Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence-Based Review

May 12, 2022

ERG Members

Name	Affiliation / Role
Alex R. Kemper, MD, MPH, MS	Nationwide Children's Hospital
Tiasha Letostak, PhD, MPH	Nationwide Children's Hospital
Margie Ream, MD, PhD	Nationwide Children's Hospital
Roshani Tasker, MS	Nationwide Children's Hospital
Jelili Ojodu, MPH	APHL
Elizabeth Jones, MPH	APHL
K.K. Lam, PhD	Duke University
Lisa Prosser, PhD	University of Michigan
Angela Rose, MS, MPH	University of Michigan
Scott Grosse, PhD	CDC
Joseph Bocchini, Jr., MD	Member
Jeffrey Botkin, MD, MPH	Member
Anne Comeau, PhD	Member
Susan Tanksley, PhD	Member
Jane DeLuca, PhD, RN, CPNP	Committee Liaison
Shawn McCandless, MD	Committee Liaison

Technical Expert Panel Members

Name	Affiliation	Role
Saadat Andrews, MD, PhD, FCCMG	University of Alberta	Metabolic Geneticist
Michele Caggana, ScD, FACMG	NY Newborn Screening Program	Director
Kim Hart, MS, LCGC	Utah Newborn Screening Program	Program Manager
Nicola Longo, MD, PhD*	University of Utah	Clinician Scientist
Marzia Pasquali, PhD*	University of Utah	Researcher and Laboratory Expert
Andreas Schulze, MD, PhD	Hospital for Sick Children (SickKids)	Clinician Scientist
Jon Daniel Sharer, PhD	University of Alabama Birmingham	Researcher, Director-Biochemical Genetics
Graham Sinclair, PhD, FCCMG	British Columbia Children's Hospital	Biochemical Geneticist
Heidi Wallis*	Association for Creatine Deficiencies	President, Association for Creatine Deficiencies; Parent Advocate

**Also a nominator of GAMT deficiency to the RUSP*

Disease Course And Epidemiology

Overview

- Disorder of creatine biosynthesis

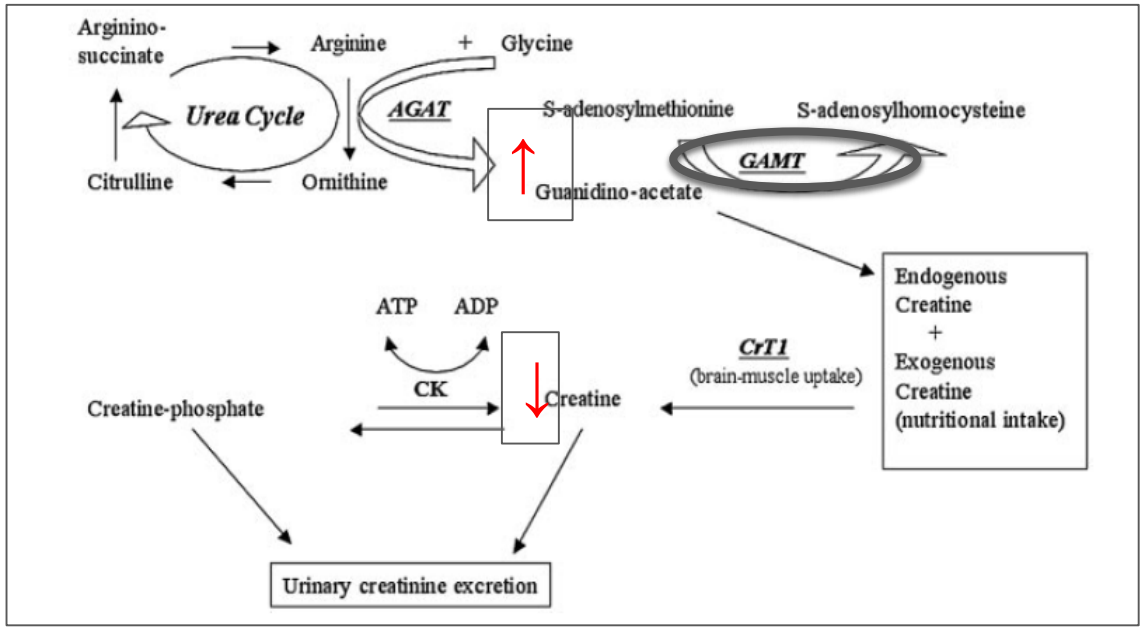


Figure A. Schematic diagram of metabolic biosynthesis

Bianchi et al. Treatment monitoring of brain creatine deficiency syndromes: A 1H- and 31P-MR spectroscopy study. *Am J Neuroradiol*. 2007; 28:548-554

Disease Course

- Fetus protected by active transport of creatine
- Progressive neurological impairments, typically not apparent until >3 months of age
- Untreated: significant intellectual disability, limited speech development, recurrent seizures, behavior problems, weakness, and movement disorder
- Not reported to be associated with increased risk of mortality

GAMT Deficiency

- Pathophysiology
  - Low creatine leads to intellectual disability
  - GUAC accumulation leads to epilepsy and movement disorder
- Biomarkers
  - Creatine and GUAC (also known as GAA)
  - MR Spectroscopy

Genetics

- Autosomal recessive disorder of the *GAMT* gene, >50 variants described
- Gene frequency studies suggest range of frequency
  - 0.038 per 100,000 (i.e., 1 in 2.64 million) based on multiple US gene databases
  - 0.4 per 100,000 (i.e., 1 in 250,000) based on dried-blood spots in the Netherlands
- Limitations of estimates
  - Generalizability of databases
  - Not all pathogenic alleles characterized

Birth Prevalence

- Baseline estimate endorsed by the TEP: 0.4 per 100,000 (i.e., 1 per 250,000)
  - 5 cases identified clinically in Utah from 2001-2011 leads to estimate of 0.88 per 100,000 (i.e., 1 per 114,000)
  - This estimate differs from case detection rate from newborn screening
  - Small numbers can lead to heterogeneity in estimates
  - May be differences in specific geographic areas

Clinical Identification

- Wide range of clinical identification
  - One study: mean age 12.3 years (range: 2-29 years)
  - A retrospective study in France evaluated 6,353 subjects with unexplained neurological symptoms and found 7 cases, of whom 6 had signs before 2 years of age

References: Mercimek-Mahmutogulu S. *Neurology*. 2006; 67:480-484. Cheillan et al. Screening for primary creatine deficiencies in French patients with unexplained neurological symptoms. *Orphanet Journal of Rare Disease*. 2012;7:96.

Registry

- The Association for Creatine Deficiencies (ACD) owns *CreatineInfo*, hosted by the National Organization for Rare Disorders
- Developed in March 2021
- Growing (by April 29, 2022: 35 subjects; 7 diagnosed in 2022), with larger pool to draw from
- No published reports yet

Screening and Diagnosis

Screening and Diagnosis in Infancy

- MS/MS for GUAC and creatine
- Diagnosis:
  - Low creatine and elevated GUAC in plasma at least one week after birth
  - Molecular analysis is supportive

Hart et al. Prospective identification by neonatal screening of patients with guanidinoacetate methyltransferase deficiency. *Mol Genet Metab*. 2021;134:60-64.

Utah Newborn Screening Program

- Two screens per infant
- Screening for GAMT deficiency began in June 2015
- Laboratory-developed test
- 2015-2019: Screening by the Associated Regional and University Pathologists (ARUP)
  - First-tier: GUAC and creatine, FIA-MS/MS derivatized assay
  - Second-tier: GUAC and creatine, LC-MS-MS
- 2019-Present: Screening by the newborn screening program
  - Laboratory-developed test
  - First-tier: GUAC and creatine, FIA-MS/MS (non-derivatized)
  - Second-tier test eliminated

Utah Newborn Screening Program

- June 2015-May 2019: Derivatized Method
  - 195,425 newborns screened
    - 365 positive first-tier screens
    - 2 positive second-tier screens referred for diagnostic evaluations (1.0 referrals per 100,000 screened)
    - 0 cases diagnosed
- June 2019-December 2021: Non-Derivatized Method
  - 125,888 newborns screened
    - 2 positive first-tier screening
    - 1 positive referred and diagnosed with GAMT deficiency (0.79 cases per 100,000 screened)
- Full period (2015-2021)
  - Referred for diagnostic testing: 0.93 per 100,000 newborns screened (1 per 107,102)
  - GAMT deficiency identified: 0.31 per 100,000 newborns screened (1 per 321,305 screened)

New York Newborn Screening Program

- Screening for GAMT deficiency began in October 2018
- Laboratory-developed test
- Initially a two-tiered screening test
  - GUAC and Creatine by FIA-MS/MS
  - GUAC by HPLC-MS/MS
- Second-tier discontinued in September 2021
- *GAMT* sequencing is part of the referral process

New York: 2021

- 211,232 newborns screened
- 82 positive first tier screen
  - 5 referred immediately
  - 77 request for a repeat (76 in the NICU)
    - 1 referred
    - 4 died for reasons not known to be related to GAMT deficiency
    - 2 pending but had an initial negative screen so unlikely to have GAMT deficiency
  - Of the 6 referrals
    - 1 with GAMT deficiency
    - 1 with arginase deficiency
    - 2 normal
    - 2 died prior to referral for reasons not known to be related to GAMT deficiency
- Referral rate: 2.8 per 100,000 newborns newborns screened (1 per 35,205)
- GAMT deficiency: 0.47 per 100,000 newborns screened (1 per 212,232)

New York: Oct 2018-Apr 2022

- 759,246 newborns screened
  - 24 referrals for diagnostic evaluation (3.2 per 100,000 newborns screened or 1 per 31,635)
  - One case of GAMT deficiency diagnosed (0.13 cases per 100,000 newborns screened or 1 case per 759,246)

Michigan Newborn Screening Program

- GAMT deficiency newborn screening approved in late 2018
- Validating approach; full population screening has not yet started

British Columbia, Canada

- 3-Tier Assay
  - First-tier: GUAC with flow-injected MS/MS
  - Second-Tier: GUAC with liquid chromatography MS/MS
  - Third-tier: targeted gene sequencing
- September 2012 – April 2022, 428,140 specimens
  - 1,228 (0.3%) with a positive first-tier assay
  - 28 with a positive second-tier assay
  - 3 with a positive third-tier assay and referred (0.7 per 100,000 newborns screened or 1 per 142,713)
  - 0 cases of GAMT deficiency (0 per 428,140)

Ontario, Canada

- GAMT deficiency newborn screening recently approved
- Plan to start Summer 2022

Victoria, Australia

- Derivatized method with flow-injected MS/MS
- From April 2002-April 2022
  - ~1.4 million screened, with one likely case
  - On an annual basis
    - ~80,000 screened
      - 20 have a second-tier test
      - 3 have a repeat sample requested
      - 0.3 are referred

Summary of Programs Screening for GAMT Deficiency

Location	Time Period	Total No. of Newborns Screened	Total No. Diagnosed with GAMT deficiency	Diagnostic Referral Rate per 100,000	Cases Detected per 100,000
UTAH (Screening conducted by ARUP)	2015-2019	195,425	0	1.0	0
UTAH (Non-derivatized Approach)	2019-2021	125,880	1	0.79	0.79
UTAH (Cumulative)	2015-2021	321,305	1	0.93	0.31
NEW YORK (1-and 2-tier screen)	2018-2021	537,408	1*	4.3	0.19
NEW YORK (1- and 2-tier screen)	2021	212,232	1*	2.8	0.47
NEW YORK (Cumulative)	2018-2022	759,246	1	3.2	0.13
BRITISH COLUMBIA	2012-2022	428,140	0	0.7	0
VICTORIA	2002 – 2022	1.4 Million	1	0.38	0.07
Pooled Screening - US	**2015-2022**	**1.08 Million**	**2**	**2.6**	**0.19**
Pooled Screening- ALL	**2002-2022**	**2.9 Million**	**3**	**1.2****	**0.1**

*Same case, reported from overlapping time periods

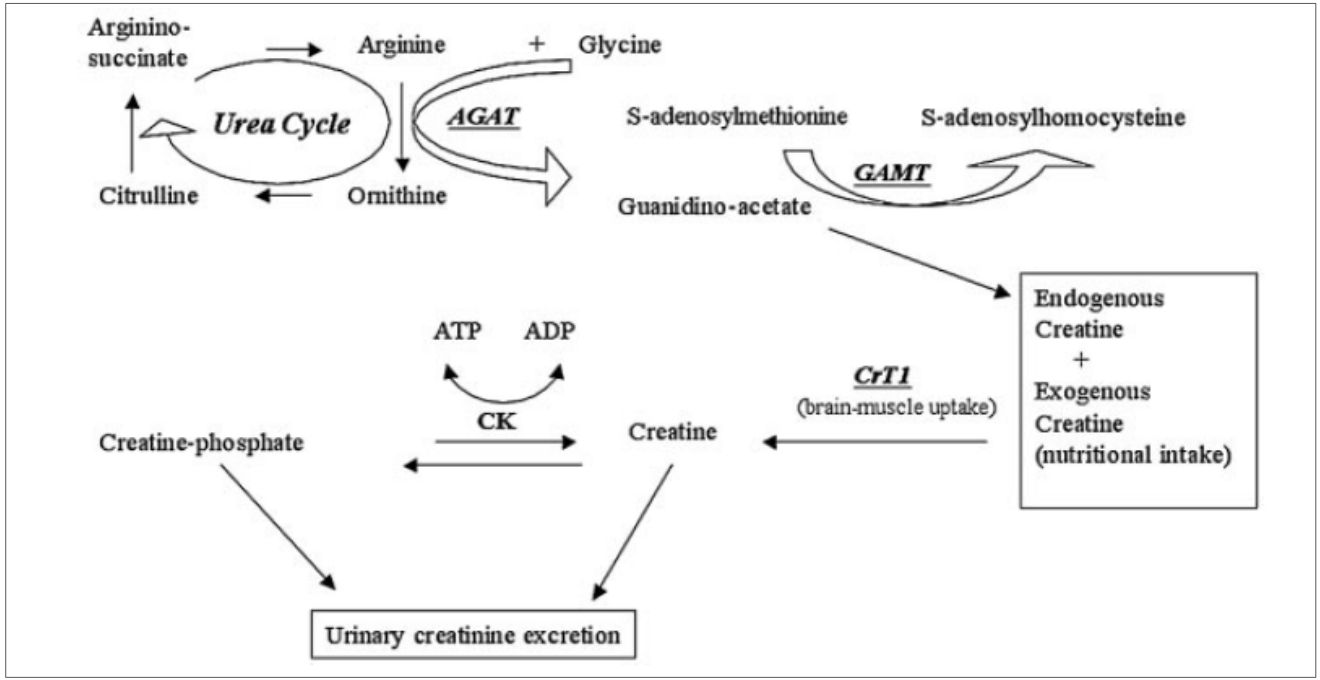
**Assuming 6 referrals from the Victoria newborn screening program based on the average number of referrals per year provided for this report

Summary: Screening

- High-throughput MS/MS incorporated into two state newborn screening programs as a laboratory-developed test
- Diagnostic referral rate is low compared to other conditions
- Three cases have been identified through newborn screening [Utah, New York, Victoria (likely case)]

Treatment

Metabolic Pathway for Creatine Biosynthesis



Bianchi et al. Treatment monitoring of brain creatine deficiency syndromes: A 1H- and 31P-MR spectroscopy study. *Am J Neuroradiol*. 2007; 28:548-554.

Standard Treatment

- Expert treatment consensus
  - Creatine and ornithine supplements, sodium benzoate
  - Protein restriction – less restrictive than for other metabolic conditions
  - Serum monitoring
- ACD helps families access creatine and ornithine
- Sodium benzoate available from compounding pharmacies

Gene Therapy

- In development
  - Delivered with AAV vector
  - Tested in a mouse model; normalized GUAC concentration

Early Standard Treatment

- 6 reports of initiation < 6 months of age

Summary of evidence reporting outcomes for early treatment (<6 months) and sibling case reports

	Outcomes with treatment onset < 6 months old			Outcomes of older sibling with later diagnosis, when available		
Publication	**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)	Prenatal	42 months	Normal	10 months (also reported in Dhar et al. 2009)[22]	6.5 years	Speech and fine motor delays
Stockler-Ipsiroglu et al. (2014)	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 DD Moderate DD Mild DD
Viau et al. (2013)	Birth	12 months	Normal			
Schulze et al. (2006)	22 days	14 months	Normal	2.75 years	2.25 years	Epilepsy, speaks “a few words”
Dhar et al. (2009)	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
Farshidi et al. (2011)	5 months	11 months	Normal	15 months	21 months	Continues to have seizures (improved), cognitive impairment, learning disability (improved)

Summary: Treatment

- Case series suggest that pre-symptomatic or earlier initiation of treatment is associated with improved neurological outcomes
- None of the reports provide outcomes based on standardized quantitative measures

Newborn Screening Program Costs of GAMT Deficiency Screening

Newborn Screening Program Costs of GAMT Deficiency Screening

- Based on interviews with representatives from the New York and Utah newborn screening programs
- Included in estimated costs
  - Equipment, reagents, added laboratory technician and scientist time
  - GAMT deficiency screening is incorporated into existing activities, so breaking out specific costs is challenging

Newborn Screening Program Costs of GAMT Deficiency Screening

- Estimated additional cost to a newborn screening program to screen for GAMT deficiency, above the operating costs of the program, may be substantially less than $1 per infant
  - Based on interviews with two state newborn screening programs that have implemented GAMT deficiency
  - Both used a laboratory-developed test (technical capacity, ability to validate)
- This cost estimate does not necessarily apply to other programs

Projected Population-Level Outcomes:

GAMT Deficiency Newborn Screening Compared with Clinical Case Detection

Goal

- Compare projected outcomes from GAMT deficiency newborn screening for all newborns in the U.S. with usual case detection in the absence of screening.

Approach

- Annual US newborn cohort of 3.6 million
- Newborn screening
- Screening outcomes
- Cases of GAMT deficiency
- Clinical identification
- Confirmed cases of GAMT deficiency

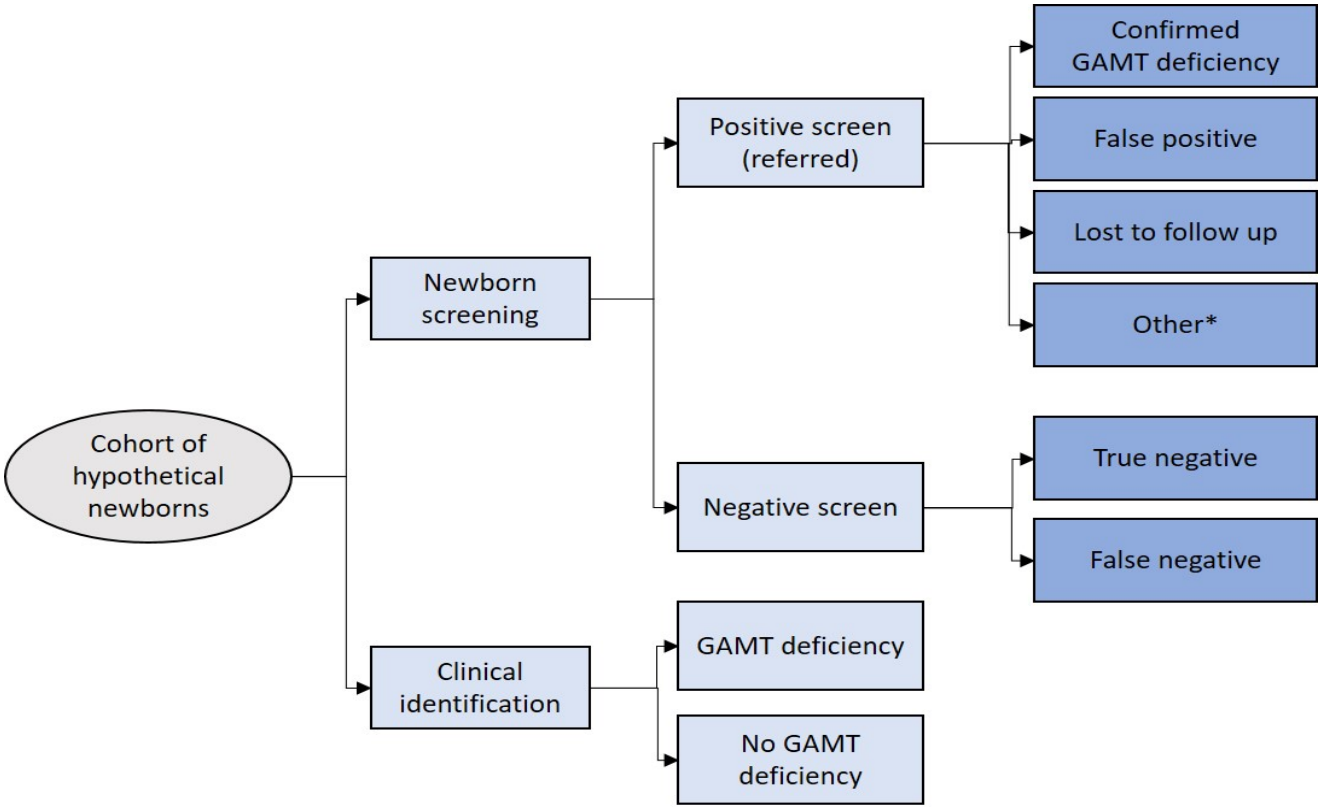
Health Outcomes

- Previous models conducted for evidence review have evaluated outcomes such as death, cognitive impairment, and need for mechanical ventilation

Decision Analysis

- Systematic approach to decision making under conditions of uncertainty
- Project ***ranges*** of short-term outcomes
- Allows decision maker to identify which alternative is expected to yield the most health benefit
- Identify key parameters and assumptions

Model Schematic



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

Model Inputs

Probability	Most Likely	Range (min-max)	Source
Positive screen, newborn screening	2.6 per 100,000	1.7 – 3.8 per 100,000	Utah and New York Newborn Screening Data
GAMT deficiency after a positive screen	0.2 per 100,000†	0.02 – 0.6 per 100,000†	
Positive screen is false	2.1 per 100,000	1.6 – 2.4 per 100,000	
Loss to follow-up after a positive screen	0.0 per 100,000	0.0 – 0.3 per 100,000	
Other‡	0.3 per 100,000	0.06 – 0.7 per 100,000	
GAMT deficiency, clinical identification	Not available	0.05 - 0.5 per 100,000	See evidence review

* 95% confidence interval derived using binomial distribution
† Conditional probability given a positive screen, ranges for conditional probability based on Utah and New York experiences
‡ Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

Projected Cases for GAMT Deficiency Newborn Screening Compared with Clinical Identification in a U.S. Cohort of 3.6 Million Newborns*

	Newborn Screening	Clinical Identification
Positive screen	93 (62 - 135)	-
GAMT deficiency 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

Summary

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

Public Health System Impact Assessment

Guanidinoacetate Methyltransferase (GAMT) Deficiency

Jelili Ojodu, MPH

BACKGROUND

Public Health System Impact

- The assessment is meant to evaluate the readiness and feasibility of NBS programs to implement screening for GAMT deficiency.
- Focuses on activities involved and time it takes to add a new disorder.
- Does not consider pre-implementation activities (e.g., funds to screen, obtaining a legislative agreement) which may add time to implementation.

Definition of Readiness

- **Ready**
  - Most NBS programs could implement within 1 year.
- **Developmental Readiness**
  - Most NBS programs could implement within 1–3 years.
- **Unprepared**
  - Most NBS programs would take longer than 3 years to implement.

Components of Feasibility

- An established and available screening test.
- A clear approach to diagnostic confirmation.
- Acceptable treatment plan.
- Established approach to long-term follow-up.

METHODS

Methods

- GAMT deficiency fact sheet
- Webinar and outreach
- Survey, revised incorporating Committee and public feedback, sent to 53 US states and territories and DC
- Interviews with 3 NBS programs that are screening for GAMT deficiency, have a mandate, or are exploring screening
- Interviews with 2 NBS programs that are not screening or planning to screen for GAMT deficiency

RESULTS

Status of GAMT Deficiency Screening in the US

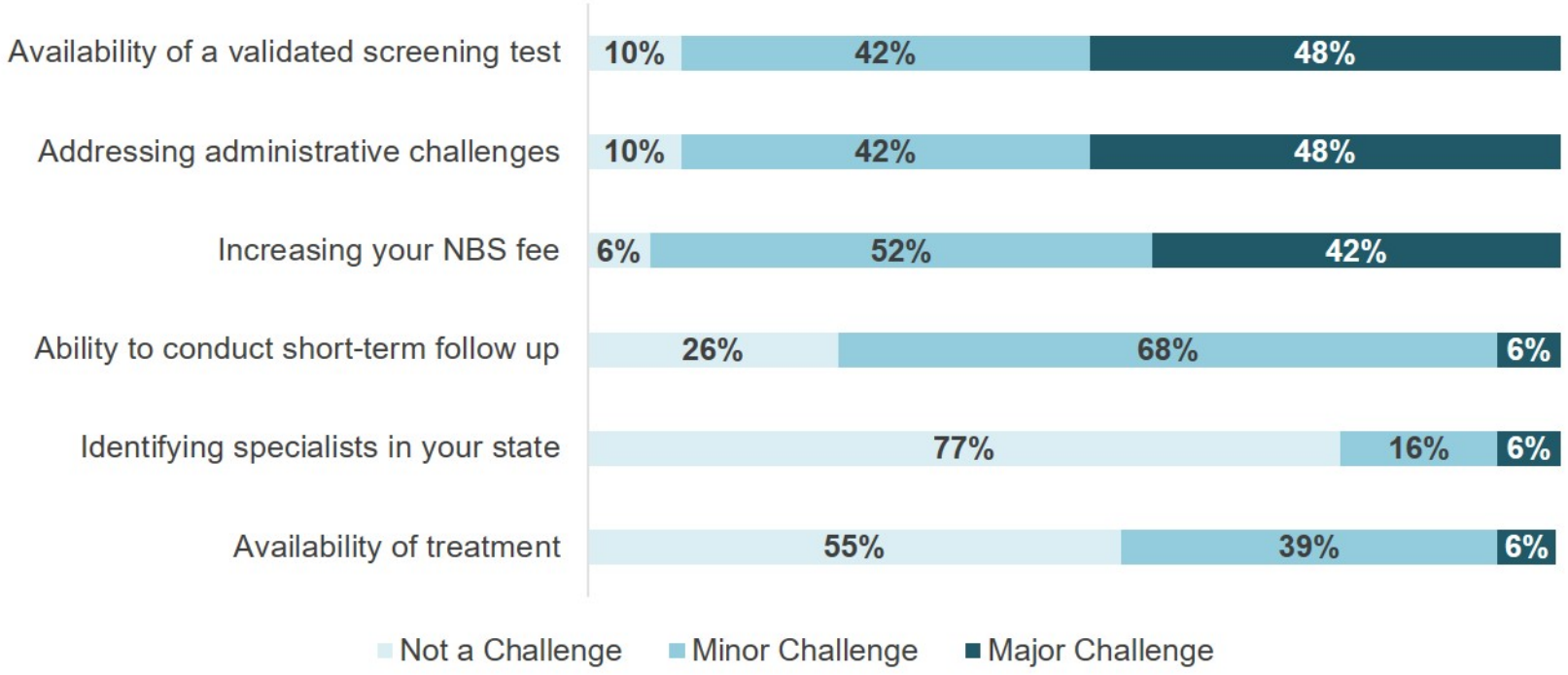
NBS Program	Universal Screening	Legislative Mandate	Considering / Performing Pilot Screening	Start Date/ Anticipated Start Date	Completed APHL Interview	Current Method
New York	Yes			2018	Yes	Derivatized MS/MS, no second-tier
Utah	Yes			2015 (ARUP)	Yes	Non-Derivatized MS/MS, no second-tier
Michigan		Yes	Yes	N/A	Yes	N/A
Connecticut			Yes	N/A		N/A

Survey Results: Respondents

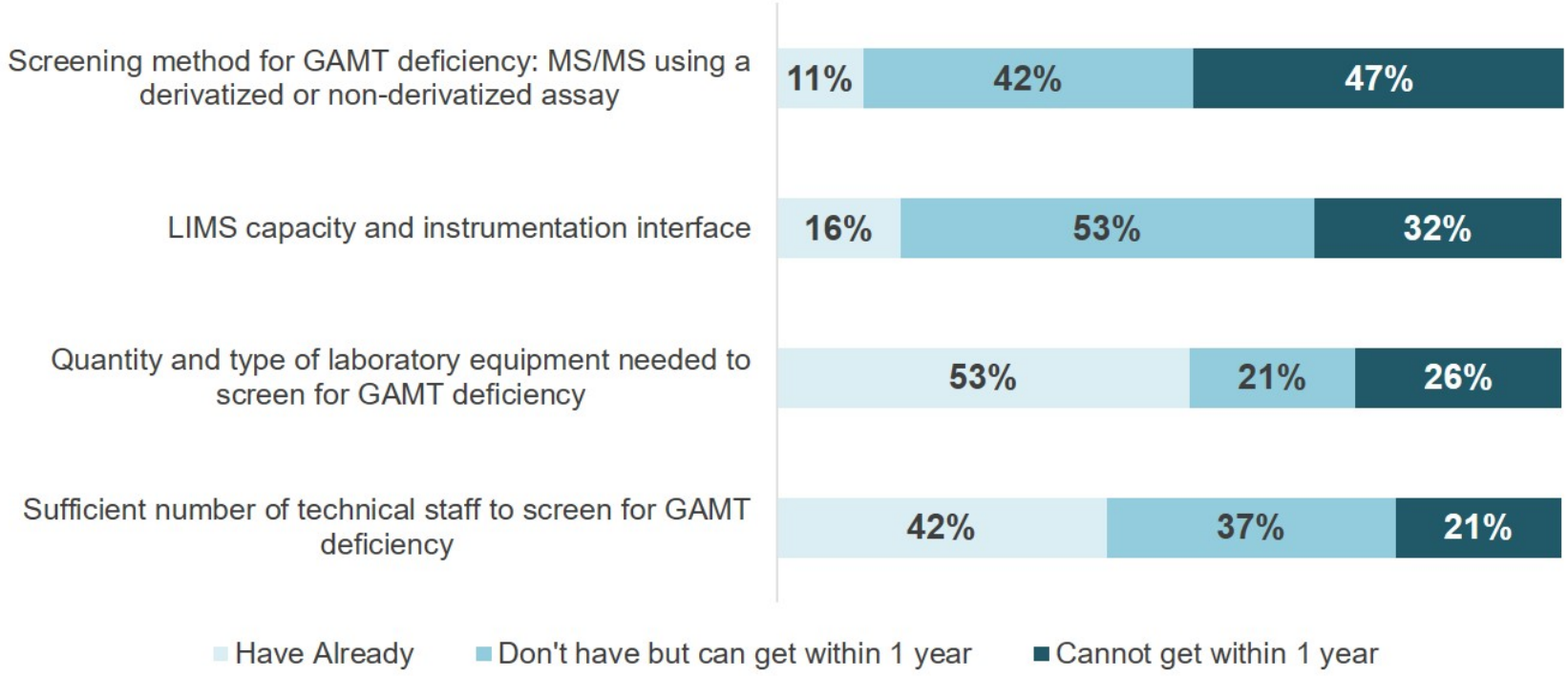
- Thirty-five of 53 NBS programs responded to survey.
- Thirty-one in survey analysis; four excluded due to screening, mandate or pilot.

Characteristics of NBS Programs in Analysis	n
State public health laboratory or NBS program	19
Regional contract for NBS laboratory services	2
State university with intra-state agency agreement for NBS laboratory services	5
Commercial contract for NBS laboratory services	3
Other	2

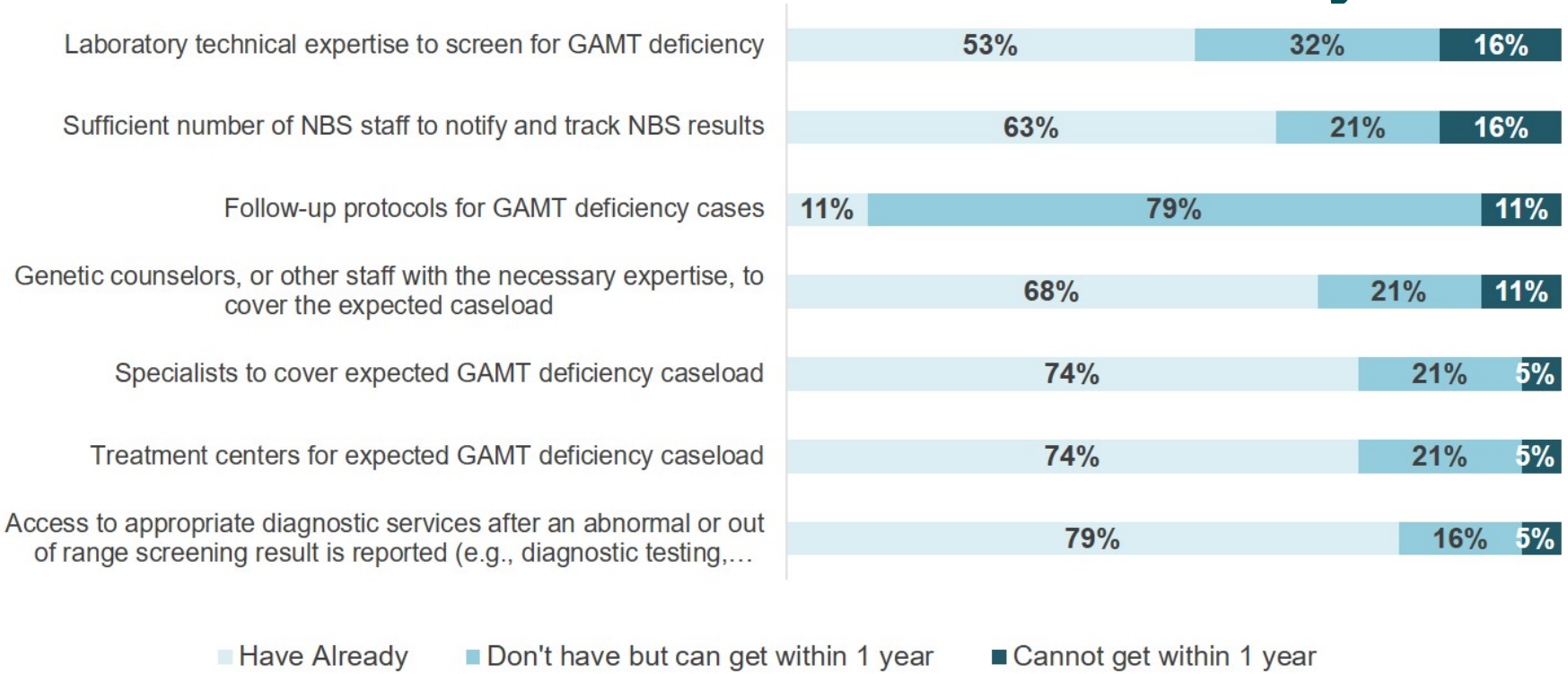
Survey Results: Implementation Challenges



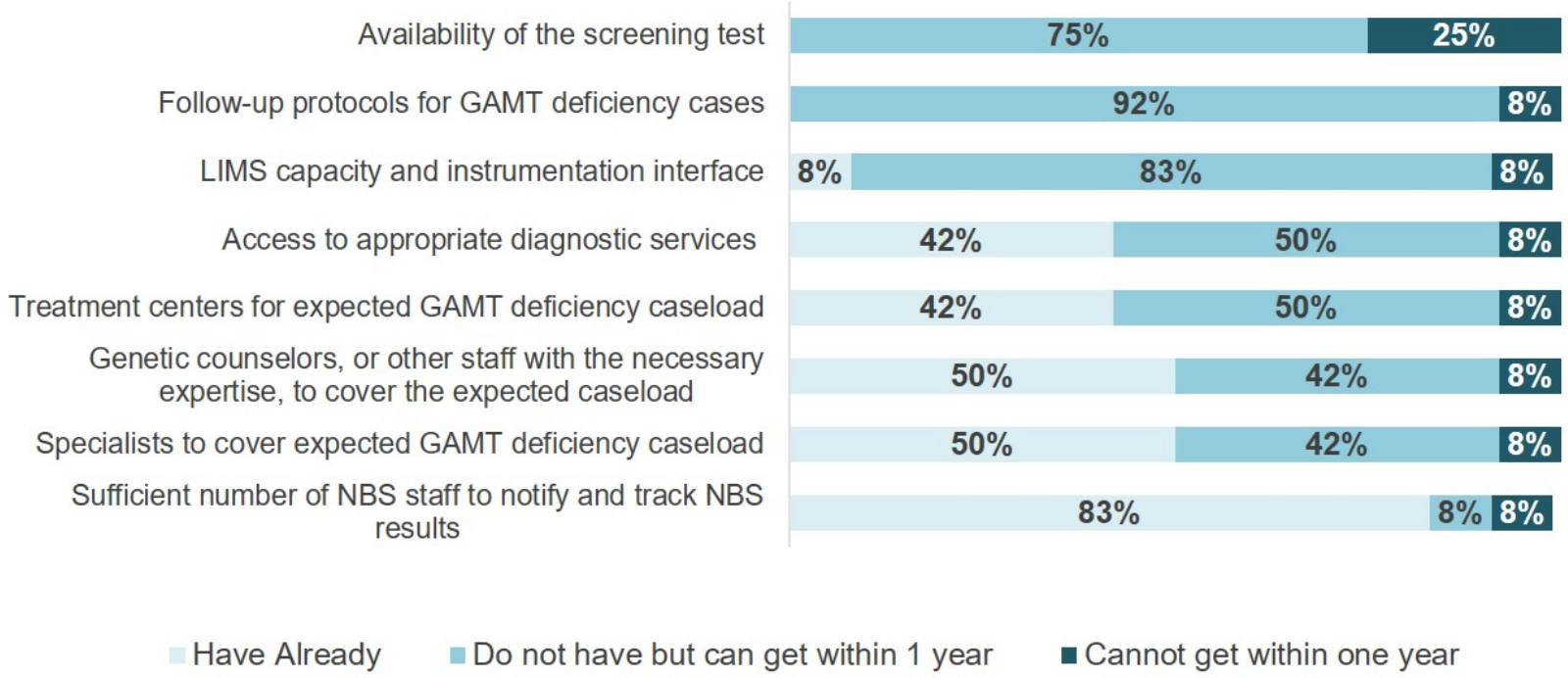
Survey Results: Resources Needed For Own State's Public Health or NBS Laboratory- Part 1



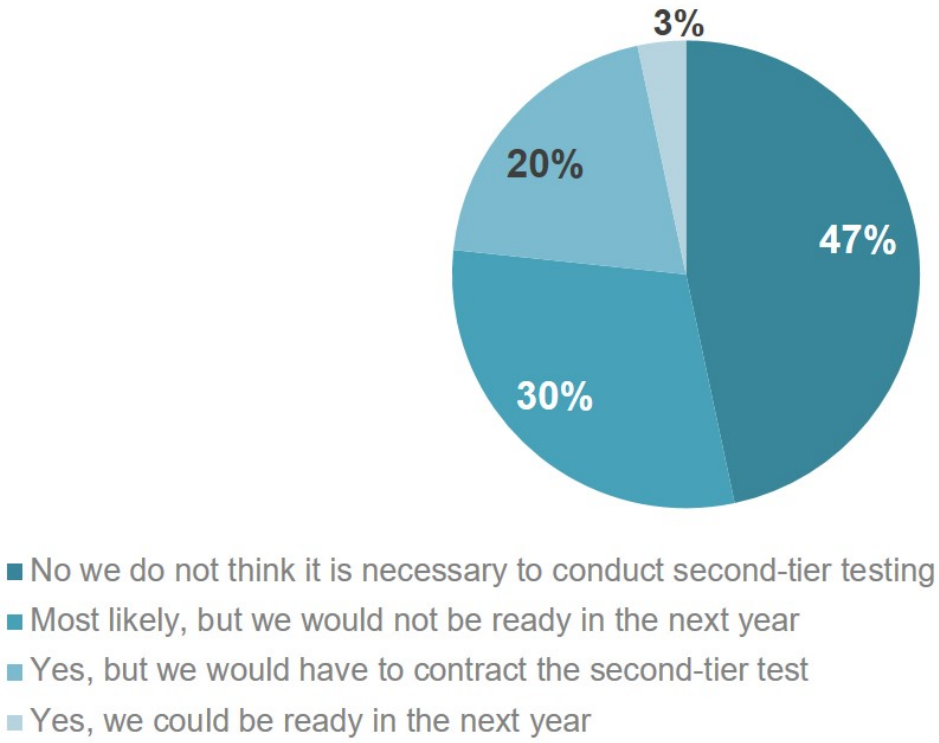
Survey Results: Resources Needed For Own State's Public Health or NBS Laboratory- Part 2



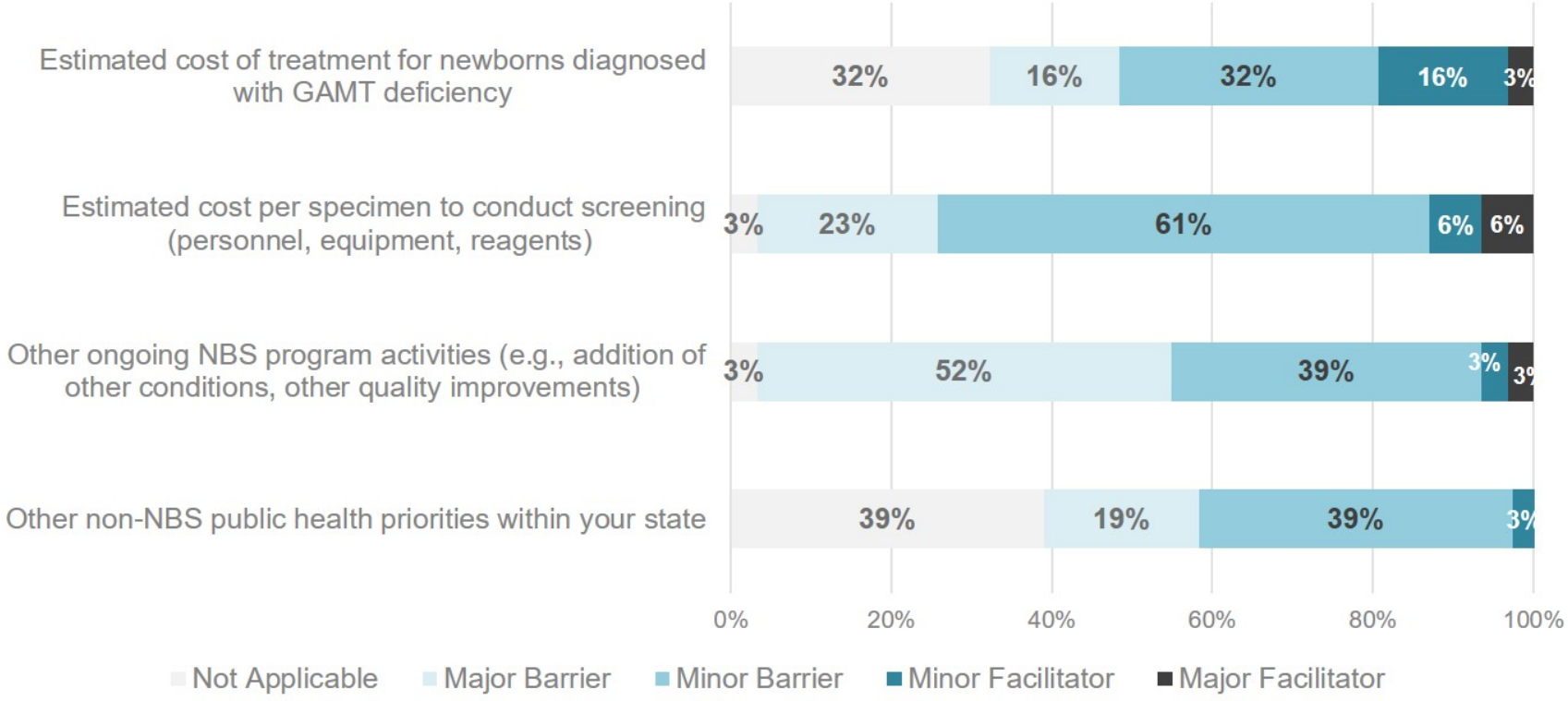
Survey Results: Resources Needed For Contracted or State University Labs with Intrastate Agreement



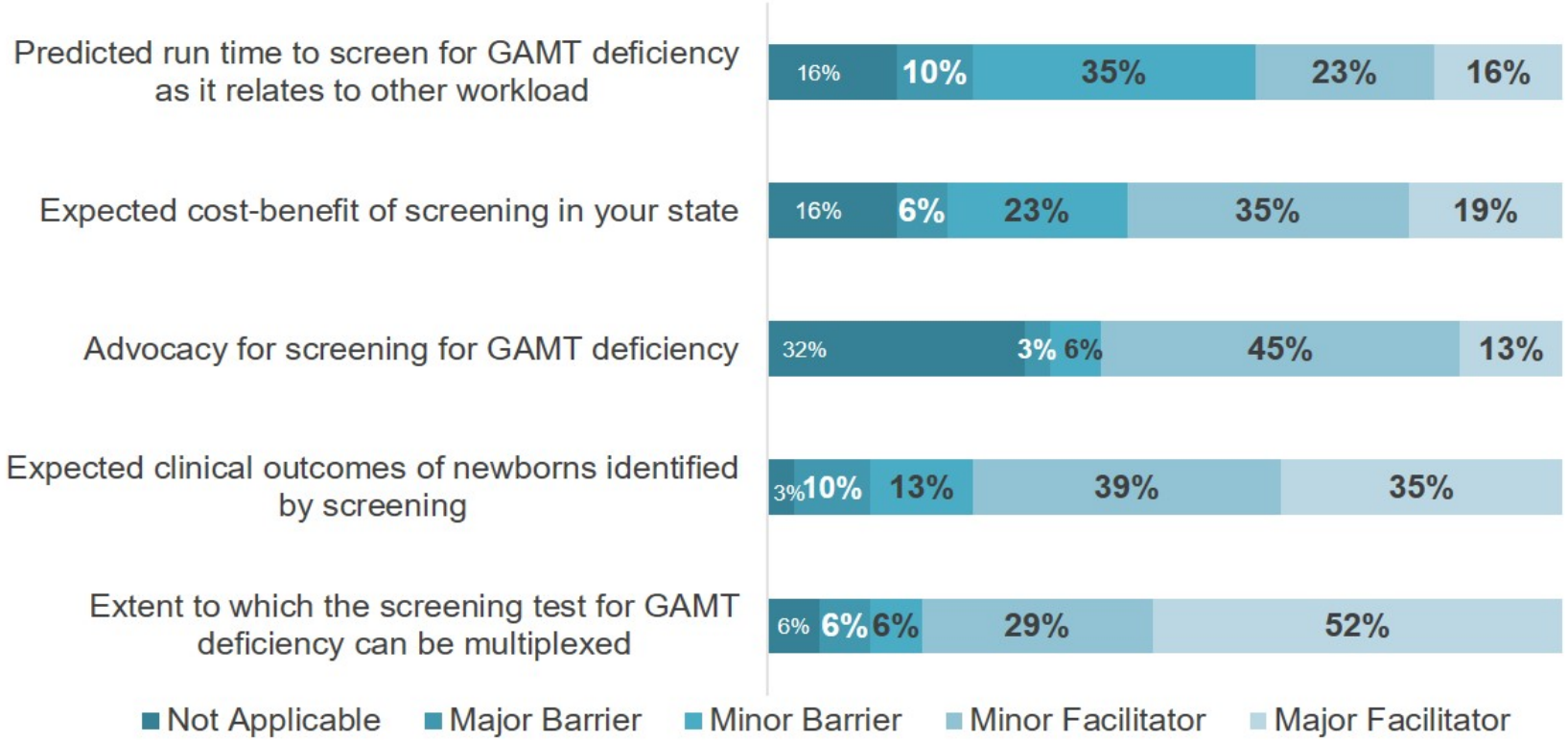
Survey Results: Second-Tier Screening for GAMT Deficiency



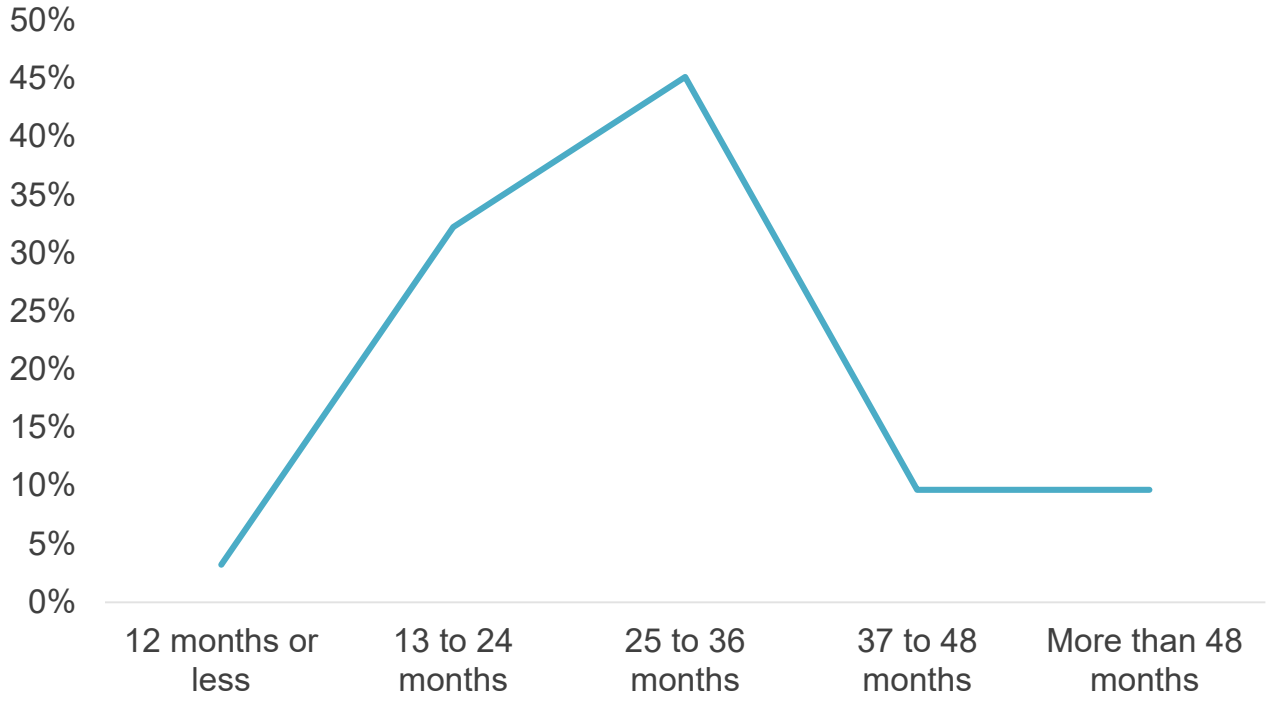
Survey Results: Barriers and Facilitators- Part 1



Survey Results: Barriers and Facilitators- Part 2



Estimated Time To Implement GAMT Deficiency in Your State



Interview Results: Lessons Learned from NBS Programs Screening

- GAMT deficiency can be multiplexed with other amino acid and acylcarnitine disorders using either a derivatized or non-derivatized method
- There is little additional staff time required
- The second-tier can be eliminated
- Both NBS programs use a laboratory developed test
- Challenges include validating GAMT deficiency with other disorders, not having an FDA-approved testing kit, and making LIMS adjustments

Interview Results: Lessons Learned from NBS Program Planning to Screen

- The Michigan NBS Program has been exploring the use of a non-derivatized MS/MS method
- Use a commercially available testing kit
- Spent over three years trying to validate the GAMT deficiency assay with their other disorders
- Difficulty with sensitivity
- Resolved some of their issues by extensively cleaning and maintaining their MS/MS equipment

Interview Results: Lessons Learned from Additional NBS Programs Not Screening

- Challenges of competing priorities, funding, hiring staff, laboratory space, and updating their laboratory information management systems.
- Concern with the growing expectations of newborn screening programs to add conditions and not having enough resources.

Strengths of PHSI

- Survey response rate was 66%.
- Webinar and factsheet for survey responders.
- Survey assessed perceptions about implementation based on experiences with other disorders.
- Interviews assessed real-world experiences.

Limitations of PHSI

- Hypothetical survey questions and subjective responses.
- Limited data on GAMT deficiency in NBS setting.
- There is great variation among NBS programs, which could limit generalizability.

SUMMARY

Summary

- Approximately half of NBS programs reported that it would take between 2 to 3 years to implement GAMT deficiency newborn screening.
- 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.

Summary

- New York and Utah are the only newborn screening programs in the US with universal GAMT deficiency NBS
- Michigan has been trying to validate GAMT deficiency screening for three years and has confronted challenges
- An FDA-approved testing kit may facilitate implementation

Summary

- The ability to multiplex GAMT deficiency screening is an important facilitator
- The states that are performing screening have been able to successfully eliminate a second-tier
- Challenges include issues of validating the test, funding, staffing, and competing priorities