a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA

A 3-year pilot study for Guanidinoacetate Methyltransferase (GAMT) deficiency in British Columbia

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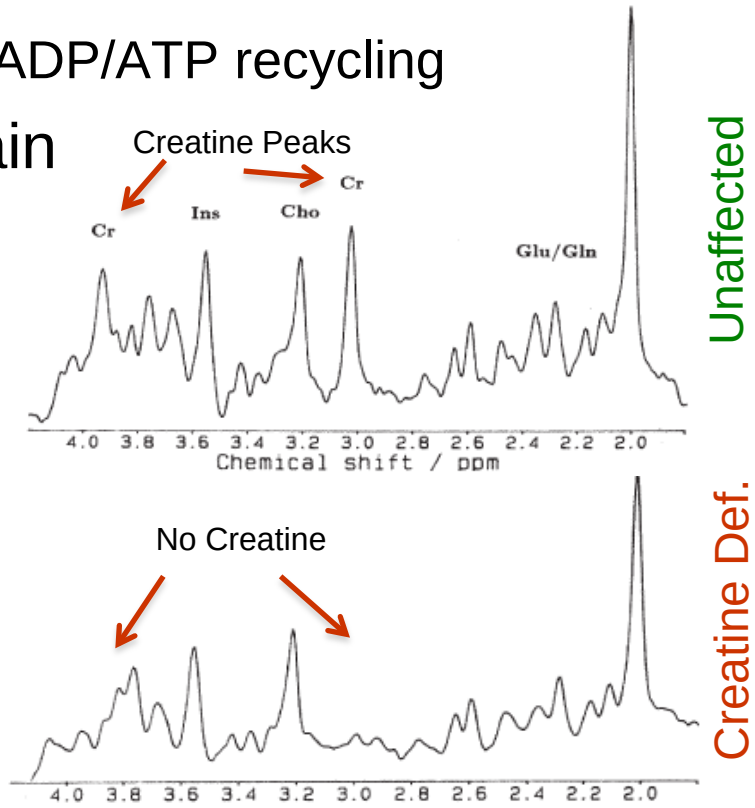
BC CHILDREN'S HOSPITAL
An agency of the Provincial Health Services Authority

Conflicts of interest

- None

Cerebral Creatine Deficiency

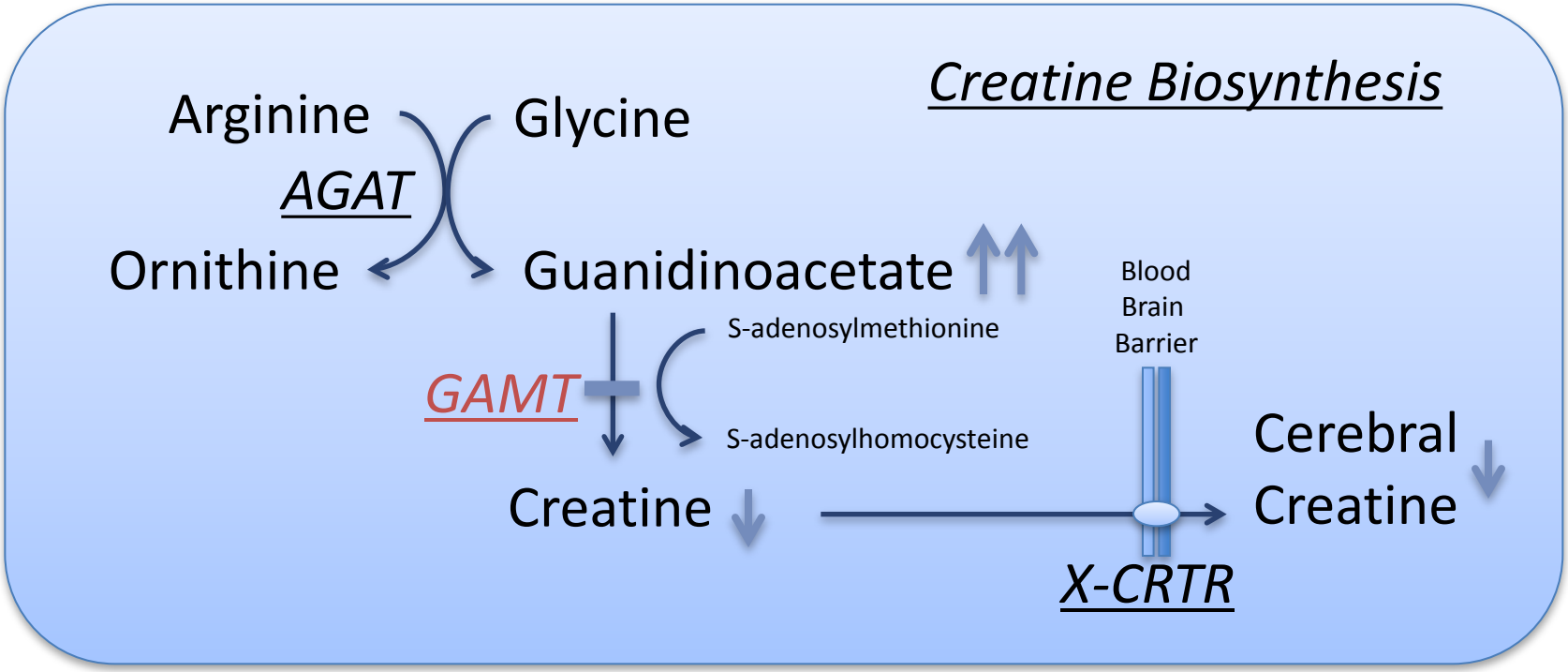
- Creatine from systemic biosynthesis and diet
- Creatine-P is a key energy source
  - Local immediate energy reserve for ADP/ATP recycling
- Little creatine synthesis in the brain
- Cerebral creatine deficiency
  - Developmental delay
  - Autistic features
  - Seizures
  - Movement disorder



Sykut-Cegielska et al (2004) Acta Biochimica Polonica 51(4):875-882

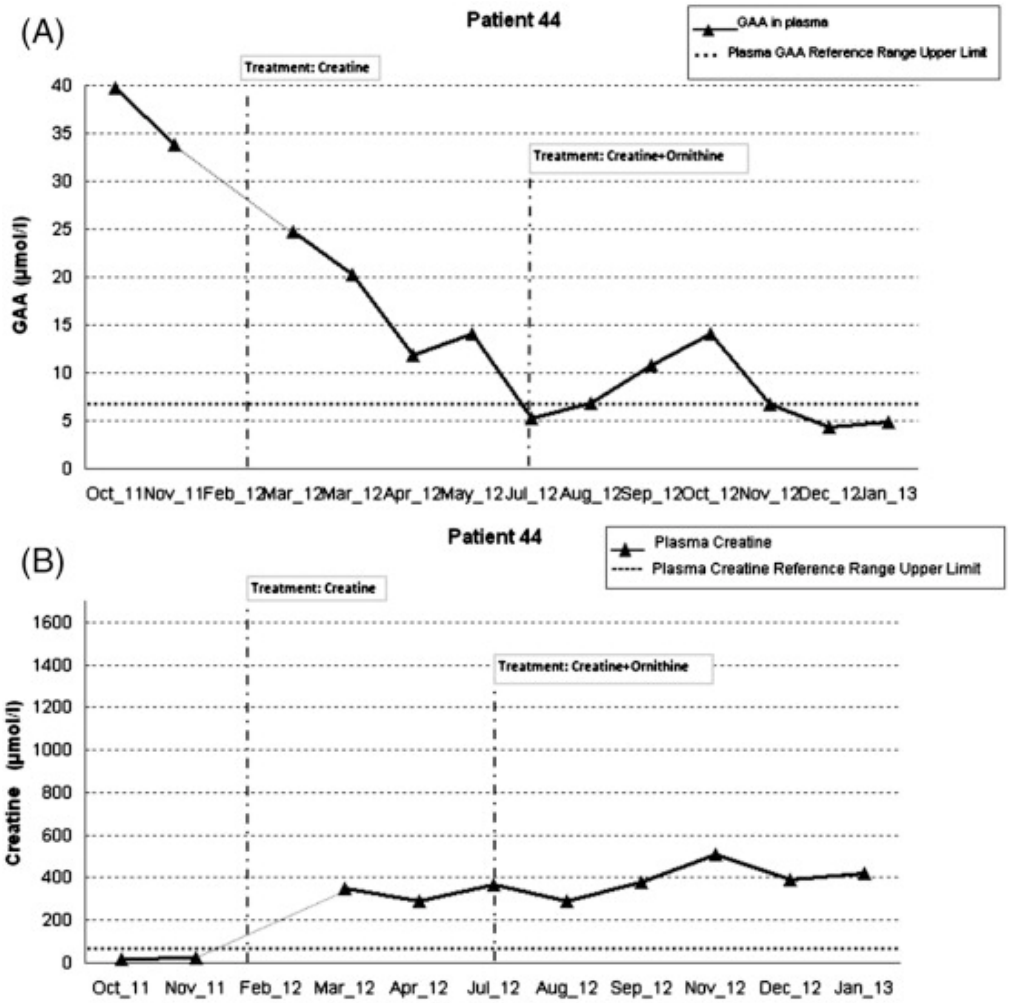
Creatine Disorders

Enzyme	Blood	Urine
Arginine:Glycine Amidinotransferase (AGAT)	↓ GAA ↓ Creatine	↓ GAA ↓ Creatine
Guanidinoacetate methyltransferase (GAMT)	↑↑ GAA ↓ Creatine	↑↑ GAA ↓ Creatine
Creatine Transporter (X-CRTR, SLC6A8)		↑ Creatine



GAMT Treatment

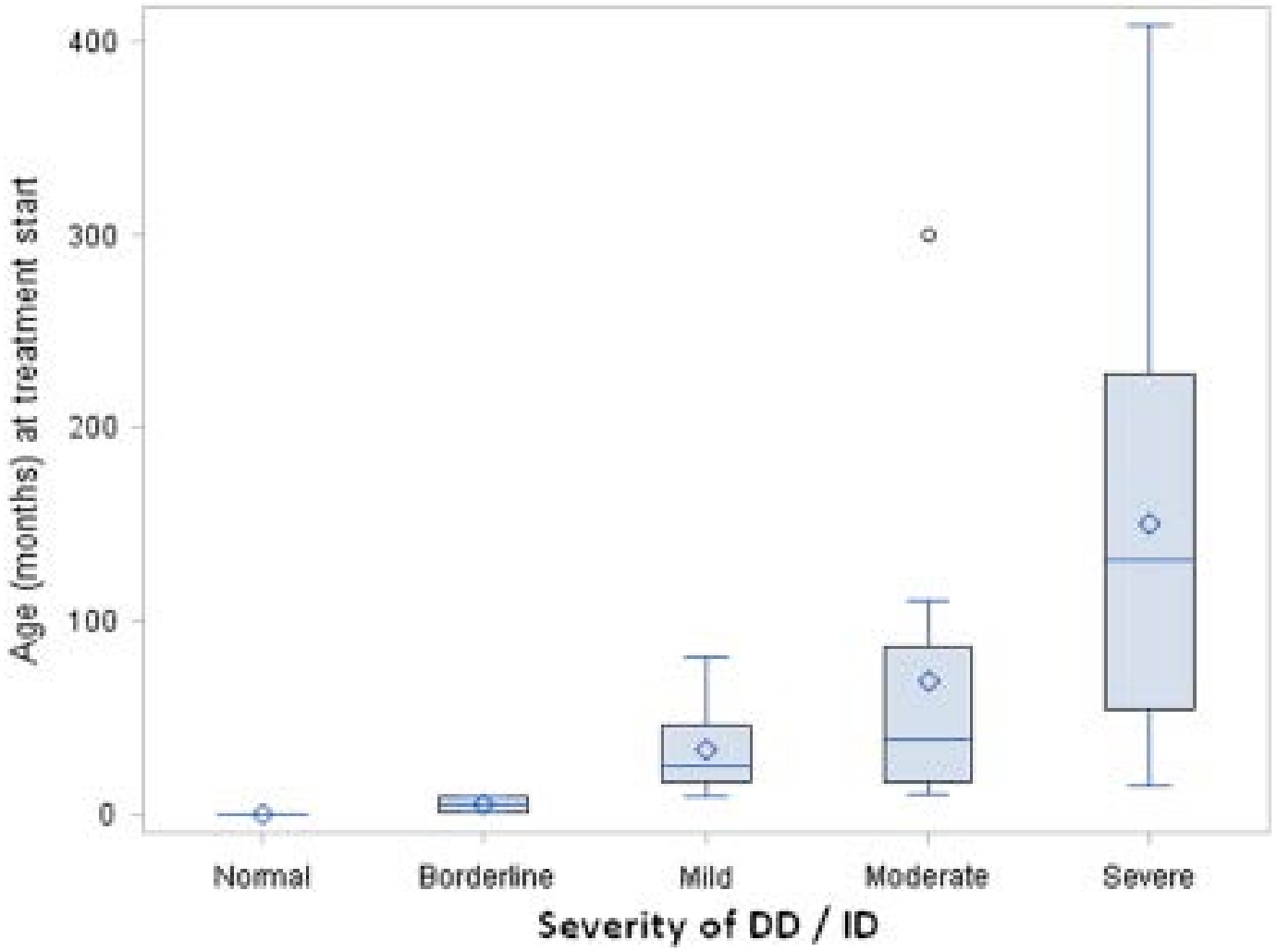
- Supplement
  - Creatine
  - Ornithine
- Restrict
  - Arginine
- Increased cerebral creatine
- Decreased GAA



Stockler-Ipsiroglu et al (2014) Mol. Genet. Metab 111(1): 16-25

✓Early Intervention improves outcomes

(only 4 infants treated from birth)



Stockler-Ipsiroglu et al (2014) Mol. Genet. Metab 111(1): 16-25

GAMT Newborn Screening

Previous Trials:

- Austria, Portugal
- Terminated due to false positive rates

Multi-tiered Approaches:

- Texas, British Columbia, Utah, Italy
- Second-tier testing reduces false positives

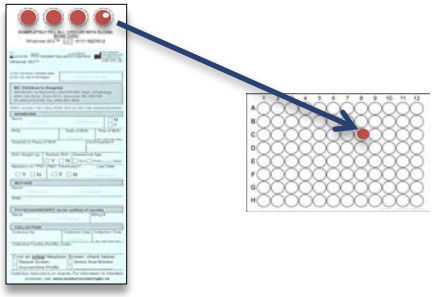
Ongoing Screening:

- Australia (Victoria) since 2002
- No cases in 770,000 infants

BC GAMT Pilot

- Clinical detection: 2 cases in 5 years
- Population-wide pilot (deidentified)
  - 3 years (~120,000 infants)
  - 3-tiers
    - GAA by FI-MS/MS (integrated into AA/AC assay)
    - GAA by LC-MS/MS (integrated into MSUD assay)
    - GAMT sequencing in bloodspot (6 exons)
  - 1 or 2 GAMT mutations = abnormal screen
  - Re-identification of abnormal screens

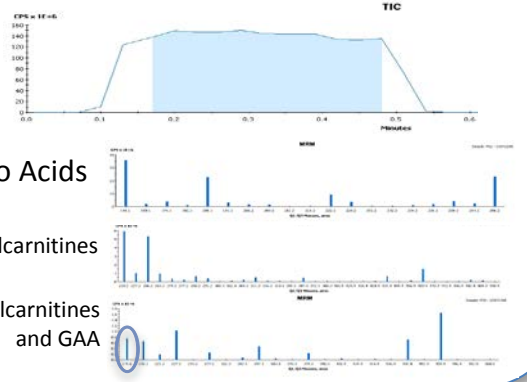
Initial Newborn Screening Card
(Punched, Extracted and Derivitized)



All samples deidentified (coded)

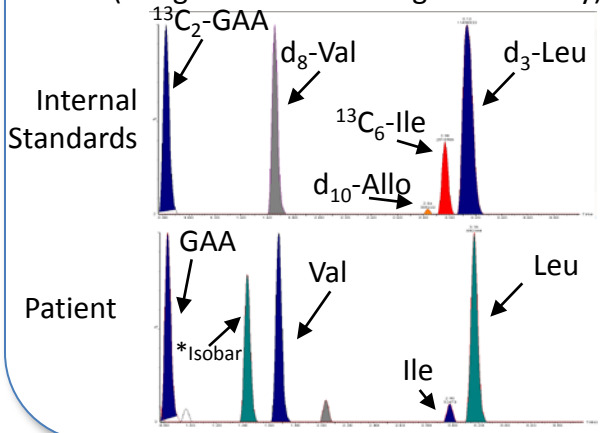
All samples

1st-Tier GAA by Flow injection
(Integrated with routine AA/AC analysis)



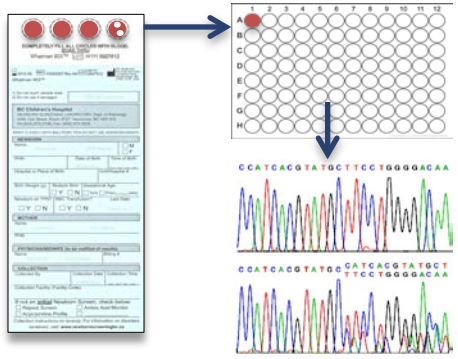
If GAA >6uM (99.9tho%)

2nd-Tier GAA by LC-MS/MS
(Integrated with existing MSUD assay)



If GAA >6uM

3nd-Tier GAMT Sequencing
(Directly from initial bloodspot card)



No mutations

1 or more mutations

NEGATIVE SCREEN = No further action

POSITIVE SCREEN = Reidentify and refer for treatment

NEGATIVE SCREEN

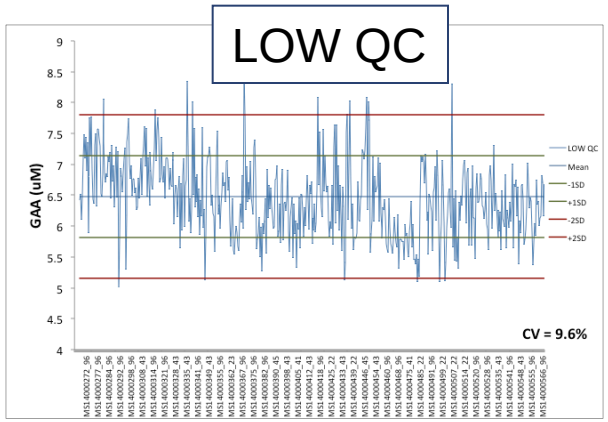
POSITIVE SCREEN

First Tier Performance

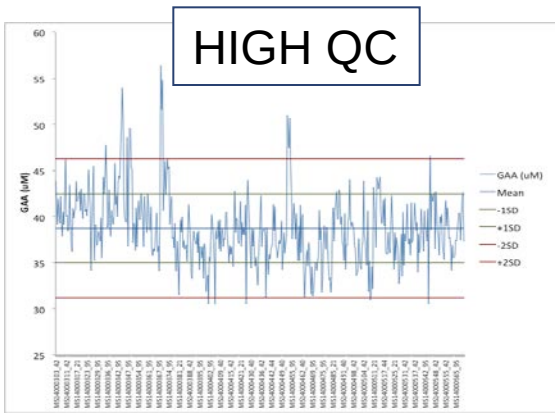
- As of Oct 2014: 91,000 infants screened

First-Tier

- Mean GAA = 1.65 uM (±0.55)
  - Consistent with the literature
- 0.14% over 1st-tier cutoff (125 newborns)

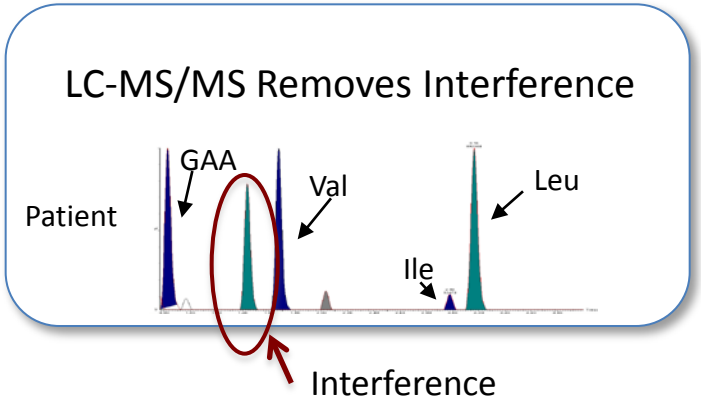


CV=9.6%



CV=9.7%

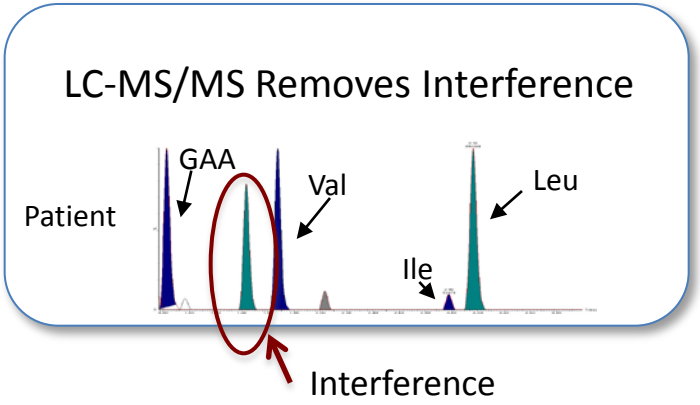
Second-Tier Performance



- Integrated with MSUD
- 5 minute run-time
- Most normal on 2nd-Tier
  - Mean = 1.52 uM (Range 0.3-6.8)
- Only one positive on 2nd tier (GAA=6.8uM)
  - **No GAMT** mutations found
- FPR= 0% but TPR =0%
- Retrospective Clinical Cases
  - GAA = 9.1 and 10.7 uM (5yr RT storage)

First-Tier Positive Screens

- Enriched for premature infants
  - **63%** <2500g (Population = 5.6%)
- Enriched for repeat specimens
  - **42%** Repeat collections
- Interference is likely a product of therapy
  - Exogenous compound?



Is GAMT a good NBS candidate?

- ✓ Natural History
  - – Universally poor outcomes without treatment
- ✓ Treatment
  - – Excellent outcomes with early intervention
  - – Inexpensive treatment (Creatine and diet)
- ✓ Test performance
  - – Two-tier approach required
  - – Integration into existing assays (very low cost)
- ? Incidence
  - – A very rare disorder (0/770,000 in Australia)

Acknowledgements

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