NOMINATION AND PRIORITIZATION WORKGROUP

REPORT #2

UPDATE ON NEWBORN SCREENING FOR GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY

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ACHDNC MEETING
NOVEMBER 3, 2016

OUTLINE OF PRESENTATION

- Brief review of initial summary and recommendation by ACHDNC at previous meeting
- Introduction and summary of new information
- Analysis of the Nomination and Prioritization Workgroup's review of this information to determine if that changes the previous recommendation

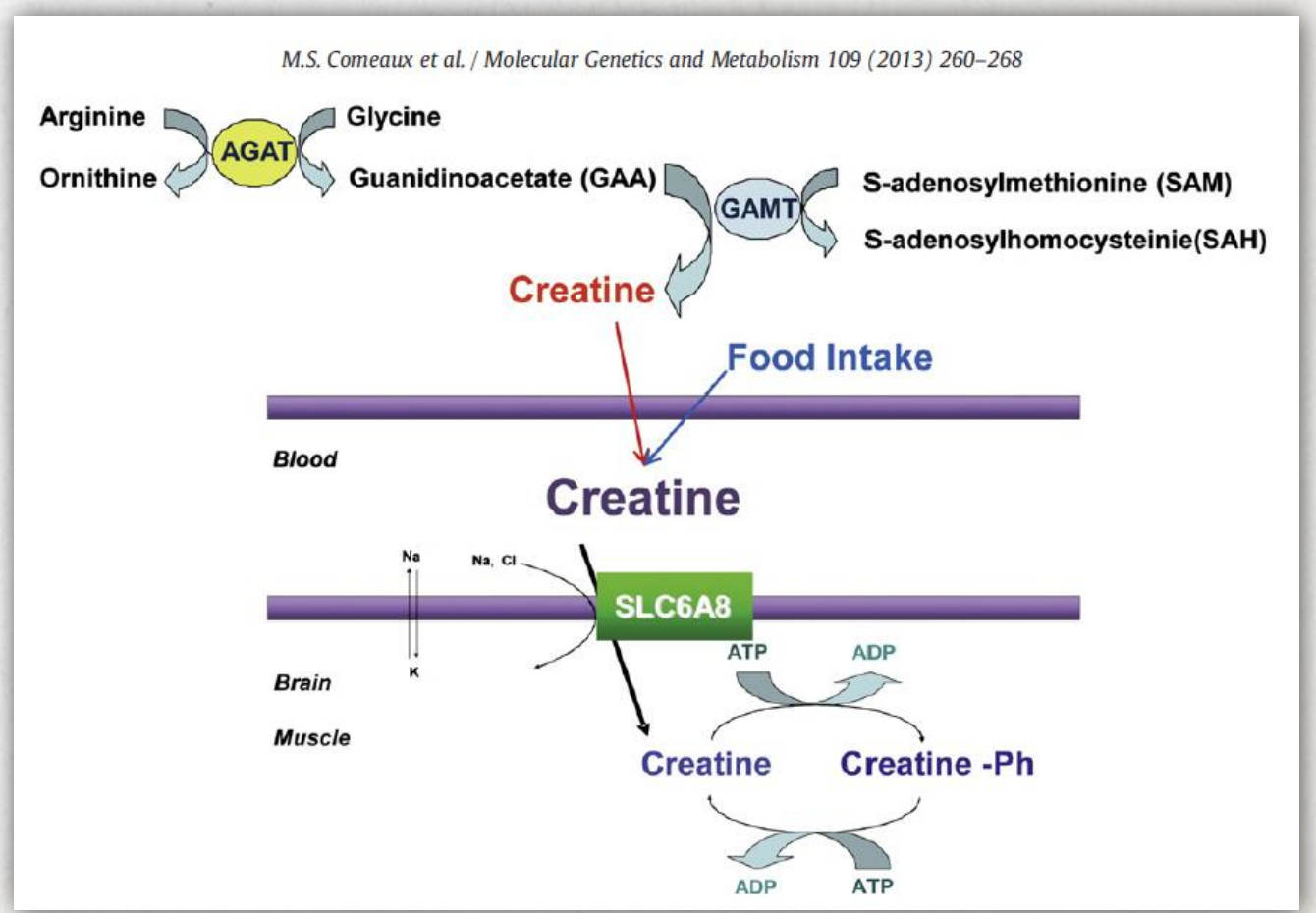
REVIEW OF INITIAL SUMMARY

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)

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

- 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)

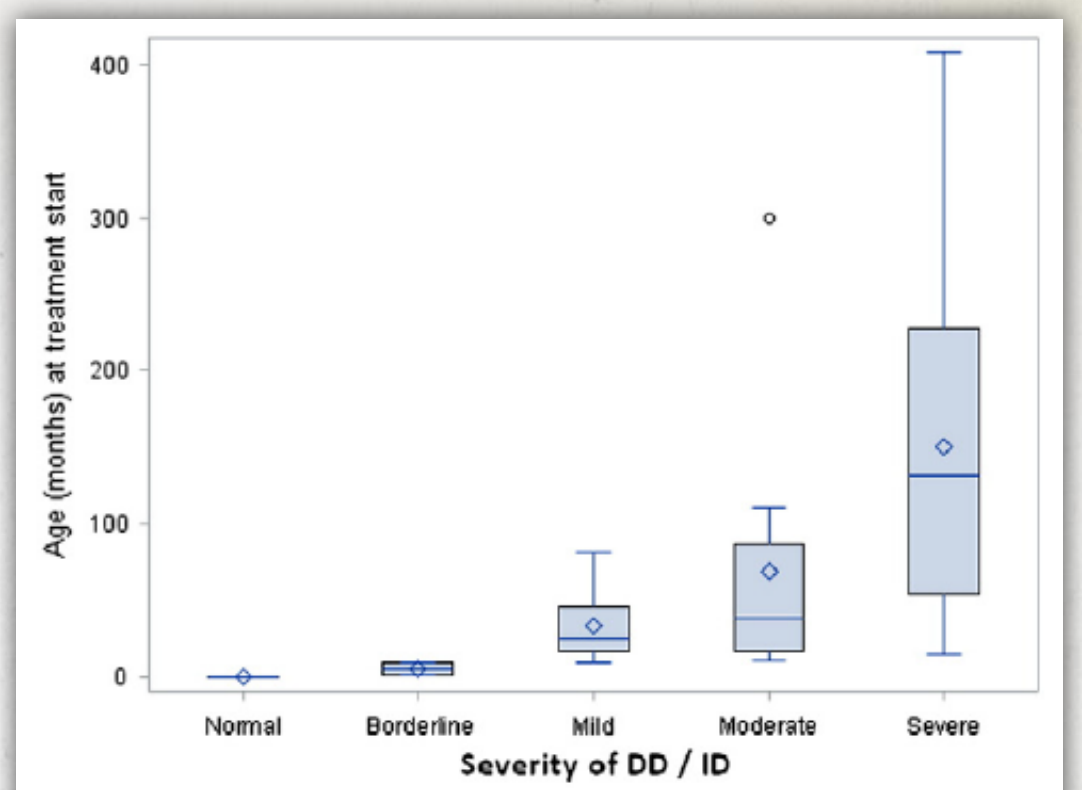


Fig. 1. Mean ages at diagnosis/treatment onset and severity of developmental delay/intellectual disability (DD/ID) in 48 patients with GAMT deficiency. (a) normal development (n = 2): min age = 0 months (treatment started prenatally), max age = 0.23 months (1 week); 25th, 50th, 75th percentile = 0, 0.12, 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.

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

STATUS OF NBS FOR GAMT DEFICIENCY

- University of Utah[1]
  - Retrospective study of 10,000 NBS samples:
    - False positive rate (FPR): 0.08% (GAA + GAA/Creatine)
    - FPR with 2nd tier test: 0%
    - True positive: 0

- Baylor Research Institute (Texas)[2]
  - Prospective study of 19,293 NBS samples (ca. 50% from Mexico) between 2008-2011:
    - FPR: 0.5% (GAA)
    - FPR with 2nd tier test: 0%
    - True positive: 0

[1]Pasquali M et al. J Inherit Metab Dis. 2014;37:231-6
[2]Mercimek-Mahmutoglu S et al. Mol Genet Metab. 2012;107:433-7

STATUS OF NBS FOR GAMT DEFICIENCY

- British Columbia (Canada)[2]
  - Retrospective study of 3,000 NBS samples:
    - FPR: 0.13% (GAA)
    - FPR with 2nd tier test: 0%
    - Also tested for 2 "common" mutations and happened to find 2 carriers of 2 novel mutations
    - True positive: 0

- Victoria (Australia)[3]
  - Prospective NBS since 2002 (~1 million babies)
    - GAA as marker; no 2nd 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.

[2]Mercimek-Mahmutoglu S et al. Mol Genet Metab. 2012;107:433-7
[3]Pitt JJ et al. Mol Genet Metab. 2014;111:303-4

STATUS OF NBS FOR GAMT DEFICIENCY

- The Netherlands[4]
  - 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[4]:**

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

[4]Mercimek-Mahmutoglu S et al. Gene. 2016 1;575:127-31

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 implemented.
- 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.

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
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.

SUMMARY OF NEW INFORMATION

NEW INFORMATION

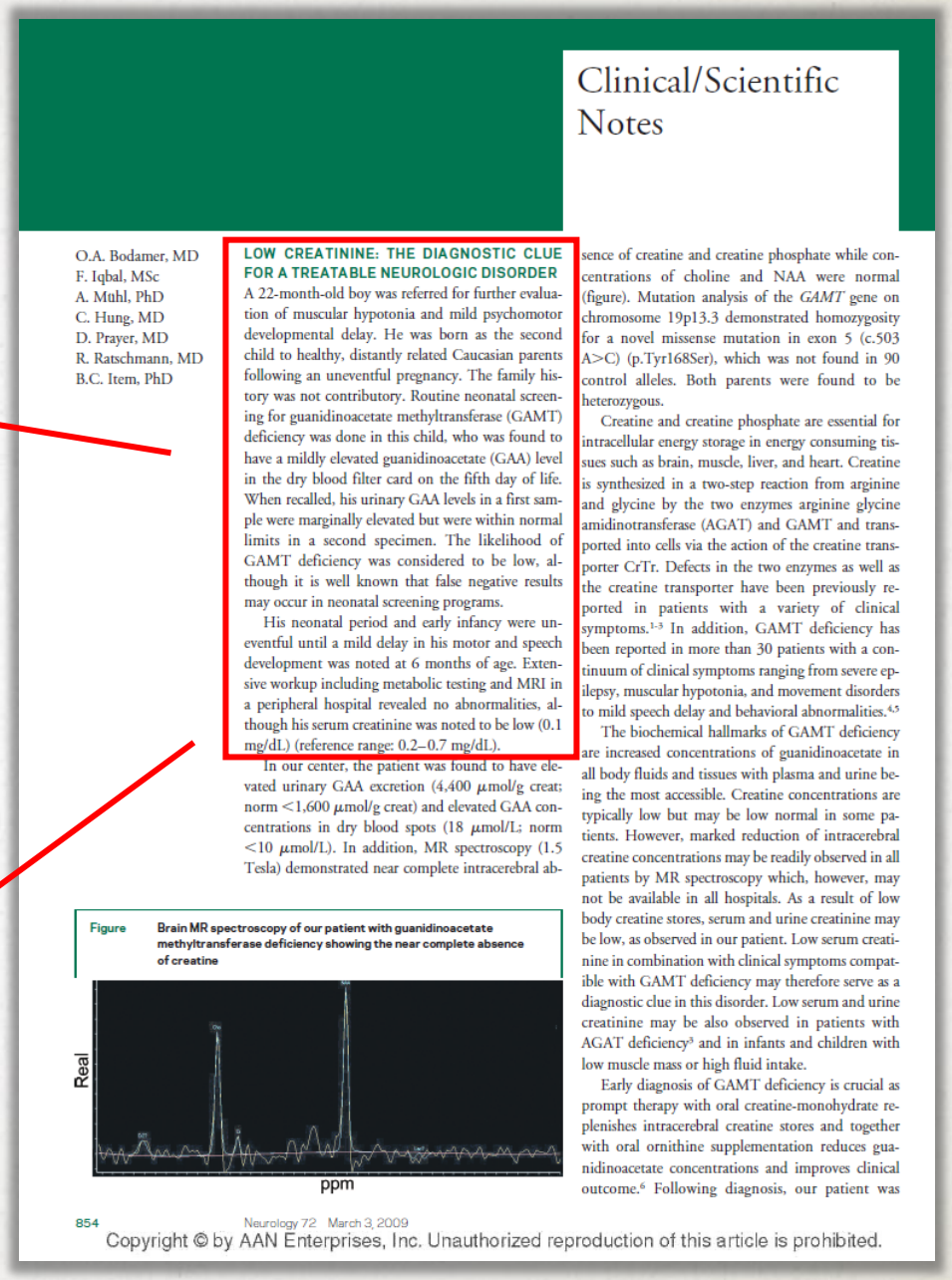
Case description by Bodamer et al

Neurology 72 ; 2009

LOW CREATININE: THE DIAGNOSTIC CLUE FOR A TREATABLE NEUROLOGIC DISORDER

A 22-month-old boy was referred for further evaluation of muscular hypotonia and mild psychomotor developmental delay. He was born as the second child to healthy, distantly related Caucasian parents following an uneventful pregnancy. The family history was not contributory. Routine neonatal screening for guanidinoacetate methyltransferase (GAMT) deficiency was done in this child, who was found to have a mildly elevated guanidinoacetate (GAA) level in the dry blood filter card on the fifth day of life. When recalled, his urinary GAA levels in a first sample were marginally elevated but were within normal limits in a second specimen. The likelihood of GAMT deficiency was considered to be low, although it is well known that false negative results may occur in neonatal screening programs.

His neonatal period and early infancy were uneventful until a mild delay in his motor and speech development was noted at 6 months of age. Extensive workup including metabolic testing and MRI in a peripheral hospital revealed no abnormalities, although his serum creatinine was noted to be low (0.1 mg/dL) (reference range: 0.2–0.7 mg/dL).



Clinical/Scientific Notes

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In our center, the patient was found to have elevated urinary GAA excretion (4,400 μmol/g creat; norm <1,600 μmol/g creat) and elevated GAA concentrations in dry blood spots (18 μmol/L; norm <10 μmol/L). In addition, MR spectroscopy (1.5 Tesla) demonstrated near complete intracerebral absence of creatine and creatine phosphate while concentrations of choline and NAA were normal (figure). Mutation analysis of the *GAMT* gene on chromosome 19p13.3 demonstrated homozygosity for a novel missense mutation in exon 5 (c.503 A>C) (p.Tyr168Ser), which was not found in 90 control alleles. Both parents were found to be heterozygous.

Figure Brain MR spectroscopy of our patient with guanidinoacetate methyltransferase deficiency showing the near complete absence of creatine

Creatine and creatine phosphate are essential for intracellular energy storage in energy consuming tissues such as brain, muscle, liver, and heart. Creatine is synthesized in a two-step reaction from arginine and glycine by the two enzymes arginine glycine amidinotransferase (AGAT) and GAMT and transported into cells via the action of the creatine transporter CrTr. Defects in the two enzymes as well as the creatine transporter have been previously reported in patients with a variety of clinical symptoms.[1-3] In addition, GAMT deficiency has been reported in more than 30 patients with a continuum of clinical symptoms ranging from severe epilepsy, muscular hypotonia, and movement disorders to mild speech delay and behavioral abnormalities.[4,5]

The biochemical hallmarks of GAMT deficiency are increased concentrations of guanidinoacetate in all body fluids and tissues with plasma and urine being the most accessible. Creatine concentrations are typically low but may be low normal in some patients. However, marked reduction of intracerebral creatine concentrations may be readily observed in all patients by MR spectroscopy which, however, may not be available in all hospitals. As a result of low body creatine stores, serum and urine creatinine may be low, as observed in our patient. Low serum creatinine in combination with clinical symptoms compatible with GAMT deficiency may therefore serve as a diagnostic clue in this disorder. Low serum and urine creatinine may be also observed in patients with AGAT deficiency[3] and in infants and children with low muscle mass or high fluid intake.

Early diagnosis of GAMT deficiency is crucial as prompt therapy with oral creatine-monohydrate replenishes intracerebral creatine stores and together with oral ornithine supplementation reduces guanidinoacetate concentrations and improves clinical outcome.[6] Following diagnosis, our patient was

REVIEW OF BODAMER PAPER

Case Summary: ***Evaluation by Newborn Screening Program***

- Newborn boy, born as second child to healthy, distantly related Caucasian parents
- Routine Newborn Screening for GAMT performed on 5th Day of life

- **NBS RESULT**:
  - Mild Elevation of guanidinoacetate (GAA)
- **Short Term Diagnostic Follow-up Testing**:
  - 1st urine sample: Urine GAA levels were ***marginally elevated***
  - Repeat urine sample: Urine GAA levels were ***in normal range***

REVIEW OF BODAMER PAPER

Case Summary: ***Beyond Newborn Screening***

NBS Program Outcome and Assessment

… Newborn low risk for GAMT deficiency

…It was inferred that the newborn was sent home and not subsequently followed

- Neonatal period and early infancy were uneventful

REVIEW OF BODAMER PAPER

Child became symptomatic and underwent clinical evaluation:

- At 6 months: Mild delay in motor and speech development
  - Clinical evaluation showed no abnormalities
    - Metabolic testing and MRI
    - Low serum creatinine was noted (0.1 mg/dL … ref range: 0.2 – 0.7)

- It is not clear whether or not any connection was made at this point to the newborn screening result

REVIEW OF BODAMER PAPER

Child became symptomatic and underwent clinical evaluation:

- At 22 months: Additional clinical workup at Specialty Center
  - Elevated urine GAA excretion (4,400 umol/g creatinine … ref range <1.600)
  - Elevated DBS GAA levels (18 umol/L ….. ref range < 10)
  - MR Spectroscopy
    - Near complete intracerebral absence of creatine and creatine phosphate
    - Normal levels of choline and N-acetylaspartate (NAA)
  - Mutation analysis of GAMT gene (chromosome 19p13.3)
    - Homozygous for novel missense mutation in Exon 5 (.c503 A>C) (p.Tyr168Ser)
    - Both parents were heterozygous for mutation
- GAMT deficiency was confirmed

NOMINATION AND PRIORITIZATION WORKGROUP

ANALYSIS AND RECOMMENDATION

NOMINATION & PRIORITIZATION WORKGROUP
REVIEW OF BODAMER PAPER

- Emphasis of workgroup discussion was whether this case satisfied the criteria for a case picked up by newborn screening

Guidance from Pilot Study Recommendation 3A

(as voted on during the Aug meeting)

The study should evaluate the newborn screening process from collection through diagnosis and identify at least one screen positive newborn with confirmation of presence of the condition under consideration.

DOES THIS CASE SATISFY CRITERIA:

Evaluate the newborn screening process from collection through diagnosis and identify at least one screen positive newborn

YES

- NSB was positive or borderline (no cutoff data was provided)
- Initial symptoms appeared at 6 months
- GAMT diagnosis was made at 22 months

NO

- Diagnostic assessment following NBS indicated that the "likelihood of GAMT deficiency was low"
- Newborn was sent home with uneventful neonatal period and early infancy and was only brought to medical attention after experiencing clinical symptoms
- NBS system which includes screen and diagnostic work-up ***failed the child*** and this case should be considered a ***"False Negative" for the NBS system***

N&P WORKGROUP ANALYSIS

- Despite the positive NBS, the follow-up and diagnosis failed for this child, resulting in permanent damage
- Since NBS is considered a system, this is not a clean representation of pickup and diagnosis by the NBS system
- Concern about trying to make this case "fit"
  - E.g. Another diagnostic test should have been used
  - E.g. This algorithm is outdated and an alternate diagnostic algorithm would have identified the case
- This case does not seem to be consistent with Recommendation 3a:
  - … "evaluate the newborn screening process from collection through diagnosis and identify at least one screen positive newborn" …

N&P WORKGROUP RECOMMENDATION

- Not recommend GAMT be referred to full evidence review at this time.
- Case does not meet the criteria of a single clear case detected by the NBS system.
- Australian study has still not detected a single case in 1 million screens, nor have any of the other studies detected a true positive.
- More detailed data on the NBS cutoff is needed and how it was arrived at would be helpful and further exploration of the low and negative urine results is needed.
- We continue to recommend all the current studies notify ACHDNC immediately when a true case is detected, diagnosed, and initiated treatment in time to improve outcome.