Overview of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency

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*Also a nominator of GAMT deficiency to the RUSP

Overview

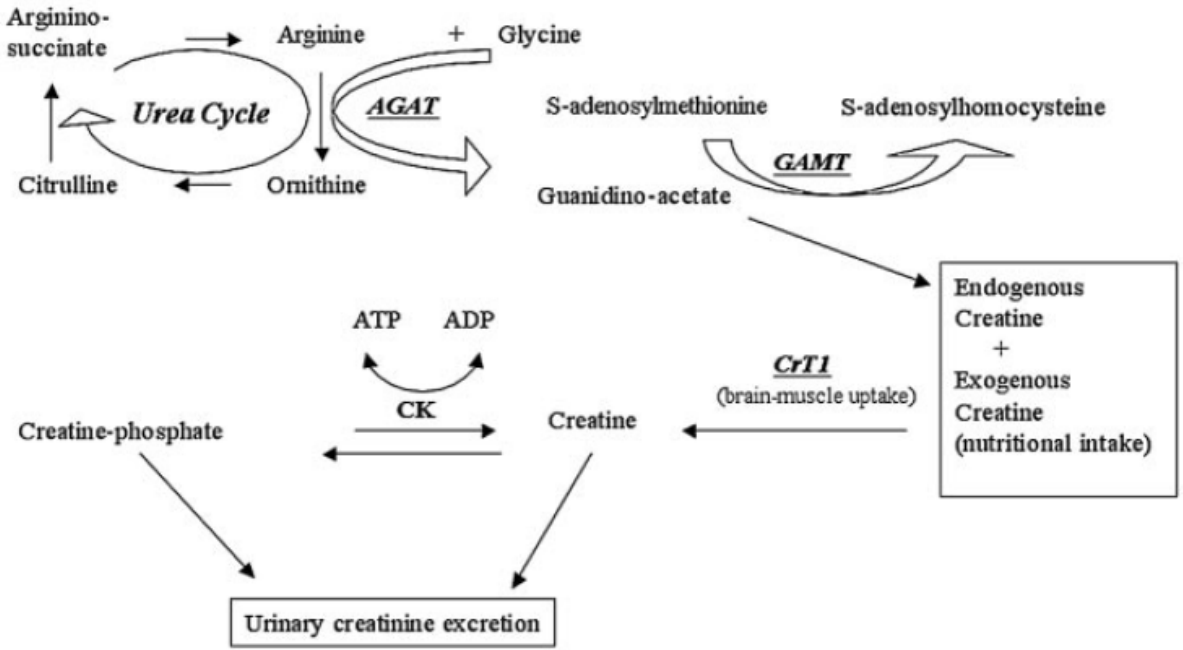
GAMT Deficiency

- Condition that causes cerebral creatine deficiency
- Untreated, global developmental delay with severe language delay, seizures, muscle weakness, movement disorders, behavior disorders

GAMT Deficiency

- Autosomal recessive mutation in the *GAMT* gene
- Location: 19.p13, 6 exons, at least 58 mutations
- Elevated guanidinoacetate (GUAC) and low plasma and brain creatine

Metabolic Pathway



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

GAMT Deficiency

- Pathophysiology
  - Low creatine leads to intellectual disability
  - GUAC accumulation leads to epilepsy and extrapyramidal disorders
- Biomarkers
  - Creatine and GUAC
  - MR Spectroscopy

Epidemiology

- Estimated prevalence: <0.2/100,000 live births
- Wide range of estimated carrier frequency (1:812-1:1475)

References: Desroches et al. *Mol Genet Genomics*. 2015;290:2163-2171; Mercimek-Mahmutoglu S. *Mol Genet Metab*. 2012; 107:433-437

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
    - Most (6/7) had signs before 2 years of age
    - Only one diagnosed before 2 years; 3 after 10 years

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.

Newborn Screening

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
  - Rule-out arginase deficiency, which can cause elevated GUAC
  - 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.

Newborn Screening in the US

New York

- 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

- In 2021
  - 211,242 newborns screened
  - 78 borderline (37 per 100,000)
  - 6 referred (3 per 100,000)
    - 1 case identified (positive predictive value 17%; 0.47 cases per 100,000)
    - 3 false positives and 2 likely false positives (infants in the NICU that died prior to diagnostic testing)

Utah

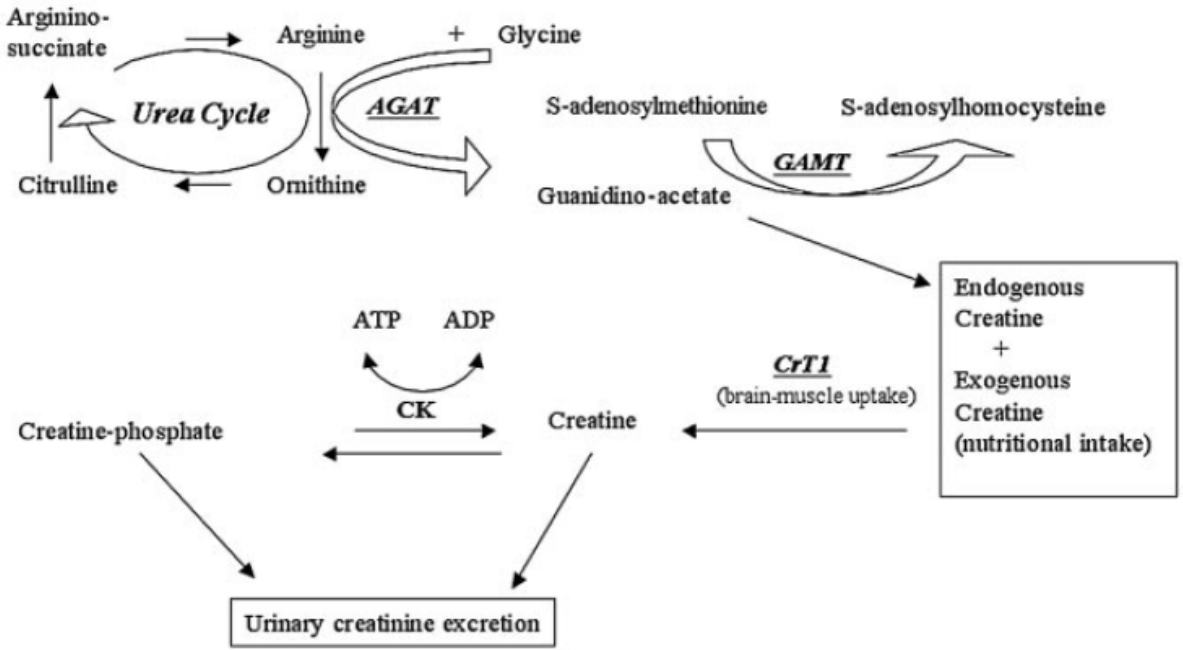
- Two screens per infant
- Screening for GAMT deficiency began in June 2015
- Laboratory-developed test
- 2015-2019
  - First-tier: GUAC and creatine, FIA-MS/MS derivatized assay
  - Second-tier: GUAC and creatine, LC-MS-MS
- 2019-Present
  - First-tier: GUAC and creatine, FIA-MS/MS (non-derivatized)
  - Second-Tier: GUAC and creatine (send-out)

Utah

- Since adoption of the current approach in 2019, 78,477 screens
  - 1 second-tier test (1.3 per 100,000 screens)
  - 1 referral (1.3 per 100,000 screens)
  - 1 case identified (1.3 per 100,000 screens)

Treatment

Metabolic Pathway



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

Treatment

- Creatine and ornithine supplements, sodium benzoate, available over-the-counter
- Dietary restriction of arginine
- Ideal timing of treatment is uncertain, but experts recommend from 2-4 weeks of age
- Serum monitoring

Effectiveness of Early Treatment

Early Treatment

- Given the rarity of the condition, clinical trials and cohort studies are challenging
- Focus on case reports and case series

Early Treatment

- Case series of 48 subjects from 38 families from a survey of clinicians
- Median age of diagnosis: 51 months (range: prenatal-34 years), with treatment soon after diagnosis
- Increasing age at treatment start was associated with greater severity of intellectual disability
- 3 subjects treated before 1 month: no developmental delay after a treatment duration of 14 months-7 years

Stockler-Ipsiroglu S et al. Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment, and monitoring. *Mol Gen Metab*. 2014;111:16-25.

Early Treatment

- Case report: subject who began treatment at 28 months followed to 6 years with persistent intellectual disability
- Case Report: subject diagnosed and treated at 8 days based on family history with normal development at 12 months

References: Mercimek-Mahmutoglu et al. *Pediatric Neurology*. 2014;51:133-137. Viau KS. Evidence-based treatment of guanidinoacetate methyltransferase (GAMT) deficiency. *Genet Metab*. 2013;110:255-262.

Early Treatment

- Sibling Case:
  - Older sibling treated at 10 months after presenting with hypotonia; at 6 years still delayed speech and fine motor skills
  - Younger sibling diagnosed prenatally normal at 42 months

Reference: El-Gharbawy et al. Elevation of guanidinoacetate in newborn dried blood spots and impact of early treatment in GAMT deficiency. *Mol Genet Metab*. 2013;109:215-217.

Early Treatment

- Sibling Case
  - Older sibling diagnosed at 2 years of age with significant developmental delay and seizures
  - Younger sibling began treatment at 22 days and developmentally normal at 14 months

Reference: Schulze A. et al. Presymptomatic treatment of neonatal guanidinoacetate methyltransferase deficiency. *Neurology* 2006;67:719-721.

Early Treatment

- Cousins reported in an abstract
  - Older cousin began treatment ~3 years, but after an unclear period of treatment, still had significant intellectual impairment but improved seizure frequency
  - Younger cousin evaluated at 5 months, with normal development at 16 months

Farshidi S et al. Creatine deficiency syndrome: a case report. Annual symposium of the Society for the Study of Inborn Errors of Metabolism, 2011.

Evidence Review Process Currently Underway

Projection of Population-Level Outcomes

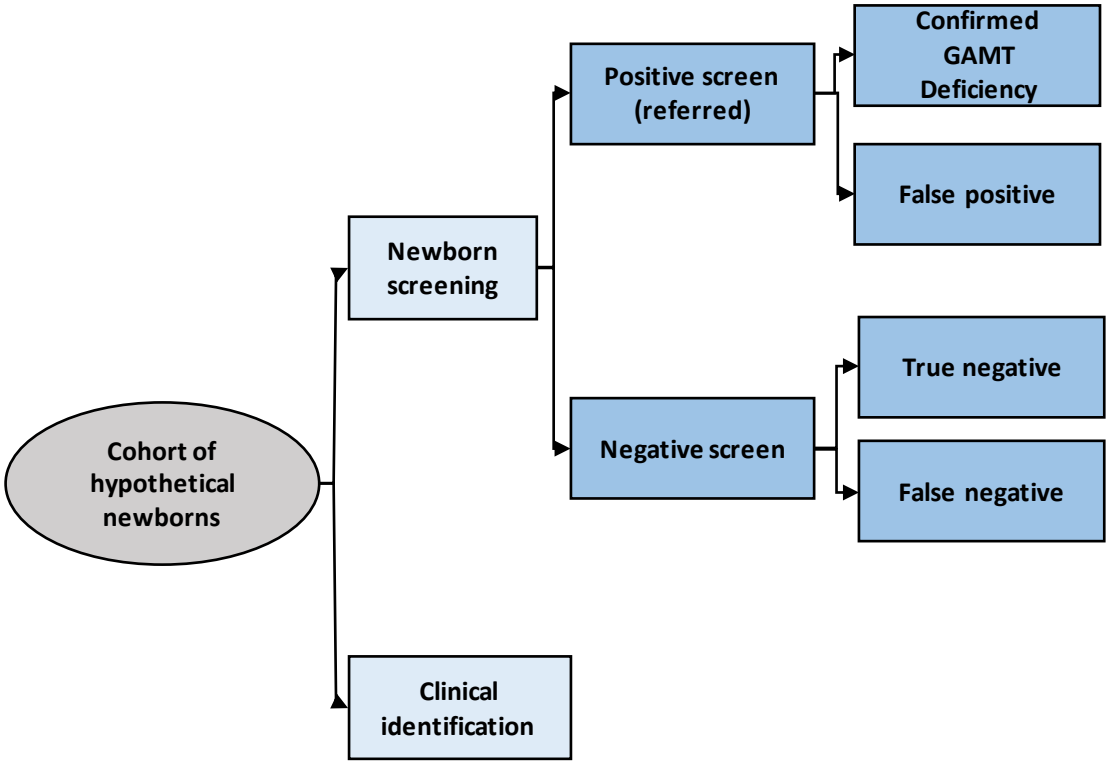
Goal

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

Projected Population-Level Outcomes

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

Model Schematic



Public Health System Impact Survey

Public Health System Impact Survey

- Webinar held on January 14
- Survey to open next week

Questions?