Recommendation to DACHDNC for Newborn Screening for MPS1

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Condition Review Workgroup

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Secretary's Discretionary Advisory Committee Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (Approved January 31, 2013)

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared	Feasibility	HIGH or MODERATE / LOW
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.		
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			—	
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			—	
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			—	
---		LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.			—	

Net Benefit

- Outcomes
  - Mortality
    - The data do not demonstrate a reduction in mortality from early intervention from newborn screening compared to treatment following clinical detection
  - Cognitive function
    - Severe MPS1
      - MPS1 report: *"Overall, it is difficult to quantify the effect of early HSCT on cognitive outcomes in severe MPSI. Although earlier treatment may improve developmental outcomes, based on the results of one study by Poe et al., quantifying the magnitude of benefit is difficult."*
      - Cognitive outcomes summary: *"…[T]wo recent analyses … reported that transplantation at less than 8 to 16 months is associated with significantly better cognitive outcomes and lower risk of cognitive impairments among affected children."*

Net Benefit

- Outcomes
  - Cognitive function
    - Attenuated MPS1
      - MPS1 report: "*It has been reported that mild cognitive impairment is common among children with attenuated MPS I (Shapiro et al. 2012), and in particular for a subset of the condition associated with the L238Q missense mutation (Ahmed et al. 2014). Cognitive outcomes in attenuated MPS I merit further attention by researchers.*"
      - No data are available regarding whether early detection through newborn screening will improve cognitive outcomes for children with attenuated MPS1.

Net Benefit

- Risks associated with newborn screening for MPS1
  - Low positive predictive values (<5%) with current test technologies
    - Relative high number of false positive results requiring re-testing and confirmation
    - The phenomenon of pseudodeficiency
  - HSCT carries risk of morbidity and mortality
    - Risk associated with HSCT also will be present for children identified clinically
    - Uncertain risk of inappropriate HSCT intervention in children with attenuated form

Net Benefit

- Conclusions:
  - The benefits of early detection via newborn screening for children with severe MPS1 are not definitive due to the lack of data from newborn screening systems
  - However, in terms of cognitive outcomes, the results of studies in other clinical contexts strongly suggest that significant benefits can be anticipated
    - Cognitive benefits of early intervention to children with attenuated MPS1 remain to be determined
  - The level of certainty about cognitive benefits for children with severe MPS1 is “High”

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Feasibility

- The most appropriate test platform and protocol for screening for MPS1 remains to be determined
  - MPS1 testing cannot be conducted with instruments currently used for the RUSP
- However, several options have been evaluated in the context of population screening with dried bloodspots
  - There is clear evidence that newborn screening for MPS1 is feasible as a component of state newborn screening programs
  - Additional work is necessary to define the most appropriate test platform and protocol

Feasibility

- The feasibility of newborn screening for MPS1 is “High or Moderate”

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Readiness

- The survey of public health impact indicates: *"Although most respondents reported that screening for MPS I could be implemented between 1 and 3 years after funding was made available* [79%]*, it is critical to recognize that obtaining funding for the screening test was seen as a major challenge by 81%."*
- Conclusion: Most public health departments are "unprepared for screening" (A3)

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Recommendations

- DACHDNC recommends that newborn screening for MPS1 be approved under matrix category A3
- Substantial work will need to be done in most states to fund, develop, and implement screening for MPS1
  - States should be encouraged to implement screening within 3 – 5 years of approval for inclusion of MPS1 on the RUSP
  - Early adopters of newborn screening for MPS1 are encouraged to obtain data in a rigorous fashion to promote continuous improvement of the evidence base regarding the risks and benefits of screening