Recommendations to the ACHDNC for Newborn Screening of Guanidinoacetate Methyltransferase (GAMT) deficiency

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ACHDNC Meeting

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Decision Matrix

- Understanding the level of certainty of net benefits of newborn screening for identification of infants affected by GAMT in the population

- Feasibility of newborn screening for GAMT

- States' readiness to implement newborn screening for GAMT

Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (RUSP)

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			---	
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			---	
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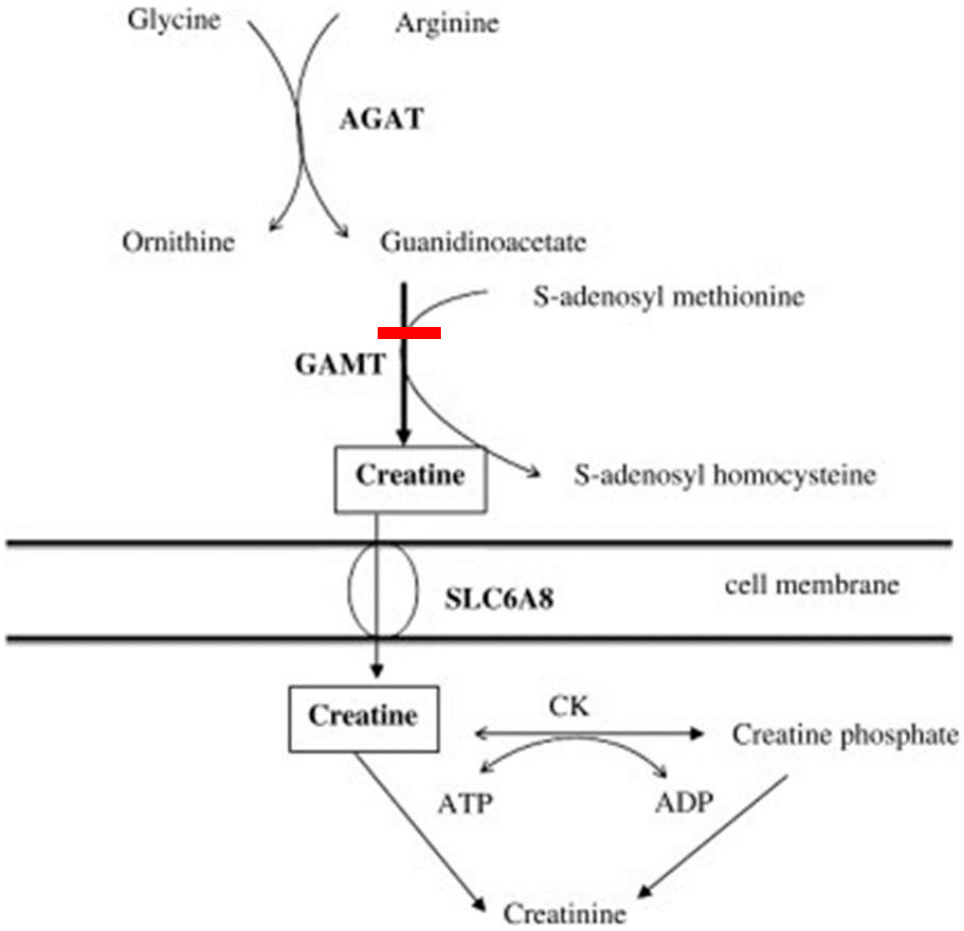
Guanidinoacetate Methyltransferase (GAMT) deficiency

Characterization and epidemiology

- Autosomal recessive disorder of creatine biosynthesis
- One of three disorders of cerebral creatine deficiency
  - Cerebral creatine transporter (X-linked) is most common
  - AGAT deficiency is rare - no available birth prevalence
- Neurological deterioration begins in early infancy
  - Decreased CNS creatine
  - Accumulation of guanidinoacetate (GUAC)
- Several more common DNA variants, but most rare or novel
- Birth prevalence based on newborn screening estimates (NY and UT) -- 0.2/100,000
  - Range 0.02—0.6/100,000



Guanidinoacetate Methyltransferase (GAMT) deficiency

Findings and symptoms

- Clinical symptom onset occurs after 3-6 months of age to 2 years
  - Clinical diagnosis often delayed -- ranges from the neonatal period to adulthood
- Poor neurocognitive outcomes
- Findings can be nonspecific
  - Intellectual and developmental disability
  - Poor speech
  - Behavior issues (social anxiety, aggression, self-injury, autism, hyperactivity)
  - Seizures (various types)
  - Hypotonia
  - Ataxia
  - Spasticity/involuntary movements/movement disorder (chorea, athetosis, dystonia)
  - MRI hyperintensities in globus pallidus
- Life expectancy may be limited due to complications (e.g., epilepsy), but not clear that the underlying disease process limits lifespan

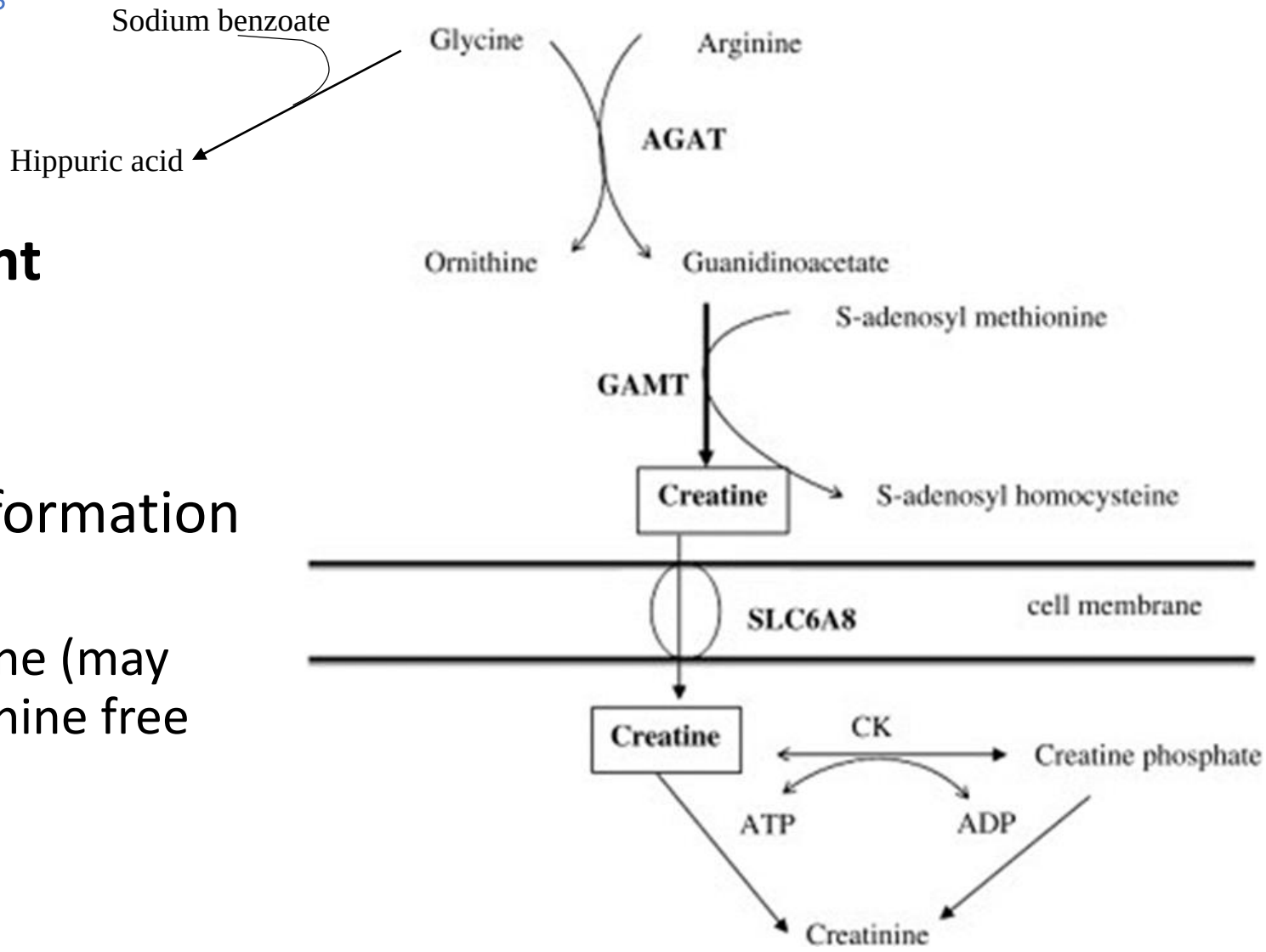
Guanidinoacetate Methyltransferase (GAMT) deficiency

Screening and Diagnosis

- **Screening currently uses Laboratory Developed Tests (LDT)**
  - Population based in Utah and New York in the US, BC in Canada, Victoria in Australia
  - UT & NY both currently using:
    - MS/MS method used to measure GUAC and GUAC:creatine ratio
      - UT underivatized; NY derivatized
    - 2nd tier test initially, now not necessary
    - Above range GUAC and GUAC:creatine defines positive screen
- **Method development and validation may vary from state to state**
  - No FDA approved kit currently available
- **Confirming diagnosis**
  - Quantitative measurement of GUAC and creatine in plasma clinically available
  - CNS creatine low (by MRS or CSF), GUAC increased
  - Sensitivity and specificity of metabolite testing thought to be high, but not documented
  - Urine only may lead to diagnostic error (missed cases - PMID: 28055022)
  - Genetic analysis can be supportive of the diagnosis, especially if metabolites not markedly abnormal
  - No definitive case definition available

Guanidinoacetate Methyltransferase (GAMT) deficiency

Treatment-no formal published guidelines



Metabolic treatment

- Increase CNS creatine
  - Oral creatine
- Reduce guanidinoacetate formation
  - Oral ornithine
  - Dietary restriction of arginine (may need supplement with arginine free formula)
  - Oral sodium benzoate

Guanidinoacetate Methyltransferase (GAMT) deficiency

Treatment-no formal published guidelines

- Care team based on developmental and health needs
  - Dietician familiar with management of protein restricted diet
- Monitoring
  - Neurodevelopmental evaluation, institution of behavioral therapies and services (PT/OT/Speech)
  - Periodic GUAC, creatine and PAA, kidney screening for creatine nephropathy
  - Neurological evaluation for seizures (EEG) and movement abnormalities
  - ^{1}H-MRS (proton magnetic resonance spectroscopy) to be obtained to monitor brain creatine levels for neurological symptoms?
- Investigational therapies
  - Gene therapy in an animal model (2022)

Benefit to affected infants/children

- Limited literature available
- **All older siblings** had developmental issues (mild -- severe)
- Case reports of 8 younger siblings (including 1 case wo older sib) all treated before 6 months of age
  - Normal development in 7 of 8 cases
  - 1 infant treated at 8 DOL has hypotonia and developmental delays later in first year of life
    - Older sibling dx at 6 y; Treatment associated with improvements in tone, autistic symptoms and motor skills,
      - Also has delayed myelination, small corpus callosum on MRI – not typical of GAMT def
    - Both sibs homozygous for the most common variant
      - Could there be other factors contributing to outcome?

Benefit to affected infants/children

Reasonable assertions based on limited data

- Presymptomatic therapy most often associated with normal neurological development
- Treatment is likely associated with better neurological outcomes, cognitive development and function
  - This should correlate with improved QOL (no data)
- Earlier initiation of treatment likely maximizes benefits of therapy

Potential Harms

- Potential harms of the NBS process
  - False positive – low concern due to reliable confirmatory testing
  - Indeterminate results are rare
  - Potential for lost to follow up - none reported by UT and NY
  - Cost and burden of confirmatory testing- may be lower than other conditions on the RUSP
- False negative – none reported yet
- Limitations that there is no clear case definition

Annual Projected Outcomes for Newborn Screening for GAMT in the U.S.

- Projected estimates for annual population-based results based on data from two existing state screening programs (UT & NY)
  - Based on 3.6 million births annually in US
- ~1 in 13 infants with a positive screen will be diagnosed with GAMT
- ~1 in 9 infants with a positive screen will die before a definitive diagnosis can be made (preemies)
- It is possible, but not yet described, that a defect in the urea cycle could be identified (this would a desirable secondary outcome)

	Newborn Screening	Clinical Identification
Positive screen	93 (62 - 135)	-
GAMT identified	7 (1 - 22)	2 - 18
False positive	77 (59 - 88)	-
Lost to follow-up	0 (0 - 12)	-
Other*	10 (2 - 26)	-

Source of data – Utah and New York Newborn Screening Data

* Includes diagnosis of non-targeted conditions and unknown determination due to death before confirmatory testing

Net Benefit is the balance of benefit and harm in the population screened

Getty Image

Net Benefit is the balance of benefit and harm in the population screened

Benefit and Harm accrue to different individuals in the population.

Is there any reason to think that different groups will be affected differently by benefits or harms? (no particular reason to think so for this condition)

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Is there significant net benefit for compulsory, population NBS?

- Limited evidence suggests significant benefit of pre-symptomatic therapy
- Extremely low risk of harm from treating patients that will not benefit from treatment
- Relatively low risk of potential harm to families with indeterminate status

High Certainty of **significant** benefit (A)

OR

Moderate Certainty of **significant** benefit (B)

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Newborn screening for GAMT deficiency

Feasibility and Readiness

- Newborn screening tests are available and appropriate for high-throughput testing
- States may struggle with adding screening within a reasonable period (1-3 years) due to challenges in method development and validating assay
- Clear case definition needed
- Proportion of true positive to all positive NBS results in the range of other conditions on the RUSP
- Screening costs are in line with other recent additions – may be less depending on method and equipment available in lab
- Follow up resources thought to be mostly adequate for demand

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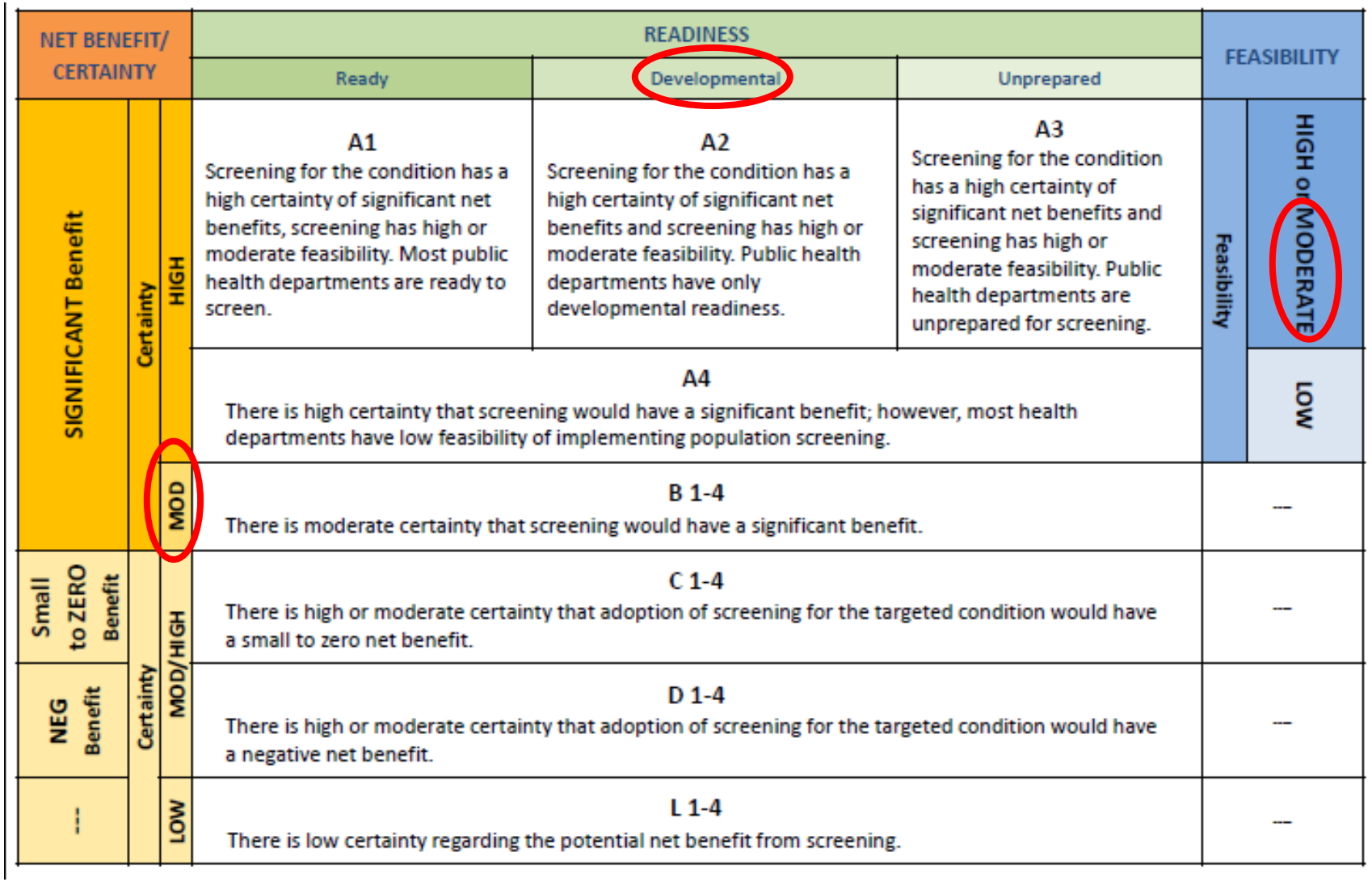

NET BENEFIT/ CERTAINTY			READINESS: Ready	READINESS: Developmental	READINESS: Unprepared	FEASIBILITY: Feasibility HIGH or MODERATE	FEASIBILITY: Feasibility LOW
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Newborn Screening for GAMT deficiency
Recommendation to the ACHDNC

- Newborn Screening for GAMT meets criteria for matrix category B2
- Developmental readiness for newborn screening programs to enact screening for GAMT
- Most states could add this to MS/MS approaches, but lack of FDA approved kit increases cost and time to implement
  - Addition to RUSP may facilitate adding GUAC/Creatine to kits

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RECOMMENDATION

GAMT deficiency should be added to the RUSP as a core condition