SACHDNC Nomination and Prioritization Workgroup Report

X-linked Adrenoleukodystrophy (ALD)

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Condition Information

- Type of Disorder: Adrenal insufficiency and neurodegeneration
- Treatment Strategy: Hormone replacement therapy for adrenal insufficiency, hematopoietic cell transplant (HCT) for cerebral demyelination
- Nominators for condition
  - Charlie Peters, MD
  - Advocate Organizations: The Stop ALD Foundation, ALD/AMN Global Alliance, Be A Hero Become a Donor, Cure ALD, Fight ALD, The Myelin Project, Run4ALD, ELA, ULF

Key Question 1

Are there prospective pilot data (U.S. and/or international) from population-based assessment available for this disorder?

- Yes. Some in, some in progress.
- Pilot #1: Hubbard, Moser, et al (2009) – LC/MSMS method. 1000 newborn samples run including 17 known blinded cases. 16 of 17 identified correctly
- Pilot #2: A. Moser (2010 personal communication) – Prospective pilot of 5000 newborns. No cases detected. Pilot study 1: true positive cases: 0; false positive cases: 0
- Pilot Study #3: Current study underway at Mayo Biochemical Genetics Laboratory (Matern, Tortorelli, and Rinaldo) 100,000 specimens plus known cases.

Key Question 2

Does the screening test have established analytic validation?

- Some published, and some currently underway but not published. Early onset cases are readily detected in current studies.

Key Question 3

Is there a widely available confirmatory test/diagnostic process FDA approved? yes

- Plasma testing at Hopkins and 4 other labs in the US (http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/2298?db=genetests)
- MRI screening semi-annually, with diagnosis by specific findings with cerebral inflammation in 80% of affected boys.

Condition Information 1

- **The nominated condition(s) is medically serious.**
  - Yes.

Condition Information 2

The case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening. yes

- Attenuated forms: adult onset form
- Some uncertain genotype-phenotype correlates
- Determined by clinical identification. In the US, the estimated combined male and female frequency of ALD is 1:17,000
- Neurologic problems are found in half of the female carriers, and ~half of the diagnosed males have late onset forms – adolescent and adult. How to address the clinical needs of these folk was not addressed in the nomination. Treatment efficacy is uncertain for those with later onset forms

Condition Information 3

Characteristics of the screening test(s) for the newborn screening system (among other aspects, a low rate of false negatives).

- Pilots 1 and 2 (KKI) : Analysis by tandem mass spectrometry with or without chromatographic separation of lysophosphatidylcholine (LPCs) species (C20 to C26). Multiplexing with acylcarnitines possible.
- Pilot 2 (Mayo): Also tandem mass spectrometry (multiplexed with 6 LSD enzyme assays).

Potential harms of screening and testing

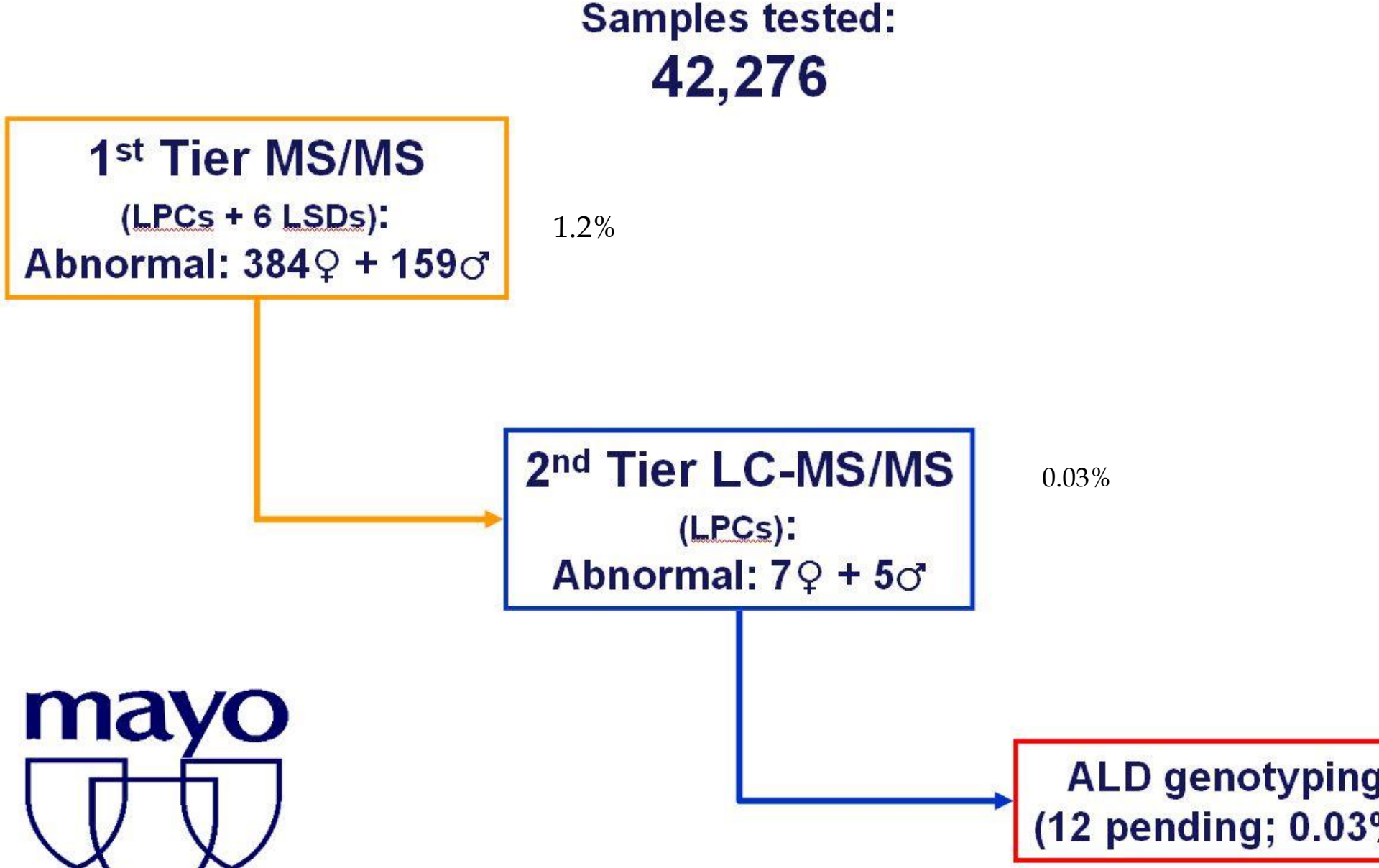
- Patients affected with peroxisomal biogenesis disorders and 70-85% of ALD heterozygous females will be detected by this assay.
- Post analytical tools based on the R4S model are available to discriminate these cases from females affected with other peroxisomal disorders.

ALD Clinical Validation (Mayo)

- **Samples:**
- Normal values were established analyzing 340 anonymyzed, leftover newborn screening blood spots (IRB study# 11-005593).
- 30 ALD* newborn blood spots; 16 received from KKI as part of a collaborative effort to develop and validate the screening test, 14 received from California Department of Public Health made available under IRB study # 10-005821.
- 2 PBD* newborn blood spots received under IRB study #10-000292 and IRB study# 11-005593.
- 6 ALD carrier newborn blood spots received from California Department of Health made available under IRB study # 10-005821. Also 11 (to date) family members of unknown genotype.
- 12 ALD non-newborn blood spots, 6 PBD non newborn blood spots, and 12 ALD carrier non-newborn blood spots received from KKI as part of a collaborative effort to develop and validate the screening test.
- 100,000 prospective DBS from CDPH (41,000 tested to date)

*ALD: X-linked adrenoleukodystrophy PBD: peroxisomal biogenesis disorders

Status of NBS Study for X-ALD



Condition Information 4

If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.

- Known early onset cases readily detectable in stored newborn screening DBS
- Adult onset is unclear at this time
- Reports have described the initial success of HCT for a patient with long-term beneficial effects of HCT and large international HCT experience. With monitoring, timely and effective HCT can be achieved i.e., 95% 5-year survival, with excellent clinical outcomes compared to 54% survival for a similar group not treated by HCT [10]. Of note, boys in the untreated group progressed to a vegetative state and death. Survival for transplanted patients is 92% for boys with early stage brain disease compared with 45% at 5 years for patients with late stage disease. Identification of ALD can lead to timely diagnosis of adrenal insufficiency and initiation of hormone replacement therapy. A metabolic crisis due to unrecognized and consequently untreated adrenal insufficiency can be fatal or result in significant morbidity with long-term sequelae including profound, rapid neurologic deterioration in boys with ALD.

Condition Information 5

Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available.

- Maintenance and stress-dosing adrenal hormone replacement therapy is the standard of care for primary adrenal insufficiency including that associated with ALD HCT* is the only effective long-term treatment for ALD; however, to achieve optimal survival and clinical outcomes, HCT must occur prior to manifestations of symptoms. Gene therapy experimental treatment has been shown to be safe and efficacious
- Urgency It is imperative to implement by 3 months the following: (a) adrenocortical function testing to detect adrenal insufficiency and by 3 yrs (b) serial neuroimaging to detect the earliest evidence of demyelination; therefore timely diagnosis is critical.

* Hematopoietic stem cell transplant

Summary and gaps noted by N&P Workgroup

- Established overall: Case definition, Screening and diagnostic protocol, Treatment protocols. Pilot testing done or underway.
- However, phenotypic spectrum requires additional investigation.
- Appeal of multiplex testing
- Although the Workgroup noted several positive aspects in most of the areas of consideration, the review should not move forward until the largest and latest pilot study on the screening test is completed and data are published or further along. Researchers at MBGL are willing to provide updated results to committee as they are obtained. We recommend the nominators resubmit the nomination at that time.

Nominations and Prioritization Group Recommendations

- No – Do not send forward to Condition Review process for evidence review and public health impact analysis.

Comments?

Questions?