

**Nomination and Prioritization  
Workgroup Report  
on  
Guanidinoacetate Methyltransferase  
(GAMT) deficiency**

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# Nomination of GAMT Deficiency

## Nominator:

Nicola Longo, MD, PhD (University of Utah)

## Co-Sponsoring Organizations:

- Marzia Pasquali, PhD (University of Utah, ARUP Labs)
- (no advocacy group mentioned)

## Advocate Organizations:

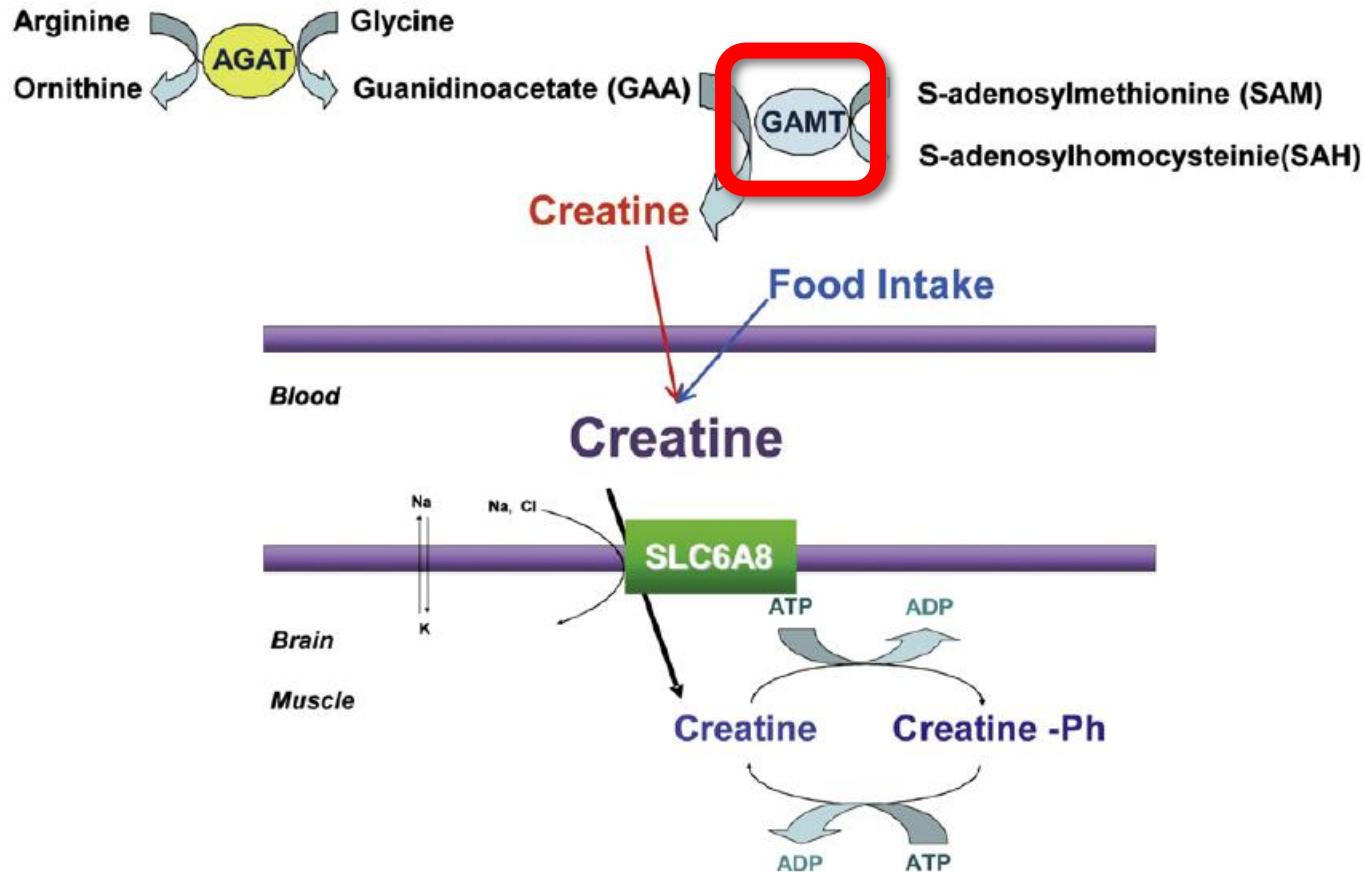
Association for Creatine Deficiencies (ACD; [creatineinfo.org](http://creatineinfo.org))

# Key Questions

1. **The nominated condition(s) is medically serious?**
2. **Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder?**
3. **A case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?**
4. **Analytic validity: The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?**
5. **Clinical utility: If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky?**
6. **Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available?**

# Creatine Deficiency Syndromes

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



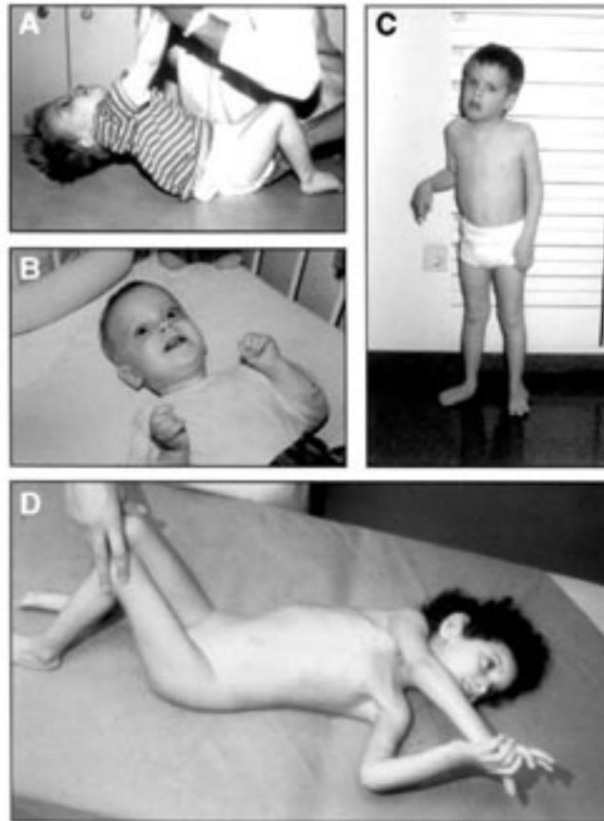
**Fig. 1.** The enzymes involved in the creatine biogenesis and metabolic pathway. AGAT: L-Arginine:Glycine amidinotransferase. GAMT: Guanidinoacetate Methyltransferase. SLC6A8: creatine transporter (CT1).

# Creatine Deficiency Syndromes

Deficiency	# of Affected Persons	Age of Onset	Intellectual Disability	Epilepsy		Movement Disorder		Behavior Problems and other Symptoms	Treatment & Outcome
				Frequency	Drug Resistance	Frequency	Severity		
<b>GAMT</b>	110	3 months – 3 years	Mild to severe	69/80 (86%)	46%	30/80 (37.5%)	Mild to severe	Hyperactivity, autism spectrum disorder, aggressive behavior, self-injurious behavior	<u>Treatment:</u> Creatine, Orn supplementation; Arg or protein restriction  <u>Outcome:</u> Improvement but best when initiated early!
<b>AGAT</b>	14		Mild to moderate	2/14 (14%)	None	None		Muscle weakness (67%)	<u>Treatment:</u> Creatine supplementation  <u>Outcome:</u> Improvement but best when initiated early
<b>CRTR (X-linked)</b>	>160	<3 years (males)	Mild to severe	59/101 (60%) males	3/59 (5%)	41/101 (40%)	Mild to severe	86/101 (85%) attention deficit hyperactivity, autism spectrum disorder	<u>Treatment:</u> Creatine, Arg, Gly supplementation; (Cyclocreatine)  <u>Outcome:</u> poor

*Adapted/modified from:* Mercimek-Mahmutoglu S, Salomons GS. Creatine Deficiency Syndromes. 2009 Jan 15 [Updated 2015 Dec 10]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK3794/>

From: Guanidinoacetate Methyltransferase Deficiency  
The Online Metabolic and Molecular Bases of Inherited Disease, 2014



**Legend:**

Two patients with GAMT deficiency. (A–C) The index patient. Oral supplementation with creatine was started at the age of 23 months. (A) Severe muscular hypotonia and weakness at 9 months. (B) Dystonia at 22 months. (C) Considerable improvement of motor abilities after treatment with creatine at 5½ years. (D) The second patient with GAMT deficiency at the age of 4 years. (Courtesy of Prof. Rating, Heidelberg.)

# Creatine Deficiency Syndromes

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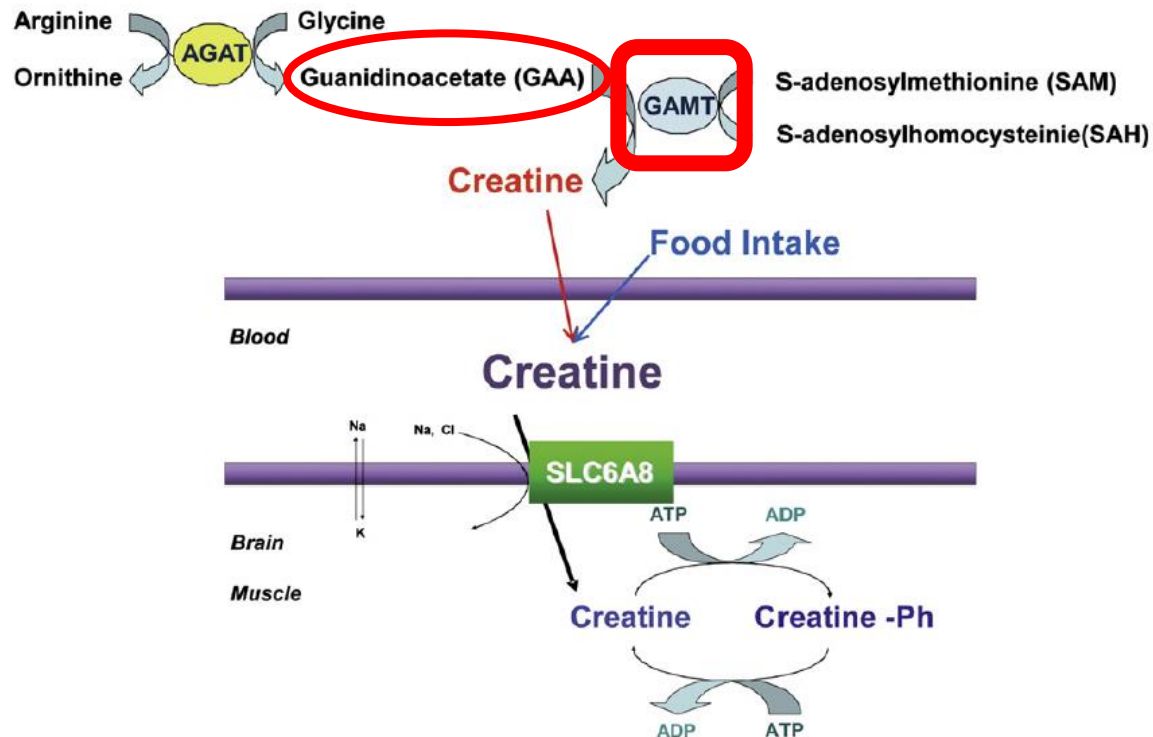
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# Creatine Deficiency Syndromes

## Biochemical Genetic Diagnosis

	Guanidinoacetate (GAA)			
	Urine	CSF	Plasma	DBS
GAMT	↑	↑	↑	↑

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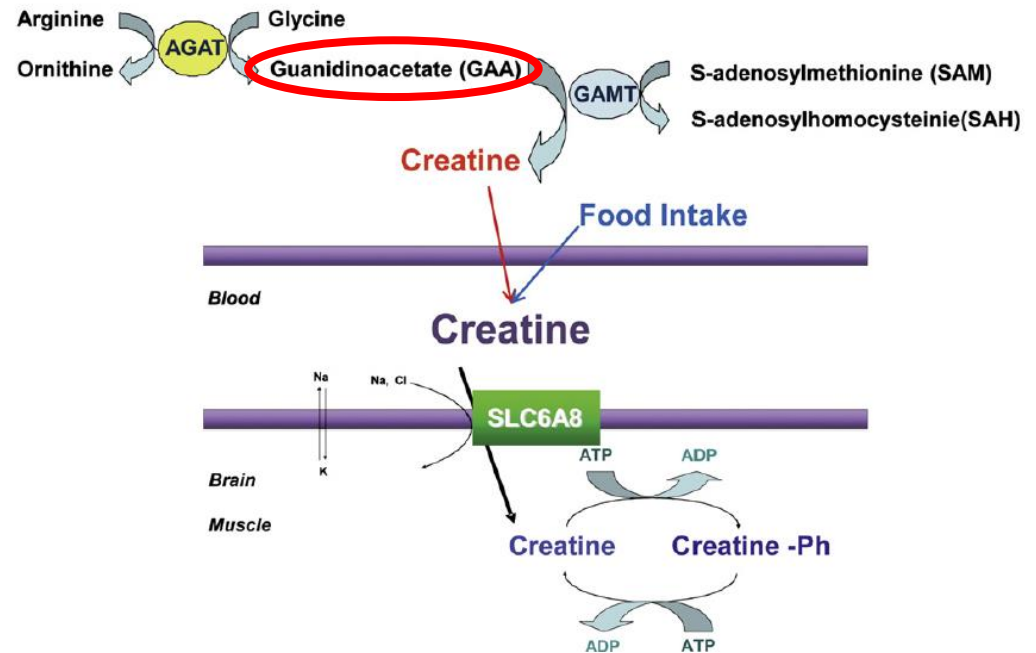


# Creatine Deficiency Syndromes

## Biochemical Genetic Diagnosis

	GAA	
	Urine	Plasma
GAMT	↑	↑
AGAT	↓ - N	↓ - N
CRTR (♀)	N	N
CRTR (♂)	N	N

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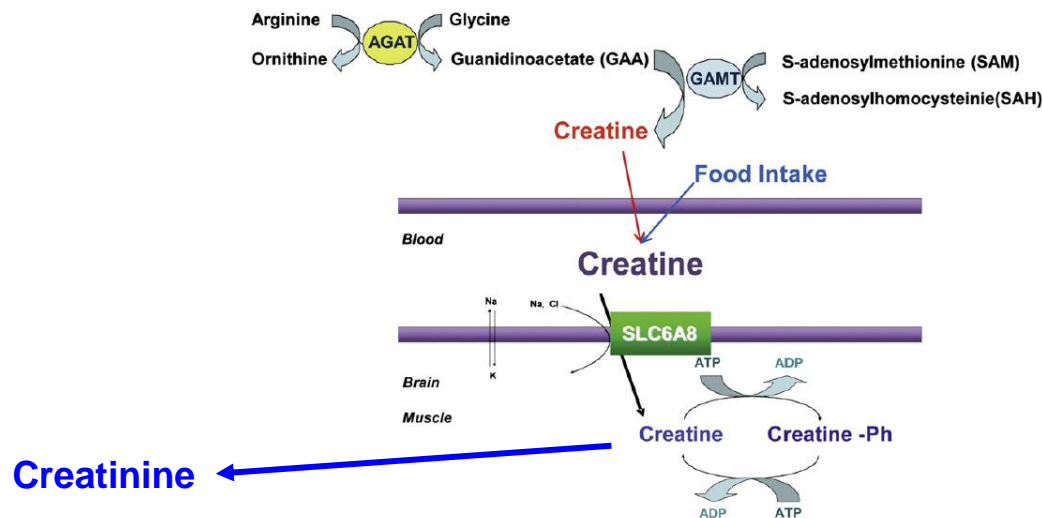


# Creatine Deficiency Syndromes

## Biochemical Genetic Diagnosis

	GAA		Creatine (Cr)		Creatinine (Crn)		Cr/Crn	
	Urine	Plasma	Urine	Plasma	Urine	Plasma	Urine	Plasma
<b>GAMT</b>	↑	↑	↓ - N	↓	↓ - N	↓ - N	↓ - N	-
<b>AGAT</b>	↓ - N	↓ - N	↓ - N	↓	↓ - N	↓ - N	↓ - N	-
<b>CRTR (♀)</b>	N	N	N - ↑	N	↓ - N	↓ - N	N - (↑)	-
<b>CRTR (♂)</b>	N	N	N - ↑	N	↓ - N	↓ - N	↑	-

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	GAA/Cr	
	Urine	Plasma
<b>GAMT</b>	↑	↑
<b>AGAT</b>	N	N
<b>CRTR (♀)</b>	N	N
<b>CRTR (♂)</b>	N	N

# Creatine Deficiency Syndromes

## Diagnostic Algorithm

### GTR: GENETIC TESTING REGISTRY

**Clinical tests** ([39 available](#))

#### Biochemical Genetics Tests

[Enzyme assay \(1\)](#)

[Analyte \(5\)](#)

#### Molecular Genetics Tests

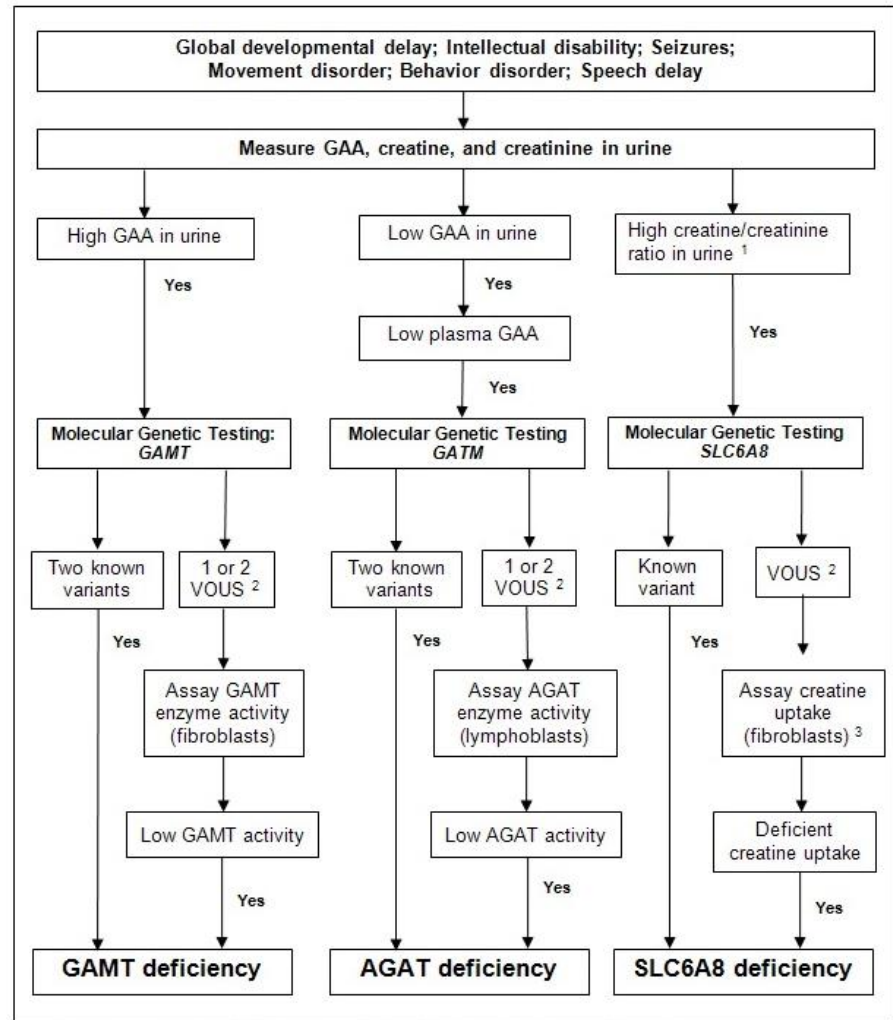
[Targeted variant analysis \(6\)](#)

[Linkage analysis \(1\)](#)

[Sequence analysis of the entire coding region \(30\)](#)

[Deletion/duplication analysis \(15\)](#)

[Sequence analysis of select exons \(1\)](#)



1. Males only. The only reliable testing for females is molecular genetic testing.

2. VOUS = variant of uncertain significance

3. Creatine uptake can be used in females when molecular genetic testing has identified either a novel variant of uncertain clinical significance or no variant despite strong clinical suspicion. Note: In some heterozygous females, creatine uptake studies are normal because X-chromosome inactivation results in expression of only the normal *SLC6A8* allele.

# Creatine

- **Source:**

- Diet
- Biosynthesis

- **Functions:**

- Regeneration of ATP
- Neurotransmitter in CNS

Vitamins & Supplements

Sort: Default ▾ View: List ▾ My Shortlist (0) ∞

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Arg  
Orn



## STS Creatine 5000 180 vcaps

**\$10.99** from 5+ stores

Muscle Growth - Capsule

Creatine Monohydrate is an athlete's ultimate supplement. Taken as part of your workout plan, it is intended to provide nutritive support for ...



## Now Foods Creatine Monohydrate 1,200 mg, Tablets - 150 count

**\$11.49** from 10+ stores

NOW - Muscle Growth - Pill

NOW Sports Creatine Monohydrate Tablets Dietary Supplement. Fast Acting Disintegration. ATP Energizer. Vegetarian/Vegan. Creatine Monohydrate is a ...



## Creatine Monohydrate 1000 mg 2 Bottles x 120 Coated Caplets

**\$12.79** from Piping Rock Health Products ★★★★★ 13,952 seller reviews

★★★★★ 2 product reviews

Energy - Capsule

Creatine Monohydrate capsules deliver natural energy support Creatine is a popular supplement because it serve as an energy reserve for physically ...



## Puritan's Pride Fitness Creatine Monohydrate 700 mg-120 Capsules

**\$5.49** from Puritan's Pride ★★★★★ 16,357 seller reviews

Capsule

Looking to get the most out of your workout? - Fitness Creatine Capsules are a key, foundational supplement for athletes, bodybuilders and anyone ...



## GAT Creatine

**\$39.99** from Walmart - Mega Retail Store

GAT Creatine

# GAMT Deficiency

- **Pathophysiology:**

- **Creatine deficiency**
- **Accumulation of neurotoxic GAA**

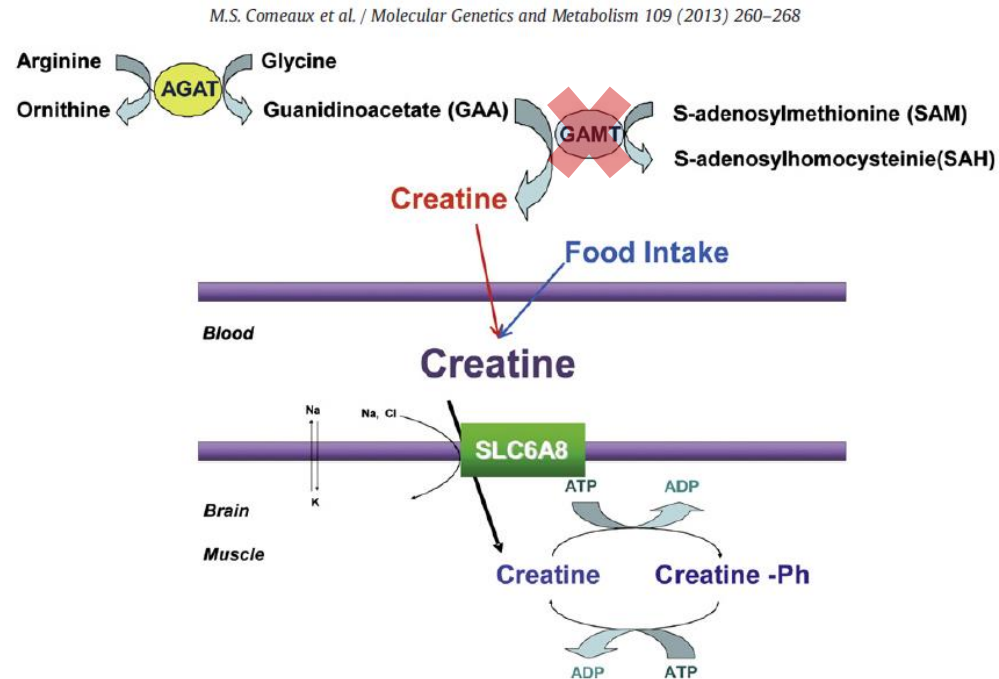
- **Treatment rationale:**

- **Restore Creatine pool:**

- Creatine supplementation in high doses to overcome poor uptake by CNS
- (SAM supplementation)

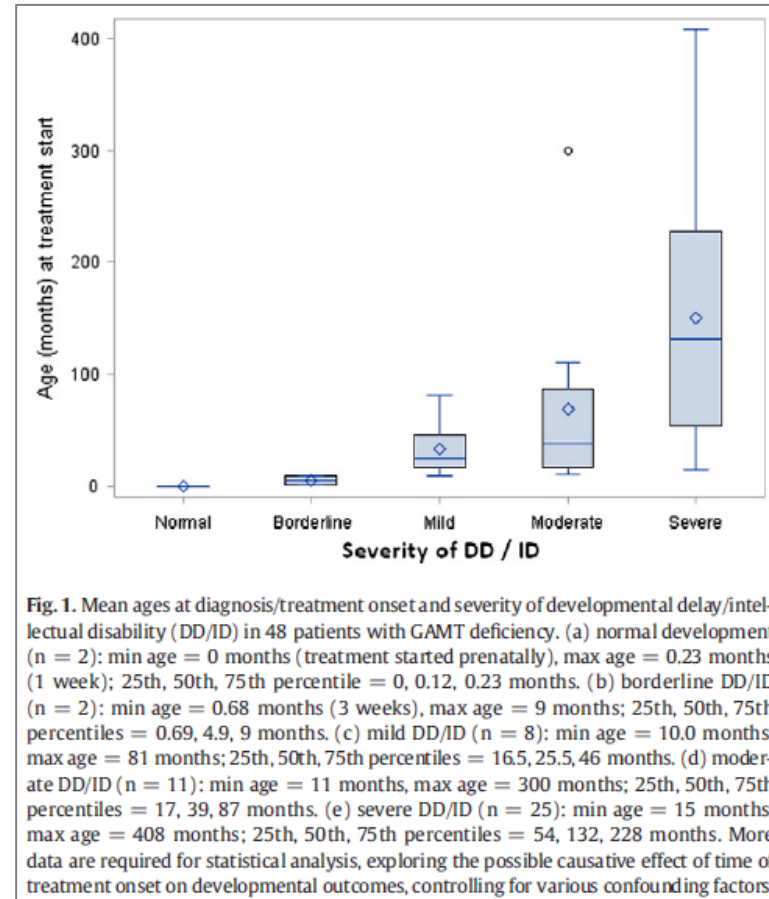
- **Reduce GAA:**

- Ornithine supplementation
- Arginine restriction
- Na-Benzoate to bind/excrete Glycine



# GAMT Deficiency

- **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)**



From: Stockler-Ipsiroglu S et al. Mol Genet Metab. 2014; 111:16–25

# Key Questions

- 1. The nominated condition(s) is medically serious?** **Yes**
2. Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder?
- 3. A case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?** **Yes (based on 110 pts.)**
4. Analytic validity: The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
5. Clinical utility: If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky?
- 6. Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available?**



# Molecular Genetics and Metabolism

Molecular Genetics and Metabolism 110 (2013) 255–262



Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: [www.elsevier.com/locate/ymgme](http://www.elsevier.com/locate/ymgme)



## Evidence-Based Treatment of Guanidinoacetate Methyltransferase (GAMT) Deficiency

Krista S. Viau<sup>a,\*</sup>, Sharon L. Ernst<sup>a</sup>, Marzia Pasquali<sup>a,b,c</sup>, Lorenzo D. Botto<sup>a</sup>, Gary Hedlund<sup>d</sup>, Nicola Longo<sup>a,b,c</sup>

<sup>a</sup> Department of Pediatrics, Division of Medical Genetics, University of Utah, 50 North Mario Capecchi Drive, 2C412 SOM, Salt Lake City, UT 84132, USA

<sup>b</sup> Department of Pathology, University of Utah, USA

<sup>c</sup> ARUP Laboratories, University of Utah, 500 Chipeta Way, Salt Lake City, UT 84108, USA

<sup>d</sup> Department of Medical Imaging, Primary Children's Medical Center, University of Utah School of Medicine, 100 N Mario Capecchi Drive, Salt Lake City, UT 84113, USA

**Recommendations for treatment of GAMT deficiency are evolving.**

Initiation of creatine treatment lead to a decrease in guanidinoacetate levels (Fig. 3A). However, once creatine levels were normalized there was no further decline in guanidinoacetate (Fig. 3B). This probably reflects the effect of creatine on AGAT, the first enzyme in creatine synthesis, whose expression and activity are upregulated in creatine-deficiency states [23–25].



# Molecular Genetics and Metabolism

Molecular Genetics and Metabolism 111 (2014) 16–25



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## Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring<sup>☆</sup>

Sylvia Stockler-Ipsiroglu<sup>a,\*</sup>, Clara van Karnebeek<sup>a,b</sup>, Nicola Longo<sup>c</sup>, G. Christoph Korenke<sup>d</sup>, Saadet Mercimek-Mahmutoglu<sup>e</sup>, Iris Marquart<sup>d</sup>, Bruce Barshop<sup>f</sup>, Christiane Grolik<sup>g</sup>, Andrea Schlune<sup>h</sup>, Brad Angle<sup>i</sup>, Helena Caldeira Araújo<sup>j</sup>, Turgay Coskun<sup>k</sup>, Luisa Diogo<sup>l</sup>, Michael Geraghty<sup>m</sup>, Goknur Haliloglu<sup>k</sup>, Vassiliki Konstantopoulou<sup>n</sup>, Vincenzo Leuzzi<sup>o</sup>, Alina Levtova<sup>p</sup>, Jennifer MacKenzie<sup>q</sup>, Bruno Maranda<sup>r</sup>, Aizeddin A. Mhanni<sup>s</sup>, Grant Mitchell<sup>p,t</sup>, Andrew Morris<sup>u</sup>, Theresa Newlove<sup>a</sup>, Deborah Renaud<sup>v</sup>, Fernando Scaglia<sup>w</sup>, Vassili Valayannopoulos<sup>x</sup>, Francjan J. van Spronsen<sup>y</sup>, Krijn T. Verbruggen<sup>y</sup>, Nataliya Yuskiv<sup>a</sup>, William Nyhan<sup>f</sup>, Andreas Schulze<sup>e,z</sup>

6. Steps towards evidence informed decision making
  - a. Overall, numerous questions regarding the evidence of the described treatment modalities, still remain to be answered.
  - b. Systematic studies are needed to determine the most effective dosages and combinations of creatine-monohydrate, L-ornithine, sodium benzoate and dietary protein restriction to correct GAA in plasma, CSF, and brain and optimize outcomes.
  - c. As an approach to achieve this goal we are planning a web-based platform ([www.gamtonline.org](http://www.gamtonline.org)) including a toolbox with standardized treatment and monitoring protocols linked to a GAMT research database allowing the clinician to choose the treatment strategy most applicable to the individual patient and to longitudinally monitor a minimum set of biomarkers and clinical outcomes.

# Key Questions

1. The nominated condition(s) is medically serious?
2. Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder?
3. A case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?
4. Analytic validity: The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
5. Clinical utility: If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky?
6. Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available?

Yes

Yes (based  
on 110 pts.)

Not yet

# Key Questions

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2. **Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder?**
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6. Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available? Not yet

# **GAMT Deficiency**

## **Newborn Screening Test**

- **Primary NBS assay:**
  - Measurement of GAA (and Creatine and Creatinine) along with acylcarnitine and amino acid analysis
  - Adds cost for reagents (but no extra equipment, space, FTE)
  - Laboratory Developed Test (currently no FDA kit available)
  - CDC Quality Assurance Program already has reference materials (GAA, Creatine)
- **2<sup>nd</sup> Tier Test (using original NBS sample):**
  - More accurate measurement of GAA (and Creatine and Creatinine?) by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
  - May require extra equipment, etc.
  - Could be regionalized
- **Molecular genetic analysis of *GAMT* gene**
  - Problem of genotypes of uncertain significance
  - Not yet common in NBS labs

# Status of NBS for GAMT Deficiency

- **University of Utah<sup>1</sup>**
  - **Retrospective study of 10,000 NBS samples:**
    - *False positive rate (FPR): 0.08% (GAA + GAA/Creatine)*
    - *FPR with 2<sup>nd</sup> tier test: 0%*
    - *True positive: 0*
- **Baylor Research Institute (Texas)<sup>2</sup>**
  - **Prospective study of 19,293 NBS samples (ca. 50% from Mexico) between 2008-2011:**
    - *FPR: 0.5% (GAA)*
    - *FPR with 2<sup>nd</sup> tier test: 0%*
    - *True positive: 0*

<sup>1</sup>Pasquali M et al. J Inherit Metab Dis. 2014;37:231-6

<sup>2</sup>Mercimek-Mahmutoglu S et al. Mol Genet Metab. 2012;107:433-7

# Status of NBS for GAMT Deficiency

- **British Columbia (Canada)<sup>2</sup>**
  - **Retrospective study of 3,000 NBS samples:**
    - *FPR: 0.13% (GAA)*
    - *FPR with 2<sup>nd</sup> tier test: 0%*
    - *Also tested for 2 “common” mutations and happened to find 2 carriers of 2 novel mutations*
    - *True positive: 0*
- **Victoria (Australia)<sup>3</sup>**
  - **Prospective NBS since 2002 (~1 million babies)**
    - *GAA as marker; no 2<sup>nd</sup> tier test*
    - *FPR: 0.02%*
    - *True positive: 0*

## \*Ethnic background:

66% of Australian, Scottish, English or Irish ancestry. Less than 1% Aboriginal. Most immigrants from British Isles, China, Italy, Vietnam, Greece and New Zealand.

<sup>2</sup>Mercimek-Mahmutoglu S et al. Mol Genet Metab. 2012;107:433-7

<sup>3</sup>Pitt JJ et al. Mol Genet Metab. 2014;111:303-4

# Status of NBS for GAMT Deficiency

- **The Netherlands<sup>4</sup>**
  - **Retrospective study of 500 NBS samples\*:**
    - *Methods: GAMT sequencing and GAA measurement*
    - *GAMT sequencing: 2 carriers (1 known, 1 novel mutation)*
    - *GAA measurement: FPR - 0%; True positive - 0*
    - *Presumed carrier frequency: 1 in 250*
    - *Calculated incidence: 1 in 250,000*

## **\*Ethnic background<sup>4</sup>:**

**“Dutch newborn population consisting of individuals with Dutch, Turkish, Moroccan, Indonesian, German, Surinamese, Latin American, other European and Asian ethnic backgrounds.”**

# How frequent is GAMT Deficiency

- **Based on calculations:**
  - **The Netherlands (Gene. 2016; 575: 127-31):**
    - **500 NBS samples tested: 2 carriers**
    - **Calculated incidence: 1 in 250,000**
  - **Utah (J Inherit Metab Dis. 2014; 37: 231-6):**
    - **5 patients diagnosed over 10 years**
    - **Calculated incidence: 1 in 114,072 live births**
  - **Portugal (Mol Genet Metab. 2007; 91: 1-6):**
    - **1,002 NBS samples tested for 1 mutation: 8 carriers**
    - **Calculated incidence: 1 in 63,000**
- **Based on prospective Newborn Screening**
  - **Australia: <1 in 1,000,000 live births (ongoing)**
  - **Utah: <1 in 50,000 live births (ongoing)**



# Summary

- **GAMT deficiency is a serious medical condition.**
- **Natural history of GAMT deficiency seems well understood - but only 110 patients are known worldwide.**
- **Treatment in principle similar to many RUSP conditions (diet/supplements, support).**
- **Best outcomes when treatment started shortly after birth.**
- **DBS based assays can be adopted for NBS quickly and at very low cost.**
- **Prospective NBS ongoing in Victoria (Australia) since 2002 (ca. 1 mill. babies screened to date; 0 true positive!).**
- **GAMT deficiency seems to be very rare.**
- **Sensitivity (likely 100%); FPR (near) 0%.**

# NBS for GAMT Deficiency?

- **YES**

- Natural history understood.
- Treatment similar to many classic inborn errors of metabolism.
- Outcomes best with early treatment.
- NBS assay cheap and easily

- **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

# Key Questions

1. **The nominated condition(s) is medically serious?** **Yes**
2. **Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder?** **Yes (AUS)**
3. **A case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?** **Yes (based on 110 pts.)**
4. **Analytic validity: The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?** **Yes**
5. **Clinical utility: If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky?** **No case identified prospectively**
6. **Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available?** **Not yet**

# **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.**