Scientific, clinical, social, and policy considerations for implementing newborn screening for Metachromatic Leukodystrophy

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We Have A Working Screen

A de-identified newborn screening (NBS) pilot study has screened well over 100,000 dried blood spots (DBS) in the State of Washington since the spring of 2016.

Most lysosomal disease newborn screens test for enzyme activity levels using Tandem Mass Spectrometry (MS/MS). Due to the high prevalence of the ARSA pseudo-deficiency allele (Pd) in the general population (1 in 12)[1], the Gelb lab at the University of Washington, with assistance from Teryn Suhr of MLD Foundation, developed a sulfatide screen that is immune to Pd and uses the same MS/MS flow that is common to most state NBS labs.

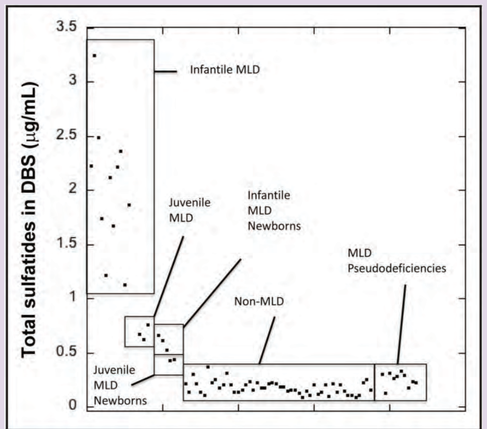


Fig. 3. Total sulfatide concentrations in blood (µg/mL) in patients already diagnosed with MLD (n = 14), non-MLD newborns (n = 50), patients with MLD pseudodeficiencies (n = 10), newborn patients who developed infantile MLD (n = 3), and newborn patients who developed juvenile MLD (n = 2).

Results to date[2] have shown a clear delineation of late infantile MLD. While juvenile MLD is showing sample separation, work is ongoing to determine if this separation is adequate for state public health use.

The current MLD NBS screening flow calls for in-lab diagnostic confirmation, where possible, using genomic sequencing prior to contacting the parents for a whole blood sample. In spite of over 300 known MLD mutations, and limited genotype-phenotype correlation data, indications are that over 50% of sequencing samples confirm or deny late infantile MLD because of higher prevalence of a handful of common mutations.[3]

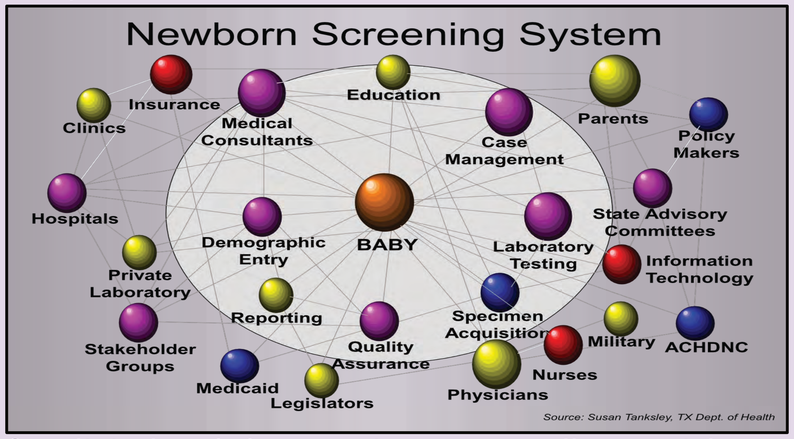
Launching an Identified Pilot – ScreenPlus

A consented identified-baby pilot called ScreenPlus[4] will be launching in portions of New York state in the spring of 2020. This study will validate the MLD NBS screen in a state lab, and will provide an opportunity to go beyond in-lab genomic sequencing to make a formal diagnosis, and to refine the screening, diagnostic, clinical and therapeutic recommendation flow.

Progress is being made to implement additional identified pilots in other states to further validate and refine the screen and the post-screen processes.

Newborn Screening – It's Complicated

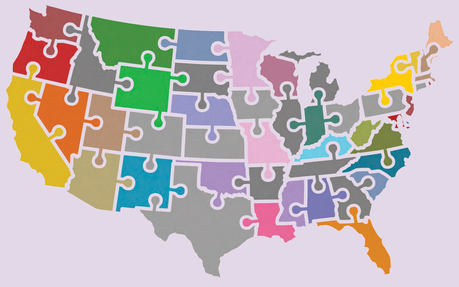
The NBS ecosystem is very complicated and consists of much more than a lab test. The screen results guide a complicated series of decisions and recommendations



for clinical and therapeutic care as well as social services. In the US, NBS can involve both the state and federal governments, insurance companies, caregivers, and many other ecosystem partners in formal and informal roles.

Newborn Screening is State Public Health

Each US state – plus the US territories, Washington DC, and the military for total of approximately 56 distinct programs – define their own philosophy, rules, regulations, flows, decision making criteria, processes, legislative oversight, and resources for newborn screening. Also, all of the ecosystem partners identified above have their own role, requirements, and needs that need to be addressed to implement a successful NBS program.



ACHDNC & The RUSP

The federal government does not manage or control state newborn screening, however, the federal Health & Human Services Secretary formally convenes an advisory committee called the ACHDNC[5] that uses an extensive evidence-based review process to maintain the Recommended Uniform Screening Panel (RUSP) which current consists of 35 core conditions. Most states, in a formal or informal manner, reference the RUSP for guidance when prioritizing the consideration and implementation of new screens.

Key MLD NBS Screen Issues

Beyond the reliability of the screen, a great number of key practical and ethical issues will need to be discussed by key domain leaders as we come to consensus and recommendations for the MLD RUSP nomination. These issues include clinical and therapeutic care recommendations for late infantile MLD newborns, what is a viable therapy for MLD newborns, what if that therapy is not available in your home state (or country), access & reimbursement for expensive therapies, what should be the role of clinical trials and emerging therapies as therapeutic options, can/should juvenile MLD be recommended to be a part of the recommended screen and if so, what clinical and therapeutic recommendations should be made for suspected juveniles, improving genotype/phenotype correlation, and more.

Next Steps

Building on over a decade of MLD ecosystem experience, 5 years of RUSP Roundtable facilitation, and the 2017 MLD NBS Summit, MLD Foundation is currently facilitating a two-pronged initiative to address the many issues and data points needed for a successful RUSP application.

The launch of a MLD NBS Expert Advisory Group is taking place in February, 2020. It is expected this group will concur with MLD Foundation, other MLD advocacy groups, and our biopharma partners that a number of Focus Group meetings will need to be organized to engage a broad, informed, and collaborative set of interested parties to inform and address the many aspects of the RUSP Nomination.

In parallel, MLD Foundation is actively preparing to use the information gathered for the RUSP nomination to formalize strategies to implement MLD NBS in the 56 US public health programs, and in parallel, internationally.

If you have an interest in MLD NBS please contact us.

1. Pseudo-deficiency of arylsulfatase A: a common genetic polymorphism with possible disease implications, Hohenschutz, C., Eich, P., Friedl, W. et al. Hum Genet 82, 45–48 (1989). https://doi.org/10.1007/BF00288270
2. Sulfatide Analysis by Mass Spectrometry for Screening of Metachromatic Leukodystrophy in Dried Blood and Urine Samples. Clinical Chemistry 62:1 (2016) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737087/
3. Unpublished and unreviewed preliminary natural history data, Dr. Laura Adang, Children's Hospital of Philadelphia
4. Identifying Rare Diseases in Newborns: Broader Screening for Better Outcomes, Dr. Melissa Wasserstein https://www.montefiore.org/body.cfm?id=1738&action=detail&ref=1607
5. Advisory Committee on Heritable Disorders in Newborns and Children, https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html

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