

Update on Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency



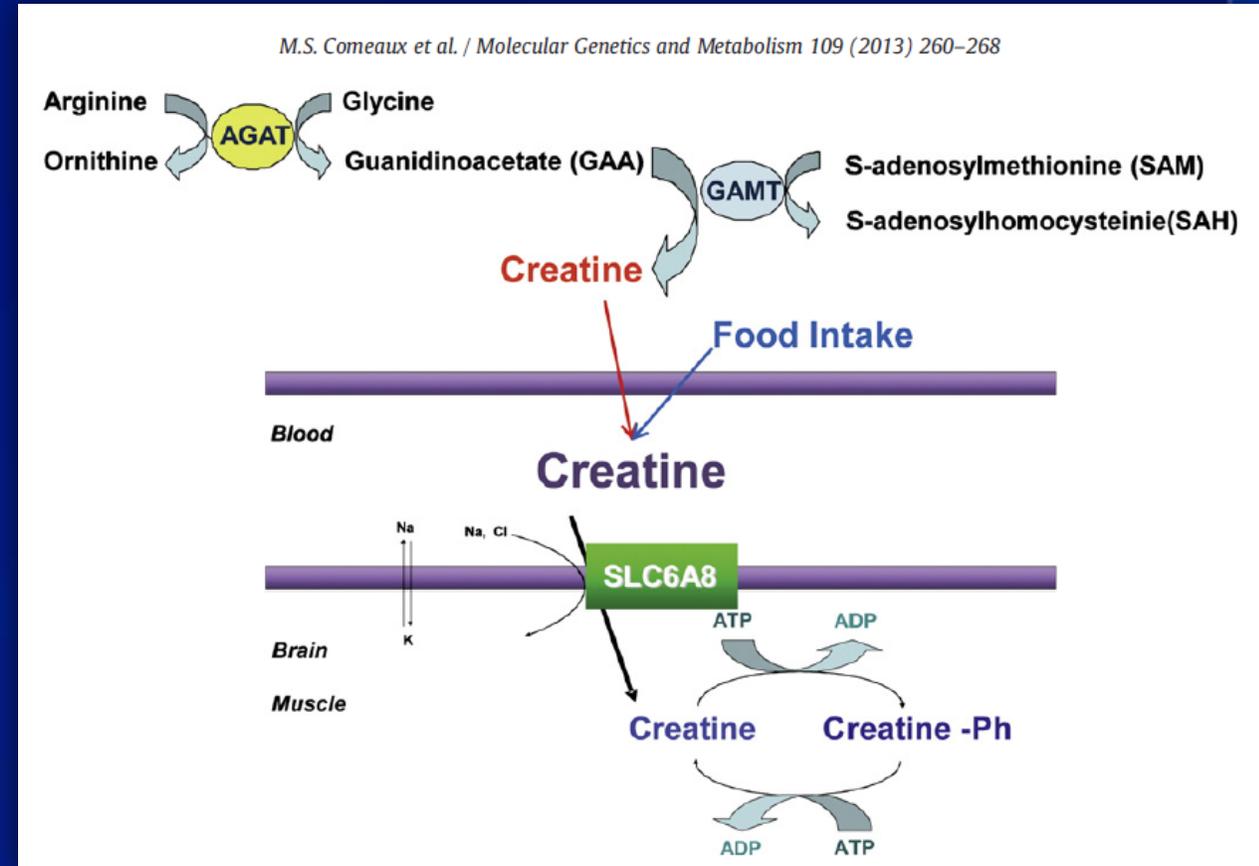
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Creatine Synthetic Pathway

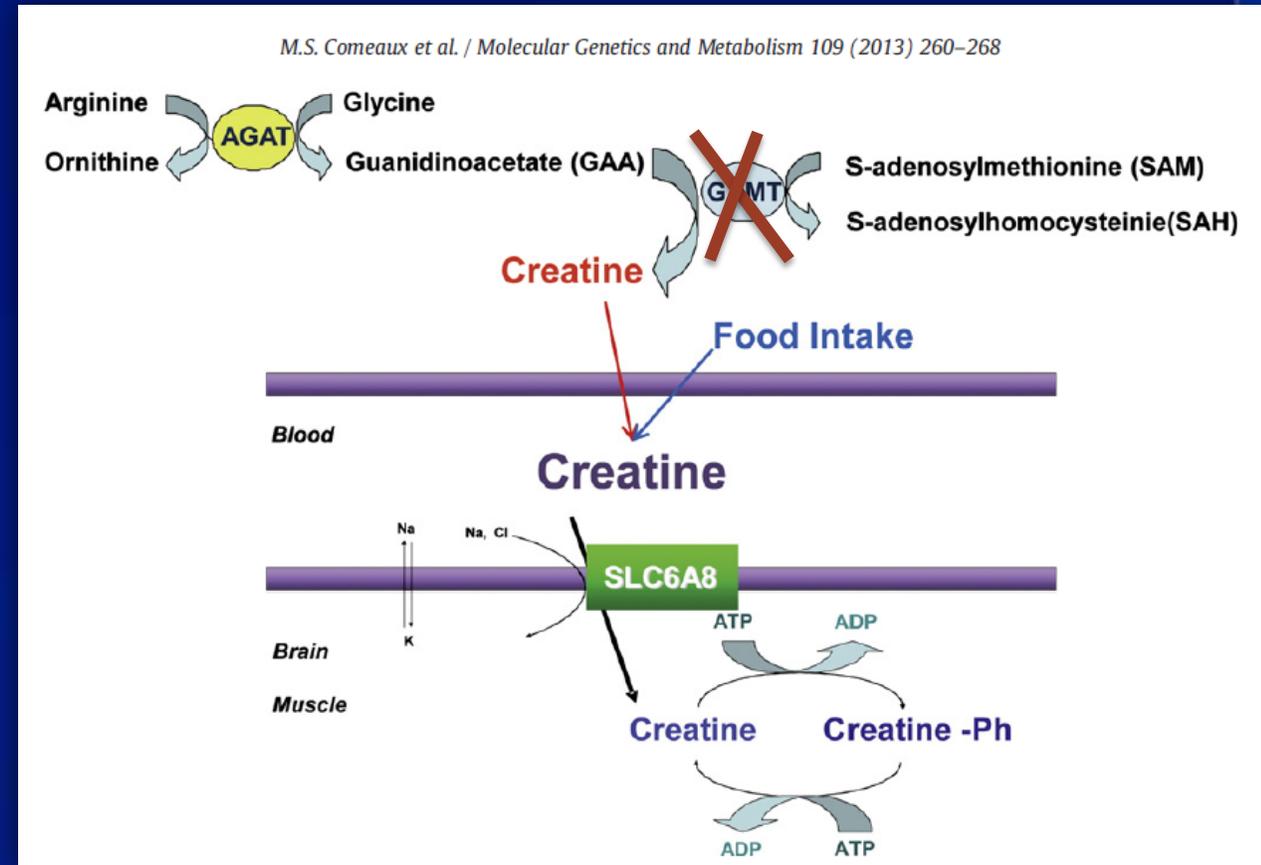
- **Guanidinoacetate Methyltransferase (GAMT) is one of the enzymes involved in the synthetic pathway for creatine**
 - AGAT: transfers the amidino group from arginine to glycine to form GAA
 - GAMT: methylates GAA to form creatine
- **Half of the Creatine in body derived from dietary sources (Meat or Fish)**
- **Circulating creatine is taken up by tissues by the creatine transporter**

AGAT (L:arginine:glycine amidinotransferase)



GAMT Deficiency

- **Pathophysiology**
 - Creatine Deficiency
 - Accumulation of neurotoxic GAA
- **Treatment Rationale**
 - **Restore Creatine pool:**
 - Creatine supplementation in high doses to overcome poor uptake by CNS
 - S-adenosylmethionine Supplementation
 - **Reduce GAA**
 - Ornithine supplementation
 - Arginine restriction
 - Na-Benzoate to bind/excrete glycine



GAMT Deficiency

- **Clinical Presentation** reflects the importance of creatine in the central nervous system
 - Symptoms occur during infancy and early childhood
 - Includes cognitive impairment, development and speech delays, muscle hypotonia, seizures, movement disorders, behavioral abnormality (autism spectrum, auto-aggressive behavior)
- **Treatment Outcomes**
 - Symptomatic patients improve
 - Patients treated early in life have (near) normal development
 - Treatment interruption may result in irreversible damage

El-Gharbawy AH et al. Mol Genet Metab. 2013; 109: 215–7)

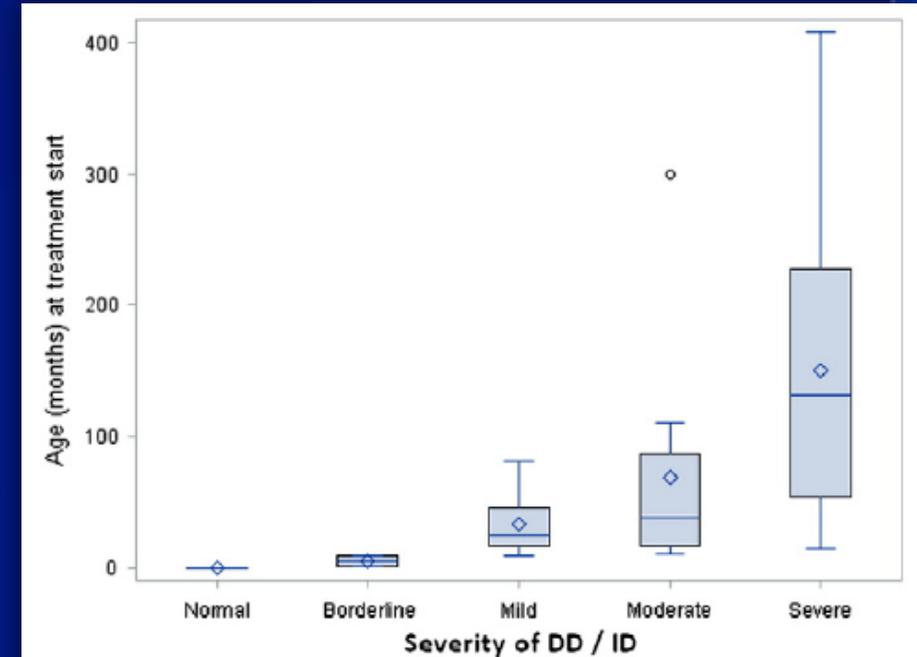


Fig. 1. Mean ages at diagnosis/treatment onset and severity of developmental delay/intellectual disability (DD/ID) in 48 patients with GAMT deficiency. (a) normal development (n = 2): min age = 0 months (treatment started prenatally), max age = 0.23 months (1 week); 25th, 50th, 75th percentile = 0, 0.12, 0.23 months. (b) borderline DD/ID (n = 2): min age = 0.68 months (3 weeks), max age = 9 months; 25th, 50th, 75th percentiles = 0.69, 4.9, 9 months. (c) mild DD/ID (n = 8): min age = 10.0 months, max age = 81 months; 25th, 50th, 75th percentiles = 16.5, 25.5, 46 months. (d) moderate DD/ID (n = 11): min age = 11 months, max age = 300 months; 25th, 50th, 75th percentiles = 17, 39, 87 months. (e) severe DD/ID (n = 25): min age = 15 months, max age = 408 months; 25th, 50th, 75th percentiles = 54, 132, 228 months. More data are required for statistical analysis, exploring the possible causative effect of time of treatment onset on developmental outcomes, controlling for various confounding factors.

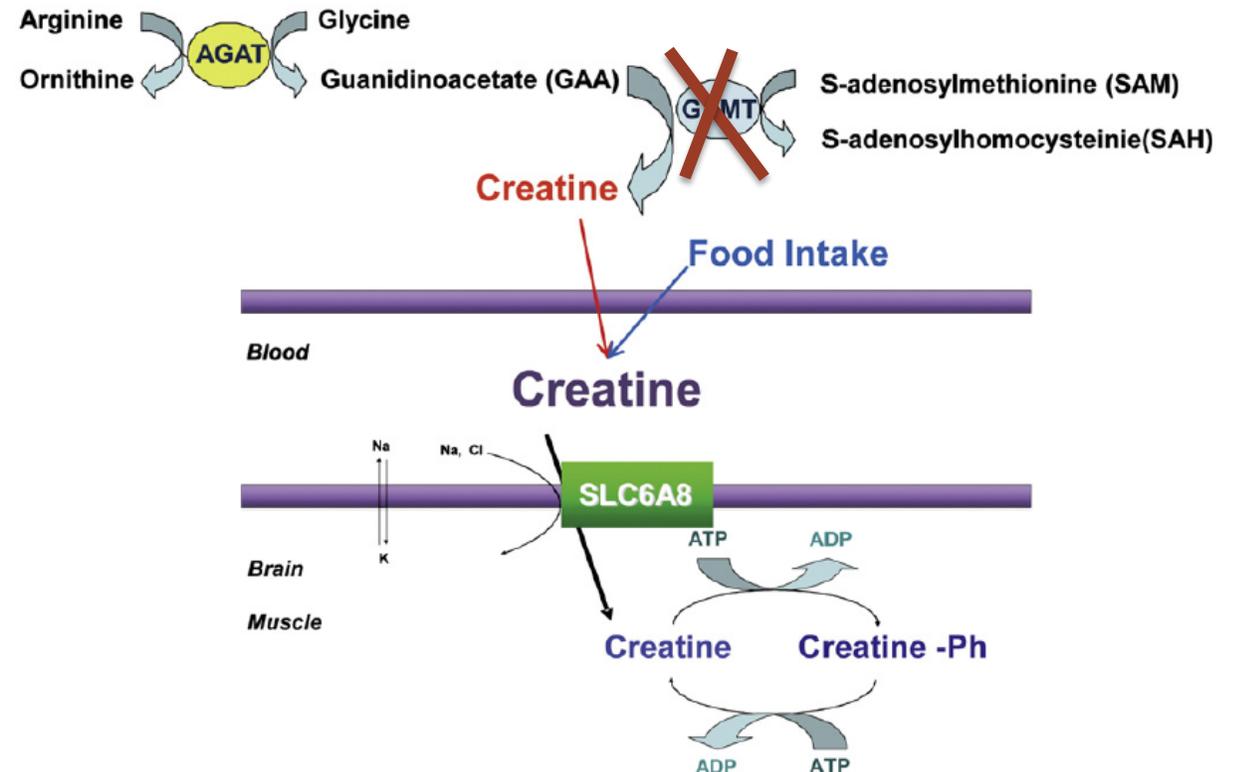
Evaluation of GAMT Deficiency

Biochemical Markers

Key Biochemical Markers

Analyte	Plasma	Urine
GAA	↑	↑
Creatine	↓	↓ - N
Creatinine	↓ - N	↓ - N

M.S. Comeaux et al. / Molecular Genetics and Metabolism 109 (2013) 260–268



Evaluation of GAMT Deficiency

Newborn Screening Programs

- **Primary Newborn Screening Assay**
 - Flow Injection MS/MS ... Measurement of GAA (+/- Creatine and Creatinine) together with Aminoacid and Acylcarnitine Analysis
 - Currently, no FDA-approved kit is available
 - Laboratory Developed Tests can be modified to include markers
- **Second-Tier Test**
 - Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) evaluation of a screen positive sample (GAA and Creatine)
 - Stand alone test or multiplexed with other second-tier markers
- **Molecular Evaluation - Sequencing**

Nomination of GAMT Deficiency

NOMINATOR

- Nicola Longo, MD, PhD (University of Utah)

Co-Sponsoring Organizations

- Marzia Pasquali, PhD (University of Utah, ARUP Labs)

Advocate Organizations

- Association for Creatine Deficiencies (ACD;
creatineinfo.org)

Newborn Screening for GAMT Deficiency

Summary of 2016 ACHDNC Deliberations

YES

- Natural history understood.
- Treatment similar to many classic inborn errors of metabolism.
- Outcomes best with early treatment.
- NBS assay can be multiplexed with existing test (LDTs).
- NBS strategy with high sensitivity and low FPR.

NO

- Understanding of natural history based on only 110 patients.
- No agreed upon treatment strategy.
- Metabolic control must be strict.
- No FDA approved NBS or diagnostic assay.
- No patient ever identified through NBS program.

NOMINATION OF GAMT DEFICIENCY FOR NBS

** RECOMMENDATION TO ACHDNC **

- **Do NOT initiate External Evidence Review because:**
 - No case has been identified prospectively through newborn screening to date which significantly hampers evidence review.
 - Treatment guidelines appear to be in development but are not finalized.
- **Recommend that proponents work with other experts to:**
 - Formalize treatment guidelines;
 - Encourage continuation of NBS for GAMT deficiency in Utah and Australia and report asap when a patient has been identified prospectively.
- **Invite proponents to resubmit nomination immediately when above has been achieved.**

**CURRENT STATUS OF PROGRAMS
SCREENING FOR GAMT DEFICIENCY**

Updates from Newborn Screening Programs State of Victoria, Australia

- **Population wide newborn screening for GAMT Deficiency in the State of Victoria**
 - **Approximate Number Births per year 70,000**
- **NBS for GAMT Deficiency - Update in 2014**
 - **Number of Newborns Screened from April 2002 to April 2013 771,345**
 - **Initial Screen: 127 newborns screened positive for elevated GAA**
 - **Repeat Testing: 3 newborns with increased GAA**
 - **Follow-up Testing: 3 newborns were false positives**
 - **Urine levels of GAA, creatine and creatinine were not consistent with GAMT deficiency**

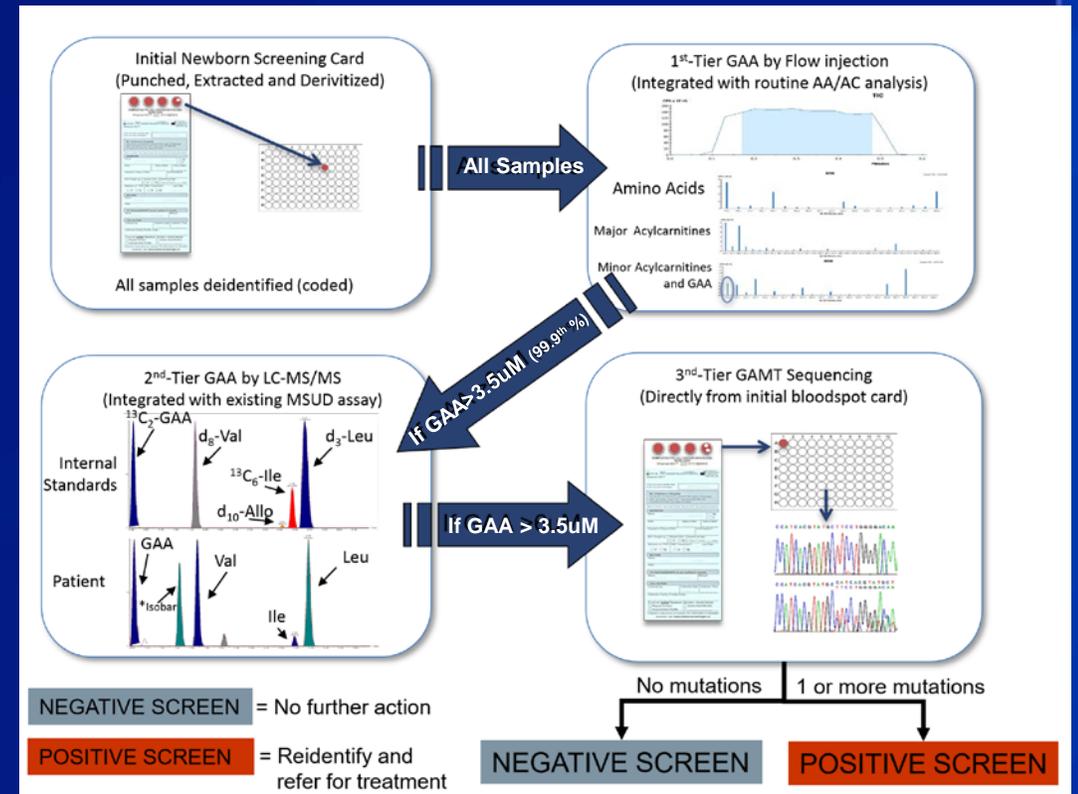
Updates from Newborn Screening Programs State of Victoria, Australia

- **NBS for GAMT Deficiency - Update in May 2018 (oral communication)**
 - Estimate of the number of newborns screened from April 2002 to April 2018 1,050,000
 - Numbers are similar to what was previously published
 - **NO TRUE POSITIVE CASES IDENTIFIED**
- **Not Aware of any False Negatives**
 - Reasonably confident that if there was a positive case of GAMT that he/she would have been picked up symptomatically
 - NBS program in same building as the Biochemical Genetics Laboratory
- **GAMT Deficiency seems to be very rare in this population**
 - Fortuitous that he decided to include biomarkers for GAMT deficiency in 2002
 - Intends to continue screening for GAMT

Updates from Newborn Screening Programs Province of British Columbia, Canada

- **Population wide screening pilot**
 - Pilot started 18th Sept 2012
 - Pilot ran for 3 years, screening all infants in BC
- **Currently – Newborn Screening for GAMT deficiency is a routine test in B.C.**
- **Current Screening Algorithm**
 - 1st Tier: Modification of routine MS/MS acylcarnitine /amino acid assay to include markers for GAA
 - 2nd Tier: Modification of the LC-MS/MS MSUD 2nd tier assay to include markers for GAA
 - 3rd Tier: Sanger sequencing of exons of the *GAMT* gene to identify one or more possible pathogenic variants

Newborn Screening Algorithm



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Updates from Newborn Screening Programs Province of British Columbia, Canada

- **Total Number of Newborns Screened: 246,995**
 - Sept 2012 to April 2018
 - **Number of Screen Positive Cases: 2**
 - Both cases were FALSE POSITIVES
 - Follow up tests of GAA and creatine in plasma and urine were normal in both cases
 - **Number of TRUE POSITIVES: 0**
 - **Not aware of any False Negatives**
 - **True Incidence is unknown in this population**
- 1st Tier Screen:
➤ 0.3% Positive Rate (741/246,995)
- 2nd Tier Screen:
➤ 2% Positive Rate (15/741)
- 3rd Tier Screen:
➤ 13% Positive Rate (2/15)

Updates from Newborn Screening Programs State of Utah, USA

- Population wide newborns screening for GAMT Deficiency in Utah – done as part of a ROUTINE SCREEN
- Number of Newborns Screened to end February 2018: 139,000
- Number of False Positives: 2
 - Both were NICU babies
 - False Positive Rate of 0.0014%
- No False Negatives identified
 - There is 1 children's hospital and 1 metabolic center
 - Any symptomatic case of GAMT deficiency would be picked up
- NO TRUE POSITIVE CASES IDENTIFIED

Updates from Newborn Screening Programs State of Michigan, USA

“Coming soon to Michigan’s Newborn Screening Program is Guanidinoacetate Methyltransferase (GAMT) deficiency.”

- **Michigan’s Newborn Screening Spring 2018 Newsletter**

Michigan will be the second state in the United States to screen for GAMT deficiency, and screening is anticipated to begin late 2018.

CDC is Available to Provide Technical Support for any NBS Program Interested in Implementing NBS for GAMT Deficiency

- CDC is available to provide technical assistance as needed to help with method development, validations and implementation of testing
 - Includes data review, conference calls
 - On-site visits in state lab, hands-on training at the CDC Campus
- CDC published a non-derivatized assay to detect GAA and Creatine
 - Modification of an existing assay for Amino Acids / Acylcarnitines
 - A derivatized method had previously been published



HHS Public Access

Author manuscript

Int J Neonatal Screen. Author manuscript; available in PMC 2017 September 01.

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Int J Neonatal Screen. 2016 ; 2(4): . doi:10.3390/ijns2040013.

Non-derivatized Assay for the Simultaneous Detection of Amino Acids, Acylcarnitines, Succinylacetone, Creatine, and Guanidinoacetic Acid in Dried Blood Spots by Tandem Mass Spectrometry

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CDC is Available to Provide Technical Support for any NBS Program Interested in Implementing NBS for GAMT Deficiency

- CDC is currently producing Quality Assurance Materials enriched with Guanidinoacetic acid (GAA) and Creatine (CRE)
- As of 2018 – There are 8 Laboratories (worldwide) participating in the CDC GAMT QC program
- Starting in 2019 - Guanidinoacetic acid (GAA) and Creatine (CRE) will be included as part of the routine Amino Acids / Acylcarnitine reference PT materials
 - Screening programs that have GAA and CRE markers integrated in the AA/AC screening test will detect these markers



SUMMARY

- GAMT deficiency is a serious medical condition and seems to be very rare.
- Treatment in principle similar to many RUSP conditions (diet/supplements, support).
- Approximately 1.4 million newborns have been screened for GAMT deficiency in 3 Programs (Victoria, Australia; British Columbia, Canada and Utah, USA)
- To Date - no Newborn has been pre-symptomatically identified through these screening programs
- Additional programs are considering the addition of GAMT deficiency to their NBS panel
- CDC is available to provide technical support for programs who seek to implement screening for GAMT deficiency

Thank you for your attention!



Newborn Screening

*Saving Lives.
Promoting Healthier Babies.
Protecting our Future.*



For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

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National Center for Environmental Health
Division of Laboratory Sciences

