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May 11, 2025

Kirsten Johnson MPH, Secretary Designee
Department of Health Services
1 West Wilson Street
PO Box 2659
Madison WI 53705
Sent by email and US Mail to kirstenl.johnson@dhs.wisconsin.gov

Dear Secretary Johnson:

Enclosed find the report of the Secretary's Advisory Committee on Newborn Screening on a proposal to add screening for Guanidinoacetate methyltransferase deficiency (GAMT deficiency) to the Wisconsin mandatory newborn screening (NBS) panel. The proposal was unanimously approved by the Committee.

On behalf of the Committee, thank you for the opportunity to contribute to Wisconsin's newborn screening program, and for the Department's outstanding support of the Committee's work.

Sincerely,

NFost

Norman Fost MD MPH
Professor Emeritus
University of Wisconsin School of Medicine and Public Health
Chair, Secretary's Advisory Committee on Newborn Screening

Secretary's Advisory Committee on Newborn Screening Meeting

Friday, March 14, 2025

Report on the Nomination to Add Guanidinoacetate methyltransferase deficiency to the Newborn Screening Panel in the State of Wisconsin

On March 14, 2025, the Secretary's Advisory Committee on Newborn Screening met via Zoom to discuss the nomination to add Guanidinoacetate methyltransferase deficiency (GAMT deficiency) to the Wisconsin mandatory newborn screening (NBS) panel. GAMT deficiency was nominated on October 18, 2024 by Dr. Jessica Scott Schwoerer, a clinician with the Medical College of Wisconsin and co-sponsored by Dr. Roberto Mendez, assistant director of newborn screening with the Wisconsin State Laboratory of Hygiene. The Metabolic Subcommittee (October 18, 2024)) and the Umbrella Committee (December 6, 2024) met previously and concluded that GAMT deficiency meets all of the criteria for inclusion on the NBS panel.

GAMT deficiency is a disorder related to cerebral creatine deficiency. It is an autosomal recessive disease caused by pathogenic variants in the *GAMT* gene, which encodes the enzyme guanidinoacetate methyltransferase. This enzyme converts guanidinoacetate (GUAC) to creatine. Lack of functioning enzyme results in an abnormal buildup of GUAC and a deficiency of creatine. Clinical manifestations of GAMT deficiency most commonly include developmental delays (particularly speech delays), intellectual disability, autism, seizures, and ataxia. GAMT deficiency has been shown to be successfully treated in pre-symptomatic individuals with dietary interventions and supplements.

At the time of this report, twelve other states - California, Arizona, Utah, Minnesota, Michigan, Kentucky, Florida, Pennsylvania, New York, Connecticut, Delaware, and Maryland - screen for GAMT deficiency.

Conditions added to the Wisconsin mandatory newborn screening panel must meet nine criteria. The committee considered each criterion in turn.

First, *mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.* GAMT deficiency impacts the central nervous system. Patients with this condition typically develop symptoms in infancy or toddlerhood after an initial presymptomatic period. The clinical features of GAMT deficiency are developmental delays (particularly speech delays), intellectual disability, autism, seizures, and ataxia. Without newborn screening, this condition would not be detected in many infants and treatment would not begin prior to the manifestation of symptoms. All eight members voted that GAMT deficiency meets Criterion 1.

Second, *for each condition, there should be information about the incidence, morbidity, and mortality and the natural history of the disorder.* GAMT deficiency is a rare condition. The precise incidence of GAMT deficiency is not known, but based on the number of clinically reported cases it is estimated to be <0.3/100,000 live births, or an estimated one case in Wisconsin every 5 years. There are several different estimated carrier frequencies that range from 1/250 to 1/1475 newborns. There is no reported decrease in life expectancy, but the long-term consequences of the neurologic symptoms may increase the risk of mortality. All eight members voted that GAMT deficiency meets Criterion 2.

Third, *conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences*. GAMT deficiency impacts the central nervous system, and symptoms arise as early as 3-6 months of age. Presymptomatic dietary interventions and supplementation are associated with improved neurologic outcomes such as reduced intellectual disability, seizures, and movement disorders. Nutritional deficiencies can occur with protein restriction. Nutrient deficiency resulting from mild protein restriction is common with treatment. Creatine supplementation can cause water retention, muscle cramps, dehydration, vomiting, diarrhea, and liver dysfunction. Evidence suggests that creatine is a safe supplement overall, but there are concerns about high dose creatine in individuals with renal disease. All eight members voted that GAMT deficiency meets Criterion 3.

Fourth, *the interventions should be reasonably available to affected newborns*. GAMT deficiency is currently treated with dietary restriction of arginine and supplementation of creatine and ornithine. Treatment is similar to other protein metabolism disorders already on the NBS panel. The appropriate medical metabolic formula is available through multiple companies. The Association of Creatine Disorders has partnered with a laboratory to make high-quality creatine and ornithine supplements. All eight members voted that GAMT deficiency meets Criterion 4.

Fifth, *appropriate follow-up should be available for newborns who have a false positive newborn screen.* The state NBS laboratory will communicate the positive screening result to the primary care provider and the metabolic clinic that will engage in confirmatory testing and clinical follow-up. The confirmatory testing for GAMT

deficiency includes biochemical testing for an elevation in GGAA, and molecular testing of the *GAMT* gene. The turnaround time for this testing is typically less than two weeks. Patients found to be true positives will be started on treatment, and families of patients found to be false positives will receive appropriate counseling and education about the NBS process and that the results indicate that their child does not have the condition. There was extensive discussion about the potential psychosocial harms – e.g., confusion and stigmatization. Based on the estimated false positive rate in the nomination form, the false positive results, could affect 30-40 families for every true positive, but NY and UT have much lower reported false positive results. There are concerns about so-called "vulnerable child syndrome," which refers to parents over-protecting a healthy child, or changes in reproductive behavior based on the false belief that an existing child has the disorder. There was agreement that further exploration is needed of how to manage these concerns, which affect other newborn screening tests. All eight members voted that GAMT deficiency meets Criterion 5.

Sixth, *the characteristics of mandated tests in the newborn population should be known including specificity, sensitivity, and predictive value or other convincing medical evidence (experience, natural history, or literature)*. Ten false positives are estimated per year in the nomination form, but there is a chance that this number could be significantly lower based on the screening experience from NY and UT. There is no risk of identifying other disorders using the proposed screening test for GAMT deficiency. All eight members voted that GAMT deficiency meets criterion. 6.

Seventh, *if a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.* A new sample collection system is not needed for GAMT deficiency.

Eighth, *before a test is added to the panel the details of reporting, follow-up, and management must be completely delineated including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.* Reporting, follow-up, and management for identified cases of GAMT deficiency will be similar to other conditions on the Wisconsin newborn screening panel. If a newborn has a positive newborn screen, the results will be communicated to the infant's primary care physician (PCP) and metabolic consultants at Children's Wisconsin or the University of Wisconsin Waisman Center. The metabolic consultants can direct the primary care provider to arrange for confirmatory testing. If the confirmatory tests are positive, the patient can establish care in the metabolic clinic and begin treatment. The metabolic center can provide ongoing management and education. Those who test positive can receive counseling on the meaning of this result. All eight members voted that GAMT deficiency meets criterion 8.

Finally, *recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions*. Screening for GAMT deficiency involves measuring guanidinoacetate concentration and the guanidinoacetate to creatinine ratio. In order to accomplish this, the current MSMS multiplex assay will need to be replaced. This is

expected to require an additional cost of approximately $10 per newborn. Confirmatory testing is typically covered by insurance.

Treatments that would be covered by the state would be the medical formula and supplements. Currently, the cost of the recommended medical formula is $140/case or $23/can. Each can contains 1968 kcal. The cost of creatine and ornithine supplementation depends on age. The cost is estimated to range from $275/year for infants to $1900/year for adults. All eight members voted that GAMT deficiency meets criteria 9.

As GAMT deficiency was determined to fulfill all nine criteria, a motion was made to approve the nomination of GAMT deficiency. The motion to approve was seconded, then unanimously approved by the committee.

Members of the Committee:

Norman Fost MD MPH (Chair)
Mei Baker MD
Jeff Britton MD
Arthur Derse MD JD
M. Bruce Edmonson MD MPH
Tim Kruser MD
Emily Singh GC
Steven Leuthner MD MA
David Wargowski MD