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Evidence and Recommendation for Guanidinoacetate Methyltransferase Deficiency Newborn Screening

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Abstract

Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive disorder of creatine biosynthesis due to pathogenic variants in the *GAMT* gene that lead to cerebral creatine deficiency and neurotoxic levels of guanidinoacetate. Untreated, GAMT deficiency is associated with hypotonia, significant intellectual disability, limited speech development, recurrent seizures, behavior problems, and involuntary movements. The birth prevalence of GAMT deficiency is likely between 0.5 and 2 per million live births. On the basis of small case series and sibling data, presymptomatic treatment with oral supplements of creatine, ornithine, and sodium benzoate, and a protein-restricted diet to reduce arginine intake, appear to substantially improve health and developmental outcomes. Without newborn screening, diagnosis typically happens after the

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development of significant impairment, when treatment has limited utility. GAMT deficiency newborn screening can be incorporated into the tandem-mass spectrometry screening that is already routinely used for newborn screening, with about 1 per 100 000 newborns screening positive. After a positive screen, diagnosis is established by finding an elevated guanidinoacetate concentration and low creatine concentration in the blood. Although GAMT deficiency is significantly more rare than other conditions included in newborn screening, the feasibility of screening, the low number of positive results, the relative ease of diagnosis, and the expected benefit of presymptomatic dietary therapy led to a recommendation from the Advisory Committee on Heritable Disorders in Newborns and Children to the Secretary of Health and Human Services that GAMT deficiency be added to the Recommended Uniform Screening Panel. This recommendation was accepted in January 2023.

Newborn screening allows for the detection and early treatment of conditions associated with significant morbidity or mortality that are not typically apparent at birth or in early infancy. In the United States, newborn screening programs operate at the state level, including the decision about which conditions are included in screening. The Recommended Uniform Screening Panel (RUSP) is a list of conditions endorsed by the US Secretary of Health and Human Services for inclusion in state newborn screening programs. The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) makes recommendations about conditions to include on the RUSP on the basis of a comprehensive evaluation of expected benefits and harms of screening.[1] Factors assessed include screening accuracy, health outcomes of cases identified through screening compared with usual clinical identification, and the feasibility of implementing population-based screening within the existing state-based newborn screening system.

In January 2023, guanidinoacetate methyltransferase (GAMT) deficiency was added to the RUSP on the basis of a recommendation from the ACHDNC in May 2022. This report summarizes the key elements leading to this recommendation. The full evidence review report, the letter from the ACHDNC to the Secretary of Health and Human Services, and the response from the Secretary of Health and Human Services are available at the ACHDNC's Web site (https://www.hrsa.gov/advisory-committees/heritable-disorders/recommendations-reports).

OVERVIEW OF GAMT DEFICIENCY

GAMT deficiency is an autosomal recessive disorder of creatine biosynthesis due to pathogenic variants in the *GAMT* gene (chromosome 19p13.3; Online Mendelian Inheritance in Man: #601240).[2] GAMT deficiency leads to low plasma and brain creatine levels and elevated concentrations of guanidinoacetate in the brain, cerebrospinal fluid, blood, and urine. The inadequate supply of creatine, a critical energy source for cellular metabolism, and buildup of neurotoxic levels of guanidinoacetate, lead to severe and progressive neurologic problems.

Over 50 cases of GAMT deficiency have been reported in the peer-reviewed literature. Common features in untreated individuals include hypotonia, significant intellectual disability, limited speech development, epilepsy, severe behavioral disorders, and movement

disorders, including ataxia and dystonia.[3–7] Newborns with GAMT deficiency are asymptomatic because they are protected in utero by active transport of creatine across the placenta.[8] Once symptoms develop, GAMT deficiency can be difficult to diagnose in the absence of family history or newborn screening because of the non-specific clinical findings. One study of 22 subjects reported that, although clinical findings (eg, developmental delay, seizures, ataxia) were first noticed at an average of 14 months (range: 3–24 months), the average age of diagnosis was 8.5 years (range: 9 months–25 years).[3]

BIRTH PREVALENCE IN UNSCREENED POPULATIONS

On the basis of identification of known pathogenic alleles in deidentified newborn screening dried-blood spots, the estimated birth prevalence of GAMT deficiency is between ~0.038 and 0.4 per 100 000 live births (eg, between ~1 per 2.6 million and 1 per 250 000 live births).[9,10] One clinical study that estimated the birth prevalence to be significantly greater (0.88 per 100 000 live births or 1 per 114 000 live births) was based on 5 patients referred to a single treatment center between 2001 and 2011.[11] The estimated birth prevalence from screening is described below.

SCREENING AND DIAGNOSIS

Normally, the enzyme GAMT produces creatine from guanidinoacetate. GAMT deficiency newborn screening is based on measuring guanidinoacetate, which accumulates when GAMT enzyme activity is low. The screening utilizes flow injection tandem mass spectrometry to measure guanidinoacetate and creatine concentrations in dried blood spots. This procedure can be multiplexed with other standard newborn screening blood spot assays for acylcarnitines and amino acids. Both derivatized and nonderivatized extracts have been used. Positive samples have elevated levels of guanidinoacetate and a high guanidinoacetate/creatine ratio.[12] Sequencing the *GAMT* gene for known pathogenic variants provides supportive data when previously documented pathogenic variants are found.

Diagnosis is based on low plasma creatine and elevated plasma guanidinoacetate. Molecular analysis of the *GAMT* gene, which has >50 known pathogenic or likely pathogenic variants, is supportive of the diagnosis but not necessary. Magnetic resonance spectroscopy, which can identify low creatine levels and elevated guanidinoacetate levels in the brain, can be helpful for following patients but is more commonly used for research purposes and is not required for diagnosis. Patients should be assessed for arginase deficiency, which can also lead to increased guanidinoacetate levels, if there is diagnostic uncertainty. Because diagnosis is primarily based on available biochemical tests, diagnostic confirmation can typically be completed within 2 months of a positive screen. Because there is no late-onset phenotype, further follow-up is not needed for infants with normal creatine levels and nonelevated guanidinoacetate levels.

Newborn screening for GAMT deficiency began in Australia in 2002, and by April 2022, 1.4 million newborns had been screened, with 1 case diagnosed.[13] A pilot screening study in British Columbia from 2012 to 2018 screened nearly 250 000 newborns, with no cases identified.[14] Utahbegan newborn screening for GAMT deficiency in 2015. Among 321 305

newborns screened, 3 were referred for diagnostic testing (ie, 0.93 per 100 000 newborns screened or 1 per 107 102 newborns screened) and 1 case was identified (ie, 0.31 per 100 000 newborns screened or 1 per 321 305 newborns screened).[15] New York began newborn screening for GAMT deficiency in 2018. Among 759 246 infants screened, 24 were referred for diagnostic evaluation (ie, 3.2 per 100 000 newborns screened or 1 per 31 635 screened) and 1 case of GAMT deficiency was diagnosed (ie, 0.13 cases per 100 000 newborns screened or 1 case per 759 246 screened).[16] On the basis of these findings and updated information provided for the evidence review, there have been 2.9 million newborns screened internationally. Of these, 1.2 per 100 000 newborns were referred for diagnostic follow-up and 0.1 cases of GAMT deficiency per 100 000 newborns were diagnosed. In the United States, the case detection rate appeared to be higher (0.19 cases of GAMT deficiency per 100 000 newborns screened as of the completion of the evidence review report).

GAMT DEFICIENCY TREATMENT

The treatment of GAMT deficiency is aimed at increasing creatine levels and decreasing guanidinoacetate concentration. Treatment includes supplementation with oral creatine (typically ~400 mg/kg daily) and ornithine (typically 100–800 mg/kg daily).[20] Additional supplements of sodium benzoate (typically 100 mg/kg daily) and dietary protein restriction with arginine-free essential amino acid supplementation may be recommended.[11,20] The US Food and Drug Administration does not consider these supplements to be pharmaceuticals, which could lead to variations in the quality of available treatment and could also impact insurance coverage.

There are no controlled trials to evaluate the optimal age for treatment initiation. However, case series, particularly those that compare siblings, suggest that presymptomatic or early initiation of treatment of GAMT deficiency is associated with improved neurologic outcomes, including reduced risk of intellectual disability and less frequent seizures (Table 1). Six studies describing 8 infants were identified by the evidence review in which treatment was started before 6 months of age. Five of these studies compared outcomes between later-treated older siblings and younger, earlier-treated siblings.[5] Seven of the 8 reported infants had normal developmental outcomes at a range of 11 to 42 months of follow-up. One limitation is that these reports do not include comparable standardized neurodevelopmental assessments.

PREDICTED GAMT DEFICIENCY NEWBORN SCREENING POPULATION-LEVEL OUTCOMES

Assuming the birth prevalence of GAMT deficiency is 0.2 per 100 000, screening all 3.6 million newborns annually in the United States would lead to 93 (range: 62–135) positive screens for infants then referred for follow-up, of whom 7 (range: 1–22) would be diagnosed with GAMT deficiency. Insufficient information is available to estimate the number of cases that would be clinically identified or to quantitatively predict the outcomes for the cases identified through newborn screening.

IMPLEMENTING GAMT DEFICIENCY NEWBORN SCREENING

On the basis of the experience in New York and Utah, the cost of adding GAMT deficiency newborn screening from the program perspective above and beyond fixed costs of the existing program is substantially <$1 per infant. Among 31 state newborn screening programs not screening for GAMT deficiency that responded to a survey in early 2022, 35% reported that GAMT deficiency newborn screening could be implemented in 2 years or less, 45% in 2 to 3 years, and 20% that it would take longer. The lack of an FDA-approved testing kit was identified as an important barrier.

FINAL RECOMMENDATION

In January 2023, the Secretary of Health and Human Services added GAMT deficiency to the RUSP on the basis of a recommendation from the ACHDNC in May 2022. Although GAMT deficiency has a significantly lower birth prevalence than other metabolic conditions recommended for newborn screening (eg, phenylketonuria ~6 per 100 000, maple syrupurine disease ~0.5 per 100 000),[21] screening for GAMT deficiency has a small additional cost and is accurate, with a low number referred for diagnostic testing. The approach to diagnosis is well described and can be completed in early infancy with available biochemical testing and there is no late-onset phenotype, so infants with normal diagnostic testing do not need additional follow-up. Treatment is based on a dietary intervention that is broadly available. Early treatment leads to significantly better neurologic outcomes, and diagnosis is significantly delayed without screening. Overall, GAMT deficiency newborn screening was assessed by the ACHDNC to have significant potential benefit despite the rarity of the condition on the basis of the relative ease of case detection and the expected impact of presymptomatic treatment.

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ABBREVIATIONS

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
GAMT	guanidinoacetate methyltransferase
RUSP	Recommended Uniform Screening Panel

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TABLE 1

Studies Comparing GAMT Deficiency Treatment Before 6 Months of Age Compared With Outcomes, When Available, in Siblings With First Treatment at an Older Age

Source	Treatment Onset Aged <6 Mo			Sibling With Later Treatment		
	Age of Diagnosis and Treatment	Duration of Treatment and Follow-up	Developmental Outcome at Follow-up	Age of Older Sibling at Diagnosis	Duration of Treatment and Follow-up	Developmental Outcome at Follow-up
El-Gharbawy et al, 2013[17]	Prenatal	42 mo	Normal	10 mo	6.5 y	Speech and fine motor delays
Dhar et al, 2009[6]						
Stockler-Ipsiroglu et al, 2014[7]	Prenatal	41 mo	Normal	10 mo	39 mo	Mild developmental delay
	1 wk	14 mo	Normal	5.5 y	30 mo	Moderate developmental delay
	3 wk	31 mo	Normal	30 mo	10 y	Mild developmental delay
Viau et al, 2013[11]	Birth	12 mo	Normal	—	—	—
Dhar et al, 2009[6]	8 d	11 mo	Central hypotonia, developmental delay persists	2.5 y	4.5 y	Improved motor skills, started walking, improved tone, improved autistic features
Schulze et al, 2006[18]	22 d	14 mo	Normal	2.75 y	2.25 y	Epilepsy, speaks “a few words”
Farshidi et al, 2011[19]	5 mo	11 mo	Normal	15 mo	21 mo	Continues to have seizures (improved), cognitive impairment, learning disability (improved)

—, no sibling comparator.