Duke Clinical Research Institute

# Newborn Screening for MPS I Disease: Condition Review Update

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# Condition Review Workgroup (CRW)

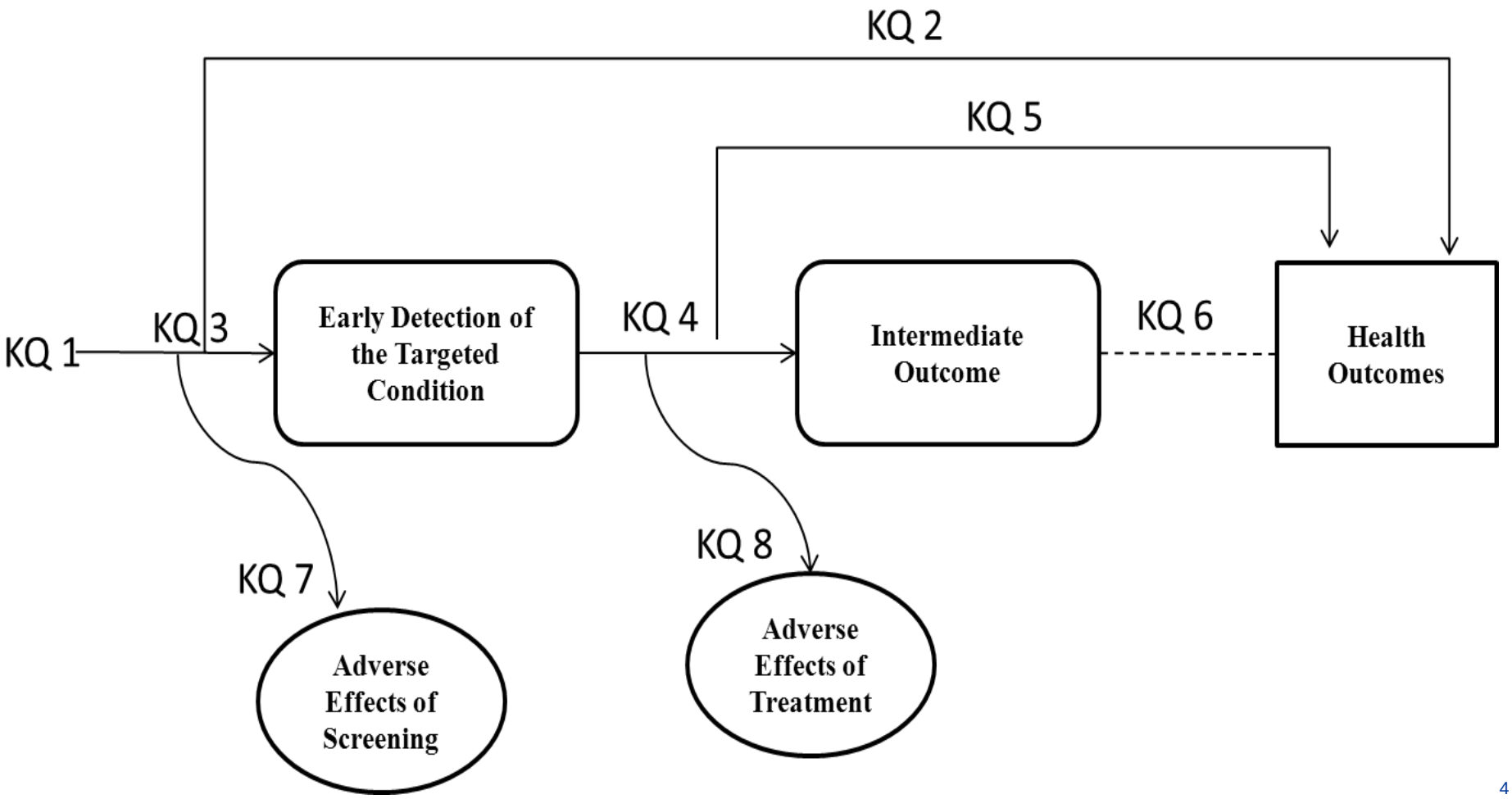
| CRW Members | Role | Institution |
|---|---|---|
| **Alex R. Kemper, MD, MPH, MS** | Chair | Duke University |
| **Anne M. Comeau, PhD** | State NBS Public Health Program | New England NBS Program, University of Mass Medical School |
| **Aaron Goldenberg, PhD, MPH** | NBS Bioethicist | Center for Genetic 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; NBS Expert | 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 |

# 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



# (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?

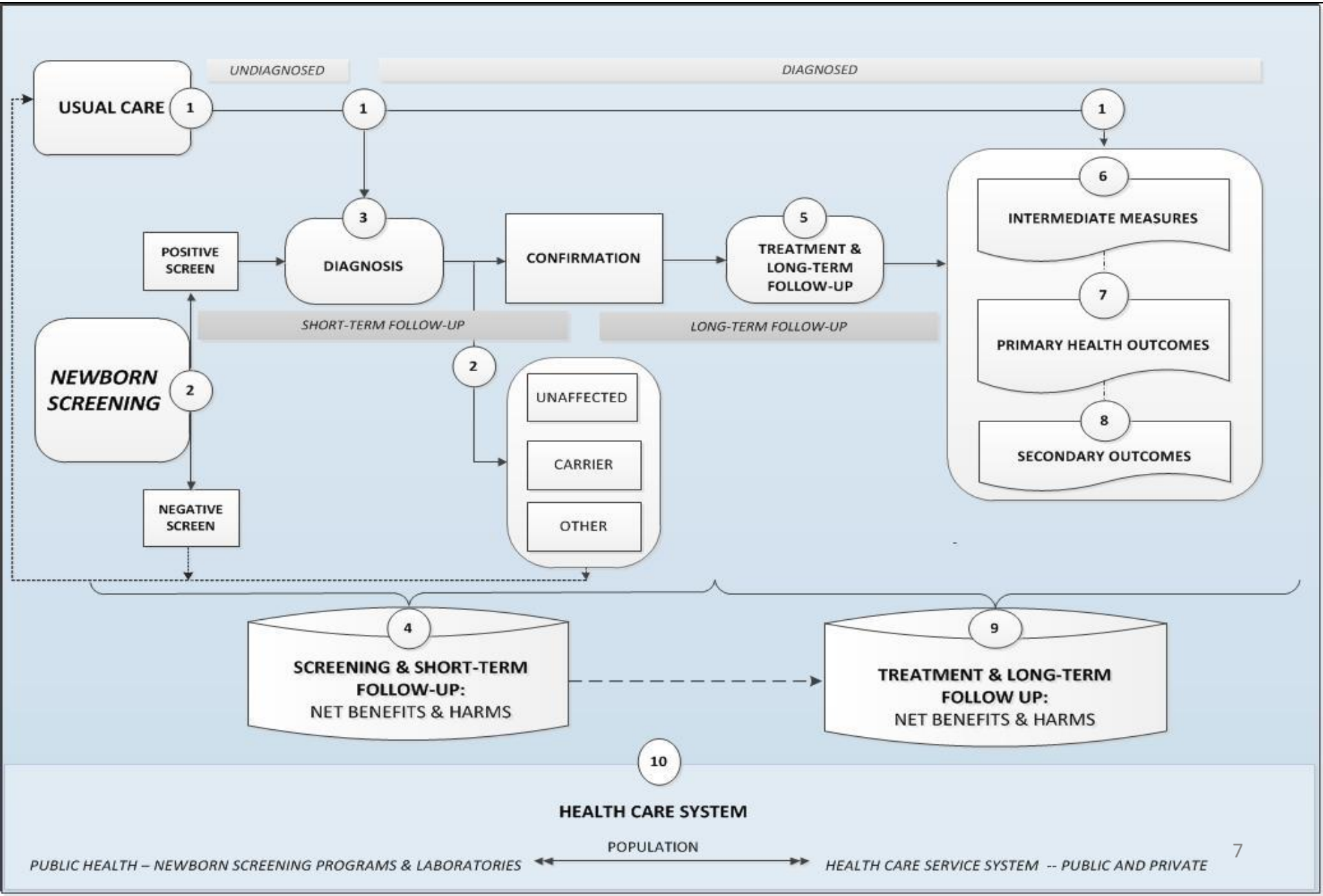
KQ7: What are the **harms associated with screening**?

KQ8: What are the **harms associated with treatment**?

# Conceptual Framework of NBS Impact-*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



# 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?*

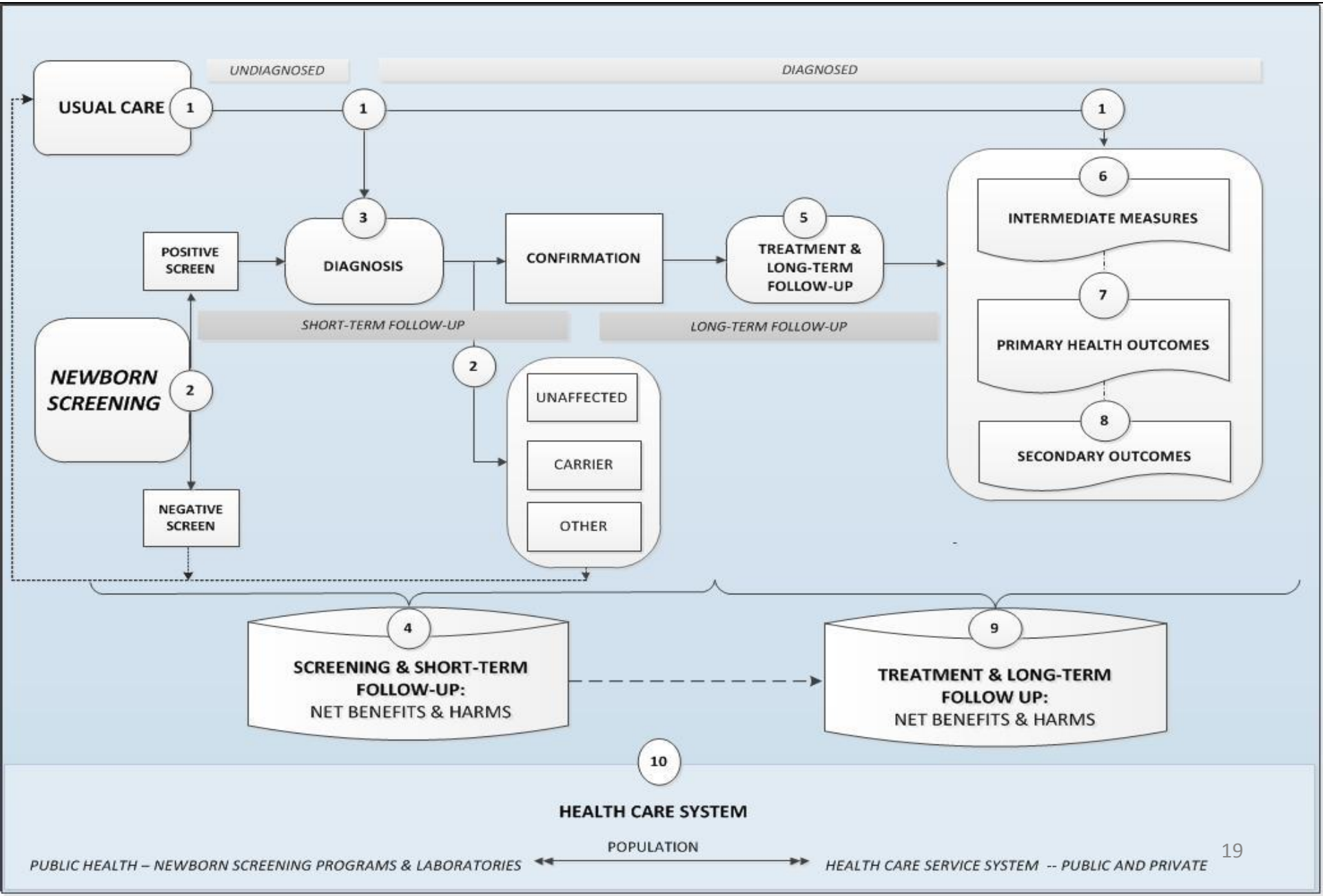
# KTQ 9: Benefits & Harms—Treatment & Long-Term Follow-up

- *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



# MPS I Technical Expert Panel (TEP)

| TEP Members | | Institution |
|---|---|---|
| **Barbara K. Burton, MD** | Professor of Pediatrics<br>Director | Northwestern Univ Feinberg School of Medicine<br>Phenylketonuria Treatment Program<br>Lurie Children's Hospital of Chicago |
| **Lorne A. Clarke, MD** | Professor of Medical Genetics<br>Medical Director<br>MPS Scientific Advisory Board | Department of Medical Genetics<br>Provincial Medical Genetics Program<br>National MPS Society<br>Child & Family Research Institute<br>University of British Columbia |
| **Patricia Dickson, MD** | Chief<br>Associate Professor of Pediatrics | Division of Medical Genetics<br>Department of Pediatrics<br>Los Angeles County – Harbor<br>UCLA Medical Center |
| **Joseph Muenzer, MD, PhD** | Professor of Pediatrics<br>Professor of Genetics | Department of Pediatrics<br>Genetics and Metabolism Clinic<br>University of North Carolina School of Medicine |
| **Barbara Wedehase, MSW, CGC** *(MPS I lead nominator)* | Executive Director | National MPS Society |
| | | |

# 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 | |
|---|---|
| **Age** | **Symptom Presentation** |
| < 1 year | Non-specific manifestations (hernia, respiratory infections) |
| > 1 year | Facial features coarsen<br>Lower spine deformity |
| > 3 years | Linear growth stops<br>Progressive and profound intellectual disability<br>Hearing loss |
| > 10 years | Death due to cardiorespiratory failure, neurodegeneration |

# 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

**MPS I Screening Results**

| | Estimate | 95% Confidence Interval |
|---|---|---|
| Estimated Prevalence | 1 in 35,700 | 1/11,100 – 1/143,000 |
| Positive Predictive Value | 0.33 | 0.08 – 0.65 |
| 3 MPS I "True Positives" | | |
| False Positives | 1 in 17,750 | 1/7,250 – 1/31,900 |
| 6 "False-Positives"<br>• 1 carrier<br>• 2 poor punch<br>• 3 low IDUA, normal alleles | | |
| *Scott et al., 2013* | | |

# MPS I: Natural Course with Clinical Detection

**Table 1. Median years of age (range) of onset, diagnosis, and death for MPS I Registry patients [N=891].**

| | Total number [#] (%) | Onset | Diagnosis | Treatment Initiation | Death [# (%)] |
|---|---|---|---|---|---|
| **Severe MPS I** *(Hurler)* | [508] (57) | **0.5** (0-6.5) [485] | **0.8** (0-23.8) [508] | **1.4** (0.1-31.2) [438] | **3.8** (0.4-27.2) [156 (30.7)] |
| **Attenuated MPS I** *(Hurler-Scheie)* | [209] (23.5) | **1.9** (0-12.4) [187] | **3.8** (0-38.7) [209] | **8.6** (0.3-47.2) [197] | **17.4** (7.5-30.3) [16 (7.7)] |
| *(Scheie)* | [97] (10.9) | **5.4** (0-33.8) [87] | **9.4** (0-54.1) [97] | **17.1** (3.1-62.9) [85] | **29** (17.4-46.6) [4 (4.1)] |
| Undetermined | [28] (3.1) | **0.8** (0.1-7.2) [24] | **1.3** (0-43.9) [28] | **2.9** (0.3-44) [23] | **5.1** (1.8-9.7) [4 (14.3)] |

*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
  - CIHAHL: 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*

- Clincaltrials.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