DEPARTMENT OF HEALTH

Protecting, Maintaining and Improving the Health of All Minnesotans

October 29, 2024

Ms. Shanna Quimby
Gavin Flying For A Cure
1382 Ridgewood Drive
Winona, MN 55987

Dear Ms. Quimby and Co-Sponsors (Dr. Paul Orchard and Senator Jeremy Miller),

The Advisory Committee on Heritable and Congenital Disorders, also called the Newborn Screening Advisory Committee (NSAC), appreciates your nomination of Metachromatic Leukodystrophy (MLD) for inclusion on Minnesota's Newborn Screening Panel. The committee is grateful for you and additional families sharing your perspectives and urging why newborn screening is important to the MLD community during the public comments at both the April 23rd and October 8th meetings.

A condition readiness workgroup composed of experts in Minnesota familiar with MLD was formed as part of the committee's formal condition consideration process. The findings from this workgroup were sent to advisors prior to the October meeting and key discussion points that arose from the work group were presented at the meeting. The committee recognizes MLD as a serious condition where early identification and treatment has better outcomes for early onset cases. However, based on review of available evidence, the committee concluded to not recommend MLD for addition to the panel at this time.

During the committee meeting on October 8th, prior to a vote on whether to recommend MLD for addition to the panel, advisors and evidence review workgroup members participated in discussion, major topics included:

- **Characteristics of the screening test**
    - **U.S.-based data** – Currently, the only universal pilot for MLD is in Germany. The only pilot in the U.S. is a consented pilot through New York's supplemental ScreenPlus program. The Germany pilot has identified 3 MLD cases (2 early juvenile and 1 late onset) and ScreenPlus has not identified any cases yet, although their sample size is still small. Much of the data and published literature around the testing algorithm has been done using European samples from confirmed MLD cases. This is notable because newborn screening samples are collected later in Europe and may have an impact on whether it is even possible to pick up cases of MLD through newborn screening at 24 hours, which

is when most dried blood spots are collected in the U.S. The state of New York has been approved for a pilot to universally screen for MLD that is set to start in 2025 and Illinois is working towards screening as well. Both states will produce U.S. based data to show how the sensitivity and specificity of the algorithm translates between Europe and the U.S.

- **2nd Tier Testing Options**
  - **ARSA enzyme activity** – Currently, this test is not available in dried blood spots through a commercial testing laboratory. ARSA enzyme activity is a spectrum and activity levels are expected to be low or absent in individuals with MLD but also those with pseudodeficiency or carriers of the condition, which are not the specific targets of screening. Additionally, due to the nature of the ARSA enzyme test, Arylsulfatase B activity could make the ARSA activity look normal which is a limitation that has not been sufficiently addressed in currently published literature. This may result in false negative cases of MLD. As the ARSA enzyme test becomes available (expected within the next six months) and more work is done in pilots utilizing this test as part of their screening algorithm, we may get more information to better understand the benefits and limitations.
  - **Molecular testing** – Currently, the pilots and approaches to screen for MLD use molecular as their 2nd tier test. There was discussion about the cost incurred by the program or the families should molecular testing be needed to improve specificity. If a more specific first tier or first tier/second-tier approach is identified that reduces the number of cases needing molecular testing, this may be a non-issue.

- **Target of screening** – MLD is a condition with variable onsets. Treatments available and their effectiveness differ based on early or late onset MLD. Current testing approaches have not proven a way to target the early onset form of MLD which is the form most likely to benefit from early identification and treatment.
- **Diagnostic ambiguity** – For a diagnosis, testing includes: elevated sulfatides in urine, decreased ARSA enzyme activity in leukocytes, and molecular analysis of the *ARSA* gene. Currently, diagnostic testing does not always provide a clear answer even in individuals with clinical suspicion of symptoms because they may have mild biochemical labs or variants of uncertain significance found on molecular testing. Applying this information to an asymptomatic newborn detected through population newborn screening brought up the possibility for creating patients in waiting with unclear clinical benefit.
- **Access to treatment and follow-up care** – Cost and insurance coverage were discussed, and how those factors may impact the accessibility of treatment and care for all individuals who may be identified through population-based newborn screening. Although this was discussed, the committee recognized this is a consideration for ensuring individuals have access to treatment and not a barrier to screening.

Although MLD is not being recommended for addition at this time, the committee will stay abreast of new evidence and information that becomes available. The condition readiness workgroup will reconvene to review new evidence and present back to the committee at the April 15, 2025 meeting. Additionally, MLD is currently under formal evidence review by the federal Advisory Committee on Heritable Disorders in Newborn Children that makes recommendations on which disorders should be added to the recommended uniform screening panel (RUSP). If MLD is added to the RUSP, the Minnesota Newborn Screening Program will re-nominate MLD for expedited review by the committee. If MLD is not added to the RUSP, we encourage you to re-nominate MLD when more evidence is available.

If you have any questions or would like to schedule time to discuss the information in this letter, please contact the NSAC coordinators at health.nsac@state.mn.us.

Thank you again for your nomination of MLD for inclusion on Minnesota's Newborn Screening Panel, and I look forward to hearing from you soon.

Sincerely,

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Rae Blaylark
Chairperson
Advisory Committee on Heritable and Congenital Disorders
Enclosure: October 8th presentation, October 8th meeting minutes, publications provided