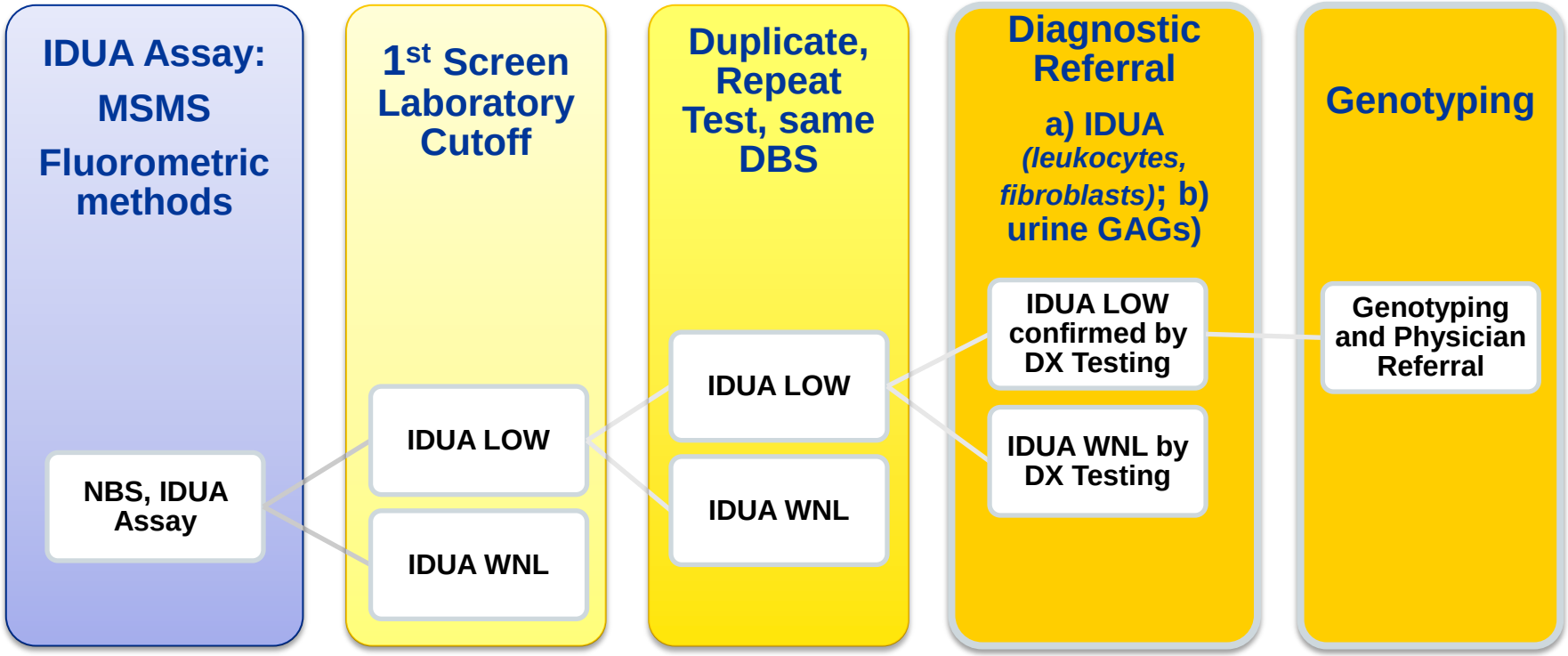
U.S. State NBS Programs – MPS I NBS Mandate

- *New Jersey – planning phase*
- *New Mexico – planning phase*
- *Illinois - ~3 years ago evaluated digital microfluidics, now implementation prep and validation with LSD multiplex MS/MS; population pilot planned for 2014*

❖ *Missouri NBS Pilot – Full Population Pilot testing LSDs with digital microfluidics platform (Jan 15, 2013 to present)*

MPS I Newborn Screening Algorithm

(based on Missouri program)



Missouri Newborn Screening Pilot

- Full population Pilot Screening (*have not yet "gone live"*)
- Screening method: Digital microfluidics ~84,000 samples *(Jan to Dec 2013; ongoing)*
- 42 positive
  - *1 affected MPS-I case (confirmed Severe [Hurler])*
  - *2 "genotypes of unknown significance" (2 mutations, low IDUA activity)*
  - *1 carrier*
  - *5 pseudodeficiency*
  - *16 false-positives*
  - *17 pending status confirmation*

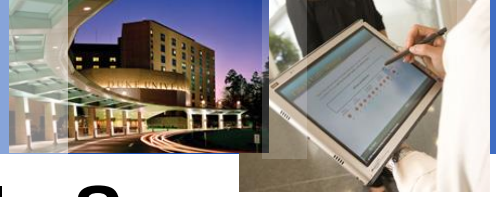
MPS I Newborn Screening – Published Studies

Anonymous Dried Blood Spots

- Washington State, U.S. (Scott et al., 2013)

Population-based Pilot Newborn Screening

- Italy (Paciotti et al., 2012)
- Taiwan (Lin et al., 2013)



Newborn Screening for MPS I - Summary

	Missouri NBS Pilot *(ongoing)*	Univ of WA	Taiwan NBS Pilot	Italy NBS Pilot
Confirmed MPS I	**(~1 to 3* in 84,000)**	**1 in 35,700**	**1 in 17,643**	**0 in 3,403**
Screening method	Digital Microfluidics	MS/MS	Fluorescence Assay	Fluorescence Assay
Total samples screened	~84,000	106,526	35,285	3,403
Total cases consistent with MPS I	~1 (3*)	"3"	2	0

**3 including the 2 cases of "Genotype of unknown significance", with IDUA mutations and low activity.*

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

What benefits and harms are associated with treatments of MPS I?

- Severe (*Hurler*)
  - HSCT
  - ERT + HSCT
- Attenuated (*Hurler-Scheie, Scheie*)
  - ERT

Does early detection improve the outcome of treatment?

Treatment – Summary – Severe MPS 1

- HSCT compared to historical controls leads to:
  - *Increased survival (<5% vs. 65% at 10 years; most HSCT mortality occurs within the first year post-transplant)*
  - *Preserved development*
  - *Improvement in mobility*
- Little evidence regarding HSCT in asymptomatic infants
- Earlier treatment likely better, but ideal timing is unclear. Previous expert panels have recommended before 2 or 2.5 years of age
- Little evidence regarding HSCT+ERT

Treatment – Summary – Attenuated MPS 1

- ERT leads to improved outcomes (RCT with follow-up)
  - *6-Minute Walk Test*
  - *Disability Index*
- Benefit of ERT in asymptomatic cases of attenuated MPS 1 is unclear
- Harms of treatment
  - *ERT: Need for chronic infusions, antibody development*

Next Steps – MPS I Condition Review

- Complete Systematic Evidence Review
- Identify Key Evidence into Public Health Impact Assessment
- Assess Population and Public Health Impact
  - *Projected Population Benefit – Decision Analysis*
  - *Evaluation of Public Health System Impact*
- Finalize Condition Review Report

Next Steps –
I. Systematic Evidence Review

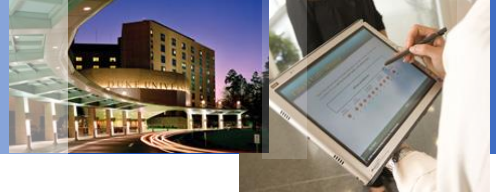
- Expert Interviews
- TEP Follow Up
- Outline evidence-based MPS I NBS Procedures
- Identify key evidence for Decision Analysis Model
- Finalize SER and report

Next Steps:
II. Decision Analysis to Project Public Health Impact on Population

- Goal - Estimate
  - *The number of newborns expected to screen positive and be diagnosed with MPS 1, stratified by form and severity vs. uncertain*
  - *Expected outcomes from screening compared to clinical case detection*
- Develop Decision Model Structure
- Translate key parameter inputs from evidence review
- Convene TEP to guide refinement of decision model inputs and estimates

Next Steps:
III. Public Health System Impact Assessment

- Develop and administer Stage I web-based survey(s) of *MPS I NBS Feasibility and Readiness*
- Conduct follow-up in-depth interviews with select state NBS programs
- Summarize NBS Feasibility and Readiness data

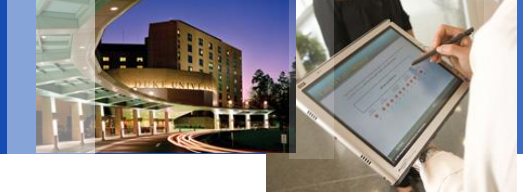


Thank You!

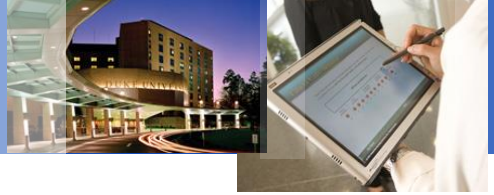
Questions?

Presentation Contact:

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



Back-ups

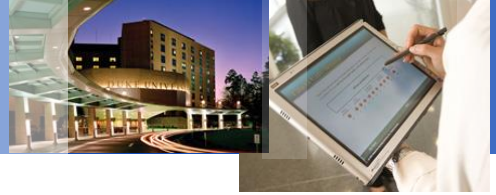


Washington NBS Study (Univ of WA)

- MS/MS IDUA assay – 106,526 anonymous dried blood spot samples (*WA State Dept of Health*)
- 9 positive screens for low IDUA activity; confirmatory DNA testing with same DBS
  - *3 consistent with MPS I disease*
  - *6 "Unaffected"*
    - 1 carrier
    - 2 poor punch samples
    - 3 no nucleotide changes consistent with MPS I

Estimated Results: MPS I – All Forms		95% CI
Overall Incidence	1 in 35,700	1/143,000 - 1/11,100
Positive Predictive Value	0.33	0.08 - 0.65
False Positive Rate	1 in 17,750	1/7,250 - 1/31,900

Scott et al. (2013). Identification of infants at risk for developing Fabry, Pompe, or MPS I from newborn blood spots by tandem mass spectrometry. J Pediatr.

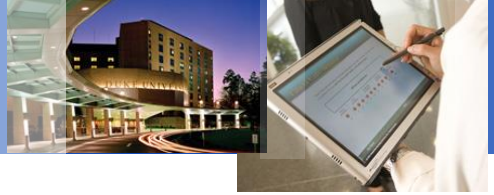


Taiwan Newborn Screening for MPS I

- Fluorometric measurement of IDUA in microtiter plates
- 35,285 newborns screened Oct 2008 to Apr 2013
  - *19 positive 1st screens recalled for re-check (for leukocyte IDUA)*
  - *3 positive recall screens (low IDUA activity in leukocytes) sent for diagnostic confirmation*
  - *Diagnostic confirmation: urine GAG analysis, leukocyte IDUA, molecular DNA*
    - 2 confirmed MPS I
    - 1 MPS I carrier

Estimated Results: MPS I, All Forms	
Overall Incidence	1 in 17,643

Lin et al. (2013). A pilot newborn screening program for Mucopolysaccharidosis type I in Taiwan. Orphanet J of Rare Diseases, 8: 147.



Italy Newborn Screening Study

- Fluorometric measurement of IDUA in microtiter plates
- 3,403 newborns screened, Umbria, Italy region
  - *13 positive 1st screens recalled for 2nd DBS retest*
  - *3 positive recall DBS screens, recalled for diagnostic confirmation via low IDUA activity assay in leukocytes/whole blood*
  - *0 confirmed low IDUA activity, MPS I*

Estimated Results: MPS I, All Forms	
Overall Incidence	0 in 3,403

Paciotti et al. (2012). First pilot newborn screening for four lysosomal storage diseases in an Italian region: Identification and analysis of a putative causative mutation in the GBA gene. Clinica Chimica Acta, 413, 1827-1831.

Severe MPS I: HSCT

- N = 20 subjects who received HSCT from Cord Blood *(single institution, 1995-2002)*
  - *Median age at diagnosis 11 months (range: prenatal – 29 months)*
  - *Median age at transplantation 16 months (2-33 months)*

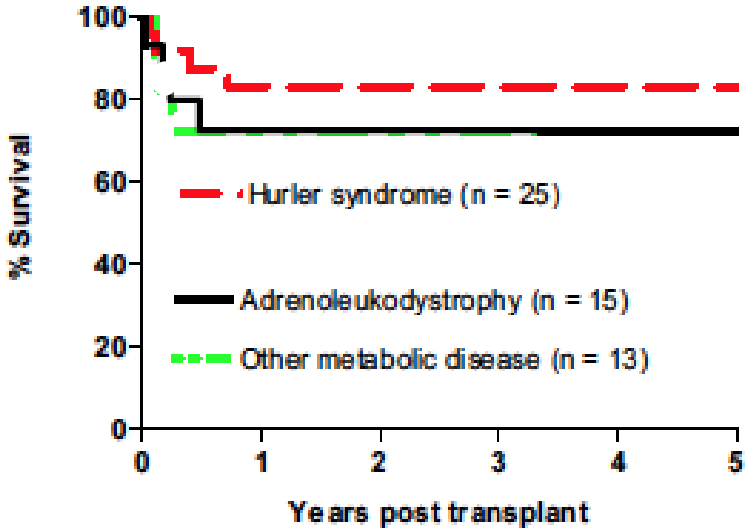
Outcomes

- 85% Event-free Survival (17/20), median 2.5 years (905 days) post-transplant
- Kyphosis
  - 4 required spinal fusion
  - 5 mild, stable kyphosis
  - 6 had decrease in kyphosis
  - 2 had no kyphosis
- 100% “stable or improved” neurocognitive function

[496] Staba et al. (2004). Cord blood transplants from unrelated donors in patients with Hurler's syndrome N Engl J Med, 350, 1960 9.

Severe MPS I: HSCT

- N = 25 subjects underwent HSCT in Australia and New Zealand, 1992-2008
- **Outcome**
  - *83% Survival (95% CI: 68%-98%) at 1 and 5-years*
  - *All deaths within first year*



[5] Mitchell et al. (2013). Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: A report from the Australian and New Zealand Children s Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. *Pediatr Transplant*. 17(6) 582-588.

Severe MPS I : HSCT

- **N = 23 subjects who underwent HSCT at a single institution from 1989-2007; follow-up to 2011**
  - *Median age of transplant 13.5 months (range: 4-24 months)*

Outcomes:

- ***78% Overall survival (n=18)***

  2 had secondary graft loss
  - *1 successfully re-transplanted*
  - *1 experienced progressive disease*
- ***22% Transplant-related mortality (n=5)***

- **Among survivors**
  - *83% (15/18) attend regular school*
  - *78% (13/18) are able to ambulate and perform daily activities*
  - *22% (4/18) have stable hydrocephalus*
  - *83% (15/18) have mild and stable corneal clouding*
  - *50% (9/18) have required some orthopedic intervention*

[175] Gassas et al. (2011). Long term adaptive functioning outcomes of children with inherited metabolic and genetic diseases treated with hematopoietic stem cell transplantation in a single large pediatric center: parents' perspective. *J Pediatr Hematol Oncol*. 33. 216-20

Severe MPS I: HSCT + pre-ERT

258 subjects identified through registries who underwent HSCT (1995-2007)

- *19% (48 of 258) received at least 4 infusions of ERT prior to HSCT*
- *Median age of HSCT: 16.7 months (range: 2.1 - 228 months)*
- *HSCT Donor Sources*
  - Unrelated Cord Blood (UCB) (116)
  - Matched Unrelated (105)
  - Matched Sibling (37)

Outcomes

- Overall survival was 74% and Event-free survival was 63%
  - Event-Free survival significantly higher for those treated earlier than median age (71% vs. 55%; *p=0.02*)
  - ERT use did not predict improved survival (univariate [*p=0.07]* or multivariate analysis)
- *Normal IDUA Enzyme activity:*
  - 98% of UCB group vs. 53 – 66% IDUA, other donor sources *(p=0.007)*

➢ ***Potentially biased because results not adjusted for multiple sources of confounding***

[18] Boelens et al. (2013). Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning *Blood*, 121 3981 7.

Severe MPS I: HSCT + pre/post-ERT

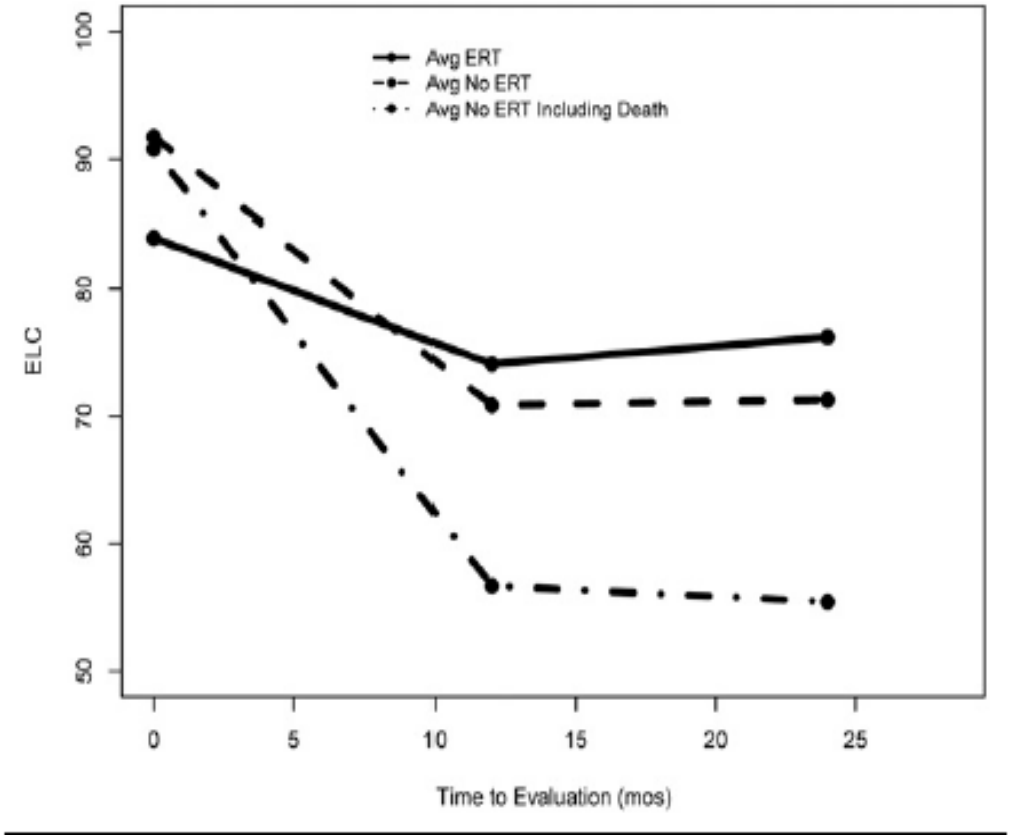
- Subjects (N=19)
  Average age at HSCT: 17.5 months
- 2 Groups
  - *HSCT only (n=10)*
    - 17.1 months at HSCT
    - No ERT
  - *HSCT + pre/post-ERT (n=9)*
    - 18 months at HSCT
    - ERT given Pre-HSCT (weekly) and Post-HSCT (8 infusions)
- Outcomes: Post-transplant Survival
  - *80% (8/10) HSCT only group*
  - *100% (9/9) HSCT + pre/post-ERT group*
- By 2-years post-transplant, 1 subject (HSCT + pre/post-ERT) had 47% engraftment and enzyme levels in the “carrier range”

[42] Eisengart et al. (2013). Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome *J Pediatr*, 162, 375 80 e1.

Severe MPS I: HSCT pre/post-ERT

… "children in the ERT group lost 9.19 fewer points per year …(p=0.031). When the 2 patients in the no-ERT group who died were excluded, this difference was reduced to 5.40 points per year…(p=0.031)."

- HSCT + ERT may confer some benefit for both survival and intellectual development, but data are based on small sample sizes



[42] Eisengart et al. (2013). Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome *J Pediatr*, 162, 375 80

Severe MPS I: HSCT and ERT

- One patient received HSCT at 2 years and then again at 2.5 years for failure to engraft
- At 14 years, developed fatigue, shortness of breath, and became wheelchair dependent
- Developed restrictive lung disease with GAG deposition
- Leukocyte enzyme level >70%
- After 2 years with ERT:
  - Resolved - Fatigue, weakness, shortness of breath
  - Improved ambulation

➢ ***This case study suggests that ERT after HSCT may be beneficial when HSCT has limited effect***

[268] Bijarnia et al. (2009). Combined enzyme replacement and haematopoietic stem cell transplantation in Hurler syndrome *J Paediatr Child Health*, 45, 469 72.

Attenuated MPS 1: ERT for Symptomatic Care

- 2-group Randomized Clinical Trial (RCT)
- 26 weeks, ERT (n=22) vs. Placebo (n=23)
- Mean age 15 years
- Outcomes
  - *Forced Vital Capacity (FVC): 3% point increase in the difference between differences in median FVC (p<0.01)*
  - *6 Minute Walk Test (6MWT): 38 meter increase in the difference between difference average 6MWT (ANOVA p=0.04; Wilcoxon Rank Sum test p=0.07)*
  - *Disability Index: No change*
  - *Shoulder Flexion: No change*
  - *ERT: 20/22 developed IgG antibodies*

[500] Wraith et al. (2004). Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double blinded, placebo controlled, multinational study of recombinant human alpha L iduronidase (laronidase) *J Pediatr.* 144, 581 8.

Attenuated MPS 1: ERT for Symptomatic Care

- **In a 3.5 year extension trial**
  - *40/45 completed the extension trial*
    - Non-completers:
      - 3 withdrew (needle phobia, scheduling difficulty, pregnancy)
      - 1 died following respiratory infection
      - 1 had anaphylaxis

  Outcomes

  - *FVC: worsened in 11/40 (0.8 points of predicted/year)*
  - *6MWT: increased by was 17.1, but variable*
  - *Mean disability index:*
    - 57% improved
    - 20% stable
    - 23% declined

  ➢ ***ERT led to statistically significant improvement compared to placebo, but clinical significance unclear***

[294] Clarke et al. (2009).Long term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I *Pediatrics*, 123, 229 40.

Attenuated MPS 1: ERT for Symptomatic Care

- 3 affected siblings
- ERT begun at different ages (6 years, 2.5 years, and 4 months)
- Outcomes after 5 years of ERT
  - *Child that began ERT at 6 years had 6 Minute Walk Test (6MWT) <10% and Forced Vital Capacity (FVC) 53% of predicted. Required orthopedic interventions*
  - *Child that began at 2.5 years had 6MWT WNL and FVC of 81% predicted. No facial coarsening but mild shoulder stiffness with full range of motion*
  - *Child that began at 4 months had 6MWT WNL and FVC of 85% predicted. No facial Coarsening or joint stiffness.*

➢ ***This case series suggests that presymptomatic ERT for Attenuated MPS I may lead to improved health outcomes***

[4] Laraway et al. (2013). Does early use of enzyme replacement therapy alter the natural history of MPS I? Experience in three siblings *Mol Genet Metab*, 109, 315 6.