RANSIP newborn screening program: working to bring early diagnostics, inclusion, and therapeutic access to metachromatic leukodystrophy patients

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WORLD*Symposium*™ 2021, Poster #249

Metachromatic Leukodystrophy – MLD

Metachromatic leukodystrophy is a rare autosomal recessive metabolic disease affecting an estimated 1 of every 40,000 births. MLD is generally thought of as presenting in three forms, although there is overlap. Late infantile symptom onset (50–60% of cases) is generally at 12–18 months. Juvenile (20–30%) is more often divided into early juvenile (3–7 yrs) and late juvenile (7–16 yrs), and adult (10–20%) with symptom onset from the late teens to the 6th decade.

HSCT and gene therapy (EU approval Dec'20) are available therapies primarily targeting pre-symptomatic individuals.

In spite of over 300 known MLD mutations and limited genotype–phenotype correlation data, indications are that over 50% of NBS sequencing samples may confirm the form of MLD because of the higher prevalence of a handful of more common mutations.[1]

MLD Has a Working Screen

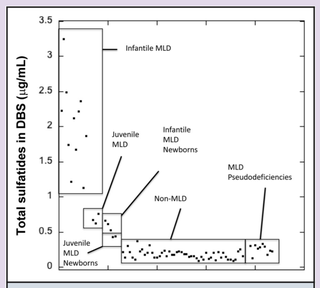


Fig. 3. Total sulfatide concentrations in blood (µg/mL) in patients already diagnosed with MLD (n = 14), non-MLD newborns (n = 50), patients with MLD pseudodeficiencies (n = 10), newborn patients who developed infantile MLD (n = 3), and newborn patients who developed juvenile MLD (n = 2).

A State of Washington de-identified newborn screening pilot study has screened well over 100,000 dried blood spots (DBS) since the spring of 2016.[2] It is a three-tier screen using MS/MS to detect sulfatide levels, then ARSA-A enzyme levels, and finally targeted genomic sequencing of dried blood spots before notifying parents of a screen positive.

ScreenPlus – Identified Pilot Study

A consented identified-baby pilot called ScreenPlus[3] will be launching in portions of New York state in early 2021 after being delayed from the spring of 2020 partially due to COVID. This study will validate 13 disorders, including MLD, in a state lab, and will improve MLD screening, diagnostic, clinical and therapeutic recommendations and processes, as well as gather key data needed to prepare a successful RUSP nomination.

Newborn Screening – It's a Gateway

NBS is much more than a lab test. In the US and most countries, NBS is run by the public health system. In the US, each state has responsibility for its own NBS system so there are over 54 independent NBS systems (50 states plus territories and the military). The screening results inform a complicated series of decisions and recommendations for clinical and therapeutic care as well as social services.

NBS is Health Equity

NBS is among the first records in a baby's health record and is one of the only places where there is universal and full equity in access to health services because (in the US) 99.9% of all new babies are screened.[4]

99.9% = Universal Access & Equity!

Improves Clinical & Therapeutic Care

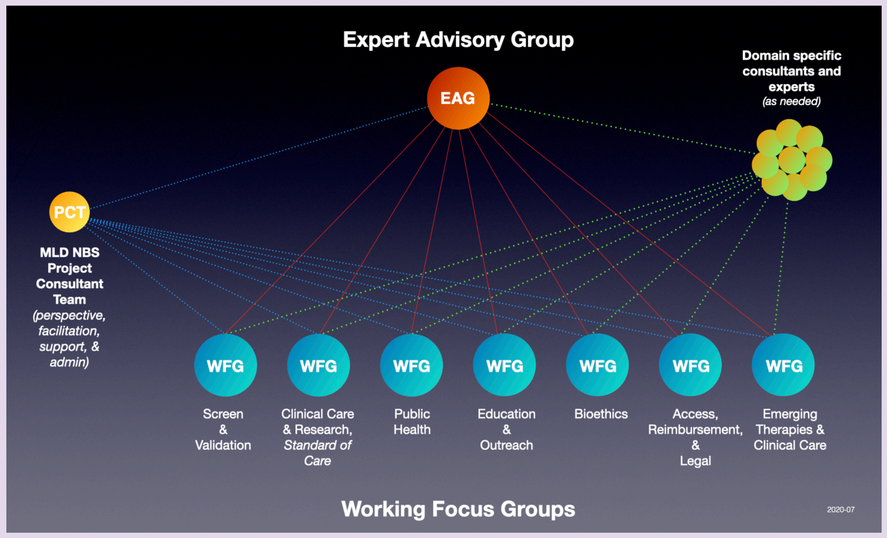
NBS is an opt-out public health program and as such is not an opportunity to advance research without additional consent, however, many of the disorders added to screening panels over the past decade are rare diseases. These families will be referred for local clinical and therapeutic care coordination, and ideally to trusted patient advocacy groups for more information about accessing disease-specific clinical and therapeutic experts who are often not local or even within a given state or country.

A Starting Point for Research and Understanding

These contacts to disease experts and advocacy groups can be the start of not only supporting care, but also engaging a family and their baby's data, outside of the public health NBS program, in research studies to better understand the disease, diagnostics, therapies, and to improve quality of life.

MLD RUSP Approval & Implementation

An organizational structure and strategy for the RUSP Approval and Newborn Screening Implementation Project (**RANSIP**)[5] was adopted by the 20 experts who attended a launch meeting organized by MLD Foundation during the 2020 WORLD*Symposium*™.



First Arm – RUSP Approval

Being added to the Recommended Uniform Screening Panel (RUSP) is an expert-reviewed, evidence-based federal endorsement (HHS/HRSA/ACHDNC)[6] that the MLD ecosystem is ready to identify and care for newborns found to have MLD. This approval is not required for public health implementation, however, a RUSP approval gives public health programs high confidence the MLD NBS program is robust, accurate, complete, and ready to launch — often resulting in an easier path to implementation.

Second Arm – Implementation

Using the data provided in the comprehensive RUSP nomination package, and likely before RUSP approval, which can be a multi-year process, we will be working to launch additional pilot studies and to add MLD to state and international newborn screening panels. RANSIP is structured to shorten the 5–10 years recent additions to the RUSP have taken to be implemented across all states so all babies can have a MLD-free life.

Expert Advisory Group

An Expert Advisory Group of MLD and NBS experts is leading the effort to prepare the RUSP nomination. They met every 4–6 weeks throughout 2020. They are supported by seven Working Focus Groups, a Project Consulting Team, and biopharma.

Working Focus Groups

The WFGs engage participants from many ecosystems: MLD, NBS, public health, clinical research, biopharma, government, advocacy, and families. Information exchange and discussion is two-way where all parties are learning from and informing each other. The WFGs provide information and feedback to the EAG to optimize the RUSP nomination effort and prepare for public health launch of MLD screening.

WFGs are established for Screening & Validation, Clinical Care & Research (including developing a MLD Standard of Care), Public Health, Education & Outreach, Bioethics, Access & Reimbursement, and Emerging Therapies.

Progress Since 2020

The EAG met 9 times over 11 months and has a draft RUSP Nomination underway, the seven WFGs met a total of 24 times over 7 months with over 900 WFG meeting invitations issued. APHL, NBSTRN, ACHDNC, individual state labs, US & international advocacy, and many other NBS ecosystem groups are engaging to be informed and contribute to the MLD RUSP and implementation efforts.

Plans For 2021

The RUSP nomination will incorporate ScreenPlus and other pilot data and experience, and perhaps be submitted to the ACHDNC by the end of the year.

Other key RANSIP activities:

- Additional pilot and launch discussions and efforts.
- Additional emphasis of the Clinical Care & Research WFG on formalizing a MLD Standard of Care.
- Develop the support infrastructure, launch, and guide the pre- and post-RUSP state legislative and policy efforts necessary to enable state MLD NBS launches and to enable policy allowing access and reimbursement for emerging therapies.
- Expand the Education & Outreach WFG efforts to include the broader public in policy.
- Collaboratively develop systems and databases to track MLD diagnostic and therapeutic outcomes and improve genotype/phenotype correlations.

1. Unpublished and unreviewed preliminary natural history data, Dr. Laura Adang, Children's Hospital of Philadelphia
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. 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
4. How many newborns are screened in the United States?, https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/infants-screened
5. MLD RANSIP – RUSP Approval and Newborn Screening Implementation Program, https://MLDnewbornScreening.org/rusp-nomination/
6. Advisory Committee on Heritable Disorders in Newborns and Children, https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html