Overview of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency

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Nationwide Children's
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Objective

- Overview
- Current Progress
- Next Steps

GAMT Deficiency: Overview

- Cerebral creatine deficiency
- Mutation in the *GAMT* gene (autosomal recessive)
- Elevated plasma and urine guanidinoacetate (GAA) and low serum creatine
- Untreated, global developmental delay, seizures, muscle weakness, movement disorders

Current Progress

- Technical Expert Panel Call
  - October 6, 2021
- Utah NBS Call
  - October 28, 2021
- Evidence Review
  - 338 articles after searching PubMed, Embase, CINAHL, and the Cochrane library

Technical Expert Panel Members

Name	Affiliation	Role
Saadat Andrews, MD	University of Alberta	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
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Jon Daniel Sharer, MD, PhD	University of Alabama Birmingham	Researcher, Director-Biochemical Genetics
Graham Sinclair, PhD, FCCMG	British Columbia Children's Hospital	Researcher, Biochemical Geneticist
Heidi Wallis	Association for Creatine Deficiencies	President, Parent Advocate

Diagnosis

- Biochemical confirmation in plasma (low creatine, elevated GAA) at least a week after birth
- Arginine deficiency can also cause an elevated GAA
- Molecular analysis can support the diagnosis

Treatment

- Creatine and ornithine supplements, sodium benzoate, dietary restriction of arginine
- Ideal timing of treatment is uncertain, but experts recommend from 2-4 weeks of age
- Serum level monitoring, which can space out to every 6 months after the first few years

Screening

- Dried blood spots and MS/MS for GAA and creatine
- In the US
  - New York – screening began in 2018
    - ~537K screened, 23 referred, and 1 diagnosed
  - Utah – screening began in 2015
    - Switched from a derivatized to non-derivatized method in 2019
    - ~274K infants, 3 referred, and 1 diagnosed

Utah

- Two-screen state
- First-tier uses UPLC
- GAA is the primary analyte, creatine is a secondary analyte
  - Identified case had markedly elevated GAA on the first screen
- Contracts for confirmatory testing (urine and serum GAA and creatine) and follow-up
- Screening is <$1 per child

Next Steps: Evidence Review

- Systematic Review
- Grey Literature
  - Registry developed by the Association for Creatine Deficiencies
- Novel therapies in early development
  - Gene therapy
  - Inhibitors to reduce the production of GAA
- Assessment of the New York experience

Other Activities

- Public Health System Impact Assessment
  - Survey in January
- Population Health Modeling
  - Limited available outcomes to model

Questions