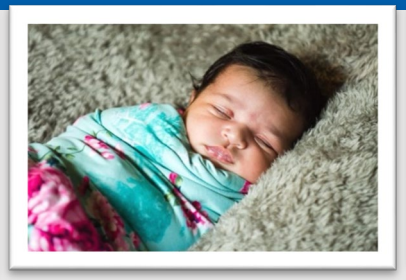
Nomination and Prioritization Workgroup Report:
Guanidinoacetate Methyltransferase (GAMT) Deficiency






Advisory Committee on Heritable Disorders in Newborns and Children
Nomination and Prioritization Workgroup:

Jeffrey Brosco
Shawn McCandless
Scott Shone
Carla Cuthbert
Cynthia Powell

Presented by:
Carla Cuthbert, PhD, FACMG

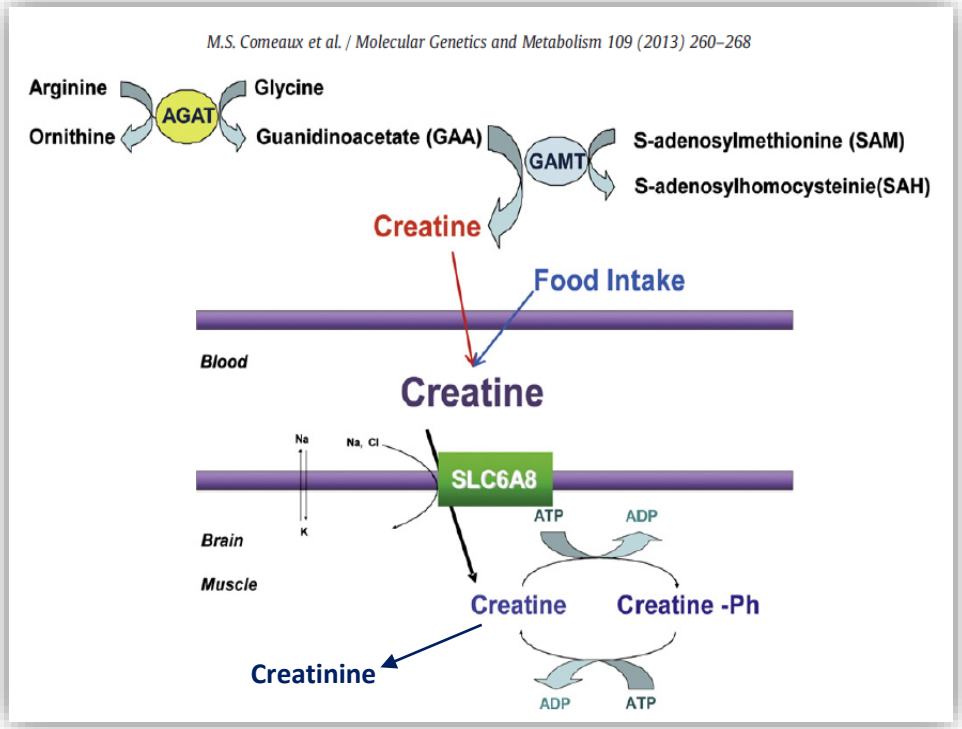
12 Aug 2021

Nomination of Guanidinoacetate Methyltransferase (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 Deficiency

The 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**
  - **Creatine Transporter 1 (encoded by the SLC6A8 gene) transfers creatine into cells and tissue**
- **Half of the Creatine in body derived from dietary sources (Meat or Fish)**
- **Circulating creatine is taken up by tissues by the creatine transporter**
- **Creatine Function**
  - **Regeneration of ATP**
  - **Neurotransmitter in the CNS**



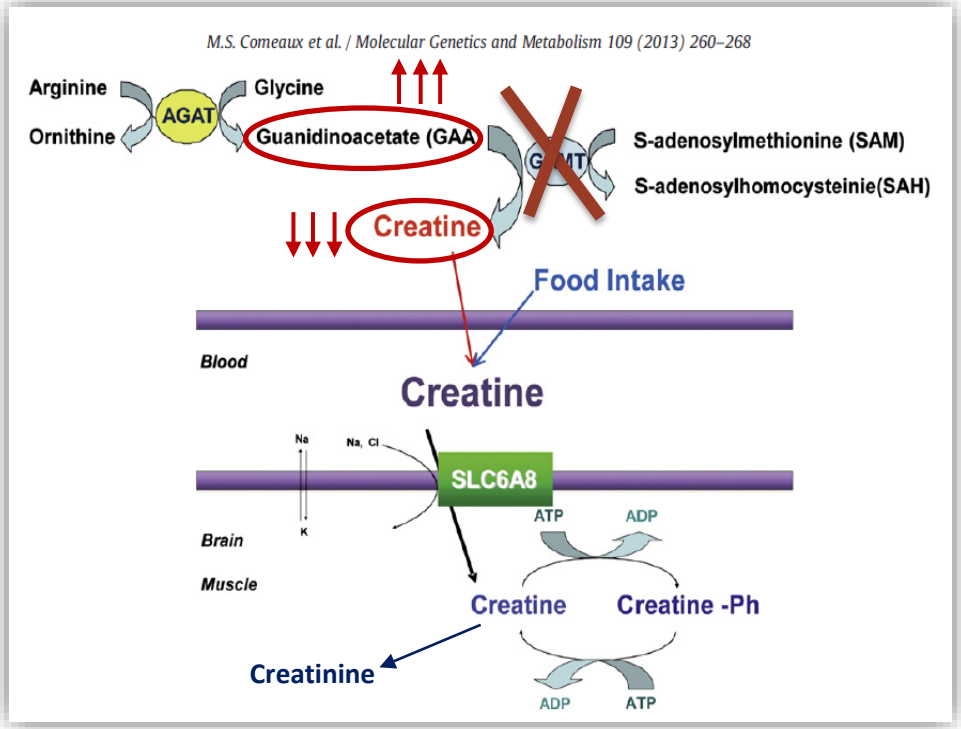
AGAT … L:arginine:glycine amidinotransferase
SLC6A8 … Solute Carrier Family 6 member 8 … Creatine Transporter

GAMT Deficiency – Biochemical Derangement

- **GAMT Deficiency: Inborn error of Creatine Synthesis**
  - One of a 3-member family of Cerebral Creatine Deficiencies
  - Caused by homozygous/compound heterozygous mutations in GAMT gene
  - GAMT Gene location: 19p13.3
  - Inheritance Pattern: Autosomal recessive
- **Pathophysiology is associated with:**
  - Creatine Deficiency
  - Accumulation of neurotoxic GAA

Analyte or Ratio	Plasma	Urine
GAA	↑	↑
Creatine	↓	↓ - N
Creatinine	↓ - N	↓ - N
GAA/Creatine	↑	↑

GAMT Deficiency Biomarker profile



GAMT Deficiency – Clinical Presentation

- ONSET: Symptoms of patients with GAMT Deficiency develop during infancy and early childhood

- Clinical Presentation includes:
  - Cognitive impairment
  - Development and speech delays
  - Muscle hypotonia
  - Seizures
  - Movement disorders
  - Behavioral abnormality
    - autism spectrum
    - auto-aggressive behavior

Comeaux MS, et al. Biochemical, molecular, and clinical diagnoses of patients with cerebral creatine deficiency syndromes. Mol Genet Metab. 2013 Jul;109(3):260-8

GAMT Deficiency – Treatment and Management

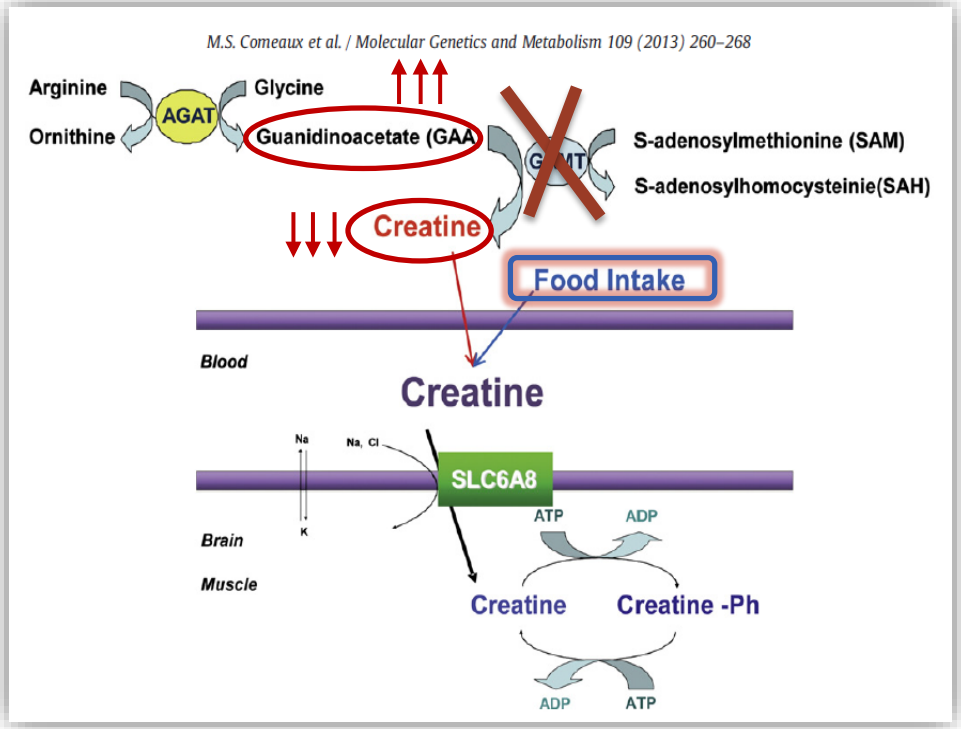
❑ Treatment Rationale

➢ Restoration of Creatine pool:

- Creatine supplementation in high doses to overcome poor uptake by CNS
- S-adenosylmethionine Supplementation

➢ Reduction of GAA

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



Core Requirements for Nomination

1. Validation of the laboratory test
2. Widely available confirmatory testing with a sensitive and specific diagnostic test
3. A prospective population-based pilot study

Key Questions to Address

1. Is the nominated condition(s) ***medically serious***?
2. Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
3. Are ***prospective pilot data*** from population-based assessments available for this disorder?
4. Does the screening test(s) have established ***analytic validity***?
5. Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
6. Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process?
7. Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?
8. Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Key Question #1

Is the nominated condition(s) medically serious?

YES

This is a health condition with a high risk of morbidity that negatively impacts daily function or quality of life

Clinical Presentation:

- Cognitive impairment
- Development and speech delays
- Muscle hypotonia
- Seizures
- Movement disorders
- Behavioral abnormality
  - autism spectrum
  - auto-aggressive behavior

Key Question #2

Is the case definition and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.

YES

- Autosomal recessive inborn error of creatine synthesis with a clinical presentation that reflects the importance of creatine in the central nervous system
- Clinical and biochemical features of GAMT deficiency have been well described
- NOTE: GAMT is so rare that we may not know the full spectrum of the phenotypic presentation until screening is more widespread
  - Clinical features are generally not very specific
  - Patients with GAMT deficiency are typically clinically identified by ~ 3 years of age
  - Is it possible that there are older patients who remain undiagnosed?

Key Question #3

Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

YES

Population -wide screening exists in at least 2 US States and other countries

Newborn Screening Program	Year Screening Began	Number of Newborns Screened	GAMT Def Newborns Identified
Utah (USA)	2015	275,000	1
New York (USA)	2018	537,000	1
British Columbia (Canada)	2012	365,000	0
Victoria (Australia)	2002	1,290,000	0

Key Question #3 — Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

Utah Case

Newborn Screening and Diagnostic Test results

		First Routine Testing > 7 days		Second Routine Testing > 7 days		
	Number Tested	GUAC (umol/L)	CRE (umol/L)	GUAC (umol/L)	CRE (umol/L)	
Derivatized NBS Testing	195,425	1.21 +/- 0.35	313 +/- 70	1.18 +/- 0.50	162 +/- 47	June 2015 to May 2019
Non-derivatized NBS Testing	78,477	1.33 +/- 0.66	453 +/- 115	1.12+/- 0.54	231 +/- 83	May 2019 to Current
Utah Patient	**1**	**13.25**	**324**	**9.26**	**100**	

GUAC: Guanidinoacetate
CRE: Creatine

- **Diagnostic Follow up**
  - GUAC (plasma) 9.16 umol/L (normal 0.5 – 1.8)
  - CRE (plasma) 16.8 umol/L (normal 37-117)

Hart K et al (2021) PROSPECTIVE IDENTIFICATION BY NEONATAL SCREENING OF PATIENTS WITH GUANIDINOACETATE METHYLTRANSFERASE DEFICIENCY. Mol Genet Metab. 2021 (Submitted June 2021)

Management and Outcome

- Started on therapy at 11 days of age
  - creatine and ornithine supplementation
    - 500 mg per kg per day
    - divided into 4 doses
  - sodium benzoate
    - 100 mg per kg per day
    - divided into 4 doses
  - moderate protein restriction
    - addition of 20-25% of estimated caloric needs as protein-free formula substituting for breastmilk

Current Status:

Remains normal, is growing and developing well and is tolerating therapies well.

Key Question #3

Are prospective pilot data (U.S. and/or international) from population-based assessments available for this disorder?

New York Case

Newborn Screening and Diagnostic Test results

		First Routine Testing	
	Number Tested	GUAC (umol/L)	CRE (umol/L)
Derivatized NBS Testing	537,408	1.34 +/- 0.57	569 +/- 155
New York Patient	1	23.35	509

Oct 2018 to Current

GUAC: Guanidinoacetate
CRE: Creatine

- **Diagnostic Follow up**
  - GUAC (plasma) 13.16 umol/L (normal 0.5 – 1.8)
  - CRE (plasma) 9.5 umol/L (normal 37-117)

Management and Outcome

- Started on therapy at 17 days of age
  - creatine and ornithine supplementation
    - 500 mg per kg per day
    - divided into 4 doses
  - sodium benzoate
    - 100 mg per kg per day
    - divided into 4 doses
  - moderate protein restriction
    - addition of 20-25% of estimated caloric needs as protein-free formula substituting for Similac

Current Status:

Tolerating the therapy, growing and developing normally.

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Key Question #4

Does the screening test(s) have established analytic validity?

Screening Tests for GAMT Deficiency

- Primary Newborn Screening Assay
  - Flow Injection MS/MS … Measurement of GAA (+/- Creatine and Creatinine) together with Amino Acid and Acylcarnitine Analysis (can be derivatized or non -derivatized)
  - 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

YES

Data provided demonstrates that methods have acceptable analytic validity

Key Question #5

Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

- The Biomarkers for GAMT Deficiency are multiplexed with the existing test for Aminoacid /Acylcarnitine analysis
  - NOTE: NBS programs using FDA approved tests would need to modify the test and perform full analytical validation before use
- Second-tier tests are available to reduce false positives
- No known FALSE NEGATIVES have been described
  - All 4 programs have indicated that they would be made aware if cases were identified clinically
  - Given the non-specific clinical features, what is the level of certainty that programs will be made aware of possible missed cases?

Key Question #5

Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

UNCLEAR

		First Routine Testing		Second Routine Testing			
	Number Tested	GUAC (umol/L)	CRE (umol/L)	GUAC (umol/L)	CRE (umol/L)	Screen Positive	True Positive
UTAH Derivatized NBS Testing	195,425	1.21 +/- 0.35	313 +/- 70	1.18 +/- 0.50	162 +/- 47	2	0
UTAH Non-derivatized NBS Testing	78,477	1.33 +/- 0.66	453 +/- 115	1.12+/- 0.54	231 +/- 83	1	1
NEW YORK Derivatized NBS Testing	537,408	1.34 +/- 0.57	569 +/- 155	N/A	N/A	23	1

- Screening characteristics are largely similar to current newborn screening tests
- NOTE: FALSE POSITIVE Cases in New York seem to be higher than we might expect
  - Presence of an interferent?

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Key Question #5

Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

New York Update

- Due to the high number of screen positives and referrals, method modifications were made to eliminate the interferent seen in the first -tier test

	INITIAL METHOD		REVISED METHOD	
Analyte	Precursor (m/z)	Product (m/z)	Precursor (m/z)	Product (m/z)
GUAC	174.1	101.1	174.1	73.1
GUAC_IS	176.1	103.1	176.1	75.1
Creatine	188.1	90.1	188.1	90.1
Creatine_IS	191.1	93.1	191.1	93.1

- The modification was evaluated and the revised method was validated
- The Revised Method was implemented into routine testing in 2020

- Summarized below are the screen positive samples for the same time period in 2019 (Original Method) and 2020 (Revised Method)
  - Performance from Days 065 to 245 are shown

	Original Method 2019	Revised Method 2020
TOTAL # samples screened	128656	123707
# Samples requiring 2nd tier HPLC analysis	1821	35
# Samples requiring DNA analysis	7	1
# Samples needing REPEAT analysis	136	17
# Samples sent for REFERRAL	7	1

- The modification demonstrates reduction in follow up testing and referrals
- Second-tier test may not be needed

Key Question #6

Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?

YES

The Following Laboratories have confirmatory tests for GAMT Deficiency

- ARUP Laboratories
- Baylor
- Duke
- Greenwood
- Kennedy Krieger
- Mayo Clinic
- Medical Neurogenetics
- University of Alabama Birmingham
- Yale University

Key Question #7

Are there defined treatment protocols, FDA approved drugs (if applicable) and is the treatment(s) available?

YES

- 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

- 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)

Thoughts for Discussion

- Generally considered that metabolic specialists will manage patients with GAMT deficiency in a similar manner to other metabolic patients

- Any special considerations of access to “Metabolic Foods” ?

Key Question #8

Do the results have *clinical utility*?

If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring
Molecular Genetics and Metabolism 111 (2014) 165
Sylvia Stockler-Ipsiroglu, Clara van Karnebeek, Nicola Longo, G. Christoph Korenke, Saadet Mercimek-Mahmutoglu, Iris Marquart, Bruce Barshop, et. al.

Evidence-Based Treatment of Guanidinoacetate Methyltransferase (GAMT) Deficiency
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Krista S. Viau, Sharon L. Ernst, Marzia Pasquali, Lorenzo D. Botto, Gary Hedlund, Nicola Longo

Presymptomatic treatment of neonatal guanidinoacetate methyltransferase deficiency
Neurology 67 (2006) 719–721
A. Schulze, G. F. Hoffmann, P. Bachert, et al.

Several reports document clinical improvement after treatment in patients with GAMT Deficiency

There are promising reports that describe the benefit of pre-symptomatic treatment of diagnosed patients

- **Eg younger siblings identified through index patient**

Table 1
Clinical characteristics, treatment modalities and outcomes in 48 patients with GAMT deficiency.

Patient # (ref)	Family #	Gender	Mutation	At treatment onset				Treatment modality	Treatment duration	Outcome/improvement on treatment
				Age	DD/ID degree	DD/ID plus	Basal ganglia changes			
1 (24)	1 (sibling P5)	f	c.327G>A/c.522G>A	Prenatal	Normal (nf)		nd	cr, orn-hd, diet-lp	41 mo	Normal (nf)
2 (28)	2 (sibling P25)	m	c.299_c.311 dup13/c.233T>A	1 week	Normal (nf)		nd	cr, orn-hd, diet-lp, benz	14 mo	Normal (nf)
3 (15, 24)	3 (sibling P17)	f	c.152A>C/c.526dupG	3 weeks	Normal (nf)		n	cr[3]orn-hd", diet-ar2 diet-pm, benz" " interrupted treatment	7 y	Normal 31 mo (f) boderline 8 y (f)
4	4 (sibling P27)	f	327G>A	9 mo	Borderline (nf)		n	cr, orn-hd, diet-ar" ", diet-lp, benz	21 mo	dd (dd,s)
5 (2)	1 (index sibling P1)	m	c.327G>A/c.522G>A	10 mo	Mild (nf)	e	y	cr, orn-hd, diet-lp	39 mo	dd,e
6 (28)	5	m	c.327G>A/c.522G>A	11 mo	Moderate (nf)	e	y	cr, orn-hd, diet-lp, benz	48 mo	dd (dd,s),e
7	6	f	Not determined	14 mo	Mild (f)	e	y	cr, orn-hd, SAM	7 y 4 mo	dd
8 (28)	7	f	c.327G>A/c.403G>A	15 mo	Severe (nf)	e	y	cr, orn-hd, diet-lp	8 y 6 mo	dd (dd,b),e
9 (2)	8	m	c.327G>A/c.36_c.37ins26	16 mo	Moderate (nf)	e	y	cr, orn-ld, diet-lp	36 mo	dd (dd,s),e
10	9	m	c.327G>A	17 mo	Moderate (nf)	m	y	cr	6 y 6 mo	dd (dd,s,b),m
11 (16)	10	m	c.503A>C	19 mo	Mild (f)		n	cr, orn-ld	36 mo	dd (dd,s)
12 (1, 18)	11 (sibling P19)	f	c.327G>A/c.48C>A	21 mo	Mild (nf)	m, e	y	cr, orn-hd	6 y 7 mo	m,e
13 (14)	12	f	c.327G>A	21 mo	Moderate (f)		n	cr, orn-hd, diet-ar	39 mo	dd (dd,s,b)
14 (3)	13	m	c.327G>A/c.309dup13	22 mo	Severe (nf)	m, ee	y	cr, orn-hd" " "	16 y	e,m
15 (17)	14	f	c.327G>A/c.522G>A	24 mo	Severe (nf)	m, e	y	cr, orn-hd, diet-ar	10 y	dd,e,m
16	15	m	c.526dupG	24 mo	Moderate (nf)		n	cr	44 mo	dd
17 (1, 18)	3 (index sibling P3)	m	c.152A>C/c.526dupG	30 mo	Mild (f)	e	n	cr", orn-hd", diet-ar" ", benz" later diet-pm	10 y	dd (dd,s),e
18 (1)	16	m	Not reported	36 mo	Severe (nf)	ee	n	cr, orn-hd	36 mo	dd (dd,s,b), e
19	11 (index sibling P12)	m	c.327G>A/c.48C>A	38 mo	Moderate (nf)		y	cr,orn-hd	6 y 7 mo	dd
20 (19)	17	m	c.491insG/IVS5-3C>G	39 mo	Severe (nf)	m, e	y	cr, orn-ld" ", orn-hd, diet-lp" ", diet-ar	11 y	dd, e,m
21	18	f	c.327G>A	39 mo	Severe (nf)	m, ee	y	cr	48 mo	dd (b)
22 (21, 22)	19	m	c.497T>C	44 mo	Mild (tbq = 55) (f)		n	cr, orn-hd	7 y 4 mo	dd (dd,s,b) (IQ = 90)
23	20	m	c.506G>A	48 mo	Mild (f)		n	cr, orn-hd	3 y 9 mo	dd (s)
24	21	m	c.327G>A/c.133T>A	4 y 6 mo	Severe (nf)	m, e	n	cr, orn-hd	20 mo	dd (dd,b), e,m
25 (28)	2 (index sibling P2)	f	c.299_c.311dup13/c.233T>A	5 y 6 mo	Moderate (nf)	e	n	cr, orn-hd, diet-lp	30 mo	dd (dd,s,b),e
26	22	m	c.522G>A/c.505T>C	5 y 7 mo	Severe (nf)	ee	y	cr, orn-hd, diet-lp	30 mo	Stable
27	4 (index sibling P4)	m	c.327G>A	5 y 9 mo	Moderate (nf)	e	n	cr, orn-hd, diet-ar" ", diet lp, benz	21 mo	dd (b)
28	23 (sibling P37)	f	Not reported	6 y 9 m0	Mild	ee	nd	cr, orn-ld, diet-lp	26 mo	dd(b), e
29 (23)	24 (cousin P47, P48)	m	c.59G>C	8 y	Severe (nf)	m, e	nd	cr, orn-ld" " ", diet-pm	7 y	dd, m
30	25	f	c.327G>A	8 y 6 mo	Severe (f)	ee	n	cr, orn-hd, diet-ar	48 mo	dd (dd,s,b), e
31	26	f	c.327G>A	9 y 3 mo	Moderate (nf)	e	y	cr	36 mo	Stable
32 (20)	27	f	c.590T>C	10 y	Severe (f)	e	n	cr, orn-hd, diet-ar 5 y then diet-lp	7 y	dd,e
33	28	m	c.327G>A	11 y	Severe (nf)	ee	y	cr	48 mo	dd (b),e
34	29	f	Not determined	11 y	Severe (nf)		n	cr	12 mo	Stable
35	30	m	Not reported	12 y	Severe (nf)	ee	n	cr, orn-hd, diet-lp" " "	8 y	id (s,b),e
36	31	f	c.59G>C/c.521G>A	13 y	Severe (f)		nd	cr, orn-ld" ", diet-lp" "	6 y	dd
37	23 (index sibling P28)	m	Not reported	13 y 9 mo	Moderate	ee	nd	cr, orn-ld, diet-lp	26 mo	dd(s), e
38	32	m	c.289C>T	14 y	Severe (nf)	ee	n	cr, orn-hd, diet-lp	4 y	id (b),e
39 (1)	33 (sibling P42)	m	c.59G>C	16 y	Severe (f)	m, e	y	cr	9 y	e
40	34	f	Not reported	18 y	Severe (nf)	ee	n	cr, orn-hd, diet-lp" " "	8 y	id (s,b),e
41 (23)	35	f	c.506G>A	19 y	Severe (nf)	m, e	nd	no treatment	0	nd
42 (1)	33 (sibling 39)	m	c.59G>C	20 y	Severe (f)	e	y	cr	9 y	e
43 (1)	36 (sibling P45)	m	c.59G>C	20 y	Severe (f)	e	y	cr	9 y	e
44	37	f	c.327G>A	21 y	Severe (nf)	m, ee	n	cr, orn-hd	11 mo	dd (b), e
45 (1)	36 (sibling P43)	m	c.59G>C	22 y	Severe (f)	e	nd	cr	9 y	e
46	38	m	c.327G>A	25 y	Moderate (nf)		n	No treatment	0	nd
47 (23)	24 (sibling P46)	f	c.59G>C	31 y	Severe (nf)	m, e	nd	cr, diet-pm	5 y	m
48 (23)	2 (index sibling P45)	f	c.59G>C	34 y	Severe (nf)	m, e	nd	cr, diet-pm	5 y	Stable

b: behavior; benz: sodium benzoate (100 mg/kg/d); cr: creatine-monohydrate (300–800 mg/kg); dd/id: developmental delay/intellectual disability; diet-ar: arginine-restricted diet (below DRI needing amino acid supplements); diet-lp: diet low protein (meeting DRI without amino acid formula); diet-pm: protein modified diet avoiding protein rich foods such as meat and milk products, no counting of protein intake); e: mild epilepsy; ee: severe epilepsy; (f): formal assessment; m: movement disorder; mo: months; n: no; nd: not determined; (nf): no formal assessment; orn-hd: L-ornithine high dose (>200–800 mg/kg); orn-ld: L-ornithine low dose (100–200 mg/kg/); P: patient; (ref): reference; s: speech; SAM: S-Adenosyl-L-Methionine; y: yes; y: years; [1]: therapy transiently discontinued; [2]: therapy permanently discontinued; [3]: therapy transiently performed.

- **48 patients from 38 families with known GAMT deficiency**
  - Includes younger siblings identified as a result of an index patient
- **Clinical Presentation at treatment onset:**
  - Developmental delay and Intellectual disability varied in degree of severity
  - Variable expression of other clinical features eg epilepsy, movement disorder and basal ganglia involvement
- **3 patients treated within 1 month of birth**
  - Appeared normal before treatment
  - Appeared normal after treatment regimen
- **Treatment onset for remaining patients was variable**
  - Clinical improvement was achieved in the majority of patients
  - General improvements noted in:
    - DD/ID ie behavior, language and self-supportive skills for 'activities of daily life'
    - Epilepsy and movement disorder

Reference:
Guanidinoacetate methyltransferase (GAMT) deficiency: Outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring .
Molecular Genetics and Metabolism 111 (2014) 125
Sylvia Stockler-Ipsiroglu, Clara van Karnebeek, Nicola Longo, G. Christoph Korenke, Saadet Mercimek-Mahmutoglu , Iris Marquart, Bruce Barshop, et al

Key Question #8

Do the results have *clinical utility*?

If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

YES

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Molecular Genetics and Metabolism 111 (2014) 1–25
Sylvia Stockler-Ipsiroglu, Clara van Karnebeek, Nicola Longo, G. Christoph Korenke, Saadet Mercimek-Mahmutoglu, Iris Marquart, Bruce Barshop, et. al.

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Several reports document improvement after treatment in patients with GAMT Deficiency

There are promising reports that describe the benefit of pre-symptomatic treatment of diagnosed patients

- **Eg younger siblings identified through index patient**

❑ POINT: Based on current information, the combination of early testing to identify at -risk newborns and pre -symptomatic intervention are likely to improve health outcomes

Key Questions - *SUMMARY*

YES	1.	Is the nominated condition(s) ***medically serious***?
YES	2.	Is the ***case definition*** and the spectrum of the condition(s) well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
YES	3.	Are ***prospective pilot data*** from population-based assessments available for this disorder?
YES	4.	Does the screening test(s) have established ***analytic validity***?
UNCLEAR	5.	Are the ***characteristics of the screening test(s)*** reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
YES	6.	Is there a widely available and CLIA and/or FDA approved ***confirmatory test/diagnostic*** process?
YES	7.	Are there defined ***treatment*** protocols, FDA approved drugs (if applicable) and is the treatment(s) available?
YES	8.	Do the results have ***clinical utility***? If the spectrum of disease is broad, will the screening and/or diagnostic test identify who is most likely to benefit from treatment, especially if treatment is onerous or risky?

Nomination and Prioritization Workgroup Recommendation

The Advisory Committee
should
move the nomination of
GAMT Deficiency
forward for a full evidence
review.

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