Recommendation to ACHDNC for Newborn Screening for X-linked Adrenoleukodystrophy

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Liaisons to the 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		
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.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			----	
Small to ZERO Benefit		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		MOD/HIGH	**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			----	
---	Certainty	LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.			----	

Net Benefit

- Outcomes
  - Mortality
    - The data do demonstrate a reduction in mortality from early intervention from (early) family testing compared to treatment following clinical detection
    - Projected benefits at 15 years from two long term studies show:
      - Averted # cases of death/survival ranged from 17-64
      - Averted # deaths ranged from 7-44 for treated patients
    - No firm published data on Addison's only to confirm or disprove net benefit for early detection. However X-ALD experts on review panel feel that there is.

Types of Disease

- Childhood Cerebral Demyelination ALD – most serious
- Adrenocortical Insufficiency – “Addison’s Only”
- Adolescent and Adult Cerebral ALD
- Adrenomyeloneuropathy (AMN)

Net Benefit

- Risks associated with newborn screening for X-ALD
- N.Y. State reports zero false positive after 1.5 years of screening (based on 2nd tier GC-MS).
- N.Y. State reports no known false negative cases
- Referral rate is low: (percentage of total infants screened referred for diagnostic workup)
- Smaller study by Dr. Moser also reported no false positives.

  - HSCT carries risk of morbidity and mortality
    - Risk associated with HSCT also will be present for children identified clinically

Net Benefit

- Conclusions:
  - The benefits of early detection via family testing or newborn screening for children with severe X-ALD are fairly definitive based on two outcome studies and unpublished data
  - Additional disorders will be detected and may benefit from early detection
  - Female carriers may benefit from early detection if they are or become symptomatic. However a certain portion of female carriers will be missed."

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Feasibility

- The most appropriate test platform and protocol for screening is now established by N.Y. data and other research studies.
- Instruments are already being used in NBS programs; however dedicated msms are needed separate from biochemical molecular testing.
- However there are multi-platform methodologies which can combine X-ALD with LSD and other diseases.
- There appear to be no significant issues with an appropriate screening test based on 1.5 years of N.Y. State screening and a second testing program at Mayo Biochemical lab.

Feasibility

- The feasibility of newborn screening for X-ALD is “High”

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Readiness

- The survey of public health impact indicates: *"Although most respondents reported that screening XALD could be implemented between 1 and 3 years after funding was made available, it is critical to recognize that obtaining funding for the screening test was seen as a major challenge*
- *Conclusion: a number have states have legislative mandates to begin screening and most are already working on test development. APHL document gives great detail on feasibility of implementation of ALD and it is mixed.*

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Recommendations

- ACHDNC recommends that newborn screening for XALD be approved under matrix category A2
- Substantial work will need to be done in most states to fund, develop, and implement screening for XALD
  - States should be encouraged to implement screening within 1-3 years of approval for inclusion of XALD on the RUSP. However, evidence from SCID indicates new programs can take up to 5 years in some states.
  - Early adopters of newborn screening for XALD are encouraged to obtain data in a rigorous fashion to promote continuous improvement of the evidence base regarding the risks and benefits of screening
  - For the most part that simply means those first screened start reaching de-myelination stage through monitoring in NY so more outcome data can be collected.