Diagnostic Proficiency Testing
Dicussion common sample 2011

George Ruijter

Geneva 30-8-2011

Patient information

The patient is a 7-year old girl with developmental retardation, in particular speech delay. She has epilepsy, for which she is treated with valproic acid.

First metabolic workup:

	Guanidinoacetate	**Creatine**	**Creatinine**
Urine	640 mmol/mol	15 mmol/mol	2.0 mmol/L
(Ref. values)	(0-129)	(0-754)	-
Plasma	28.8 µmol/L	14 µmol/L	31 µmol/L
(Ref. values)	(0.5-3.6)	(17-109)	(31-68)

Mutation analysis GAMT

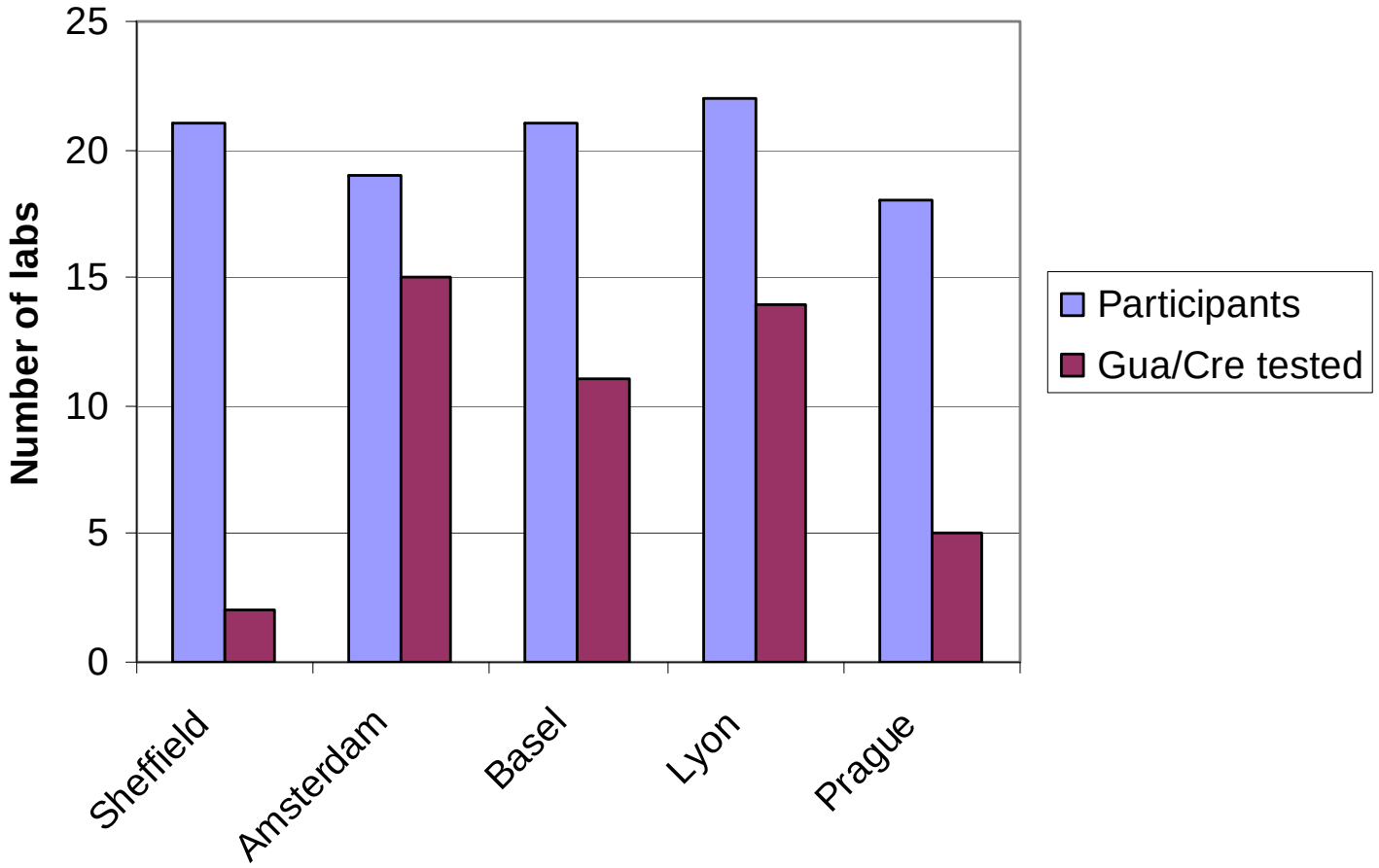
Diagnosis and target values

Guanidinoacetate methyl transferase (GAMT) deficiency

Target values:

Analytical:	Elevated guanidinoacetate (Low creatine)
Interpretation:	GAMT deficiency
Advice:	Urine/plasma/CSF guanidinoacetate, creatine and/or GAMT enzyme assay and/or GAMT mutation analysis

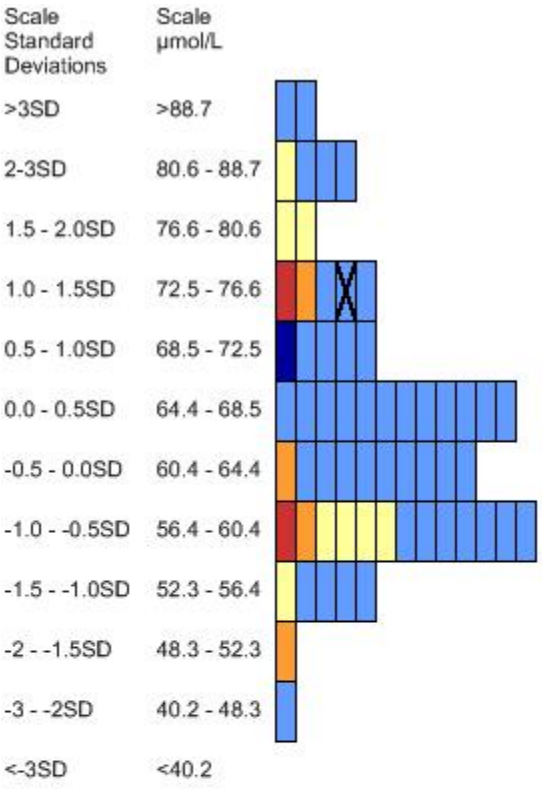
Laboratories with Gua/Cre test results

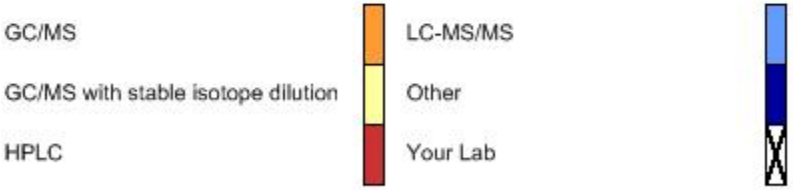


DPT participants: 101

Gua/Cre tested: 47

Gua/Cre analytical methods





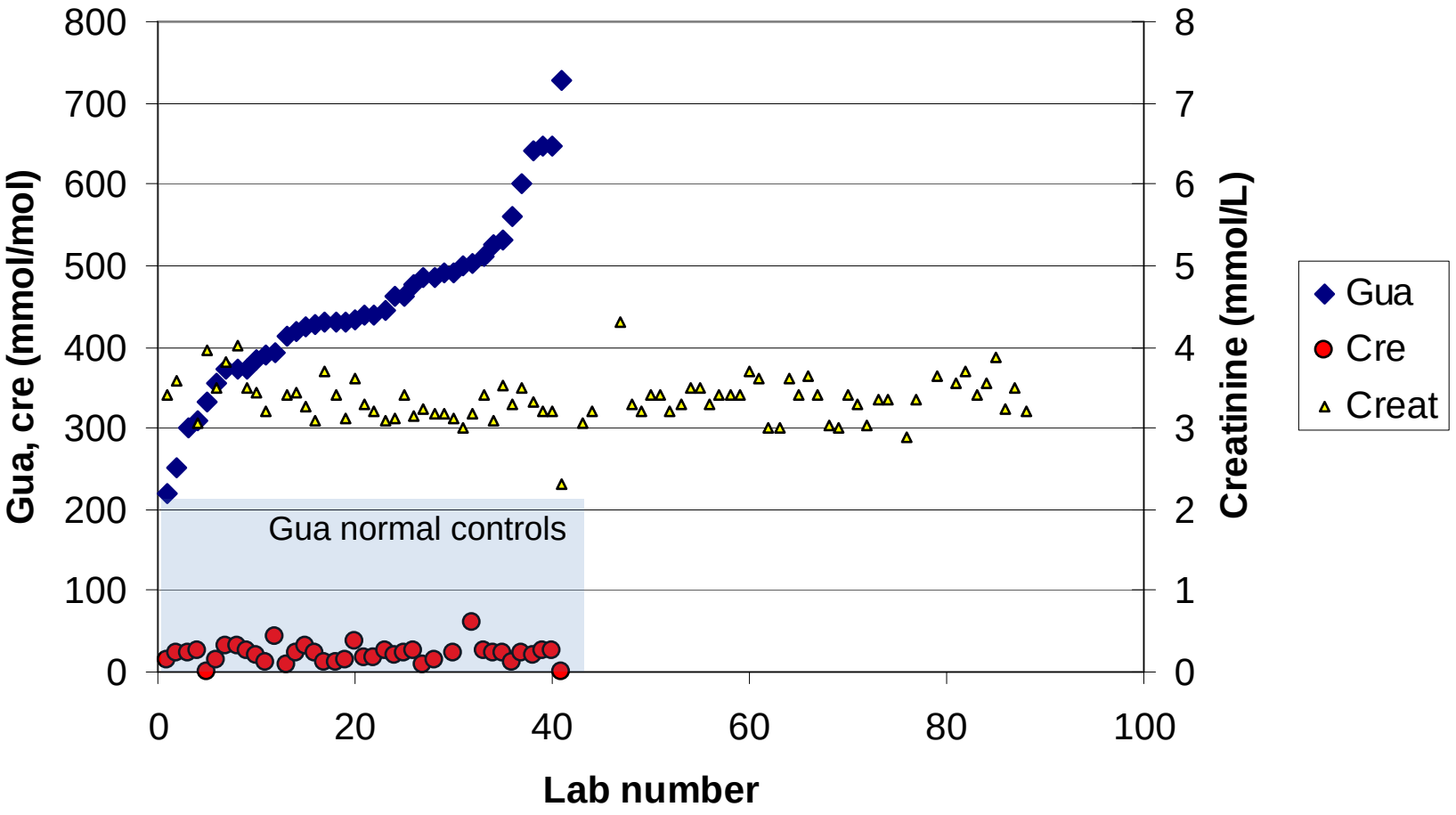
SA urine:

Gua/Cre: 60 participants

45 LC-MS/MS (75 %)

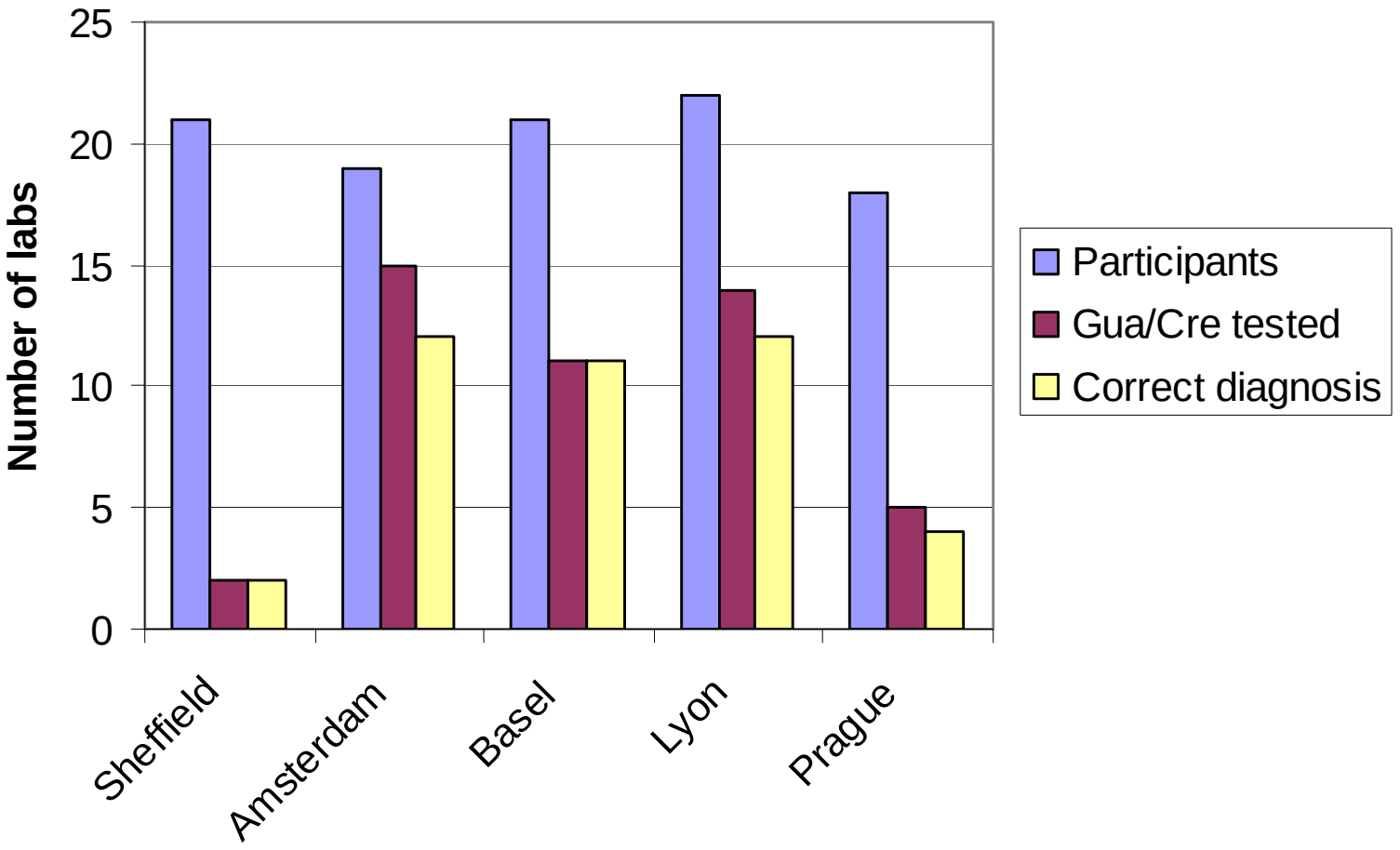
12 GC-MS (20 %)

Gua/Cre test results



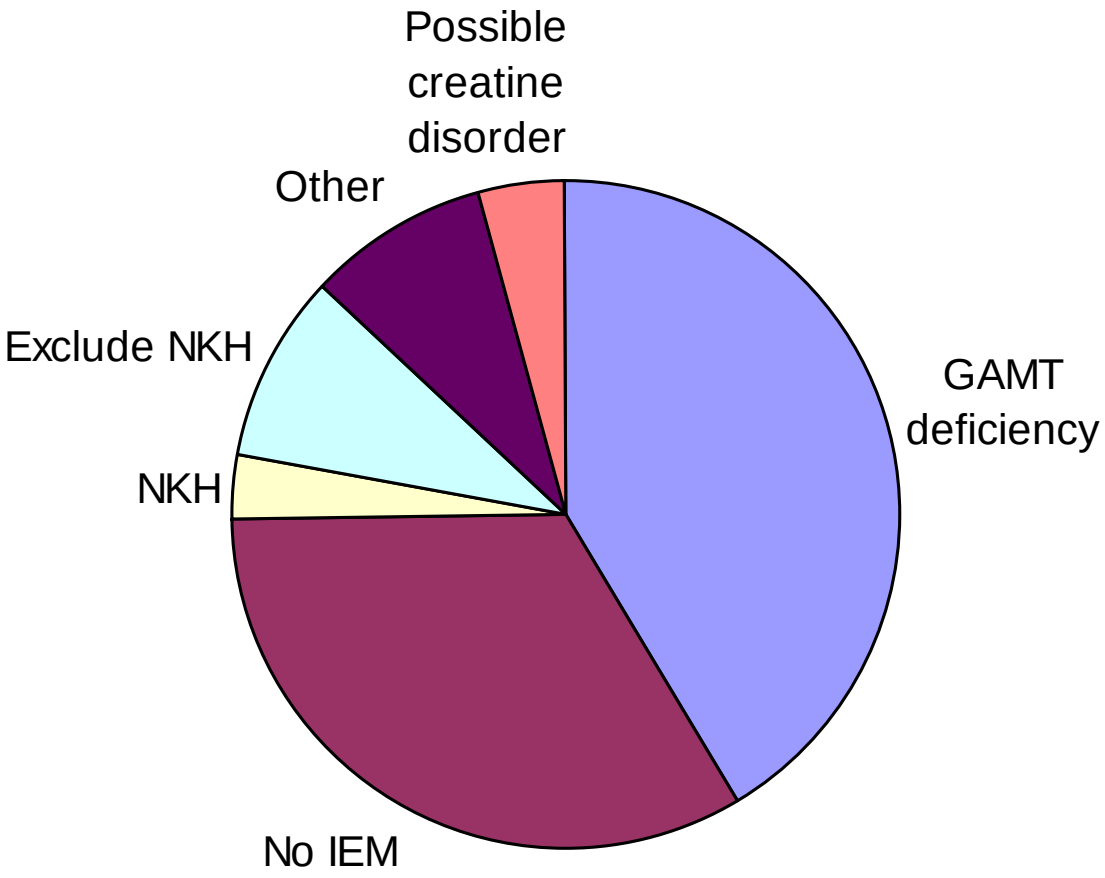
Gua: 452 ± 105 mmol/mol (CV 23 %)

Diagnostic proficiency

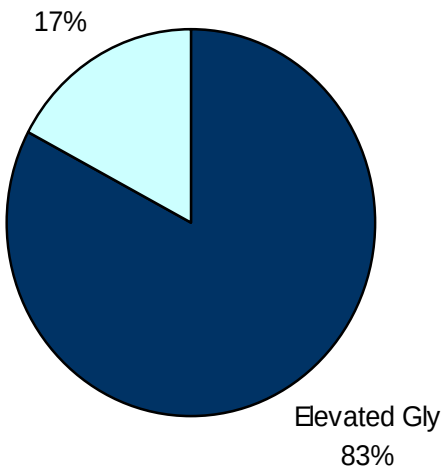


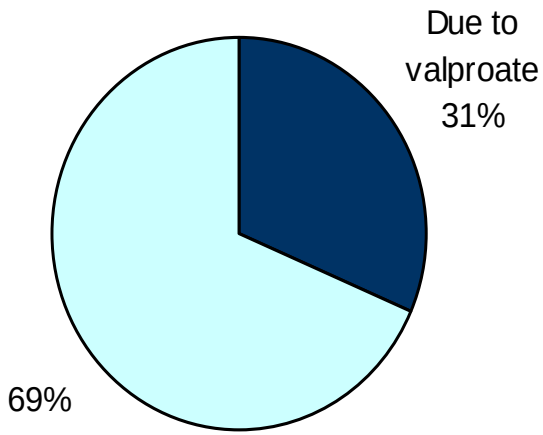
DPT participants: 101
Gua/Cre tested: 47
Correct diagnosis: 41

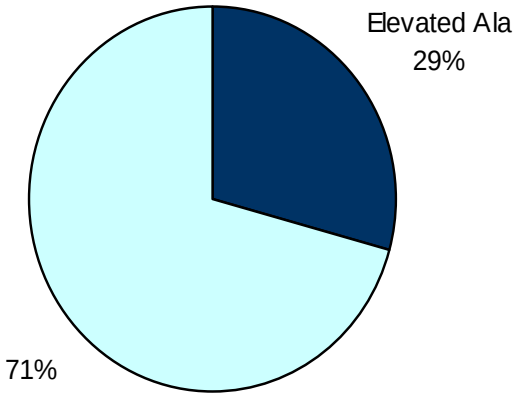
Diagnoses summary

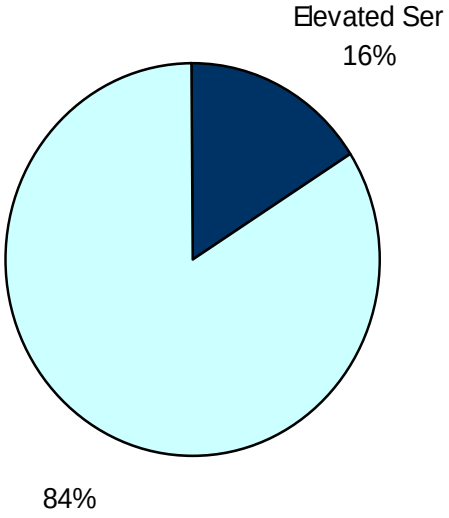


Amino acids

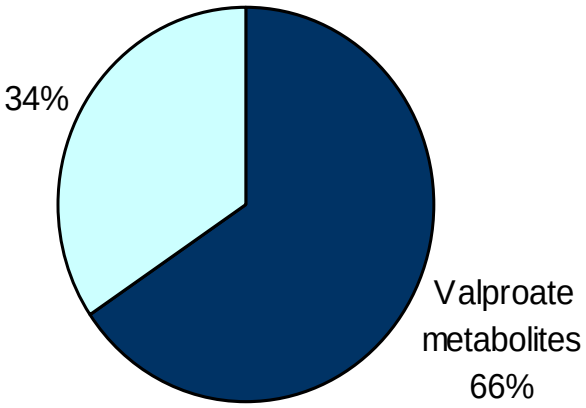

17%
Elevated Gly
83%

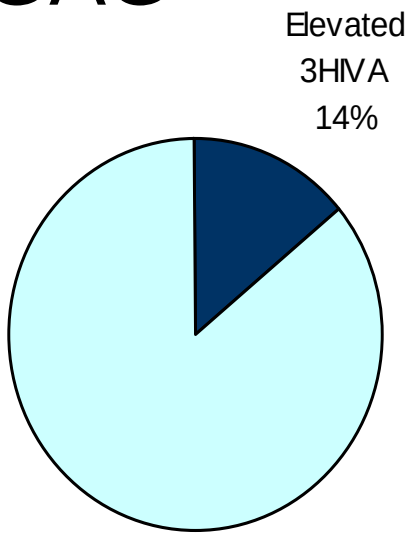

Due to
valproate
31%
69%

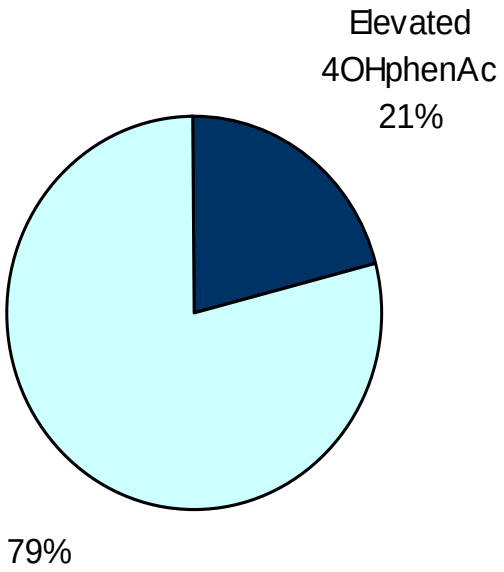

Elevated Ala
29%
71%

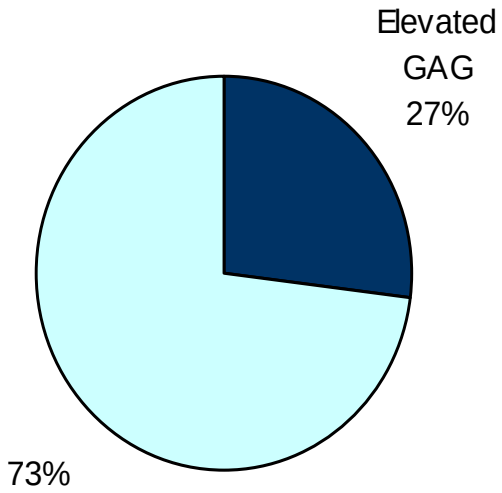

Elevated Ser
16%
84%

Organic acids, quantitative GAG









Creatinine

Elevated levels of Ala, Ser, 4OHphenAc, GAG due to decreased creatinine?

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Clinica Chimica Acta 361 (2005) 1–9

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Review

Laboratory diagnosis of defects of creatine biosynthesis and transport

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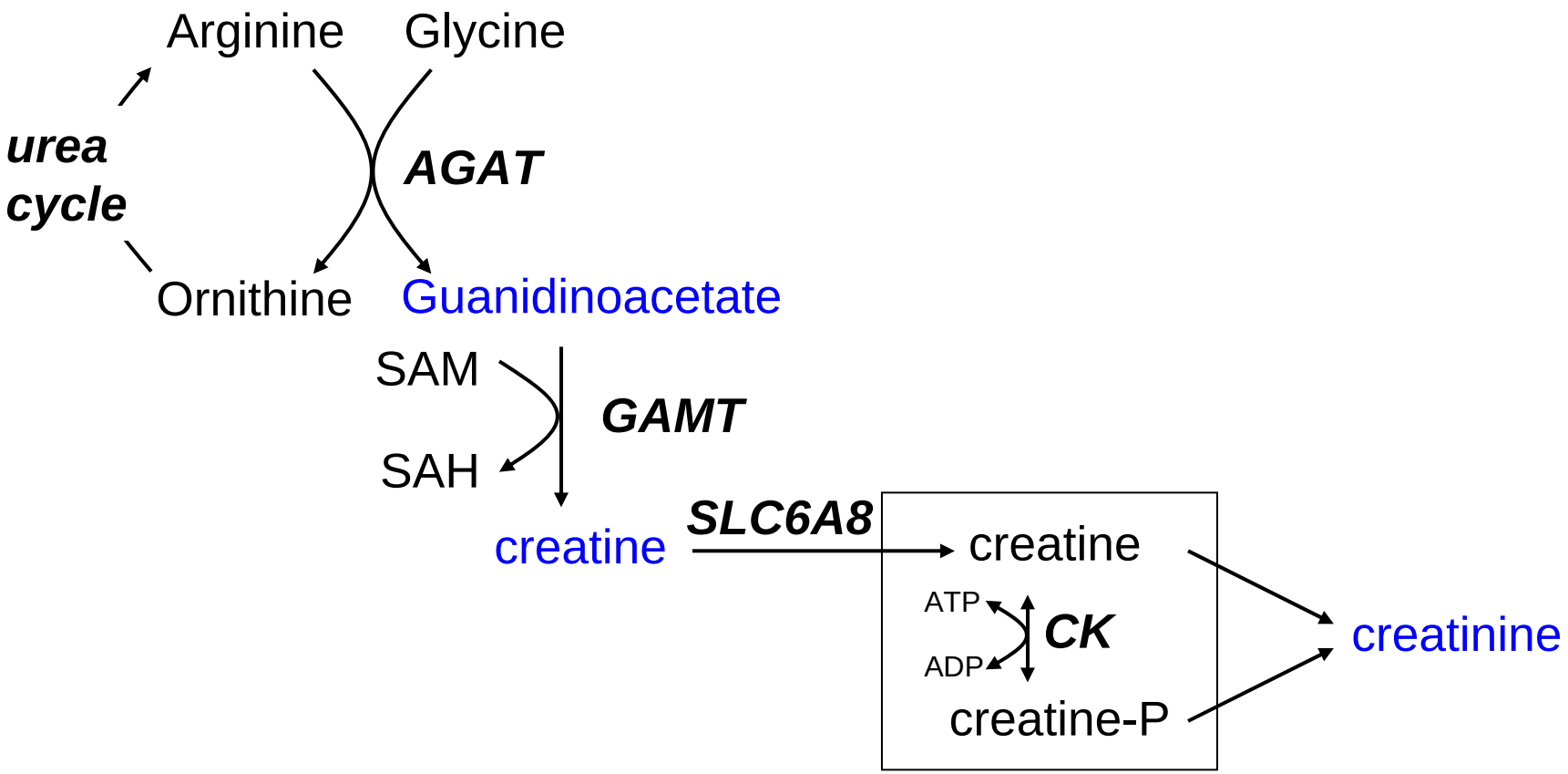
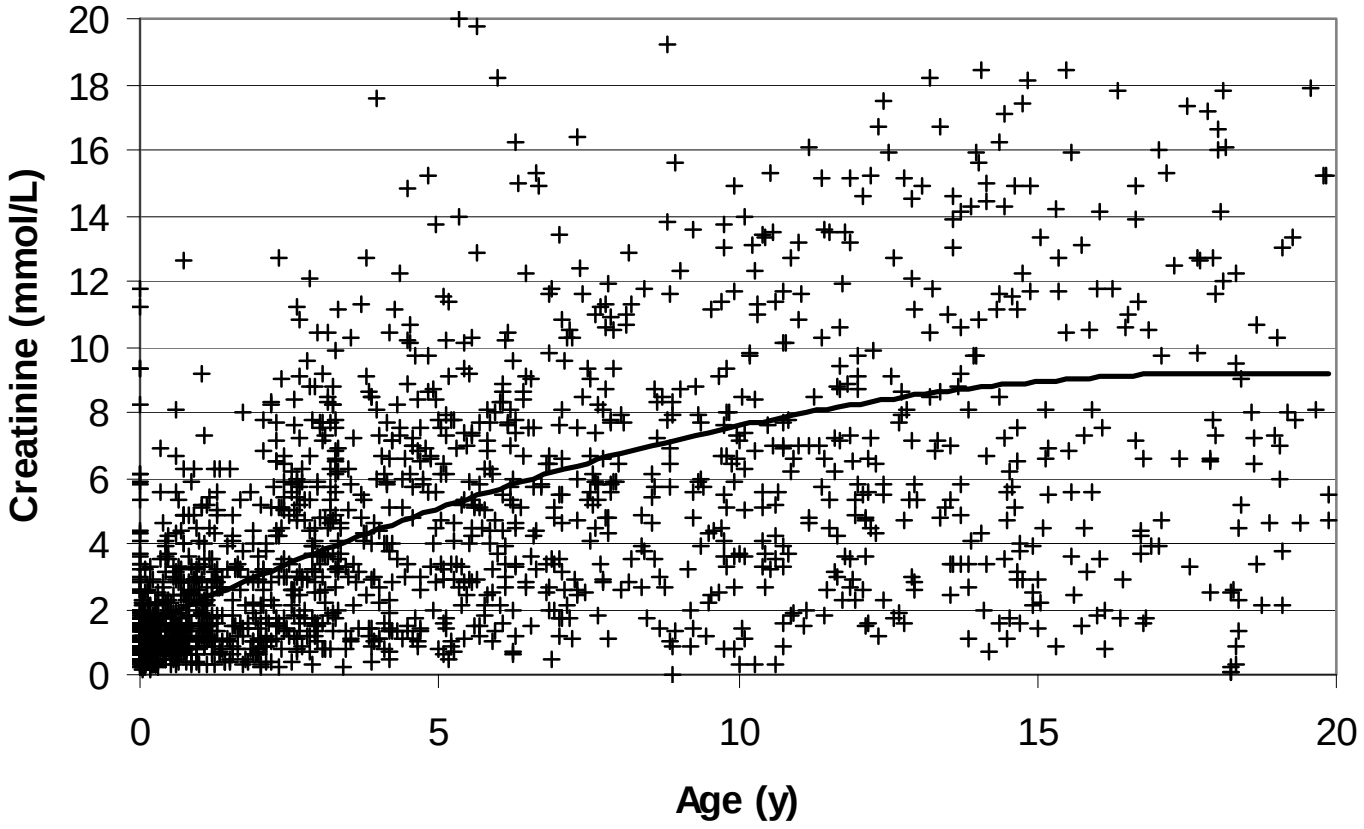
Received 25 January 2005; received in revised form 5 April 2005; accepted 12 April 2005

Creatine biosynthesis



AGAT = Arginine:glycine amidinotransferase
GAMT = Guanidinoacetate methyltransferase
SLC6A8 = Creatine transporter
CK = Creatine kinase

Creatinine vs. age (n=1768)



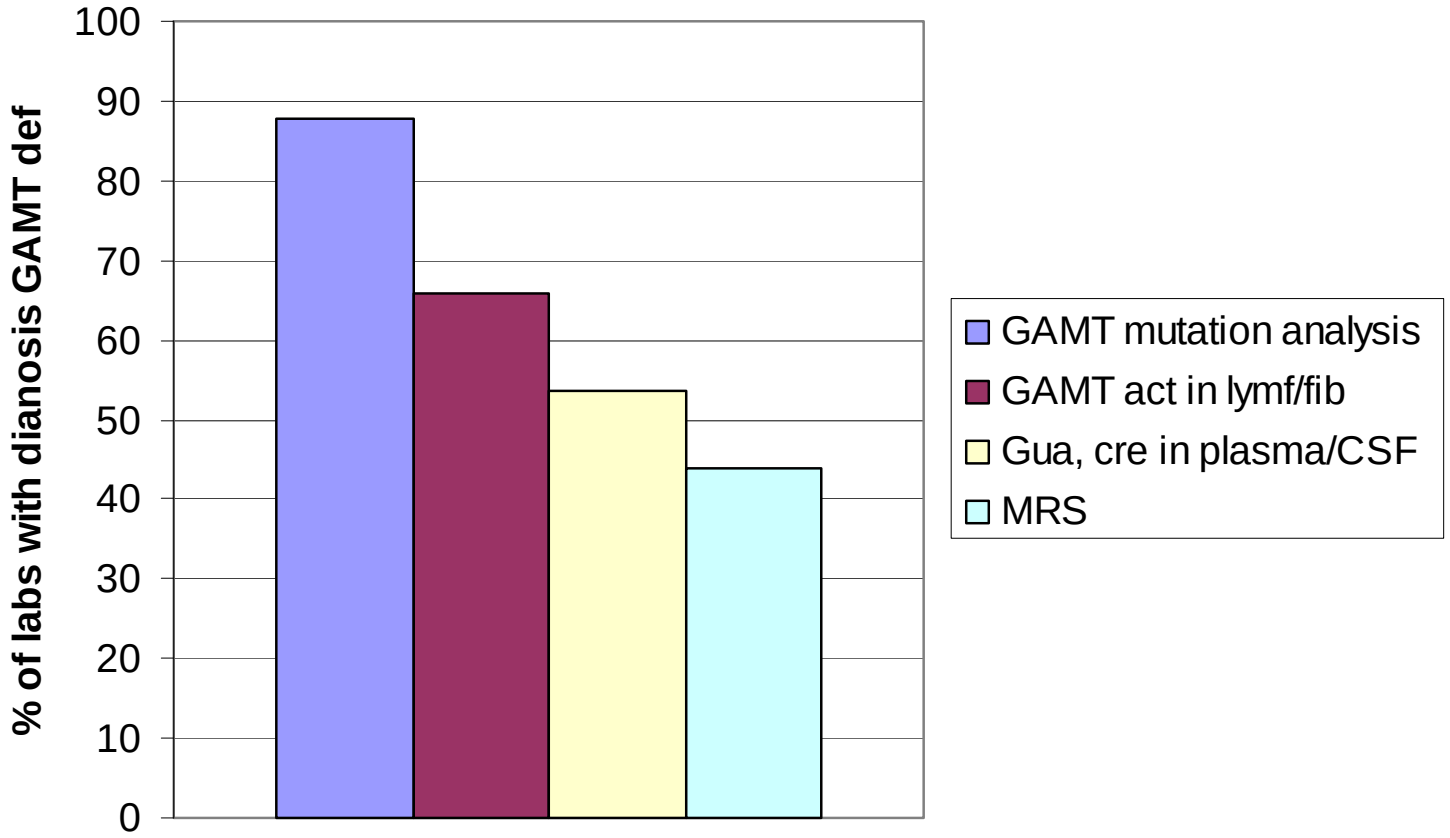
Children 6-8 y

Creatinine	average	6.5 mmol/L
	SD	3.9
	n	147

Secondary changes Gua /Cre

	Gua	Cre
Duchenne muscular dystrophy	n	↑
Hyperornithinemia	↓	↓-n
Hyperargininemia	↑	↑
Urea cycle defects	↓	n
Ketosis (?)		↑

Advice for further investigations



Response to treatment

Mercimek-Mahmutoglu et al, Neurology 2006, 67:480-484

23 / 27 patients: creatine-monohydrate
5 / 23 patients: creatine plus arginine restricted diet, ornithine suppl

Improvement of:	**no.of patients**	**(%)**
Intellectual disability	0/23	(0)
Epileptic seizures	19/21	(90)
Movement disorder	7/12	(58)

Decrease of Gua concentration in

urine	0-83 %
plasma	57-99 %
CSF	50-84 %

Conclusions

- Increased guanidinoacetate with low creatine: GAMT deficiency
- Gua/Cre tested by 47 of 101 participants
- Correct diagnosis by 41 participants
- Elevated levels of Ala, Ser, GAG, 4OHphenylacetate possibly due to relatively low creatinine
- Number of GAMT patients: ~100
- GAMT is a treatable disorder