Meeting Minutes: Advisory Committee on Heritable and Congenital Disorders (Newborn Screening Advisory Committee) Fall 2024 Meeting

October 8, 2024

Minutes prepared by: Jessica Cavazos, McKayla Gourneau, and Amy Dahle
Location: The Wilder Foundation Center
451 Lexington Pkwy N., St. Paul, MN 55104

Attendance

- Rae Blaylark (chair)
- Katie Pfister (vice-chair)
- Susan Berry
- Alex Boucher
- Kaitlyn Campbell
- Christen Ebens
- Tricia Hall
- Bob Jacobson
- Courtney Jarboe
- Dietrich Matern (attended virtually)
- Brooke Moore
- Randal Richardson
- Emelia Rogers
- Annamarie Saarinen
- Kali Schreiner
- Kathy Stagni
- Queenie Tan
- Renee Temme

Absent: Jennifer Arveson, Teresa Rink

Decisions Made

- Decision: Metachromatic leukodystrophy (MLD) is not recommended for addition at this time.
- Decision: MLD evidence review committee will reconvene and present any new evidence at the April 2025 NSAC meeting.

Meeting notes

Roll Call – Rae Blaylark

Welcome & Program Updates – Carrie Wolf

- Implementation status of currently approved disorders
  - Duchenne muscular dystrophy (DMD): added to MN newborn screening panel in January 2024, expected to begin screening in early 2025. Screening approach will be looking for elevated CK-MM levels in dried blood spots (DBS). If elevations are present, a repeat specimen will be requested at 1-2 weeks of age. If elevations persist, newborns will be referred to a neuromuscular specialist for a diagnostic workup.
    - Sue Berry: When we talked about DMD screening, we discussed the importance of having a molecular method, where does that stand?

    - Carrie Wolf: We don't have an available vendor with a contract to perform 2nd tier molecular testing. If it becomes available, we will look into it, but as of today, a 2nd tier molecular screen is not available to us.
  - Guanidinoacetate methyltransferase (GAMT) deficiency: added to the recommended uniform screening panel (RUSP) in January 2023, and MN's panel in August 2023. Screening expected to begin in early 2025.
  - Mucopolysaccharidosis type II (MPS II): added to the RUSP in August 2022 and MN's panel in August 2023, method development is in process and go-live is planned for late 2025.
  - Krabbe disease: started screening on February 26, 2024.
    - One confirmed early infantile case has been found and transplanted, one other case has screened positive with outcome pending.
- FDA Ruling on Lab Developed Tests
  - In May 2024, the FDA said that all laboratory tests must be submitted to the FDA for approval. Many of our tests are lab developed meaning a lot would need to be done.
  - The FDA ruling is currently being contested in pending litigations.
  - If the FDA ruling stands, we will need to submit our tests to the FDA and that could change the timeline of our implementation of these new conditions. Even if we are using an FDA-approved kit, if we multiplex a new condition with it, the kit is now considered a laboratory developed test and will need reapproval.
- The Newborn Screening Program has also received two nominations for new conditions: Gaucher disease and Fabry disease. These are under steering committee review right now.

MLD Condition Readiness Workgroup Report Out – McKayla Gourneau

- The evidence review workgroup consisted of experts throughout the state of Minnesota to review available literature and assess criteria spanning the following areas related to MLD: clinical characteristics, the screening test, diagnosis, follow-up, treatment, and management. The workgroup met three times and completed their work on August 1st. Full discussion summary was provided prior to the meeting to advisors for their review. The presentation at this meeting focused on discussion points and questions that came up during the workgroup for further discussion at this meeting.
- Clinical Factors: The clinical presentation of MLD was provided at the April 2024 meeting by Dr. Pillai and Dr. Orchard and summarized for attendees. Additional discussion points from evidence review included:
  - Variable onset condition: MLD is a condition with variable onsets ranging from late-infantile (within 30 months of age) to adult (> 16+ years). Late infantile is the most common and most form accounting for 50-60% of cases. The nomination and testing approaches are inclusive of all onsets.

- Treatment approach: varies depending on onset. Early onset can be treated before symptoms present with gene therapy via autologous stem cell transplant. Late onset involves monitoring visits every 6-12 months until treatment via hematopoietic stem cell transplant is appropriate.
    - Available evidence for gene therapy shows significant improvements in those with early onset MLD in comparison to those who do not receive treatment, however length of follow up data is limited. Treatment available for all types of MLD cannot prevent all condition related morbidity and mortality.
- Management guidelines: consensus-based guidelines have recently been published in Europe and the US (Laugwitz 2024 and Adang 2024).

- Testing Approaches: Three tiers of screening have been discussed in the literature and during evidence review.
    - Sulfatides using LC-MS/MS: Screening for sulfatides can be done in most newborn screening labs on a high throughput assay. This can be multiplexed with other conditions screened for such as X-ALD or other lysosomal storage disorders which can reduce costs for screening and needed resources.
        - Sulfatide species have different false positive rates. C16:0 is reported to have rates around 1% of newborns tested over cutoffs whereas a recent study reported C16:1-OH has a predicted 0.048% refer rate.
        - Limitation was brought up that much of the testing done is based on dried blood spots collected in European countries which routinely collect DBS specimens later than in Minnesota and may impact reported sensitivities and ability to pick up cases of MLD.
    - ARSA enzyme activity assay: ARSA enzyme activity will be low or absent individuals with MLD, but can also be low in carriers, those with pseudodeficiencies (10% of general population), or individuals with multiple sulfatase deficiency. This assay is not currently available in DBS. It is expected to be available within six months.
    - Molecular analysis of *ARSA* gene: evidence review workgroup brought up this could be a method utilized as a part of the screening algorithm or something done clinically
- Current Screening Efforts: No state is actively universally screening for MLD. Consented, supplemental pilot in NY (ScreenPlus) screens for MLD using C16:0 and molecular analysis of *ARSA*, but has not yet identified any cases of MLD.
    - The only universal pilot to date has taken place in Germany and has screened 109,259 newborns using a 3-tier approach screening for sulfatides, ARSA enzyme activity, and molecular analysis of the *ARSA* gene. This pilot has identified two early juvenile onset cases, one late onset case, and three MLD carriers.
    - MLD has been nominated to the RUSP. At the meeting on August 9th, the federal Advisory Committee on Heritable and Congenital Disorders voted to move MLD to full evidence review and a vote is expected in 9 months.

- Public Health Considerations
  - DBS is recommended to be collected between 24-48 hours in MN, with a majority of screens being collected at 24 hours. Results are typically reported within the first week of life which is when a diagnostic workup for an abnormal screen typically happens.
  - Need to consider the impact on families regarding false positives, identifying late onset forms of MLD, and the needed effort for undergoing a diagnostic workup in the newborn period and likelihood of benefiting from that workup.
  - Clear case definition is needed to confirm or rule out a diagnosis in an asymptomatic newborn which should be seen for a majority, however as with other conditions, concerns around variants of uncertain significance and mild or conflicting biochemical labs were brought up during evidence review.
  - A diagnostic work up must be done at a specialty center. Gene therapy is only offered at 5 locations throughout the country and one location in Minnesota (University of Minnesota).
    - The limited number of treatment centers and the cost of the gene therapy (~$4.35 million) called into question impact on availability and accessibility of treatment for all babies who may be identified with MLD through newborn screening with consideration to public versus private insurance and in-state versus out-of-state residents.

MDH Specific Considerations – McKayla Gourneau

- In 2023, MDH screened 60,400 newborns. A breakdown was provided comparing projected numbers to what would be expected in Minnesota if similar refer rates were seen to the universal pilot in Germany as well as some limitations.
  - 0.349% had elevated sulfatides, 8.7% had reduced ARSA activity in DBS. DBS specimens are recommended to be collected between 36-72 hours in Germany. It was projected 211 specimens would need 2nd tier ARSA activity testing and 18 specimens would need molecular based on 2023 birth rate. These projections are estimates and could vary significantly depending on testing approach in a US based universal NBS system.
  - The projected numbers from the Germany pilot do vary from what could be possible using the C16:1-OH sulfatide species as a primary analyte, however that analyte has not been used, published, and shown outcomes in screening pilots yet.
- For a first-tier approach, multiplexing with X-ALD would be the most feasible for the MN program. The projected refer rate after first tier testing necessitates a second-tier and that would need to be sent out due to complexity of the assay and the expected volume would not be cost effective to do in-house as is the case for most second-tier tests.
- Briefly, the current fee for MN NBS was presented ($235). The cost of implementation and screening for currently approved conditions is accounted within the fee. Although we can try to make estimates and approximations based on European data, there is too much

variability and too many limitations to know for certain if the current cost of the NBS fee can cover implementation and sustainability for screening for MLD. It is unknown if a fee increase is needed or not.

- Sue Berry: Minnesota is currently the most expensive newborn screen in the country.
- It was noted that screening algorithms that have high refer rates for complex second tier assays or necessitate molecular analysis for specificity use more funding to do.

Decision Making Tool – Matrix: The matrix provides a determination of Ready, Investigative, or Not Ready based on how many criteria in each category are deemed met by the evidence review workgroup. MLD is determined to be **Investigative**.

Discussion – Rae Blaylark, all advisors & participants in evidence review workgroup

- Sue Berry: If you pass the expense of the molecular test to the families, it's even more than $1000, because it's the cost of the clinical appointment, the lab fee, the visit to evaluate them, and everything else. You can't just pass the molecular test to the clinical side because that's passing a multi-thousand dollar test onto the families.
- Amy Dahle: (Sharing on behalf of Dieter Matern) New York was just funded to do an MLD pilot starting in 2025, looking at sulfatides, ARSA activity, and molecular. It's a non-consented pilot for 2 years and 200,000 newborns.
- Christen Ebens: Paul Orchard wanted to share a recent publication the German group put out in the New England Journal where they did screening of 109,000 newborns and identified 3 positive cases, two of which went to gene transplant. This brings up the question of strategy – considering various tiers and false positive rates and how they can be lower with better testing. How can we get to that and make it financially viable as well as emotionally viable for families and practitioners dealing with potential false positive results? The current strategy doesn't look fantastic, but there's good evidence there are better tests in development.
- Sue Berry: We mention availability of treatment, but we need to be very thoughtful that every child who is diagnosed will have access to that care, particularly when considering the cost of this treatment.
- Annamarie Saarinen: Other LSDs that have been previously added to the panel, what do we see from the presumptive numbers before addition compared to screening?
  - Tricia Hall: You find about the expected number of target cases and a lot more milder onset cases.
- Annamarie Saarinen: Clarification on frequency and timing of treatment? Is it critically important to know in the first couple of days of life?
  - Sue Berry: It's a one dose treatment but does require a transplant so all of the care and time associated with that piece. It does not have a newborn presentation.

    - Christen Ebens: Finding out about a diagnosis of MLD by symptoms at 2 years of age is too late, so early identification is still important. The disease progresses quickly in the late-infantile and early juvenile forms making identifying affected individuals through family history or newborn screening the best ways to get them to treatment in time.
- Christen Ebens: Individual hospital systems cannot undertake the cost burdens of gene therapy products and they will not offer these treatments in an inequitable manner. The treatment would not be offered to a private insured patient if it won't be offered to an uninsured patient. There are people thinking and working on these issues and it is important, however I don't know that it should play a role in this committee's decision to identify patients early.
- Rae Blaylark: A couple of questions.
    - Cost of screening should be taken into consideration to the cost of a diagnostic odyssey families face, although that can be hard to measure. On both sides, the family pays that cost. Is there a cost analysis being done to answer this question?
    - With screening for other disorders like sickle cell disease, we reliably identify individuals with trait. Is that the same likelihood with screening for this condition?
        - Sue Berry: The testing approach won't pick up carriers in the same way testing for sickle cell or cystic fibrosis (CF) does. However, we may pick up on pseudodeficiencies or carriers depending on the sensitivity of the assay, but not with as high of a degree of certainty that we see for sickle cell or CF. If we end up doing DNA testing as a part of screening, we learn about the genetic status of the child and potentially their family members. That's one of the tensions in newborn screening today is that adding DNA testing goes beyond screening and risk assessment on into a more diagnostic framework.
- Tricia Hall: A few comments.
    - It's been published that screening for MLD does identify carriers. ARSA enzyme activity is a spectrum so to catch our target we will likely pick up carriers and pseudodeficiencies along the way.
    - To take this a step further, the confirmatory testing for MLD is not always clearly diagnostic and can give a yes or no answer even when there is a clinical suspicion: they have variants of uncertain significance, they have slightly reduced enzyme activity that overlaps with carriers, there are mild sulfatide elevations in urine. I anticipate these uncertain cases increasing if we start screening the general healthy population and have the absence of a phenotype to consider as well.
    - Screening may identify carrier children with affected parents who may not be presenting clinically with symptoms.
    - Arylsulfatase A is probably the enzyme most prone to false negative results because there's crosstalk with arylsulfatase B and currently published methods for ARSA have not evaluated that. There is a hard cut point in the algorithm that shows if ARSA is normal, you don't report it out when it could be falsely normal due to interference from

arylsulfatase B. This interference is typically associated with the assay and not the genotype so although the sulfatide, ARSA activity, molecular approach may reduce false positives, it may be prone to missing cases of MLD. No one has been screening for MLD long enough to know if cases are being missed yet since they've only been happening for one or two years.

- Sue Berry: Recently, the ACHDNC made a recommendation to add Krabbe, another lysosomal storage disorder with variable onsets, specifying a screening approach to target the most severe infantile form of the condition. Has a screening target been specified for MLD or will we potentially be screening for all onsets? If we are screening for all onsets, who will be following the adult-onset cases?
  - McKayla Gourneau: The nomination did not specify a specific onset of MLD as a target – the screening approach suggested could detect all forms of MLD. The ARSA enzyme assay is not currently available and there isn't evidence to show the screening algorithm with sulfatides and ARSA activity alone can separate between early and late onset MLD.
- Sue Berry: Can we get a clarification on the matrix? There are three categories with red, yellow, and green and I know we are talking about changing it, but for MLD we are in a very ambiguous setting.
  - Bob Jacobson: Back when we first made this matrix, the idea was investigative makes more sense when we are waiting for a year or two's worth of data and there is work in progress. Not ready is more if all of the data is available and we intend to put it away for years and not revisit the condition.
- Bob Jacobson: We had a similar price tag with treatments for Krabbe and severe combined immune deficiency, what makes this treatment different?
  - Sue Berry: In some ways, it's not different. But the treatment for MLD is more expensive. Another issue the committee hasn't regularly talked about is access to treatment for every child who may receive a diagnosis after identification through mandated newborn screening. Availability does not equal access.
- Courtney Jarboe: The testing for the screen itself has been done through pilots in other countries. Will that be able to translate to screening here and effectively address false positives and false negatives? It seems previous nominated conditions have had more certainty around feasibility and sustainability in the long term for a testing approach.
  - McKayla Gourneau: It is difficult to know if the screen will be directly translatable – we don't have evidence to say that it will or won't be possible. With previous conditions, there was data available from US-based pilots or other states that were already screening that just isn't available for MLD which leaves us more uncertain. The upcoming pilot NY was approved for would be able to answer many of those questions in terms of how well the testing could translate to a US based NBS system.
- Amy Dahle: (sharing on behalf of Dieter Matern) The cost issue came up at the ACHDNC when Krabbe was discussed and the HRSA rep stated that adding Krabbe to the RUSP could promote better coverage for the affected babies. I don't think the Minnesota Advisory

Committee is the place to worry about the treatment cost, but whether the NBS can be efficient to detect affected babies for whom treatment makes a significant positive difference without causing too much anxiety for cases with false positive results.

- Christen Ebens: what would potential next steps look like depending on our vote today?
  - McKayla Gourneau: There are three ways the vote could go today: recommend the addition of MLD, not recommend the addition of MLD at this time, or delay the vote to a future meeting.
    - If recommended, NSAC coordinators put together a package of information for the Commissioner of Health who makes the final decision on whether or not to add MLD to the newborn screening panel in Minnesota. If it is added, implementation efforts begin.
    - If not recommended at this time, NSAC coordinators and the NSAC chair put together a summary letter of the decision to respond to nominators with points discussed during the nomination process and vote.
    - If there is additional information the committee believes is needed to make a decision that will be coming out in the near future, a motion can be made to delay the vote to make a recommendation on the addition of MLD.
- Sue Berry: A nomination was made for MLD to the RUSP and the secretary's committee will be doing a full evidence review. That information should be coming out in the next six months. [Vote expected in May 2025 with updates of evidence periodically at quarterly meetings until then.]
- Tricia Hall: If we were to wait for an ACHDNC milestone of some sort, would that be delaying anything based on MDH's capacity to start working on MLD? We would get more information from the thorough evidence review done through the federal committee and time to get more information about an ARSA blood spot assay.
  - Carrie Wolf: In the laboratory, we are already doing some work looking at MLD feasibility. Waiting for more information wouldn't hold anything up for what we have capacity to do right now.
- Katie Pfister: I move to close the discussion.
  - Christen Ebens: I second.
  - Unanimous in favor.

Vote: Voting at the meeting occurred via anonymous ballot. Two advisors voted absentee, and 17 advisors voted in-person.

- Motion made by Sue Berry: I move that we recommend the addition of MLD to the newborn screening panel.
  - Second by Christen Ebens

    - In favor: 8
    - Opposed: 11
    - Abstain: 0
  - Motion does not pass.
- Kaitlyn Campbell: Could we have another vote? Can another committee member make a motion to delay the vote until there is certain evidence that has been published to help inform the vote?
  - Annamarie Saarinen: Yes, could we do another vote at our April meeting when more data may be published or information from the ACHDNC might be available early (ahead of their May meeting) instead of asking the community advocates to go through the renomination process?
  - Sondra Rosendahl (previous NSAC coordinator): Following the committee bylaws, the motion was made to approve the condition. It was seconded. The committee voted. A motion to delay a vote needs to be made before a vote happens to recommend a condition be added. In the case of MLD, the vote can no longer be delayed to a future meeting because the vote already happened.
  - McKayla Gourneau: If the ACHDNC determines there is sufficient evidence to recommend MLD to the RUSP, we do have an abbreviated process here in MN for RUSP approved conditions where the NBS program makes a nomination for that condition.
- Renee Temme: I motion that the expert review committee convene again before the April 2025 meeting to review new information that has been published between August 1, 2024, and when they reconvene, and to summarize it for the committee at the April 2025 meeting.
  - Second by Annamarie Saarinen
    - In favor: 12
    - Opposed: 4
    - Abstained: 0
  - Motion passes.

Updates on the Condition Nomination Process Work Group—Amy Dahle

- Workgroup has not met yet. Committee coordinators have been putting together background information including compiling key persons involved, pieces of the process, and reviewing other state and federal condition consideration processes.
- Internal planning meetings have been held. The first workgroup meeting will be scheduled in the next couple months. Nominations are still being accepted but will not be reviewed until pieces of the process have been reviewed. Nominators are made aware of this when submitting their nomination. Updates will be given at the next advisory committee meeting.

Advisor Updates & Closure—Rae Blaylark

- Multiple advisors brought up cost considerations and where cost comes into the scope of decisions for this committee's activities.
    - Rae Blaylark: I'd appreciate if we could integrate looking at things with a health equity lens into all our processes, instead of an afterthought. One of the things that concerns me deeply is the rapidly rising cost of healthcare. While there are potential options for care, for families affected, especially those on public insurance, there are barriers to how and if they can access those same treatments.
    - Sue Berry: Agreed. In Minnesota we also need to consider the gap for children whose parents have high-deductible private insurance. They aren't often eligible for public insurance or Medicaid. In both cases, this an issue for some of these very expensive therapies, we have made some great headway talking with our Medicaid teams, but what about private insurance?
    - Emelia Rogers: I agree. We also have this other spot and it's hard to figure out exactly where to talk about it. SMRT (The State Medical Review Team, makes disability determinations for people not certified disabled by the Social Security Administration) has moved from being something based on diagnosis to being based on ADLs (Activities of Daily Living). So when we talk about newborn screening and babies who wouldn't have any symptoms, they wouldn't qualify for SMRT. And then, when there are commercial plans echoing the difficulty of not having that secondary medical assistance because of the SMRT piece. This comes to my mind, as a social worker, when we talk about cost.
    - Rae Blaylark: I agree. I think cost helps inform our decision making. We don't have access to that information. The criteria doesn't rely on it, but it's a contributing factor. Presentations from experts about the direction insurance is taking or how institutes are making decisions could be helpful. How do they define health equity? It would be a good opportunity to hear from Dr. Chomilo from DHS.
- Brook Moore: An update on our newborn screening process for cystic fibrosis. Renee Temme and I have been working with Carrie Wolf on this. Currently we screen for 39 gene variants. But there are over 2000 different gene variants that cause cystic fibrosis. We are missing historically marginalized groups and people of color by screening for only these 39 more prevalent mutations.
- Sue Berry: I'd like to have an open conversation amongst this committee about the utility of using molecular technologies to improve screening. Is this feasible as a public health measure? If molecular sequencing is needed to determine a newborn screening condition, should we make sure that everyone can be sequenced. We have disorders where 2nd tier testing is needed before we know what to do about treatment. Our committee would benefit from a discussion about the pros and cons of sequencing in a public health venue.
- Courtney Jarboe: I'd like to talk about screening in the past year. Like some of the challenges with cCMV screening. Have those challenges been addressed? Do they still exist? Are there things that we can learn from this as we move forward, especially as other conditions getting implemented?

Next meeting

Date: Tuesday, April 15th, 2025

Time: 1:00 – 4:00 PM

Location: Wilder Foundation
451 Lexington Pkwy N
St. Paul, MN 55104

Minnesota Department of Health
Newborn Screening Program
PO Box 64899
St. Paul, MN 55164
651-201-5466
health.nsac@state.mn.us
www.health.state.mn.us

10/16/2024

To obtain this information in a different format, call: 651-201-5466.