Evidence-Based Review of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency: Final Report (06/2/2022)

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

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EXECUTIVE SUMMARY

Overview

This report summarizes the evidence regarding the benefits and harms of newborn screening (NBS) for Guanidinoacetate Methyltransferase (GAMT) deficiency and the capability of state NBS programs to offer comprehensive testing and follow up for the condition.

This executive summary highlights key findings from the final version of the complete report developed for the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children regarding NBS for GAMT deficiency. This summary is not intended to replace the complete report, which describes the methods for evidence identification and synthesis, and a full discussion of findings. This summary instead provides a high-level review of findings from the complete report.

GAMT Deficiency: Epidemiology and Clinical Course

GAMT deficiency is a disorder of creatine biosynthesis. When untreated, the inadequate supply of creatine and build-up of neurotoxic levels of guanidinoacetate (abbreviated as GUAC in this report, but sometimes abbreviated as GAA elsewhere) leads to severe and progressive neurological problems that typically do not become apparent until after 3 months of age at the earliest. Untreated GAMT deficiency is associated with significant intellectual disability, limited speech development, recurrent seizures, behavioral problems, and involuntary movements, but no reported decrease in life expectancy.

Newborn Screening for GAMT Deficiency

NBS for GAMT deficiency is based on measuring GUAC and sometimes creatine in dried-blood spots with flow injection tandem mass-spectrometry (MS/MS). Depending on a NBS program's protocol, an out-of-range-GUAC concentration or the ratio of GUAC concentration to creatine concentration would lead to a repeat screen to confirm a positive newborn screen for GAMT deficiency. Although it is not a screening requirement, some NBS programs include a second-tier liquid chromatography MS/MS test to increase specificity. If a specimen is out-of-range after a repeat or second-tier screen, the newborn is referred for diagnostic evaluation. Diagnosis of GAMT deficiency is established by finding an elevated GUAC concentration and low creatine concentration in blood after a positive screen. Urine can also demonstrate an elevated GUAC concentration but may lead to diagnostic misclassification. Genetic testing can support the diagnosis when known variants are identified.

The New York and Utah NBS programs include GAMT deficiency on their NBS panels. GAMT deficiency NBS is also conducted in Canada (British Columbia) and Australia (Victoria). Other NBS programs are planning to implement GAMT deficiency screening in the United States (Michigan) and Canada (Ontario).

Treatment for GAMT Deficiency

Treatment for GAMT deficiency involves lifelong oral supplementation with creatine and ornithine, oral sodium benzoate, and a protein restricted diet to reduce intake of arginine. Affected individuals are recommended to have regular monitoring of blood GUAC and creatine concentrations, as well as an amino acid profile. Measurements are suggested every 1-2 months

in the first 6-12 months of life, with less frequent monitoring once the biochemical profile is stable. Because clinical decisions are based primarily on laboratory findings, patients can receive remote care from subspecialists and metabolic dieticians.

Case series suggest that presymptomatic treatment reduces the risk of developing the neurological sequelae (e.g., intellectual disability, behavior problems, epilepsy, movement disorders). However, the available studies are limited by small sample size, lack of standardized measures at specific ages, and variable length of follow-up.

Impact on the Health of the Population

Modeling projections estimate 7 cases of GAMT deficiency (range: 1-22) would be identified annually through NBS of all 3.6 million infants born each year, in comparison to the estimated 2-18 expected to be detected clinically sometime over their lifecourse. There is insufficient evidence to model any clinical outcomes beyond case identification to quantify the potential benefits of screening.

Impact on Public Health Systems

Approximately half of NBS programs reported that it would take them between 2 and 3 years to implement GAMT deficiency NBS. An FDA-approved testing kit would facilitate the implementation of GAMT deficiency screening. Challenges to GAMT deficiency NBS implementation include issues of validating the test, funding, staffing, and competing priorities.

The estimated additional cost to a NBS program to screen for GAMT deficiency, above and beyond the operating costs of an existing NBS program, may be substantially less than $1 per infant. This cost estimate is based on interviews with the two state NBS programs that have implemented NBS for GAMT deficiency. Both states use a laboratory-developed test because they had the technical capacity to develop and validate their own tests, unlike most states. Therefore, this cost estimate does not necessarily apply to other programs.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACD	Association of Creatine Disorders
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
APHL	Association of Public Health Laboratories
ARUP	Associated Regional and University Pathologists, Inc.
CGMP	Current Good Manufacturing Practice
ERG	Evidence-based Review Group
FDA	United States Food and Drug Administration
FTE	Full-time Equivalent
GAMT	Guanidinoacetate Methyltransferase
GUAC	Guanidinoacetate
HHS	Health and Human Services
LIMS	Laboratory Information Management System
MRS	Magnetic Resonance Spectroscopy
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NICU	Neonatal Intensive Care Unit
RUSP	Recommended Uniform Screening Panel
TEP	Technical Expert Panel
US	United States

1 SCOPE AND METHODS OF THE REVIEW

Scope of Review

This report was developed to support the Secretary of Health and Human Services' (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in making recommendations to the Secretary, HHS, about whether newborn screening (NBS) for Guanidinoacetate Methyltransferase (GAMT) deficiency should be added to the Recommended Uniform Screening Panel (RUSP).

Nomination and Request for Review

In 2016, the ACHDNC decided against referring GAMT deficiency NBS for evidence review because no case had been identified prospectively through NBS. GAMT deficiency NBS was nominated again on April 21, 2021, by Nicola Longo, MD, PhD, Professor of Pediatrics and Pathology and Chief of the Division of Medical Genetics, University of Utah, Marzia Pasquali, PhD, Professor of Pathology and Pediatrics, University of Utah, and Director of Associated Regional and University Pathologists, Inc. (ARUP) Biochemical Genetics and Newborn Screening Laboratory, and Heidi Wallis, President of the Association for Creatine Deficiencies (ACD). The ACHDNC voted to refer GAMT deficiency NBS for an evidence-based review on August 12, 2021.

Purpose of the Condition Review of Evidence

The condition review will present the evidence regarding the likely benefits and harms of expanding NBS to include GAMT deficiency, estimated health impacts of population-based screening in the United States (US), and potential impact on state NBS programs. The review focuses on the decision-making criteria considered by the ACHDNC. The Evidence-based Review Group (ERG) does not make specific recommendations to the ACHDNC about addition of a condition to the RUSP.

Case Definition and Establishing the Diagnosis of GAMT Deficiency in Early Infancy

GAMT is an enzyme needed for the synthesis of creatine, which provides energy for cellular metabolism. GAMT deficiency, an autosomal recessive disorder, leads to low plasma and brain creatine levels and elevated concentrations of guanidinoacetate (GUAC) in the brain and cerebrospinal fluid, blood, and urine. Signs of GAMT deficiency (e.g., hypotonia, seizures, developmental delay) do not typically present before 3 months of age and early findings, when they do develop, are often nonspecific. Because newborns are asymptomatic, identification would only happen if there was known increased risk (e.g., family member with GAMT deficiency) or through NBS. Diagnosis is based on the biochemical findings of low plasma creatine and elevated plasma GUAC concentrations at least 1 week after birth. Elevated concentrations of GUAC can also be found in cerebrospinal fluid and urine. Genetic analysis can be supportive of the diagnosis. Because arginase deficiency can also lead to increased GUAC levels, experts recommend evaluating for this condition if there is uncertainty. Magnetic resonance spectroscopy (MRS) can be used to identify low creatine levels and elevated GUAC levels in the brain.

Methods – Systematic Evidence Review

The methods guiding this systematic evidence review followed approaches outlined in the Condition Review Workgroup – Manual of Procedures (2012, 2014) and revised in 2016 to address requirements in the 2014 Reauthorization of the Newborn Screening Saves Lives Act (Public Law No: 113-240, 12/18/2014). These methods address the limited evidence that is typically available for rare conditions and the recognition that the evidence base for conditions considered for NBS is often rapidly changing. These methods were also developed to be completed within the timeline required for the ACHDNC. This section describes specific procedures that guided this Condition Review of NBS for GAMT deficiency.

Literature Search

Published Literature Search

An experienced medical librarian in partnership with the ERG conducted the initial literature search regarding NBS and treatment of GAMT deficiency. We identified published research articles from MEDLINE, EMBASE, CINAHL, and the Cochrane library using the following MeSH terms and associated key words for each database. Published articles could be included if the full text was written in English and included human subjects and they met the criteria for at least one key question.

Appendix A lists the specific search criteria for each database and process leading to article inclusion. As described in the manual of procedures, each database was searched and identified articles were placed into an electronic database. Two reviewers independently evaluated the titles and abstracts for potential inclusion. If either reviewer thought that the article was potentially relevant, then the full text of the article was reviewed. For excluded articles, both reviewers had to agree on the reason for exclusion based on a hierarchical list.

Key Questions for Evidence Review: GAMT Deficiency

Key Questions and Inclusion/Exclusion Criteria

The following describes the key questions for the systematic evidence review and the inclusion/exclusion criteria for published articles to provide evidence for each of the key questions.

1. What is the natural history and epidemiology of GAMT deficiency?

Relevant study designs include cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized studies. Outcomes of interest include the incidence or prevalence, timing of the development of signs or symptoms of GAMT deficiency, age of diagnosis, age at treatment initiation, and quality or length of life. This review excluded epidemiological studies of GAMT deficiency in high-risk patients (e.g., those with autism or with undiagnosed neurodevelopmental disorders) because these analyses do not provide key information on the expected prevalence in the average population.

The term “natural history” is complex. Traditionally it refers to disease outcomes in the absence of targeted interventions. However, a more useful approach for NBS decision making is to consider natural history as what happens to the individual following clinical identification, which often includes targeted therapy. When the term “natural history” is used throughout this report, information is provided to clarify its use and the implications of the findings.

2. What is the analytic or clinical validity of newborn screening for GAMT deficiency?

Relevant study designs include cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized studies. The studies should include at least 5,000 infants at average risk (e.g., not known to have GAMT deficiency), be screened for GAMT deficiency in the first month of life, and those with a positive screen should have diagnostic confirmation. Outcomes of interest include sensitivity, specificity, positive predictive value, negative predictive value, reliability, diagnostic yield, or the cost of screening. Although studies of anonymized dried-blood spots are important in the development of NBS tests, the evidence-based review focuses on studies of dried-blood spots linked to specific newborns, which provides direct insight into the validity of NBS. However, anonymous dried-blood spot tests provide important contextual information regarding the epidemiology of rare conditions such as GAMT deficiency.

3. What are the harms associated with newborn screening for GAMT deficiency?

Relevant study designs include cross-sectional, case-control, longitudinal (retrospective or prospective), randomized, case reports, and case series studies. Studies should include at least one average-risk newborn screened in the first month of life for GAMT deficiency. Outcomes include any reported adverse event related to NBS for GAMT deficiency, including the harms related to false-positive or false-negative screening.

4. What are the benefits and harms of pre-symptomatic or early treatment of GAMT deficiency compared to when GAMT deficiency is usually identified?

Relevant study designs include longitudinal (prospective or retrospective observational or interventional) studies with at least 6 months of follow-up after diagnosis or until death if that occurred before 6 months of follow-up after treatment. Studies should include at least one subject diagnosed with GAMT deficiency before 12 months of age. Such diagnosis could be based on NBS or diagnosis based on having an affected family member. Outcomes of interest include mortality, cognitive development, social and emotional development, speech and language development, fine motor development, gross motor development, muscle tone, movement disorders, and the presence of epilepsy or seizure frequency. Changes in biomarkers (e.g., creatine levels, MRS findings) can provide indirect evidence regarding early treatment benefit and would be included only if there is linkage to person-centered outcomes.

In addition to these key questions, we also considered contextual questions that provide important background information. These included:

1. What is the relationship between *GAMT* genotype and phenotypic expression? What other factors predict phenotypic expression?
2. What clinical practice guidelines are available for the diagnosis and treatment of GAMT deficiency?
3. What is the availability of specialists to provide care for newborns identified with GAMT deficiency?
4. How accessible is treatment for GAMT deficiency? Are the over-the-counter supplements used for treatment known to be of sufficient quality?
5. What are the barriers and facilitators to diagnosis or treatment experienced by affected individuals or families?

6. What is the impact of GAMT deficiency newborn screening on newborn screening programs, public health programs, or the population? How feasible is GAMT deficiency newborn screening in the US? To what degree are newborn screening programs ready to screen for GAMT deficiency?

Technical Expert Panel

A panel of technical experts was convened to advise the development of this review. Members of this Technical Expert Panel (TEP) are listed in Table 1. List of Technical Expert Panel Members. The first meeting (October 5, 2021) reviewed the scope of the review and methods, outlined the process of GAMT deficiency diagnosis and treatment, and identified current issues in research and health care delivery for children suspected or known to be affected with GAMT deficiency. The second TEP meeting (January 6, 2022) focused on the availability of evidence regarding treatment outcomes for presymptomatic or early treatment of GAMT deficiency. The third TEP meeting (April 11, 2022) focused on assessing the potential population health impact of NBS for GAMT deficiency.

Table 1. List of Technical Expert Panel Members

Name	Role
Saadet Andrews, MD, PhD, FCCMG	Metabolic Geneticist; University of Alberta
Michele Caggana, ScD, FACMG	Director, New York Newborn Screening Program
Kim Hart, MS, LCGC	Program Manager, Utah Newborn Screening Program
Nicola Longo, MD, PhD*	Clinician Scientist, University of Utah
Marzia Pasquali, PhD*	Researcher and Laboratory Expert, University of Utah, and Director, ARUP Biochemical Genetics and Newborn Screening Laboratory
Andreas Schulze, MD, PhD	Clinician Scientist, Hospital for Sick Children, Toronto, ON
Jon Daniel Sharer, PhD	Clinician Scientist, University of Alabama, Birmingham, AL
Graham Sinclair, PhD, FCCMG	Biochemical Geneticist, British Columbia Children's Hospital, Vancouver, BC
Heidi Wallis*	President, ACD

*Also a nominator of GAMT deficiency to the recommended uniform screening panel.

2 REVIEW OF EVIDENCE: NEWBORN SCREENING FOR GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY

2.1 Epidemiology and Natural History of GAMT Deficiency with Usual Clinical Detection

Gene and Gene Frequency

GAMT deficiency (OMIM: #601240) is an autosomal recessive disorder (19p13.3) that leads to cerebral creatine deficiency. According to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GAMT), more than 50 variants of the *GAMT* gene have been described. Because GAMT deficiency is rare and some affected individuals might not ever be diagnosed, there are gaps in the evidence related to the epidemiology, including the birth prevalence and whether there are higher risk populations.[1]

A study of 2,950 de-identified dried blood spots did not find the two most commonly reported variants (c.59G>C in exon 1 and c.327G>A in exon 2), but did identify two novel and potentially pathogenic variants, for an estimated carrier frequency of these novel variants of 1/1475.[2] A subsequent report evaluated the National Heart, Lung Exome Sequencing Project Exome Variant Server, which includes >200,000 individuals from 18 different databases, including the Women's Health Initiative, Framingham Heart Study, Chronic Obstructive Pulmonary Disease Genetic Epidemiology, and the Cleveland Clinic Genebank.[3] This analysis focused on 6,503 individuals, of whom 8 had a pathogenic mutation (1/812) associated with GAMT deficiency, with a carrier frequency of 0.123%. Based on this, the study estimated the incidence of GAMT deficiency to be 1 in 2,640,000 (equivalent to 0.038 cases per 100,000). An important limitation of this work is that the sample's generalizability to newborns in the US cannot be directly assessed. The TEP also reported that since the full range of pathogenic alleles has not been characterized, assessment of the frequency of specific variants in existing databases could underestimate the expected birth prevalence of GAMT deficiency.

Based on carrier frequency and gene sequencing in a sample of 500 de-identified dried blood spot samples from the Netherlands' NBS program, the birth prevalence of GAMT deficiency was estimated to be about 0.4 per 100,000 (i.e., 1 in 250,000).[4]

Estimated Birth Prevalence Based on Identified Cases

One report described that in Utah five patients were diagnosed with GAMT deficiency between 2001 to 2011.[5] Four of these subjects were diagnosed clinically and one was diagnosed at birth based on family history. The overall average age at diagnosis was 25.8 months. According to the study authors, these subjects were all born in Utah.[6] Based on the number of deliveries in Utah between 2001 and 2011, the birth prevalence was estimated to be 0.88 per 100,000 newborns (i.e., about one per 114,000 newborns). The subjects in this study were identified based on chart review at the University of Utah.[1] Findings from Utah might not be generalizable to the US overall. However, the TEP supported a baseline estimate of the birth prevalence of GAMT deficiency to be 0.4 per 100,000 births (i.e., one per 250,000) based on the case detection rate of Utah through 2021.

Natural History of GAMT Deficiency

The fetus is protected from GAMT deficiency because there is active transport of creatine across the placenta.[7] The neurodevelopmental morbidity associated with GAMT deficiency does not typically develop until after 3 months of age. Although it is difficult to evaluate prospectively, the behavior problems and intellectual disability associated with GAMT deficiency are thought to be due to the creatine deficiency and the recurrent intractable seizures and movement disorder are thought to be due to the elevated GUAC concentration. No studies have reported an increase in mortality risk directly related to GAMT deficiency, although studies are limited in follow-up and the sequelae (e.g., epilepsy) may be related to an increased risk of mortality.

One study described 27 subjects with GAMT deficiency based on a physician survey and a review of published literature.[8] Included in this study were four sets of siblings, including two who were twins, with a mean age at diagnosis of 12.3 years (range: 2 years-29 years). Most (78%) had an IQ estimated to be between 20 and 34 by qualitative assessment, 28% had intractable seizures, and 48% had a movement disorder. The specific mutation was not associated with phenotype. Although treatment normalized cerebral creatine and improved seizure frequency and the degree of movement disorder, the intellectual disability based on qualitative assessment was not improved.

A subsequent study[9] using similar methods of case detection included 20 subjects (7 previously reported, including 3 in Mercimek-Mahmutoglu et al. 2006[8]), with a median age at diagnosis of 6.5 years (range: 10 months-20 years). All subjects had developmental delay or intellectual disability. Overall, 15 had seizures, starting between 9 months and 7 years, 8 had a movement disorder, and 19 had a significant behavioral disorder. Treatment information and related outcomes were not provided.

One study describes 22 subjects cared for by physicians from Vrije Universiteit Medical Center, Amsterdam, The Netherlands.[10] Of these subjects, 16 had been reportedly previously including 11 in Mercimek-Mahmutoglu et al. 2014.[9] All results were reported into a database by the physicians. Clinical findings were first noted at an average of 14 months (range: 3 months-24 months) and the average age of diagnosis was 8.5 years (range 9 months-25 years). At diagnosis, all subjects had global developmental delay or intellectual impairment and most (18, 82%) had epilepsy, and some (8, 36%) had a movement disorder (e.g., dystonia, ataxia). Follow-up was available to an average age of 14 years 7 months (range: 5 years-31 years). Overall, treatment was associated with improvement in developmental delay/intellectual disability in 5, including in one of the two subjects who began treatment at 1 year of age. However, insufficient information was presented to quantify the magnitude of improvement. Of the 18 subjects with seizures, 11 had full resolution after treatment.

One study describes 48 subjects (22 who have been reported previously, 7 of which were reported in Mercimek-Mahmutoglu et al. 2006[8]) identified through an international study.[11] The median age at treatment initiation was 4 years 6 months (range: birth-34 years). Overall, the 44 subjects who began treatment after 9 months had developmental delay or intellectual disability and 35 of these had epilepsy. The three that started treatment by 3 weeks of age were reported as neurodevelopmentally normal.[11] Refer to the section on GAMT Deficiency Treatment for further details.

Information about specific cases of GAMT deficiency often appear in multiple reports. Repeated study of individuals is important because of the need to understand the progression of the condition and because additional cumulative evidence and analysis is important given the rarity

of the condition. However, multiple reports of the same individuals can also make the evidence base appear larger than it is. Table 2. Summary of Natural History Studies and Subject Overlap highlights this overlap.

Table 2. Summary of Natural History Studies and Subject Overlap

Reference	Total cases	Unique cases, not previously reported	Overlap with other citations in the evidence review
Khaikin et al. (2018)[10]	22	6	11 cases previously reported in Mercimek-Mahmutuglu et al. (2014)[9]
Stockler-Ipsiroglu et al. (2014)[11]	48	26	7 cases previously reported in Mercimek-Mahmutuglu et al. (2006)[8]
Mercimek-Mahmutoglu et al. (2014)[9]	20	7	3 cases previously reported in Mercimek-Mahmutoglu et al. (2006)[8]
Mercimek-Mahmutoglu et al. (2006)[8]	27	8	No overlap with other citations in this review

Registry Findings

ACD is an advocacy organization focused on improving early identification and timely treatment as well as research into Cerebral Creatine Deficiency Syndromes, including GAMT deficiency. The ACD owns CreatineInfo, a patient registry and natural history study hosted on a platform created by the National Organization for Rare Disorders (https://creatineinfo.iamrare.org). This registry was developed in March 2021. In April 2022, the registry included 35 subjects with GAMT deficiency. The number of subjects is expected to grow given that there are >90 individuals with GAMT deficiency in the ACD support group, including seven diagnosed in 2022 by April 29, 2022. No published reports are available from the registry as of this report. The ACD has developed a partnership with ClinGen to share variant information and use registry data to advance understanding about GAMT deficiency.[12] In the future, this registry will likely be an important source of information to understand factors related to case detection and the relationship between the timing of detection and health outcomes.

2.2 Screening, Short-Term Follow-Up, and Diagnostic Confirmation

Newborn screening for GAMT deficiency in the US

Utah

Since 2015, the Utah NBS program has screened newborns for GAMT deficiency twice, once at 24 hours after birth and again between 7 and 16 days after birth. All dried-blood spot based NBS in Utah follows this approach. Prior to 2019, the Utah NBS program contracted NBS laboratory

services to ARUP. ARUP began screening for GAMT deficiency in 2015 using a derivatized method. Then in June 2019, laboratory services for all NBS disorders including GAMT deficiency, moved into the NBS program. The Utah NBS program uses laboratory-developed tests for all MS/MS-screened conditions, including GAMT deficiency. A non-derivatized MS/MS method is used to measure GUAC and the GUAC:creatine ratio. A second-tier test for GAMT deficiency had been conducted by a reference laboratory; however, this second-tier test was eliminated in 2019.[13]

Based on information provided for this report, from June 2015 to May 2019, 195,425 newborns were screened with the derivatized method. During this period, 365 babies had a positive first-tier screen, and 2 had a positive second-tier screen leading to a referral for diagnostic evaluation (1.0 referrals per 100,000 screened). Neither of these infants were diagnosed with GAMT deficiency. From June 2019 to December 2021, 125,880 newborns were screened, of whom two required second-tier screening, with one referred and diagnosed with GAMT deficiency (0.79 referrals per 100,000 screened; 0.79 cases per 100,000 screened in this time period).

For the full period of June 2015 to December 2021, there were 321,305 newborns screened, with 3 referred for diagnostic testing (i.e., 0.93 per 100,000 newborns screened or 1 per 107,102 newborns screened) and one case of GAMT deficiency identified (i.e., 0.31 per 100,000 newborns screened or 1 per 321,305 newborns screened).

New York

The New York NBS program recommends that all newborns receive newborn screening for GAMT deficiency and the other dried-blood spot based disorders between 24 and 36 hours after birth. New York began screening for GAMT deficiency in October 2018 with a state laboratory-developed test using flow-injected MS/MS to measure GUAC and the GUAC:creatine ratio as part of the routine screening for amino acids and acylcarnitines in the first-tier analysis. Initially, a second-tier MS/MS test (liquid chromatography MS/MS for GUAC) was used. Referral for diagnostic evaluation was made based on this testing. According to the program, gene sequencing was provided as a courtesy to help specialists in the diagnostic evaluation.

In the first year of GAMT screening, 3382 of the 263,740 samples (1.28%) required second-tier testing, of which 210 had borderline results for GUAC concentrations requiring repeat specimens. Ten newborns screened positive after second-tier testing (3.8 per 100,000) were referred. Upon review, it was determined that most infants requiring second-tier screening were from the neonatal intensive care unit (NICU). To reduce the number of second-tier screens required, the program developed and tested an alternative algorithm with a modified first-tier screen that used a second transition marker for GUAC. The modified first-tier method had acceptable analytic performance and was highly correlated with the original second-tier test. In March 2020, the modified method was implemented. This change led to a substantial decrease in the proportion of samples needing further testing.[14] In September 2021 New York discontinued the liquid chromatography MS/MS second-tier screen.[14] *GAMT* sequencing is still done by the screening program with results provided to the specialist evaluating any screen-positive infant.[13]

In 2021, 212,232 newborns were screened by the New York NBS program, of whom 82 had a positive first-tier screen. Of these, five were immediately referred for diagnostic evaluation and 77 had a request for a repeat dried-blood spot. Among those requested to have a repeat dried-blood spot, most (76/77, 99%) were in the NICU. Overall, one of the 77 was referred for

diagnostic evaluation because of a positive repeat screen, four died for reasons not known to be related to the positive GAMT screen prior to the repeat dried-blood spot, and two infants in NICU were still pending repeat screening. Among the six referrals, one was diagnosed with GAMT deficiency, one was diagnosed with a non-targeted condition (arginase deficiency), two were normal, and two died prior to diagnostic evaluation and are suspected to be false positives. Based on the 2021 New York NBS data, the referral rate is 2.8 per 100,000 newborns screened and the number of cases of GAMT deficiency detected is 0.47 per 100,000 newborns screened (i.e., 1 per 212,232 newborns screened).

In separate information provided by the New York NBS program, for the full period of GAMT deficiency screening, from October 2018 to April 2022, there were 759,246 infants screened, with 24 referrals for diagnostic evaluation (i.e., 3.2 referrals per 100,000 newborns screened or 1 per 31,635 screened) and one case of GAMT deficiency diagnosed (i.e., 0.13 cases per 100,000 newborns screened or 1 case per 759,246 screened).

Michigan

NBS for GAMT deficiency was approved in 2018 in Michigan. Initially the program anticipated screening for GAMT deficiency in late 2018, however challenges have prevented the program from implemented screening for this condition as of April 2022. This is further described in Section 4 Assessment of the Public Health Impact of Newborn Screening for GAMT Deficiency.

Newborn screening for GAMT deficiency outside of the US

Canada

Population-wide pilot screening for GAMT deficiency started September 18, 2012, in the province of British Columbia.[15] During the 3-year pilot study, dried-blood spot samples submitted through routine screening were screened using a 3-tier assay with GUAC measurement in the standard acylcarnitine/amino acid first-tier assay. Samples with elevated GUAC levels underwent second-tier assay testing with liquid chromatography MS/MS, integrated into the maple syrup urine disease second-tier assay. Samples with elevated GUAC levels on second-tier testing underwent third-tier targeted gene sequencing on the original blood spot specimen. Samples with one or two likely GAMT mutations were identified for referral. Of the 135,372 specimens tested during the 3-year pilot study, 259 (0.19%) had elevated GUAC levels on the first-tier test and were tested with the second-tier assay. Three samples with elevated for GUAC at second-tier testing were genotyped and found to be normal. Review of the pilot study results indicated feasibility. Full population-based NBS has continued since the pilot evaluation. From September 2012 to April 2018, the program had screened 246,995 newborns, with no cases of GAMT identified.[16]

Based on an update provided for this report, as of April 2022, there have been 428,140 newborns screened, of which 1,228 (0.3%) had a positive first-tier screen, 28 had a positive second-tier screen, and 3 were referred for specialty follow-up based on genetic testing, all of whom were carriers. No cases of GAMT deficiency have been identified (see Table 3. Summary of Population-Based GAMT Deficiency Newborn Screening).

Ontario's Ministry of Health and Long-Term Care and the Ministry of Children, Community and Social Services recently approved NBS for GAMT deficiency. Newborn Screening Ontario

(NSO) is currently finalizing its introduction and start up activities and plans to begin screening during Summer 2022.[17]

Australia

NBS for GAMT deficiency began in Victoria, Australia in April 2002 using flow injected MS/MS with a derivatized method. From April 2002 through April 2013, among 771,345 newborns screened using a cut-off of 5.5 multiples of the median, equivalent to GUAC concentrations of about 5 µmol/L, 127 babies (0.02%) had increased levels and were retested on a repeated dried-blood spot, with three of these newborns having increased GUAC in the second sample. Subsequent urine testing for GUAC, creatine and creatinine did not indicate GAMT deficiency in any of the newborns.[18]

In an interview on April 8, 2022, Dr. James Pitt, a biochemical geneticist and Head of the Victorian Clinical Genetics Services Newborn Bloodspot Screening and Metabolic Screening Laboratories, provided an update on their screening experience. Of the approximately 1.4 million total newborns screened, one likely case of GAMT deficiency was recently identified. On an annual basis, about 80,000 newborns are screened, of which about 20 require the second-tier test, about 3 have a repeat dried-blood spot requested, and about 0.3 are referred to the metabolic clinic for further evaluation. Dr. Pitt is unaware of any false-negative cases.

Table 3. Summary of Population-Based GAMT Deficiency Newborn Screening describes the screening results and pooled results. These pooled results are intended to provide a general estimate for the rate of referral and diagnostic yield. However, heterogeneity across screening programs and within geographic areas could limit generalizability of the pooled estimate.

Table 3. Summary of Population-Based GAMT Deficiency Newborn Screening

Location	Time Period	Newborns Screened	Newborns Diagnosed with GAMT deficiency	Diagnostic Follow-up Referral Rate per 100,000 Newborns Screened	Cases Detected per 100,000 Newborns Screened
Utah (Screening conducted by ARUP)	June 2015-May 2019	195,425	0	1.0	0
Utah (Non-derivitized Approach)	June 2019-Dec 2021	125,880	1	0.79	0.79
Utah (Cumulative)	**May 2015-Dec 2021**	**321,305**	**1**	**0.93**	**0.31**
New York (1- and 2-tier screen)	Oct 2018-July 2021	537,408	1*	4.3	0.19
New York (1- and 2-tier screen)	Jan 2021-Dec 2021	212,232	1*	2.8	0.47
New York (Cumulative)	**Oct 2018-April 2022**	**759,246**	**1**	**3.2**	**0.13**
British Columbia, Canada	**Oct 2012 – April 2022**	**428,140**	**0**	**0.7** (following second-tier testing and genetic analysis)	**0**
Victoria, Australia	**April 2002 – April 2022**	**1.4 Million**	**1**	**0.38**	**0.07**
Pooled Screening Results – US Only	**May 2015-April 2022**	**1.08 Million**	**2**	**2.6**	**0.19**
Pooled Screening Results - All	**April 2002-April 2022**	**2.9 Million**	**3**	**1.2****	**0.1**

*Same case, reported from overlapping time periods
**Assuming 6 referrals from the Victoria NBS program based on the average number of referrals per year provided for this report

Screening Summary

- High-throughput NBS with MS/MS has been incorporated into two U.S. state NBS programs using a laboratory developed test and each program has identified one case each.

- Including programs in Australia and Canada as well as the US, 3 cases have been detected in about 2.9 million infants screened, or about 0.1 case per 100,000 newborns screened (i.e., about 1 case per 970,000 newborns screened).
- The number of infants each year requiring diagnostic evaluation is low compared to other conditions included in the RUSP.
- Diagnostic evaluation can be completed in <1 month following a positive screen.

2.3 GAMT Deficiency Treatment

Dietary modifications to supplement creatine, lower GUAC and glycine, and arginine

The treatment for GAMT deficiency is aimed at increasing creatine levels and decreasing GUAC concentrations. Treatment includes supplementation with oral creatine (typically around 400 mg/kg daily) and ornithine (typically 100-800 mg/kg daily).[19] Additional supplements of sodium benzoate (typically 100 mg/kg daily) and dietary protein restriction with arginine-free essential amino acid supplementation may be prescribed.[5,19] According to the TEP, sodium benzoate can be used to decrease glycine levels, but it is generally less important than the creatine and ornithine supplementation. The TEP also highlighted that the protein restriction is substantally less than other metabolic conditions (e.g., phenylketonuria). The TEP also highlighted that infants can still breastfeed.

GAMT Deficiency Treatment Guidelines

The review did not identify any treatment recommendations endorsed by national subspecialty groups. However, the TEP reported that there is consensus regarding the approach to treatment and the benefit of presymptomatic treatment. There are no other targeted treatments currently available. A gene therapy has been tested in a mouse model and found to normalize GUAC.[20]

Overview of Safety and Effectiveness of GAMT Dietary Supplements

GAMT Deficiency Treatment Regulatory Status

The treatments for GAMT deficiency are classified as dietary supplements by the Food and Drug Administration (FDA). As dietary supplements, the Dietary Supplement Health and Education Act of 1994 authorizes the FDA to use current good manufacturing practice (cGMP) guidelines, requires regulation and monitoring of pre-marketing notifications, and allows bans on supplements posing imminent hazards. In contrast to pharmacological treatments, clinical trial data demonstrating safety or efficacy are not required and introducing new ingredients in supplements is legal until explicitly ruled otherwise by U.S. courts. Agencies (i.e., FDA, Federal Trade Commission) are limited in enforcement authority, increasing potential risk of unknown substances in the manufacturing and distribution of dietary supplements necessary to treat GAMT deficiency.[21]

To mitigate potential risks of GAMT deficiency treatment associated with the relatively loose regulatory status of dietary supplements, the ACD patient advocacy group has developed a partnership to make available high-quality creatine and ornithine supplements for individuals with GAMT deficiency. The creatine is sourced from a laboratory that is cGMP certified. Sodium benzoate is typically purchased from compounding pharmacies.[12]

Treatment < 12 months of age

The evidence review identified 6 publications and abstracts describing treatment initiation prior to 12 months of age. While there are no controlled treatment trials, cases series suggest that earlier treatment is associated with better developmental outcomes. This is best demonstrated by reports of sibling pairs in which the younger sibling is diagnosed at birth because of a known family history of GAMT deficiency in an older sibling (see Table 4. Summary of GAMT Deficiency Studies).

One report describes an infant with GAMT deficiency who began treatment at 22 days based on the diagnosis of her brother. The younger sibling is described as "healthy and developing normally." In contrast, the brother, who was diagnosed at age 2.75 years had previously developed seizures and developmental delay (e.g., speaks few words) and has no further speech development. This report does not provide specific information about the impact of treatment on the older sibling.[22]

One case series describes a subject diagnosed and treated at 10 months of age who after 6.5 years of treatment continued to require therapy for delayed speech and fine motor skills (also described in Dhar et al. 2009).[21] This subject had a sibling diagnosed prenatally who at 42 months of age had normal developmental milestones with no cognitive, motor, or speech delays.[23]

The previously described case series of 48 subjects included 6 subjects who began treatment < 12 months of age., three of whom began treatment ≤ 3 weeks. None of the subjects who initiated treatment in the newborn period had developmental delay or intellectual disability after 14 months to 3.5 years of treatment although this was not confirmed with formal testing. In contrast, older siblings of these three subjects who were diagnosed between 10 months and 5.5 years and treated for 30 months to 10 years had mild to moderate developmental delays. The three subjects from this report, who began treatment from 9-11 months of age and were treated for 21-48 months had borderline-moderate developmental delay or intellectual disability and two had epilepsy.[11]

Another case series describes a subject that was diagnosed at 10 months of age after developing gross motor delay, hypotonia, movement disorders, and failure to thrive at 5 months. The subject was reported to be developmentally appropriate at 24 months of age and by 35 months "no longer required physical or occupational therapy and used 2-to-4-word sentences." This report also describes a subject who was diagnosed based on having a sibling with GAMT deficiency who began treatment at 8 days after birth who "remains developmentally normal at 12 months of age." Insufficient information was provided to directly compare outcomes between these siblings.[5] A series of eight subjects with GAMT deficiency reported a sibling pair in which the older sibling was diagnosed at 2.5 years old due to hypotonia, ataxia, speech delay and autistic features. Treatment was associated with "improved motor skills, started walking, improved tone, improved autistic features." The younger sibling was diagnosed at birth. After 11 months of treatment this child has "central hypotonia, developmental delay persists."[24]

A meeting abstract described a subject who was identified at 5 months based on having an affected sibling who began treatment after 3 years of age. According to the abstract, the younger sibling is "now 16 months old with normal development."[25]

Table 4. Summary of GAMT Deficiency Studies with Treatment Within the First Few Months After Birth

	Outcomes with treatment onset < 6 months old			Outcomes of older sibling with later diagnosis, when available		
	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)[23]	Prenatal	42 months	Normal	10 months (*also reported in Dhar et al. 2009*)[24]	6.5 years	Speech and fine motor delays
Stockler-Ipsiroglu et al. (2014)[11]	Prenatal 1 week 3 weeks	41 months 14 months 31 months	Normal Normal Normal	10 months 5.5 years 30 months	39 months 30 months 10 years	Mild developmental delay Moderate developmental delay Mild Developmental delay
Viau et al. (2013)[5]	Birth	12 months	Normal	---	---	---
Dhar et al. (2009)[24]	8 days	11 months	Central hypotonia, developmental delay persists	2.5 years	4.5 years	Improved motor skills, started walking, improved tone, improved autistic features
Schulze et al. (2006)[22]	22 days	14 months	Normal	2.75 years	2.25 years	Epilepsy, speaks "a few words"
Farshidi et al. (2011)[25]	5 months	11 months	Normal	15 months	21 months	Continues to have seizures (improved), cognitive impairment, learning disability (improved)

Treatment Summary

- Case series suggest that pre-symptomatic or earlier initiation of treatment of GAMT deficiency is associated with improved neurological outcomes, including reduced risk of intellectual disability and less frequent seizures.
- None of the reports provide developmental results based on a standardized quantitative measure.

3 ESTIMATED POPULATION IMPACT OF NEWBORN SCREENING FOR GAMT DEFICIENCY

This aspect of the review answers the question "What would be the impact of newborn screening at the population level if GAMT deficiency newborn screening were adopted by all newborn screening programs in the US compared to clinical case detection in the absence of GAMT deficiency newborn screening?"

Overview of Process

Evidence Evaluation and Methods Workgroup

In April 2011, an Evidence Evaluation and Methods Workgroup met to consider the methods and used by the ERG for the ACHDNC. One of the recommendations from this group was to incorporate the application of decision analysis into the evidence review process. An April 2012 publication[26] coauthored by some of the workgroup members noted that a decision analytic model "could provide an estimate of the range of cases prevented, deaths prevented, and/or number of children requiring treatment, as well as other health outcomes, for universal screening compared to clinical ascertainment." Since the recommendations were made, decision analytic modeling has been used as part of the evidence review process for hyperbilirubinemia, Pompe disease, mucopolysaccharidosis type I disease, X-linked adrenoleukodystrophy, spinal muscular atrophy, and mucopolysaccharidoisis type II. GAMT deficiency is the seventh condition to incorporate decision analytic modeling into the evidence review process.

Objectives of Decision Analysis

Decision analysis is a systematic approach to decision making under conditions of uncertainty that has been applied to clinical and public health problems.[27] Decision analytic models can be used to simulate randomized clinical trials for new health interventions, to project beyond the clinical trial time frame, or to compare treatment protocols not directly compared in head-to-head trials. The decision analytic approach allows the decision maker to identify which alternative is expected to yield the most health benefit. It can also allow researchers to characterize the uncertainty associated with projections of clinical and economic outcomes over the long-term,[28] which is important given the lack of long-term outcomes data for most conditions considered for NBS.

A decision analytic model (or decision tree) defines the set of alternatives and short- and long-term outcomes associated with each alternative. In the application to screening for GAMT deficiency, this approach was anticipated to aid in the estimation of the range of screening outcomes that could be expected for universal NBS of GAMT deficiency compared with clinical identification.

Applying Decision Analysis to Screening for GAMT Deficiency

Published literature for rare disorders such as GAMT deficiency is limited with respect to data for prevalence, natural history, and response to treatment. This is especially true for GAMT deficiency given the even rarer nature of this condition compared with conditions already on the RUSP.

For this review, we used data from the Utah and New York NBS programs supplemented by published and unpublished data. Through modeling, we aim to add to the evidence base provided

by the systematic review by providing projections of key screening outcomes at the population level for NBS compared with clinical identification. The modeling analysis also serves to highlight evidence gaps as well as the areas with the greatest uncertainty.

Expert Panel Meeting Process

Clinical and scientific experts in the screening and treatment of GAMT deficiency were identified and invited to serve on the TEP (see Table 1. List of Technical Expert Panel Members). TEP members were asked to provide input on the design and assumptions of the decision analysis model. A series of three TEP meetings (see Table 5. Timeline of Decision Analytic Modeling for GAMT Deficiency Disease Screening) were conducted to provide feedback on the evidence review and the decision analysis model. The model structure was discussed in the second TEP meeting to identify sources for input probabilities; to provide feedback on the structure of the decision analytic model; and to develop assumptions where little or no data were available. All meetings were conducted via webinar. Assumptions for the incidence of GAMT deficiency in the absence of screening were discussed as part of the third TEP meeting. The identification of data sources and the development of a decision analytic model is typically an iterative process.

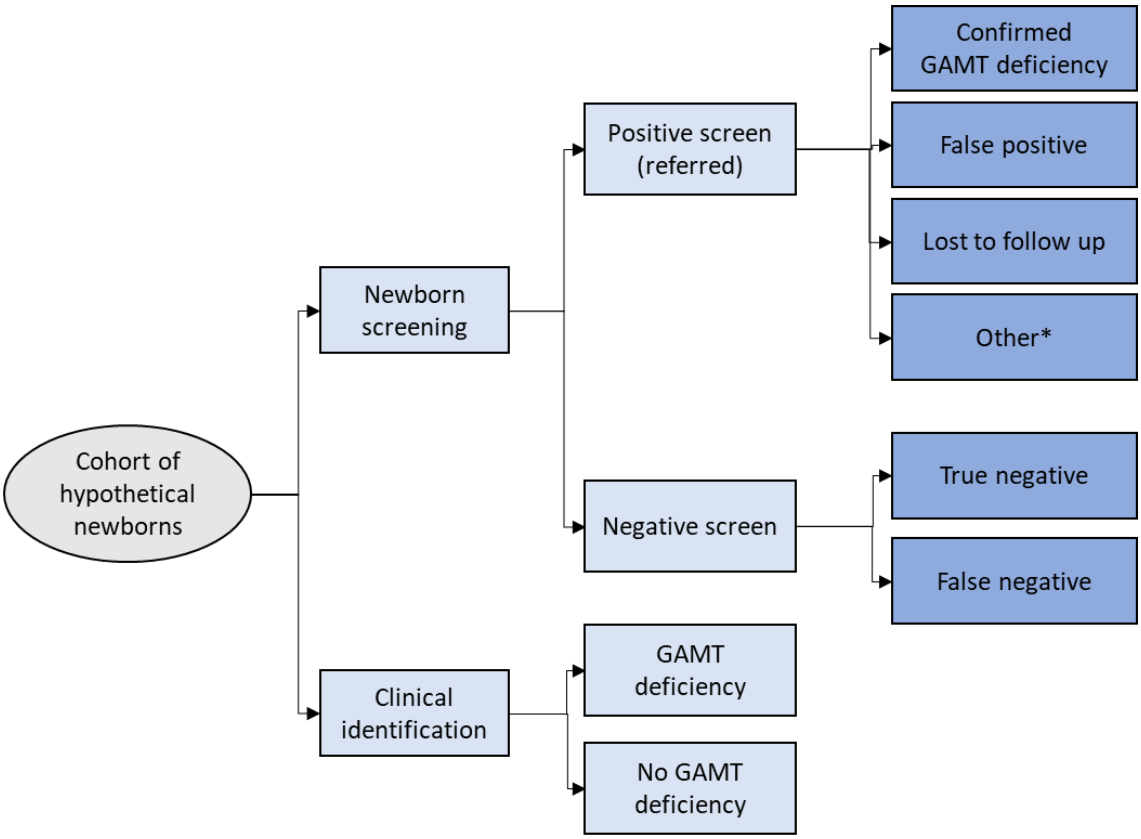
Table 5. Timeline of Decision Analytic Modeling for GAMT Deficiency Disease Screening

Date	Milestone
August 2021	GAMT deficiency nominated for addition to uniform newborn screening panel; referred to external ERG
October 2021	TEP meeting #1
December 2021	Initial development of decision analytic model to evaluate newborn screening for GAMT deficiency
January 2022	TEP meeting #2 – review of model structure and preliminary evidence review summary
April 2022	TEP meeting #3 – review of topics related to screening, treatment, and implementation of GAMT deficiency screening for NBS programs

Methods

An initial decision analysis model was developed concurrently with the evidence review process. The initial model was reviewed with the expert panel in January 2022. A schematic of the final GAMT deficiency NBS decision model is shown in Figure 1. GAMT Deficiency Model Schematic.

Figure 1. GAMT Deficiency Model Schematic



*Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

The key features of the decision analytic model are as follows:

- Target population: Annual newborn cohort for the U.S. (i.e., 3.6 million newborns).
- Interventions: Universal NBS compared with diagnosis through clinical identification.
- Timeframe: up to 3 months for NBS; lifetime for clinical identification.
- Key endpoints: Screening outcomes (positive screens, confirmed GAMT deficiency, false positives, and cases of clinically identified GAMT deficiency).

Parameter inputs were based on published and unpublished data. The model structure and parameter estimates were revised following each TEP meeting based on additional data sources identified and supplemented by expert opinion in cases where no data were available. The final set of parameter inputs and associated ranges for the analysis are shown in Table 7. Parameter Inputs, Newborn Screening for GAMT Deficiency.

Overall Approach

The model estimates outcomes for two identical cohorts of newborns for GAMT deficiency, one cohort receives NBS for GAMT deficiency, and one cohort does not. The key endpoint is number of cases of confirmed GAMT deficiency. The model also estimates screening outcomes. Each parameter in the model is defined with a point estimate and a range reflecting plausible estimates. The model was programmed using Treeage Pro Healthcare 2021 R2.1 (Williamstown, MA).

The evidence base on natural history and treatment effectiveness was insufficient to support the modeling of longer-term outcomes for individuals with GAMT deficiency due to the extremely low incidence of this disorder. This is the second condition for which the ERG had insufficient evidence to model health outcomes beyond the screening timeframe.

Key Assumptions

As described in the systematic evidence review, the birth prevalence of GAMT deficiency in the U.S. is unknown. The likely range is from 1 per 200,000 births to 1 per 2,000,000 births.

The estimated probability of outcomes from screening including probability and range of having a positive screen, identifying GAMT deficiency, identifying cases with diagnostic uncertainty needing follow-up, false positive screens, and cases lost to follow-up were based on data from the Utah and New York NBS programs (Table 7. Parameter Inputs, Newborn Screening for GAMT Deficiency).

Table 6. Estimated Birth Prevalence of GAMT Deficiency Based on Clinical Case Detection and Newborn Screening

Description	Most Likely	Range (min-max)	Source
Birth Prevalence of GAMT deficiency, clinical identification	Not available	0.05 – 0.5 per 100,000*	Published and unpublished literature on the prevalence of GAMT deficiency, TEP discussion
Birth prevalence of GAMT deficiency, NBS	0.2 per 100,000†	0.02 – 0.6 per 100,000‡	Utah and New York NBS Data

* 1 in 2 million to 1 in 200,000
† 1 in 540,276
‡ 1 in 4.4 million to 1 in 164,000. Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution

Table 7. Parameter Inputs, Newborn Screening for GAMT Deficiency

a. Summary data from Utah and New York Newborn Screening Programs

Category	Utah		New York		Combined	
	n	Incidence (per 100,000)	n	Incidence (per 100,000)	n	Incidence (per 100,000)
Total newborns screened	321,305	-	759,246	-	1,080,551	-
Positive screen	4	1.2	24	3.2	28	2.6
GAMT after a positive screen	1	0.3	1	0.1	2	0.2
Positive screen is false	3	0.9	20	2.6	23	2.1
Lost to follow-up after a positive screen	0	0.0	0	0.0	0	0.0

Other*	0	0.0	3	0.4	3	0.3

* Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

b. Parameter Inputs

Probability	Most likely	Range (min-max)	Source
Positive screen	2.6 per 100,000*	1.7 – 3.8 per 100,000†	Utah and New York NBS Data
GAMT after a positive screen	7%‡ 0.2 per 100,000	1% - 24%‡ 0.02 – 0.6 per 100,000	
Positive screen is false	82% 2.1 per 100,000	63% - 94% 1.6 – 2.4 per 100,000	
Loss to follow-up after a positive screen	0% 0.0 per 100,000	0% - 12% 0.0 – 0.3 per 100,000	
Other§	11% 0.3 per 100,000	2% - 28% 0.06 – 0.7 per 100,000	

* 1 in 39,000

† 1 in 58,000 to 1 in 27,000. 95% confidence interval derived using binomial distribution.

‡ Conditional probability given a positive screen, ranges for conditional probability based on the Utah and New York NBS experiences

§ Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

Results

Projected Cases of GAMT Deficiency

We projected the annual number of confirmed GAMT deficiency cases that would be identified with NBS in the U.S., with 3.6 million births per year, compared with clinical identification.

Using combined data from the Utah and New York NBS programs, the projected number of positive screens referred for follow-up per year is 93 (range: 62- 135) each year for a U.S. newborn cohort of 3.6 million. These newborns would require confirmatory testing. Following confirmatory testing, an estimated 7 (range: 1 - 22) newborns would be diagnosed with GAMT deficiency. The projected number of false positives each year is 77 (range: 59 - 88) newborns (Table 8. Projected Cases from Newborn Screening for GAMT Deficiency Compared to Clinical Identification for a Cohort of 3.6 Million Children in the U.S.). Based on screening experiences

in Utah and New York, there would be 10 (range: 2-26) newborns with a diagnosis of a non-targeted condition or unknown determination due to death before confirmatory testing.

Table 8. Projected Cases from Newborn Screening for GAMT Deficiency Compared to Clinical Identification for a Cohort of 3.6 Million Children in the U.S.

	Newborn Screening	Clinical Identification
Positive screen	93 (62 - 135)*	-
GAMT identified	7 (1 - 22)	2 - 18
False positive	77 (59 - 88)	-
Lost to follow-up	0 (0 - 12)	-
Other**	10 (2 - 26)	-

*Results are rounded; **Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

Limitations

The analysis uses a simplified model to evaluate projected screening outcomes for identified cases of GAMT deficiency by NBS in the US. Limited data were available for many parameter inputs. Insufficient data were available to project long-term outcomes for GAMT deficiency, either through NBS or clinical identification. The birth prevalence of GAMT deficiency in the U.S. is unclear, making comparisons of number of identified cases with and without screening to be characterized by substantial uncertainty.

Given the rare nature of newborn screened conditions, data are typically scarce for conditions being considered for addition to the recommended uniform screening panel. Compared with other conditions that have been nominated and considered for addition to the panel, data for the consideration of GAMT deficiency were considerably sparser.

Summary

- Modeling projections estimate 7 cases of GAMT deficiency (range: 1-22) would be identified annually through national NBS.
- There is insufficient evidence to compare to the estimated cases detected in the absence of NBS.
- There is insufficient evidence to model any clinical outcomes beyond case identification to quantify the potential benefits of screening.

4 ASSESSMENT OF THE PUBLIC HEALTH IMPACT OF NEWBORN SCREENING FOR GAMT DEFICIENCY

In partnership with the ERG, the Association of Public Health Laboratories (APHL) evaluated state NBS' ability to screen for GAMT deficiency according to the Manual of Procedures. The purpose of the public health impact assessment is to assess the readiness and feasibility of NBS programs to implement screening for GAMT deficiency. Readiness refers to the ability to adopt GAMT deficiency NBS onto the program's existing panel and is classified as ready (could implement within one year), developmentally ready (could implement within 1 to 3 years), and unprepared (would take more than 3 years). Feasibility is based on the degree to which there is an established and available screening test, a clear approach to diagnostic confirmation, an acceptable treatment plan, and an established approach to long-term follow-up.

The public health system impact assessment focuses on the activities involved and time it takes to implement NBS for GAMT deficiency. The evaluation does not consider other factors that may be involved prior to implementing a disorder. Examples of these other factors include, but are not limited to, getting funds to screen, obtaining a legislative agreement, or procuring new technology for screening. These pre-implementation activities can add several years to the process. NBS programs vary with regards to their activities and requirements to add new conditions.

Methods

Survey Administration

APHL, the ERG, and representatives from state NBS programs currently screening for GAMT deficiency developed a fact sheet (see Appendix B: Public Health Impact Assessment Fact Sheet for GAMT Deficiency Newborn Screening) to provide baseline knowledge about GAMT deficiency NBS to survey respondents. The fact sheet provided information on the incidence of GAMT deficiency, screening methods, resources and materials needed for screening, workstation capacity, personnel requirements, the process for quality control, the process for reporting screening, the process for short-term follow-up, typical treatments, and summary information about treatment outcomes and costs from programs already screening for GAMT deficiency. APHL hosted a webinar in January 2022 to discuss GAMT deficiency and prepare respondents for the survey. The screening outcomes included on the factsheet were what was known at the time of the webinar in January 2022; programs provided subsequent updates that were included elsewhere in this report.

A web-based survey approved by the Office of Management and Budget, was designed to assess readiness and feasibility components to add GAMT deficiency onto state NBS panels (see Appendix B: Public Health Impact Assessment Fact Sheet for GAMT Deficiency Newborn Screening). The survey was administered to 53 US public health programs via email from February 17 to April 7, 2022. The survey focused on activities directly related to public health programs and not personal medical care services. The email with the survey link emphasized the importance of working collaboratively with stakeholders in the state (e.g., laboratory experts, follow-up staff, medical specialists, Title V directors, advocates, public health commissioners) to complete the survey. All survey results were submitted directly to APHL for analysis. In March 2022 reminders were sent to survey non-respondents.

Interviews

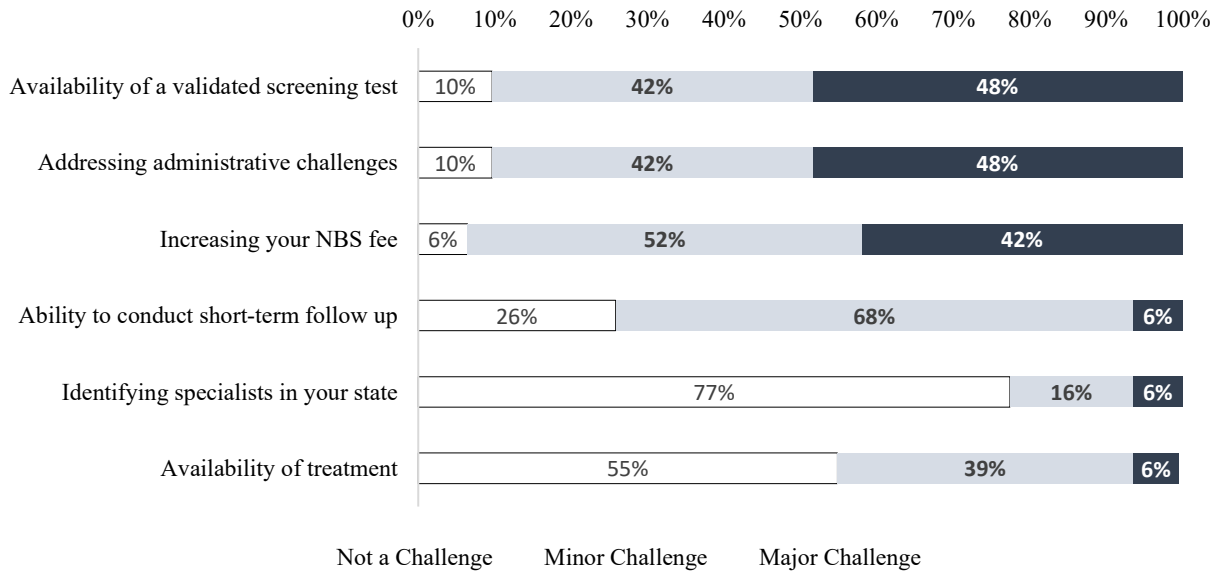
Representatives from NBS programs that had begun screening for GAMT deficiency, had a mandate to screen, or had conducted a pilot were interviewed by APHL. In addition to the NBS program designee, relevant stakeholders were encouraged to join in the interview. These interviews focused on understanding facilitators and barriers to GAMT deficiency NBS and to collect information on screening outcomes. APHL also interviewed two additional NBS programs to better understand the impact on their programs.

Survey Results

Overall, 35 of 53 NBS programs (66%) responded to the survey. Thirty-one programs were included in the analysis and four were excluded due to screening for GAMT deficiency, having a mandate, and/or a pilot. Three NBS screening programs were interviewed instead of completing the survey because they currently screen for GAMT deficiency (New York and Utah) or are preparing for GAMT deficiency NBS (Michigan). Among the survey respondents, 19 were from the public health or NBS laboratory, two from programs that contract NBS laboratory services regionally, five came from laboratory where there was a state university laboratory for which there is an intra-state agency agreement, three from programs that contract NBS laboratory services commercially, and two had an "other" designation.

Most respondents (90-94%) reported that the availability of a validated screening test, addressing administrative challenges, and increasing the NBS fee were challenges for implementing GAMT deficiency. Please see Figure 2. Reported Barriers to GAMT Deficiency Newborn Screening for details on implementation challenges.

Figure 2. Reported Barriers to GAMT Deficiency Newborn Screening (n = 31)



Approximately half of the NBS program respondents reported not having a screening method for GAMT deficiency and not being able to get it within a year. This may reflect the lack of an FDA-approved testing kit available or the need to create a laboratory developed test. Thirty-two percent reported not having Laboratory Information Management System (LIMS) capacity and

not being able to get it within one year. Although 74% reported having access to specialists and treatment centers necessary for the potential caseload, 37% reported challenges with having sufficient short-term follow-up staff to track cases. For the 12 NBS programs that contract services, 83% of them reported having enough short-term follow-up staff on hand. One-quarter of the programs that contracted services expressed concerns with having a validated screening test [Figure 3. Resources Needed for Own State's Public Health or NBS Laboratory (n = 19) and Figure 4. Resources Needed for Contracted or State University Laboratories with Intrastate Agreement (n = 12)].

Figure 3. Resources Needed for Own State's Public Health or NBS Laboratory (n = 19)

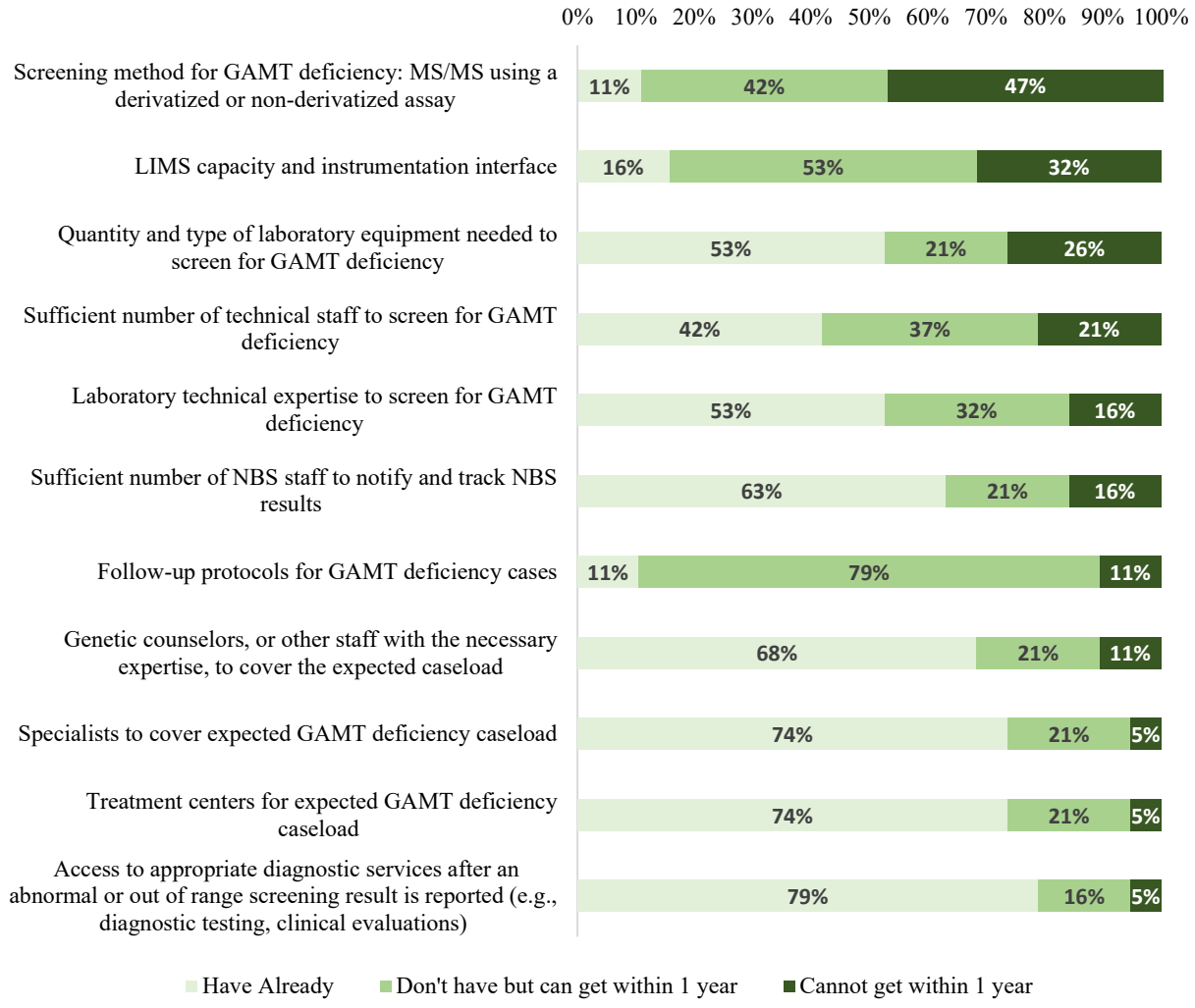
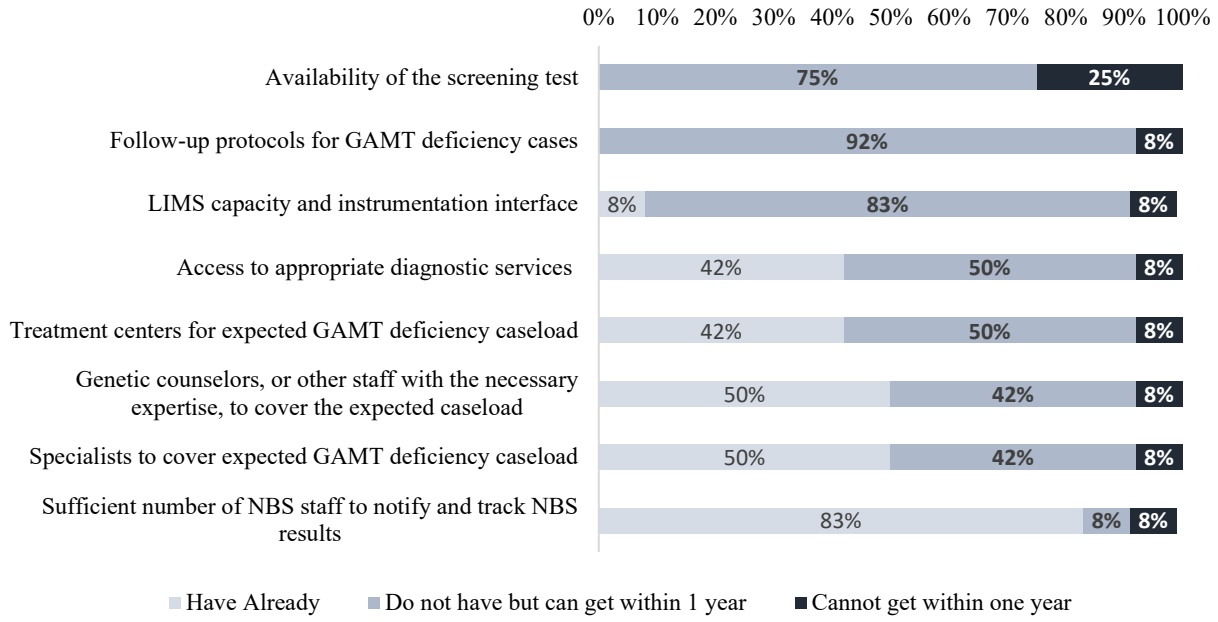
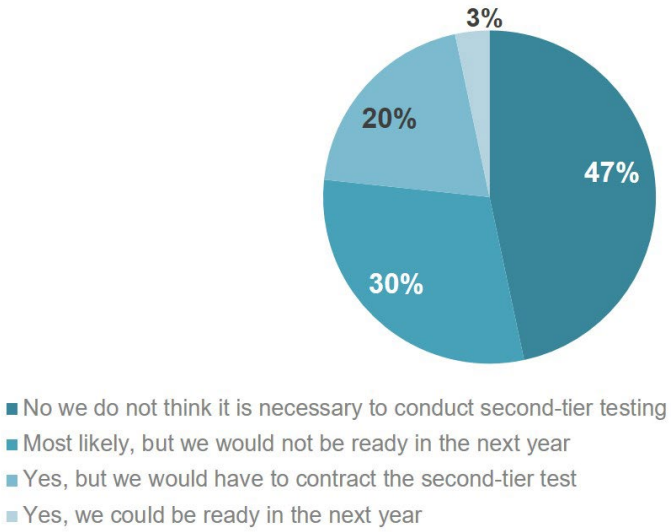


Figure 4. Resources Needed for Contracted or State University Laboratories with Intrastate Agreement (n = 12)



Approximately half of respondents did not think it would be necessary to conduct a second-tier test for GAMT deficiency. Three percent of laboratories were ready with a second-tier, 30% stated that they would likely conduct a second-tier test but would not be ready in one year, and 20% reported that they would contract this service to an outside laboratory. Please see Figure 5. Second-Tier Screening for GAMT (n = 30) for more details.

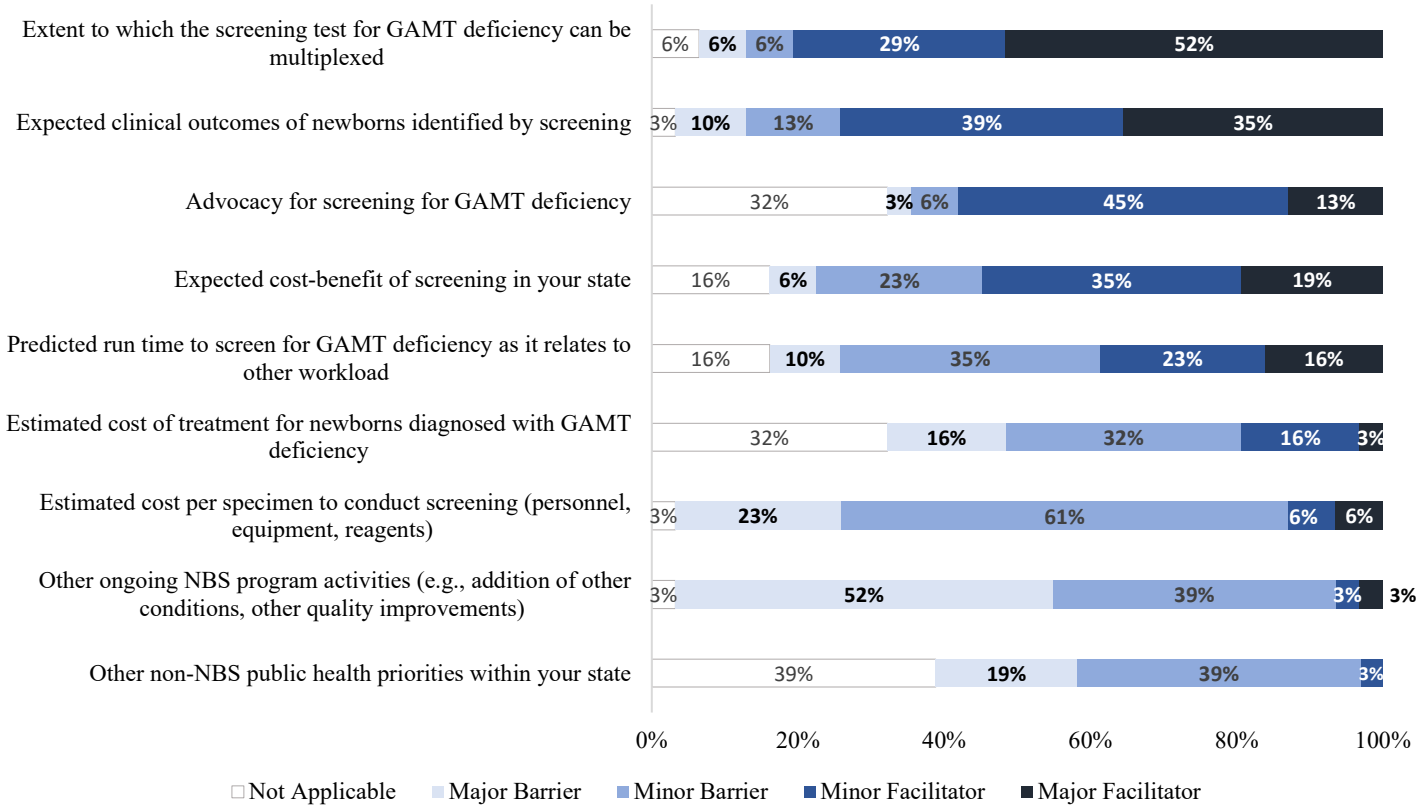
Figure 5. Second-Tier Screening for GAMT (n = 30)



Most NBS programs reported the following facilitators for screening: existing advocacy, ability to multiplex testing, the expected cost-benefit of screening, and the expected clinical outcomes. Barriers for most included competing with other NBS program activities, the estimated cost per specimen to conduct screening, and other public health priorities within the state. These barriers

and facilitators are summarized in Figure 6. Barriers and Facilitators for GAMT Deficiency (n = 31).

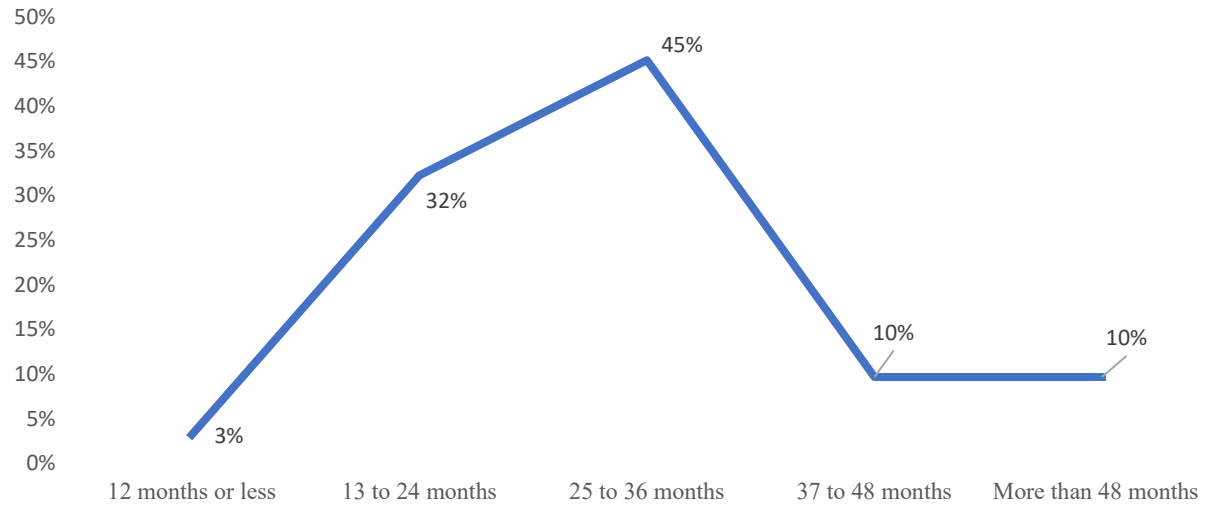
Figure 6. Barriers and Facilitators for GAMT Deficiency (n = 31)



Among open-ended responses, 12 of the 19 respondents that conduct their own screening reported that they need or at least desire an FDA-approved testing kit to screen for GAMT deficiency. Other frequently cited barriers on the open-ended section included the challenge of getting fee increases, staffing issues, and obtaining approvals. Facilitators that were frequently cited included whether GAMT deficiency is added to the RUSP, potentially having an FDA-approved testing kit, and receipt adequate funding and staff.

Nearly half of NBS programs reported that it would take 2 to 3 years to implement GAMT deficiency NBS. Thirty-five percent reported being able to implement faster than 2 years and 20% reported implementing slower than 3 years. Please see Figure 7. Estimated Time it Would Take to Implement GAMT Deficiency Screening in Your State for additional details. Some of the activities that the majority of programs noted would take more than one year included obtaining authorization to screen, getting funds, validating the assay, and setting up a results and reporting system

Figure 7. Estimated Time it Would Take to Implement GAMT Deficiency Screening in Your State



Interviews With Programs That Have Universal GAMT Deficiency Newborn Screening

New York

In 2018, the New York NBS screened for GAMT deficiency using a derivatized laboratorydeveloped assay for GUAC and creatine (CRE)multiplexed with the other acylcarnitine and amino acid disorders. Samples with GUAC >2.80 µmol/L and GUAC*1000/(creatine concentration) >12 were tested with liquid chromatography MS/MS second-tier screen to quantify the GUAC concentrations. This second-tier test was eliminated in October 2021 because the New York program was able to add a product ion to make the first-tier test more specific.

The New York program is unique in that it includes gene sequencing as a third-tier screen. However, these findings are not used when determining whether to refer for diagnostic evaluation.

Utah

Utah requires two newborn screens, once at 24-48 hours of life and again at 7 to 16 days of life. Prior to 2019, the Utah NBS program contracted laboratory NBS services to the Associated Regional and University Pathologists, Inc. ARUP screened for GAMT deficiency beginning in 2015 using a derivatized method. In 2019, laboratory testing moved in-house and the Utah NBS program simultaneously began screening for GAMT deficiency. The Utah program uses a non-derivatized laboratory developed MS/MS method to measure GUAC and creatine concentrations. The condition is multiplexed with the other acylcarnitine and amino acid disorders. Newborn screens that have out-of-range GUAC concentrations after the second screen and are referred for diagnostic confirmation if their results are out-of-range after the repeat.

Staff from the New York and Utah programs reported that GAMT deficiency was easily multiplexed with other amino acid and acylcarnitine disorders. Staff from both programs did not believe that a second-tier test was necessary. They reported that there was very little additional staff or follow-up time required for this disorder. Both the New York and Utah programs use a

laboratory-developed test for GAMT deficiency. Although laboratory-developed tests can be less expensive and more flexible than commercially available testing kits, they also require a significant amount of time and expertise to develop. NBS programs that use commercially available testing kits for other disorders may not be able to easily transition to a laboratory developed test. Currently, there is not a commercially available FDA-approved testing kits, which is not unlike the situation for many other disorders that have been nominated to the RUSP. Centers for Disease Control and Prevention provides quality assurance samples to NBS programs for GAMT deficiency.

The New York program discussed that the validation process can be a major undertaking. For example, a NBS program may need to re-validate all their amino acid and acylcarnitine disorders when adding GAMT deficiency. It took approximately one year to complete validation. Since Utah began its NBS program in 2019, it did not have pre-existing assays that had to be validated.

Interviews With Programs Planning for GAMT Deficiency Newborn Screening

Michigan

The Michigan NBS program has been exploring the use of a non-derivatized MS/MS method to screen for GAMT deficiency. It uses a similar approach for other amino acid and acylcarnitine disorders. The non-derivatized assay has the advantage of being more efficient and not requiring harsh chemicals that are required for a derivatized assay. In contrast to the New York and Utah NBS programs laboratories, the Michigan NBS program uses a commercial testing kit. Adding GAMT deficiency in effect converts the entire testing process to a laboratory-developed test. Since the NBS testing kit is provided by a vendor and proprietary, determining the impact of adding GAMT deficiency NBS is challenging.

The Michigan NBS program has spent over three years trying to validate a multiplex assay in which a analyte to screen for GAMT deficiency is added to a pre-existing testing kit with proprietary reagents. They report difficulties with the sensitivity of the screening test, which may be explained by the use of a commercial testing kit, the impact of the non-derivatized assay on their current equipment (e.g., requiring more frequent cleaning), and the age of their MS/MS equipment. During the validation process, the Michigan program identified hundreds of false positive samples daily, consuming many resources. Michigan resolved some of these issues by more frequently maintaining the MS/MS equipment. Ultimately, the MS/MS equipment may need to be replaced to continue with GAMT deficiency NBS.

Interviews With Programs Not Currently Considering GAMT Deficiency Newborn Screening

The two programs we interviewed that are not currently screening or exploring adding GAMT deficiency highlighted challenges of competing priorities, funding, hiring staff, laboratory space, and updating their LIMS. One of the programs also discussed that there were issues not having enough metabolic specialists in their state for many of their NBS disorders. The programs expressed concern with the growing expectations of NBS programs to add conditions and not having enough resources.

Readiness

Approximately half of NBS programs reported that it would take between 2 and 3 years to implement GAMT deficiency, which would make them developmentally ready for implementation. Readiness varies greatly across the country, with 35% percent reporting being able to implement faster than 2 years and 20% reported implementing slower than 3 years.

Feasibility

GAMT deficiency can be multiplexed with other acylcarnitine and amino acid disorders using a derivatized or nonderivatized MS/MS method. Screening can be conducted with a single-tier test. Laboratories have been successful using both derivatized and nonderivatized methods. It is possible that a nonderivatized method may require more cleaning steps or that the age of the MS/MS equipment may affect sensitivity. Many programs will likely need to re-validate their amino acid and acylcarnitine disorders screening tests with the addition of GAMT deficiency NBS. An FDA-approved testing kit would facilitate GAMT deficiency NBS. Additionally, laboratory information systems will likely need to be updated.

Summary Of Key Findings

- New York and Utah are the only NBS programs in the U.S. with universal GAMT deficiency NBS. Michigan has been trying to validate GAMT deficiency screening for three years and has confronted screening technology challenges.
- The ability to multiplex GAMT deficiency NBS as a single-tier screen is an important facilitator
- An FDA-approved testing kit would facilitate the implementation of GAMT deficiency newborn screening.
- Challenges to GAMT deficiency NBSNBS implementation include issues of validating the test, funding, staffing, and competing priorities.
- Approximately half of NBS programs reported that it would take them between 2 and 3 years to implement GAMT deficiency NBS.

Newborn Screening Program Costs of Screening for GAMT Deficiency

Representatives from the Utah and New York NBS programs and the ACD were interviewed to estimate the costs of adding GAMT deficiency. Both programs, along with programs in other countries, modified an existing MS/MS acylcarnitine/amino acid assay as a first-tier screening test. No additional time nor equipment were needed. After test development and validation and LIMS modification, operating costs were minimal. The estimated additional cost of adding GAMT deficiency NBS from the program perspective, above and beyond fixed costs based on the experience of the New York and Utah NBS programs is substantially less than $1 per infant. Since both program use a laboratory developed test, generalizability of this estimate could be limited.

Appendix A. SYSTEMATIC EVIDENCE REVIEW TECHNICAL METHODS

Literature Search

The following tables list the search terms for each of the four databases that were queried to identify articles for the systematic evidence review. The initial literature search was conducted for references published from January 1, 2001 to September 1, 2021, and a bridge search was conducted to update the references with publications from September 1, 2021 through April 1, 2022.

PubMed

Set	Terms	1/1/01-9/1/21	9/1/21-4/1/22
#1	"guanidinoacetate methyltransferase deficiency"[Supplementary Concept] OR "guanidinoacetate methyltransferase deficiency"[All Fields] OR "GAMT"[All Fields] OR "gamt deficiency"[All Fields] OR ("Guanidinoacetate N-Methyltransferase"[Mesh] AND deficiency[tw])		
#2	English, Humans, 2001-2021		
#3	#1 AND #2	145	1

EMBASE

Set	Terms	1/1/01-9/1/21	9/1/21-4/1/22
#1	#1 'guanidinoacetate methyltransferase'/exp AND deficiency		
#2	'guanidinoacetate methyltransferase deficiency'/exp		
#3	‘gamt gene’/exp		
#4	Gamt		
#5	gamt AND deficiency		
#6	#1 OR #2 OR #3 OR #4 OR #5		
#7	#6 AND [1-1-2001]/sd		
#8	#6 AND [1-1-2001]/sd AND [english]/lim	405	38

CINAHL

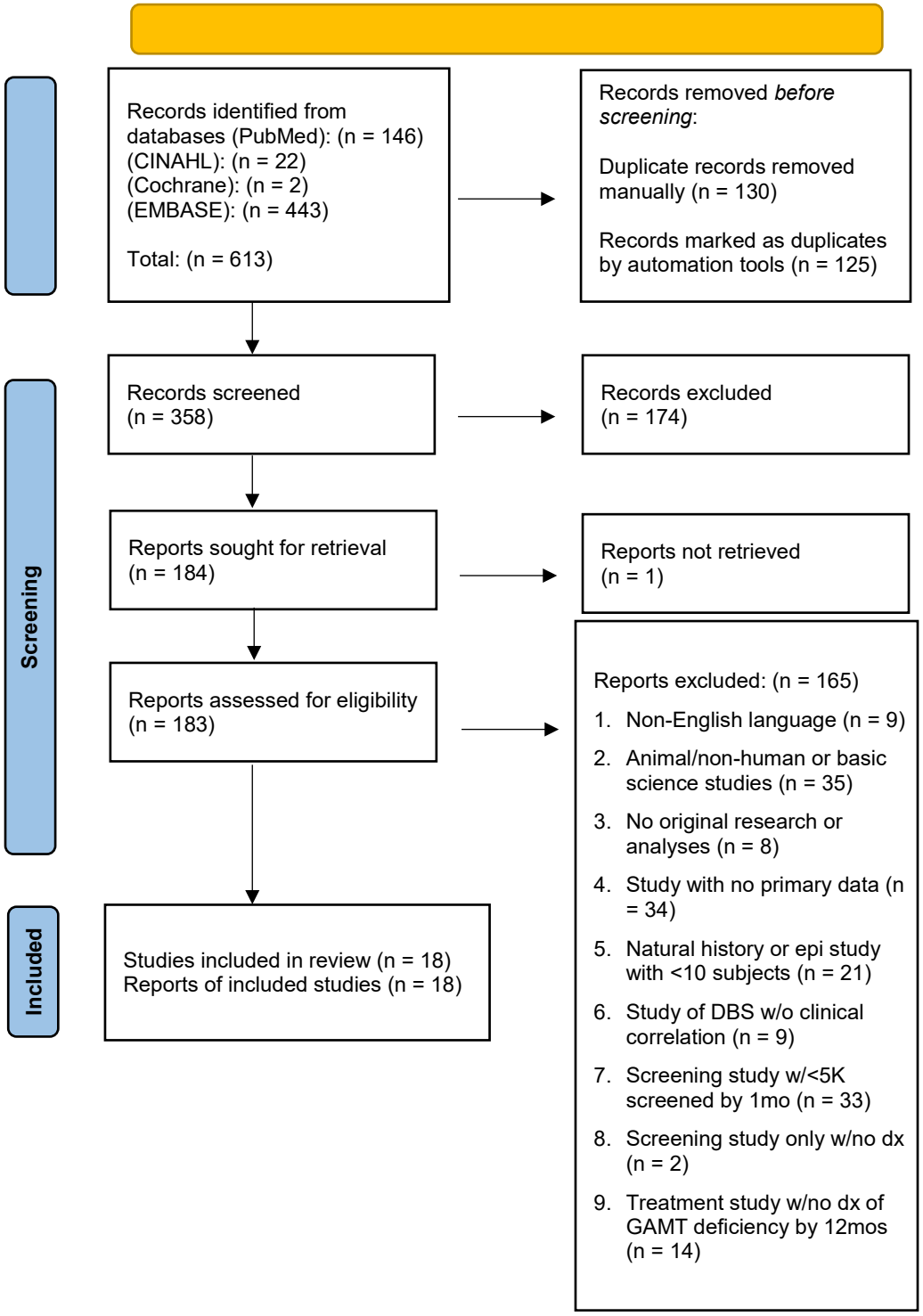
Set	Terms	1/1/01-9/1/21	9/1/21-4/1/22
#1	guanidinoacetate methyltransferase deficiency OR gamt OR gamt deficiency OR gamt gene OR (Guanidinoacetate N-Methyltransferase AND deficiency)		
#2	Filters: English, 2001-2021		
#3	#1 AND #2	20	2

Cochrane Library

Set	Terms	1/1/01-9/1/21	9/1/21-4/1/22
#1	#1 (guanidinoacetate methyltransferase deficiency):ti,ab,kw OR (GAMT):ti,ab,kw OR (gamt gene):ti,ab,kw OR (gamt deficiency):ti,ab,kw		
#2	MeSH descriptor: [Guanidinoacetate N-Methyltransferase] explode all trees		
#3	(deficiency):ti,ab,kw		
#4	#2 AND #3		
#5	#1 OR #4	2	0

The following figure describes the process leading to the articles included in this review.

Figure 8. Identification of Studies Via Databases



Quality Assessment of Screening and Treatment Reports

Following the methods for developing reports for the ACHDNC, the risk of bias was assessed for the published reports of GAMT deficiency NBS in the US and for published reports comparing treatment in the first year of life versus treatment that was begun later based on clinical identification.

Screening Studies
Risk of bias was assed related to newborn selection, standard use of a screening test, standard application of a reference standard, and the appropirate flow and timing of screening. One study met the criteria for risk-of-bias assessment:

Hart K, Rohrwasser A, Wallis H, et al. Prospective identification by neonatal screening of patients with guanidinoacetate methyltransferase deficiency. *Mol Genet Metab.* 2021; 134(1-2):60-64.
The risk of bias in this report is low. Consecutive newborns were screened with well-defined screening tests, standard approaches were used for diagnosis, and the flow and timing of screening was appropirate for NBS in New York and Utah.

Treatment Studies
No treatment study met the criteria for formal risk-of-bias assessment. The treatment studies were based on case series, which have significant risk of bias related to selective identification, measurement bias because assessment is often not blinded, and confounding because of the many uncontrolled factors related to treatment and outcomes.

Appendix B. PUBLIC HEALTH IMPACT ASSESSMENT FACT SHEET FOR GAMT DEFICIENCY NEWBORN SCREENING

Fact Sheet

This fact sheet provides newborn screening programs with background information on Guanidinoacetate Methyltransferase (GAMT) deficiency so they can complete a public health impact assessment survey that evaluates their program's readiness and feasibility to add GAMT deficiency onto their newborn screening panels. The factsheet discusses background information pertaining to the condition, screening methods, resources/materials, screening results, personnel requirements, costs, short-term follow up, and treatment for GAMT deficiency. Contact Jelili Ojodu (jelili.ojodu@aphl.org) for more information.

Condition	GAMT Deficiency
Description	GAMT deficiency is an autosomal recessive disorder caused by mutations in the GAMT gene. It is characterized by elevated plasma guanidinoacetate (GUAC) and low plasma and brain creatine. Individuals with untreated GAMT deficiency often present with developmental delay, seizures, muscle weakness, movement disorders, and behavioral disorders.
Expected Incidence	Based on clinical detection, GAMT deficiency is present in < 0.3/100,000 live births Screening detections to date are: New York: ~<0.2/100,000 live births Utah: ~0.4/100,000 live births

First-Tier Screening Methods	
Screening Strategy and Markers	Flow injection analysis (FIA) by tandem mass spectrometry (MS/MS) is most commonly used as the primary screening method. First-tier screening can be done by either a non-dervivatized or derivatized tandem mass spectrometry (MS/MS) method to detect guanidinoacetate (GUAC) and creatine.

Second-Tier Screening Methods	
Screening Strategy and Markers	Ultra performace liquid chromatography (UPLC) MS/MS analysis to measure levels of GUAC and creatine may be used for second-tier screening. New York has been able to eliminate the second-tier test by adding a new product ion into their derivatized assay to get improved specificity. Molecular analysis may be performed as a third-tier screen and can assist with diagnosis.

Resources and Materials	
Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually (Includes Conventional Redundancies)	First-tier screening by FIA MS/MS, using derivatized or non-derivatized assay methodologies, is integrated with existing acylcarnitine and amino acid testing. UPLC MS/MS instrumentation may be used as a second-tier test to increase specificity.
Equipment Suppliers and Availability of Kits, Reagents and Consumables	Standard instrumentation and reagent suppliers can be used for laboratory developed test assays. PerkinElmer is planning integration of GUAC and creatine into their NeoBase kit.

Workstation Resources and Capacity	
Instrument Time	The test is multiplexed with other disorders so instrument time is not relevant.
Maximum Number of Specimens to Be Analyzed at One Workstation In A Day	NBS programs can analyze the same number of samples that they currently analyze within a day since the test is multiplexed.
Minimum Space Requirements (Supporting Equipment Not Included)	No additonal space is required since this is multplexed with acylcarnitine and amino acid screening.

Personnel Requirements	
FTE Needed to Process 100,000 Specimens Annually	The laboratory and follow-up do not require additional FTEs assuming that the assay is multiplexed with existing assays and incorporated into the workflow. The referral rate is sufficiently low so that current follow-up staffing is adequate.

Other Considerations	
LIMs Adjustments	Variable (dependent on vendor). LIMs revisions for new conditions may require additonal staff time and cost for initial set up.
Training	Laboratory staff should be trained on SOP updates and cutoff logic similar to the current methodologies in place. Second-tier testing, if implemented, may require additional training and experience with UPLC. Follow-up staff should be trained on the workflows related to an out-of-range result.

QC and Reported Screening Results	
Availability of Quality-Control Specimens	Quality control material is available from the CDC, through contract manufacturing or FDA cleared test solutions (PerkinElmer, in development).
Reported Rate of Repeat Requests (Independent Specimen)	N/A
Reported Rate of Second-Tier Test	**New York** 45/100,000 using revised method; New York discontinued second-tier testing in Sept. 2021 **Utah** 1/100,000 using current method (previous ~185/100,000)
Rate of Referrals	**New York** ~3.1/100,000 (6 referrals in 2021) **Utah** ~1.1/100,000 (3 referrals total)
Reported Outcomes	**New York** GAMT deficiency = <0.2 per 100,000 infants screened (1 total) False positives = ~1.5 to 2.6 per 100,000 infants screened From 2021 3 confirmed false positives; no GAMT deficiency* 2 likely false positives; NICU babies that expired prior to diagnostic testing *One case later determined to have ARG. False negatives = None reported **Utah** GAMT deficiency = 0.4 per 100,000 infants screened False positives = ~1 per 100,000 infants screened False negatives = None reported

Estimated $$ Costs	
Estimated Cost (Total)	N/A
Estimated Cost to Laboratory of Reagents or FDA-Approved Kit	Less than $1 for a laboratory developed test with the assumption that GAMT deficiency is being multiplexed with the existing MS/MS tests. The cost may be greater than $1 for an FDA approved test.
Estimated 2nd Tier Testing Costs	If second-tier testing is required, it will depend on the resources available to the laboratory. This testing can be outsourced if necessary. Utah's second-tier testing costs are ~$65. Reagents and equipment necessary for second-tier testing will mostly be the same reagents and equipment as required by first-tier testing. UPLC columns can cost up to $1000 each.
Estimated Reagent Rental Cost	N/A

Estimated $$ Costs	
Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)	N/A
Estimated Diagnostic Assay Cost	~$300 for Plasma and Urine Creatine Deficiency Panel
Other Cost Considerations for Implementation	Validating the assay is a major piece of the overall cost. New York and Utah use a laboratory developed test. An FDA approved test is not currently available.

Short-Term Follow-Up	
Description	A clinician will perform confimatory testing for GAMT deficiency by evaluating levels of creatine and GUAC in plasma and urine. Prematurity and total parental nutrition (TPN) can affect these biomarkers so guidance around when to best test may be warranted for these groups. Arginase deficiency can also cause elevated GUAC.
Case Definition	GAMT deficiency is an autosomal recessive disorder that impairs the production of creatine and leads to build up of guanidinoacetate. It results in seizures, intellectual disability, movement disorders, and muscle weakness.
Diagnostic Method & Criteria	• Low plasma/urine creatine • Elevated plasma/urine GUAC • Creatine depletion in brain MR spectroscopy • *GAMT* gene variant may be found • Clinical findings • Family history
Availability of Diagnostic Testing Laboratories	The diagnostic testing can be performed in a number of laboratories.

Current Treatment(s)	
Description and Current Treatment Guidelines with Clinical Identification	Creatine and ornithine supplements, sodium benzoate, and dietary restriction of protein with addition of an essential amino acid medical protein (arginine-restricted diet) are used as standard treatments. Treatment should begin as soon as possible. Clinicians measure serum levels to monitor treatment.

References

Hart, K., A. Rohrwasser, H. Wallis, H. Golsan, J. Shao, T. Anderson, X. Wang, N. Szabo-Fresnais, M. Morrissey, D. M. Kay, M. Wojcik, P. A. Galvin-Parton, N. Longo, M. Caggana, and M. Pasquali. 2021. 'Prospective identification by neonatal screening of patients with guanidinoacetate methyltransferase deficiency', *Mol Genet Metab*, 134: 60-64.

Mercimek-Mahmutoglu S, Sinclair G, van Dooren SJ, Kanhai W, Ashcraft P, Michel OJ, Nelson J, Betsalel OT, Sweetman L, Jakobs C, Salomons GS. Guanidinoacetate methyltransferase deficiency: first steps to newborn screening for a treatable neurometabolic disease. Mol Genet Metab. 2012 Nov;107(3):433-7. doi: 10.1016/j.ymgme.2012.07.022. Epub 2012 Aug 3.

Pasquali, M., E. Schwarz, M. Jensen, T. Yuzyuk, I. DeBiase, H. Randall, and N. Longo. 2014. 'Feasibility of newborn screening for guanidinoacetate methyltransferase (GAMT) deficiency', *J Inherit Metab Dis*, 37: 231-36.

Schulze, A. 2013. 'Creatine deficiency syndromes', *Handb. Clin Neurol*, 113: 1837-43.

Schulze, A., F. Ebinger, D. Rating, and E. Mayatepek. 2001. 'Improving treatment of guanidinoacetate methyltransferase deficiency: reduction of guanidinoacetic Acid in body fluids by arginine restriction and ornithine supplementation', *Mol Genet Metab*, 74: 413-19.

Sharer, J. D., O. Bodamer, N. Longo, S. Tortorelli, M. M. Wamelink, and S. Young. 2017. 'Laboratory diagnosis of creatine deficiency syndromes: a technical standard and guideline of the American College of Medical Genetics and Genomics', *Genet Med*, 19: 256-63.

Sinclair, G. B., C. D. van Karnebeek, M. Ester, F. Boyd, T. Nelson, S. Stockler-Ipsiroglu, and H. Vallance. 2016. 'A three-tier algorithm for guanidinoacetate methyltransferase (GAMT) deficiency newborn screening', *Mol Genet Metab*, 118: 173-7.

Stockler-Ipsiroglu, S., vanKarnebeek C., N. Longo, G.C. Korenke, S. Mercimek-Mahmutoglu, I. Marquart, B. Barshop, C. Grolik, A. Schlune, B. Angle, H.C. Araujo, T. Coskun, L. Diogo, M. Geraghty, G. Haliloglu, V. Konstantopoulou, V. Leuzzi, A. Levtova, J. MacKenzie, B. Maranda, A.A. Mhanni, G. Mitchell, A. Morris, T. Newlove, D. Renaud, F. Scaglia, V. Valayannopoulos, F.J. van Spronsen, K.T. Verbruggen, N. Yuskiv, W. Nyhan, and A. Schulze. 2014. 'Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring', Mol Genet Metab, 111: 16-25.

Viau KS, Ernst SL, Pasquali M, Botto LD, Hedlund G, Longo N. Evidence-based treatment of guanidinoacetate methyltransferase (GAMT) deficiency. Mol Genet Metab. 2013;110:255–62.

Initial Survey of the Advisory Committee on Heritable Disorders in Newborns and Children's Public Health System Assessment

The purpose of this survey is to inform the Advisory Committee on Heritable Disorders in Newborns and Children (Committee) about states' ability to add newborn screening (NBS) for [condition x] using information gathered from most of the state and territorial NBS programs in the U.S. Your input will provide valuable information and aid the deliberations of the Committee.

Please refer to the Guanidinoacetate methyltransferase (GAMT) deficiency screening factsheet to help you answer the following questions about the ability of your state or territory to add screening for [condition x] to your NBS program. Please consult with others, as needed, including laboratory and follow-up staff, medical professionals and specialists, to complete the survey. When unsure about a response, please provide your best estimate. If you were to answer every question, we estimate it will take an average of 10 hours to complete this form.

1. Within the last three years, has your state: (*check all that apply)*
    - Included GAMT deficiency as part of the routine NBS panel? (*end survey*)

- Planned, implemented, or completed any type of pilot study or pilot evaluation for GAMT deficiency? (*end survey*)
- Issued a mandate or state-level decision to start screening for GAMT deficiency? (end survey)
- None of the above (*go to question 2*)

2. Which of the following entities provide NBS laboratory services for your state's NBS program? (multiple choice*)*
   - Your own state's public health or NBS laboratory
   - A state university laboratory for which there is an intra-state agency agreement
   - A contracted regional NBS laboratory
   - A contracted commercial laboratory
   - Other – please specify: _____

NBS programs consider many factors when deciding to add a condition to their NBS panel. The following question asks you to consider, in general, how much the following factors would be an issue when considering adding GAMT deficiency to your NBS panel.

3. Please indicate if the following implementation factors for [condition x] would present
   - *a major challenge*
   - *a minor challenge,*
   - *would not be a challenge*

   given the current status of the NBS Program in your state. Please describe any additional overarching challenges.

   Implementation Factors

   — Availability of a validated screening test in your state

   — Ability to conduct short-term follow-up for out-of-range screening results, including tracking and follow-up testing

   — Identifying specialists in your state (or region) who can treat newborns and children with GAMT deficiency

   — Availability of treatment for in your state GAMT deficiency

   — Increasing your NBS fee

   — Addressing administrative challenges (please specify in comments section)

For questions 5-7 please assume that GAMT deficiency has been authorized for addition to your state's panel and funds for laboratory testing and follow-up have been made available.

5. The following question considers the various resources needed (e.g. human resources, facilities, etc) by your NBS program in order to implement screening for GAMT deficiency.

5.a. Please complete the following table if you answered "your own state's public health or NBS laboratory" on question #2. If your answer on question #2 was any of the other options, please skip to 5.b.

Resources Needed For Own State's Public Health or NBS Laboratory

5.a. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Screening method for GAMT deficiency: MS/MS using a derivatized or non-derivatized assay				
Quantity and type of laboratory equipment needed to screen for GAMT deficiency				
Laboratory technical expertise to screen for GAMT deficiency				
Sufficient number of technical staff to screen for GAMT deficiency				

5.a. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
LIMS capacity and instrumentation interface				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is reported (e.g., diagnostic testing, clinical evaluations)				
Genetic counselors, or other staff with the necessary expertise, to cover the expected caseload				
Specialists to cover expected GAMT deficiency caseload				
Treatment centers for expected GAMT deficiency caseload				
Follow-up protocols for GAMT deficiency cases				

SKIP PATTERN (respondents fill out either 5.a.or 5.b., but not both)

5.b. Please complete the following table if you answered "a state university laboratory for which there is an intra-state agency agreement", "a contracted regional NBS laboratory", "a contracted commercial laboratory", or "other – please specify" on question #2.

Resources Needed For Contracted or State University Labs with Intrastate Agreement

5.b. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Availability of the screening test in the state university laboratory for which there is an intra-state agency agreement, or contracted regional laboratory, or commercial laboratory				
LIMS capacity and instrumentation interface				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is				

5.b. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
reported (e.g., diagnostic testing, clinical evaluations)				
Genetic counselors, or other staff with the necessary expertise, to cover the expected caseload				
Specialists to cover expected GAMT deficiency caseload				
Treatment centers for expected GAMT deficiency caseload				
Follow-up protocols for GAMT deficiency cases				

5.c. Would you conduct a second-tier test for GAMT deficiency? (Multiple choice)

- No we do not think it is necessary to conduct second-tier testing
- Most likely, but we would not be ready in the next year
- Yes, but we would have to contract the second-tier test
- Yes, we could be ready in the next year

6. Please indicate the degree* to which these factors impede or facilitate your ability to adopt screening for GAMT deficiency in your state.

Barriers and Facilitators

Factor	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Not Applicable
Predicted run time to screen for GAMT deficiency as it relates to other workload					
Extent to which the screening test for GAMT deficiency can be multiplexed with screening for other conditions					
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)					
Estimated cost per specimen to conduct screening (personnel, equipment, reagents)					

Factor	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Not Applicable
Estimated cost of treatment for newborns diagnosed with GAMT deficiency					
Expected clinical outcomes of newborns identified by screening					
Expected cost-benefit of screening in your state					
Advocacy for screening for this GAMT deficiency					
Other non-NBS public health priorities within your state					

**Major barrier- Will prevent testing from being implemented effectively and/or timely.*
**Minor barrier- May compromise testing so it is not performed effectively and/or timely.*
**Minor facilitator- May allow testing to be done effectively and/or timely.*
**Major facilitator- Will allow testing to be done effectively and/or timely.*

7. Please describe any additional factors that impede or facilitate adoption of screening for GAMT deficiency in your state.

8a. What are the most significant barrier(s) to screening for GAMT deficiency in your state?

8b. What would most facilitate screening for GAMT deficiency in your state?

9. Please estimate the time it would take your NBS program to initiate screening for GAMT deficiency in your state (i.e. get authority and funds to screen for [condition x], go through administrative processes, meet with your state NBS committees and complete all activities needed to implement and commence screening for all newborns in your state)?

- 12 months or less
- 13 to 24 months
- 25 to 36 months
- 37 to 48 months
- More than 48 months

10. The question above related to the overall timeline. We recognize some of the activities happen in tandem and some cannot begin until a previous activity has been completed. Please estimate the total time needed, in general, for each individual activity listed below within your NBS program. If needed, please consult with laboratory and follow-up staff, medical professionals and specialists, prior to completing the survey.

Please complete the following table if you answered "your own state's public health or NBS laboratory" on question #2. If your answer on question #2 was any of the other options, please skip to 10.b.

10a. Estimated Time to Complete Activities toward Implementing Expanded Newborn Screening for a Condition.

Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	N/A	Comment
Obtain authorization to screen for GAMT deficiency							
Availability of funds to implement screening for GAMT deficiency							
Meet with Advisory committees and other stakeholders							
Obtain and procure equipment for screening for GAMT deficiency							
Hire necessary laboratory and follow-up staff							
Select, develop, and validate the screening test within your laboratory							
Develop a screening algorithm, follow-up protocols, and train follow up staff							
Set up reporting and results systems for added condition (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result							
Add the screening test to the existing outside laboratory contract							
Conduct an internal validation study for GAMT deficiency							
Pilot test the screening process within your state, after validation has taken place							
Implement statewide screening for all newborns, including full reporting and follow-up of abnormal screens after validation and pilot testing							

SKIP PATTERN (respondents fill out either 10.a.or 10.b., but not both)

10b. Estimated Time to Complete Activities toward Implementing Expanded Newborn Screening for a Condition *(For states reporting contracting out for external laboratory services, see Question #2)*

Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	Not Applicable	Comment
Obtain authorization to screen for GAMT deficiency							
Availability of funds to implement screening for GAMT deficiency							
Meet with Advisory committees and other stakeholders							
Develop follow-up protocols, and train follow up staff							
Set up reporting and results systems for added condition (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result							
Add the screening test to the existing outside laboratory contract							
Implement statewide screening for all newborns, including full reporting and follow-up of abnormal screens after validation and pilot testing							

12. Are there any special considerations regarding GAMT deficiency that need to be taken into account when assessing the impact on the public health system? (e.g. variants of unknown significance, pseudodeficiencies, age of onset, access to specialists, access to treatment, cost of treatment, etc.). Please describe:

13. Please share any additional information regarding implementation of NBS for GAMT deficiency.

14. Please provide information about the respondent:

Name:

Phone number:

Email address:

Job title:

15. Who did you consult with to answer these questions? *Please check all that apply*.
    - o State NBS laboratory experts
    - o Other NBS program staff
    - o State NBS advisory board
    - o State Title V Director
    - o [Condition x] Specialists
    - o Primary care providers
    - o Advocates within your state for [condition x] screening
    - o Others- please specify: _____
    - o None of the above

Thank you for completing the survey!

REFERENCES

1. Cheillan D, Joncquel-Chevalier Curt M, Briand G, et al. Screening for primary creatine deficiencies in French patients with unexplained neurological symptoms. *Orphanet J Rare Dis.* 2012;7:96.
2. Mercimek-Andrews S, Sinclair G, van Dooren SJM, et al. Guanidinoacetate methyltransferase deficiency: First steps to newborn screening for a treatable neurometabolic disease. *Molecular Genetics and Metabolism.* 2012;107(3):433-437.
3. Desroches CL, Patel J, Wang P, et al. Carrier frequency of guanidinoacetate methyltransferase deficiency in the general population by functional characterization of missense variants in the GAMT gene. *Molecular Genetics and Genomics.* 2015;290(6):2163-2171.
4. Mercimek-Mahmutoglu S, Pop A, Kanhai W, et al. A pilot study to estimate incidence of guanidinoacetate methyltransferase deficiency in newborns by direct sequencing of the GAMT gene. *Gene.* 2016;575(1):127-131.
5. Viau KS, Ernst SL, Pasquali M, Botto LD, Hedlund G, Longo N. Evidence-based treatment of guanidinoacetate methyltransferase (GAMT) deficiency. *Molecular Genetics and Metabolism.* 2013;110(3):255-262.
6. Longo N. Personal Communication. In:April 5, 2022.
7. Ellery SJ, Della Gatta PA, Bruce CR, et al. Creatine biosynthesis and transport by the term human placenta. *Placenta.* 2017;52:86-93.
8. Mercimek-Mahmutoglu S, Stoeckler-Ipsiroglu S, Adami A, et al. GAMT deficiency: Features, treatment, and outcome in an inborn error of creatine synthesis. *Neurology.* 2006;67(3):480-484.
9. Mercimek-Mahmutoglu S, Ndika J, Kanhai W, et al. Thirteen New Patients with Guanidinoacetate Methyltransferase Deficiency and Functional Characterization of Nineteen Novel Missense Variants in the GAMT Gene. *Human Mutation.* 2014;35(4):462-469.
10. Khaikin Y, Sidky S, Abdenur J, et al. Treatment outcome of twenty-two patients with guanidinoacetate methyltransferase deficiency: An international retrospective cohort study. *European Journal of Paediatric Neurology.* 2018;22(3):369-379.
11. Stockler-Ipsiroglu S, van Karnebeek C, Longo N, et al. Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. *Molecular Genetics and Metabolism.* 2014;111(1):16-25.
12. Wallis H. Personal Communication. In:April 2022.
13. Hart K, Rohrwasser A, Wallis H, et al. Prospective identification by neonatal screening of patients with guanidinoacetate methyltransferase deficiency. *Molecular Genetics and Metabolism.* 2021.
14. Wojcik M, Morrissey M, Borden K, et al. Method modification to reduce false positives for newborn screening of guanidinoacetate methyltransferase deficiency. *Molecular Genetics and Metabolism.* 2022;135(3):186-192.
15. Sinclair GB, van Karnebeek CDM, Ester M, et al. A three-tier algorithm for guanidinoacetate methyltransferase (GAMT) deficiency newborn screening. *Molecular Genetics and Metabolism.* 2016;118(3):173-177.
16. Cuthbert C. Update on newborn screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency. Paper presented at: Federal Advisory Committee on Heritable Disorders in Newborns and Children. 2018 May;

https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/May18CuthbertGAMT.PDF.
17. Schulze A. Personal Communication. In:April 6, 2022.
18. Pitt JJ, Tzanakos N, Nguyen T. Newborn screening for guanidinoacetate methyl transferase deficiency. *Molecular Genetics and Metabolism.* 2014;111(3):303-304.
19. Stöckler-Ipsiroglu S, Braissant O, Schulze A. Disorders of Creatine Metabolism. In: *Physician's Guide to the Diagnosis, Treatment, and Follow-Up of Inherited Metabolic Diseases.*2022:235-249.
20. Khoja S, Lambert J, Nitzahn M, et al. Gene therapy for guanidinoacetate methyltransferase deficiency restores cerebral and myocardial creatine while resolving behavioral abnormalities. *Mol Ther Methods Clin Dev.* 2022;25:278-296.
21. Starr RR. Too little, too late: ineffective regulation of dietary supplements in the United States. *Am J Public Health.* 2015;105(3):478-485.
22. Schulze A, Hoffmann GF, Bachert P, et al. Presymptomatic treatment of neonatal guanidinoacetate methyltransferase deficiency. *Neurology.* 2006;67(4):719-721.
23. El-Gharbawy AH, Goldstein JL, Millington DS, et al. Elevation of guanidinoacetate in newborn dried blood spots and impact of early treatment in GAMT deficiency. *Molecular Genetics and Metabolism.* 2013;109(2):215-217.
24. Dhar SU, Scaglia F, Li FY, et al. Expanded clinical and molecular spectrum of guanidinoacetate methyltransferase (GAMT) deficiency. *Molecular Genetics and Metabolism.* 2009;96(1):38-43.
25. Farshidi S, Gaphari SR, Farokhi B, Hooshmand M. Creatine deficiency syndrome: Case report. *Journal of Inherited Metabolic Disease.* 2011;34:S125.
26. Prosser LA, Grosse SD, Kemper AR, Tarini BA, Perrin JM. Decision analysis, economic evaluation, and newborn screening: challenges and opportunities. *Genet Med.* 2012.
27. Haddix A TS, Corso PS, ed *Prevention effectiveness: a guide to decision analysis and economic evaluation. 2nd ed. .* 2nd ed. New York: Oxford University Press; 2002.
28. Goldie SJ CP. Decision analysis. In: Haddix A TS, Corso PS, eds., ed. *Prevention effectiveness: a guide to decision analysis and economic evaluation.* New York: Oxford University Press; 2003:103-126.