The use & benefit of cognitive & interpretative quality schemes

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Definitions (Collins English Dictionary)

interpretation *n*. (interpretive or interpretative *adj*.)

- the act or process of interpretation or explaining; elucidation
- the result of interpreting; an explanation
- a particular view of an artistic work, esp. as expressed by stylistic individuality in its performance
- explanation, as of the environment, a historical site, etc., provided by the use of original objects, personal experience, visual display material, etc.
- *logic*, an allocation of the significance to the terms of a purely formal system, by specifying ranges for the variables, denotations for the individual constants, etc.

cognition *n*. (cognitive *adj*.)

- the mental act or process by which knowledge is acquired, including perception, intuition and reasoning
- the knowledge that results from such an act or process

Use and benefit

- adherence to guidelines
  - newborn screening, sweat testing, molecular
- interpretation of result against reference range
  - orotic acid, G6PDH
- qualitative assays

  amino acids, organic acids, acyl carnitines etc
- proficiency scheme
- interpretative comments
- cognitive amino acid scheme

EQA schemes - ERNDIM

ERNDIM	?interpretive?
special assays	✗
quantitative amino acids	✗
organic acids	✓
acyl carnitines	✓
white cell cystine	✗
mucopolysaccharides	✓
transferrins	✓
white cell enzymes	✗
proficiency scheme	✓

EQA schemes - NEQAS

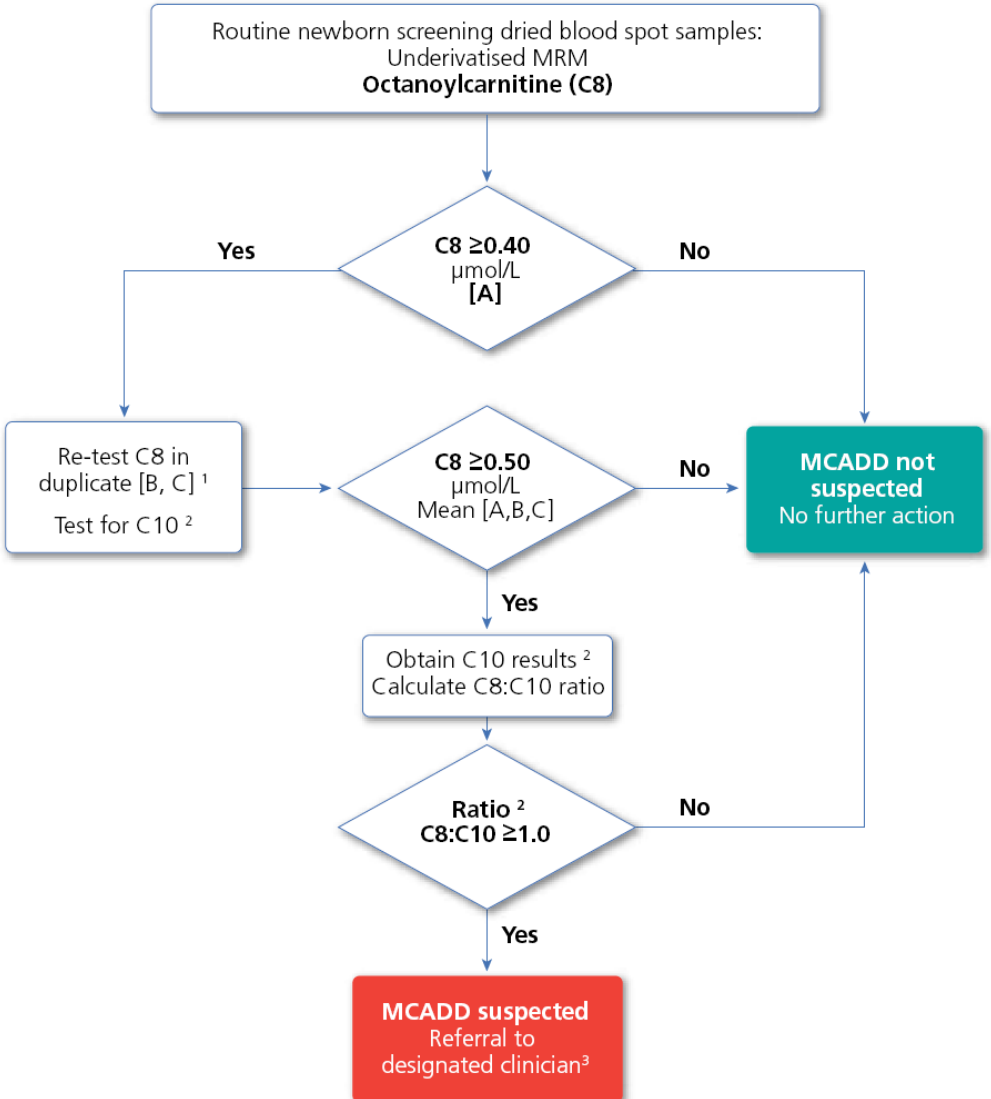
NEQAS	?interpretive?
newborn screening	✓
phe, tyr, bcaas	✗
orotic acid	✓
amino acids	✓
molecular genetics	✓
interpretive comments	✓
cognitive amino acid	✓

Quantitative assays

NEQAS Newborn screening

NEQAS Newborn screening

- quantitative results
- interpretation ***assesses*** and ***promotes*** compliance with flow-chart



NEQAS sweat testing

Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK, November 2003

The following definitions are recommended for interpretation:-

- A sweat chloride concentration of > 60 mmol/L supports the diagnosis of CF
- Intermediate chloride concentration of 40 - 60 mmol/L is suggestive but not diagnostic of CF
- A sweat chloride of less than 40 mmol/L is normal and there is a low probability of CF.
- Sodium should not be interpreted without a chloride result.
- Pending further data on conductivity measurements a value below 60 mmol/L (NaCl equivalents) is unlikely to be associatedwith cystic fibrosis. Values above 90 mmol/L support a diagnosis of cystic fibrosis.
- Cystic fibrosis should not be diagnosed based on conductivity measurement alone.

Guidelines for the Performance of the Sweat Test for the Investigation of Cystic Fibrosis in the UK, November 2003

The following definitions are recommended for interpretation:-

- A sweat chloride concentration of > 60 mmol/L supports the diagnosis of CF
- Intermediate chloride concentration of 40 - 60 mmol/L is suggestive but not diagnostic of CF
- A sweat chloride of less than 40 mmol/L is normal and there is a low probability of CF.

Newborn screening & sweat testing

- assess adherence to flow-chart/protocol
- promote adherence to flow-chart/protocol

- value
  - reminds personnel of cut-offs
  - awareness of variation in outcome for a specimen with result at 'cut-off' concentration

- disadvantages
  - complicated QA returns and reports

NEQAS orotic acid

NEQAS orotic acid

- assesses interpretation of quantitative result
  - age related reference ranges
  - opportunity to assess how very dilute or concentrated specimens are reported
- other similar schemes
  - G6PD (haematology scheme)

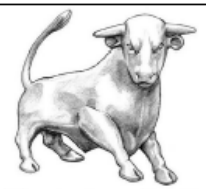
Qualitative tests

NEQAS amino acids

NEQAS urine amino acids

- Analyse specimen and classify results
  - N — no further investigation – patient 'normal'
  - O — further investigation for other reason
  - F — further investigation as 'abnormal'
  - A — no further investigation required – patient clearly 'abnormal'

NEQAS urine amino acids



Birmingham Quality

UKNEQAS Urinary Aminoacid Surveys

Laboratory :

Distribution : **28** Date : 01-Mar-2009

Analyte : Aminoacid interpretation N or F

Spec.	Pool	Pool description / Treatments / Additions
28A	155	Male, 17 years old, neurological problems
28B	156	Male, 8 years old, feeding problems
28C	157	Female, 7 days old, skin rash
28D	158	Female, 2 months old, failure to thrive

Specimen : 28A

N	0.0 %
O	3.0 %
F	78.8 %
A	18.2 %
O Your result	
F Consensus	

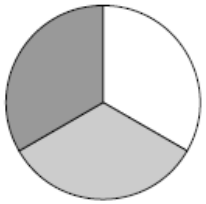
Your result	O
Total responses	33
[N] Normal	0
[O] Other	1
[F] Abnormal, further action	26
[A] Abnormal	6

Specimen : 28B

N	84.8 %
O	12.1 %
F	3.0 %
A	0.0 %
N Your result	
NConsensus	

Your result	N
Total responses	33
[N] Normal	28
[O] Other	4
[F] Abnormal, further action	1
[A] Abnormal	0

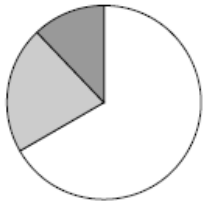
Specimen : 28C



N	33.3 %
O	33.3 %
F	33.3 %
A	0.0 %
O Your result (N O F) Tied Response	

Your result	O
Total responses	
[N] Normal	
[O] Other	
[F] Abnormal, further action	
[A] Abnormal	

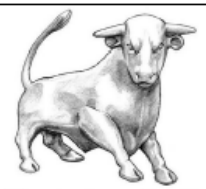
Specimen : 28D



N	66.7 %
O	21.2 %
F	12.1 %
A	0.0 %
N Your result	
NConsensus	

Your result	N
Total responses	33
[N] Normal	22
[O] Other	7
[F] Abnormal, further action	4
[A] Abnormal	0

NEQAS urine amino acids



UKNEQAS Urinary Aminoacid Surveys | Laboratory :

Distribution : **28** Date : 01-Mar-2009 | Page 1 of 6

Analyte : Aminoacid interpretation N or F

Spec.	Pool	Pool description / Treatments / Additions
28A	155	Male, 17 years old, neurological problems
28B	156	Male, 8 years old, feeding problems
28C	157	Female, 7 days old, skin rash
28D	158	Female, 2 months old, failure to thrive

A citrullinaemia
B normal (1-methylhistidine)
C normal
D normal

Specimen : 28A

N	0.0 %
O	3.0 %
F	78.8 %
A	18.2 %
O Your result	
F Consensus	

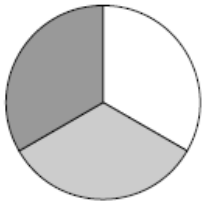
Your result	O
Total responses	33
[N] Normal	0
[O] Other	1
[F] Abnormal, further action	26
[A] Abnormal	6

Specimen : 28B

N	84.8 %
O	12.1 %
F	3.0 %
A	0.0 %
N Your result	
NConsensus	

Your result	N
Total responses	33
[N] Normal	28
[O] Other	4
[F] Abnormal, further action	1
[A] Abnormal	0

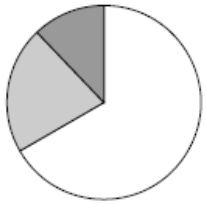
Specimen : 28C



N	33.3 %
O	33.3 %
F	33.3 %
A	0.0 %
O Your result (N O F) Tied Response	

Your result	O
Total responses	
[N] Normal	
[O] Other	
[F] Abnormal, further action	
[A] Abnormal	

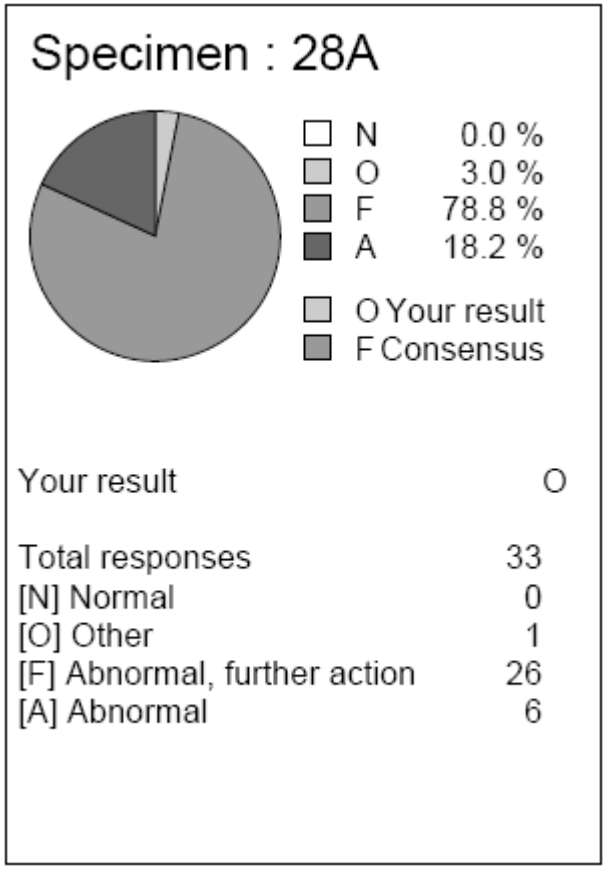
Specimen : 28D



N	66.7 %
O	21.2 %
F	12.1 %
A	0.0 %
N Your result	
NConsensus	

Your result	N
Total responses	33
[N] Normal	22
[O] Other	7
[F] Abnormal, further action	4
[A] Abnormal	0

NEQAS urine amino acids



	n
citrullinaemia	18
abnormal (not specified)	4
argininosuccinic aciduria	1
raised glycine/non ketotic hyperglycinaemia	2
elevated glutamine/glycine ?urea cycle disorder	1
hypertaurinaemia ?sulphite oxidase deficiency	1
abnormal spot (?homocystine)	1
abnormal glycine (and ?homocystine)	1

NEQAS amino acids

- advantages
  - aimed at DGH labs
    - now down to ~30 participants
    - of value as an educational tool, provides useful information to participants

- disadvantages
  - N/O/F/A!
  - can get full score but incorrect abnormality
    - is it time to change?

ERNDIM qualitative schemes

ERNDIM organic acids

- major analytical findings
  - provide labelled TIC
- most likely diagnosis (one only)
  - fairly certain/tentative
- other possible diagnoses (if applicable)
- further investigation required to confirm/clarify
- any additional comments
- scoring

2	satisfactory
1	helpful but incomplete
0	unhelpful
-1	somewhat misleading
-2	seriously misleading

ERNDIM acyl carnitines

- major analytical findings
  - provide labelled TIC/scan
- relevant quantitative data (optional)
- most likely diagnosis (one only)
  - [fairly certain/tentative]
- other possible diagnoses (if applicable)
- further investigation required to confirm/clarify
- clinical information/advice
- any additional comments

ERNDIM proficiency scheme

ERNDIM provides:

- urine specimen
- clinical details

Participant reports:

- pre-investigations
- amino acids
- organic acids
- purines and pyrimidines
- mucopolysaccharides
- other analyses
- conclusions
- advice for follow-up investigations
- advice to attending clinician (optional)

ERNDIM proficiency scheme

ERNDIM provides:

- urine specimen
- clinical details

Participant reports:

pre-investigations amino acids organic acids purines and pyrimidines mucopolysaccharides other analyses	scored 0, 1 or 2
conclusions	scored 0, 1 or 2
advice for follow-up investigations	scored 0 or 1

advice to attending clinician (optional)

ERNDIM qualitative schemes

- advantages
  - well established schemes
  - enormous educational value
  - scoring (except acyl carnitines)
  - expanding to other metabolites
    - mucopolysaccharides, transferrins
  - European flavour

- disadvantages
  - European flavour!

NEQAS molecular schemes

NEQAS molecular schemes

Mitochondrial diseases
Scheme 2010

Question 1
Mary Arthur (dob 15/02/1989) presented with an acute bilateral central vision loss and a suspected diagnosis of Leber hereditary optic neuropathy (LHON). Your local Consultant Ophthalmologist has forwarded a sample from Mary for assessment of common LHON mutations.

Question 2
Samuel Hill (dob 31/12/1993) presented to Neurology with stroke-like episodes. He has short stature and deafness and his older sister has sensorineural hearing loss which has been shown to be due to the m.3243A>G mutation. Please analyse the referred sample, including in your report the level of m.3243A>G mutation detected.

Question 3
A local Consultant Paediatric Neurologist has referred a sample from Liam Robson (dob 07/07/2002) for diagnostic testing, querying a possible diagnosis of NARP (Neurogenic weakness, ataxia and retinitis pigmentosa). Liam has developmental delay, a sensory neuropathy and vision loss.

Validated Results

Question	Results
2	Samuel HILL is heteroplasmic for the m.3243A>G mutation. This mutation is present at low levels of heteroplasmy (mutation load calculated to be 28%) in the DNA sample extracted from his blood sample.

Validated Results

Question	Results
2	Samuel HILL is heteroplasmic for the m.3243A>G mutation. This mutation is present at low levels of heteroplasmy (mutation load calculated to be 28%) in the DNA sample extracted from his blood sample.

2	Genotyping	m.3243A>G mutation detected.	2.0 marks
	Interpretation	Pathogenic m.3243A>G mutation detected. Confirmation that the patient has mtDNA disease/m.3243A>G mutation the cause of his clinical phenotype (stroke-like episodes, short stature, deafness). m.3243A>G mutation is maternally-transmitted and therefore will not transmit the mutation to his own children but other maternal relatives are at risk.	0.5 marks 1.0 mark 0.5 marks
	Comments	Recommend testing of maternally-related family members. Further non-invasive testing of a urinary epithelial cell DNA sample may give some useful prognostic advice as the level of m.3243A>G mutation in this tissue closely correlates with levels in muscle and clinical severity.	-

Surname	**WALKER**	**Reg No.**	Z.07.0163053	**D.o.B.** 03/09/2009	**Sex** F	**Lab No**	**C.10.0018855**
Forename	Lily	**Location**	Local Hospital			**Sample**	DNA
Clinician	Consultant Paediatrician	**Specialty**	Paediatric Emergency Department			**Ext.Reg**	UKNEQAS
Diagnosis						**Report destination**	Consultant Paediatrician
Clin Info		EQA				**Page No**	1 of 1

Mutation Analysis for MCADD

***ACADM* c.985A>G (p.Lys329Glu) NOT DETECTED**

Lily does not have the common mutation in the *ACADM* gene (c.985A>G) associated with medium chain Acyl-CoA dehydrogenase deficiency (MCADD).

This result substantially reduces the likelihood of a diagnosis of MCADD in Lily but does not entirely exclude this possibility. Approximately 1% of individuals of European-origin diagnosed with MCADD on the basis of clinical symptoms do not have this mutation in either the homozygous or heterozygous state (1).

A diagnosis of MCADD should rely on clinical evaluation and the results of plasma acyl-carnitine and urine organic acids analysis. If a diagnosis of MCADD remains suspicious following these biochemical investigations we shall be pleased to to forward an aliquot of DNA for extended *ACADM* gene mutation analysis at your request.

Methodology: PCR followed by *Nco*I restriction digestion and polyacrylamide gel electrophoresis. *ACADM* mutation nomenclature is according to GenBank accession number NM_000016.2 with numbering starting at the A of the ATG initiation codon.

(1) Grosse et al (2006) The epidemiology of medium chain acyl-CoA dehydrogenase deficiency: an update. *Genetics in Medicine, 8*, 205-212

Test(s)	**Collected**		**Received**	**Report printed**	**Authorised**
DNAMCAD	N/K	N/K	04/08/2010 16:17	17/08/2010 10:03	XXX

NEQAS molecular schemes

- strict marking criteria for scoring
- marks deducted for clerical errors
  - eg omitting dob from report
  - non-adherence to good clinical practice for molecular reporting
- provisional score
  - subject to appeal

NEQAS interpretative comments

- developed from the ‘cases for comment’
- assesses interpretive comments added to patients’ results by individuals
- purely educational
  - exposure to wide range of scenarios
  - useful exam preparation?
- adjunct to CPD

- 22 cases/year

UKNEQAS for Interpretative Comments [C]

Distribution : **244** Date : 09-Nov-2007

Specimen : 244

A 9 year-old boy was admitted to the Children's ward of the Hospital. He had been generally unwell. The clinical details on the request form were 'abdominal pain & hypoglycaemia'.

Serum results were as follows:

Sodium 117 mmol/L (136 - 145), Potassium 6.2 mmol/L (3.5 - 5.1), Urea 7.5 mmol/L (adult range 3.5 - 7.2), Creatinine 70 umol/L (adult range 53 - 115), Amylase 44 IU/L (30 – 110), Glucose 1.7 mmol/L.
Liver function tests, calcium and phosphate were within normal limits.

The sample was not haemolysed and was received promptly by the laboratory.

Your comment

Exclude Addsions as cause of low Na and glucose (short synacthen test). If normal suggest Inx hypoNa (POsmo, UOsmo/Na, 17OHP) and hypoglycaemia (insulin, cPep, TFTs, GH, Blood gases, Osmolar gap, FFA/3OHBA, UOrganic acids, salicylate).

Summary from the Scheme Organisers

This Case attracted 173 participants, 165 scoring positive marks (25th percentile 0.75, median 1.00, 75th percentile 1.33). Most participants mentioned the possibility of Addison's disease even though this is rare in children (some authorities mention that in Addison's, hypoglycaemia is often more severe in children than in adults, and it can also be linked to multiple endocrine problems). Many also suggested the possibility of congenital adrenal hyperplasia. Overall in this Case there was little consistency in the suggestions for follow-up tests.

For this patient, a 9am cortisol was within the reference range at 320 nmol/L (although several participants suggested that it should be considerably higher with this degree of hypoglycaemia), but showed no rise in a short Synacthen test. ACTH was markedly elevated at 1900 ng/L, and a test for adrenal cortex antibodies was positive suggesting autoimmune destruction. Thyroid function tests and a full blood count were normal, so this Case was not apparently linked to hypothyroidism or pernicious anaemia. The child is now doing well on replacement therapy.

Low scoring comments were:
'Add on osmolality. Phone ward to see if been vomiting/ diarrhoea. Hypoglycaemic –suggest repeat, and send sample for insulin (has to be recd immediately by lab)' and *'Poisoning, sepsis, I.E.M? Assess A/B status, CRP, ketones, osmolar and anion gap, cortisol, 10-OHP, insulin, TFTs and NH3. Send urine for pH, osmol/vol/Na, reducing substances, organic acids. When stable, will discuss further investigations'.*

A median scoring comment was:
'Results suggestive of Addison's disease, test cortisol and adrenal antibodies on remaining sample/ request more. Suggest immediate dose of hydrocortisone'.

A high scoring comment was:
'This is acute adrenal insufficiency until proved otherwise. A short synacthen test should be performed but treatment should not be withheld until the results are known. 17-OH progesterone and ACTH (suitably collected) should also be measured'.

Cognitive amino acid scheme

Information and slides provided by Steve Krywawych

Initial intentions

- 3 cases every 3 months
- one return per laboratory
- comment contents
  - identify abnormalities
  - propose diagnosis where possible
  - suggest further possible investigations
- comment scored
- 4 assessors
- similar to general clinical chemistry comments: –1 through 0 up to +3

Proposed guide for scoring

- -1 completely misleading comments
- 0 comments highlighting abnormal findings with no further elaboration
- 1 comments highlighting abnormal findings with incomplete number of appropriate recommendations
- 2 comments highlighting abnormal findings with incomplete number of appropriate recommendations and correct diagnosis where available
- 3 comments highlighting abnormal findings with correct diagnosis where available and correct appropriate recommendations

Case 1 – seizures from day 1
pyridox(am)ine phosphate oxidase deficiency

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	367 *	100 - 290
Serine	77 *	90 - 290
Threonine	165	70 - 220
Proline	74 *	85 - 290
Leucine	48 *	65 - 220
Isoleucine	10 *	26 - 100
Valine	68 *	90 - 300
Alanine	145 *	150 - 450
Glutamine	243 *	480 - 800
Arginine	11 *	40 - 120
Ornithine	17 *	25 - 120
Lysine	44 *	100 - 300
Methionine	12	10 - 60
Taurine	52	40 - 140
Phenylalanine	35	35 - 100
Tyrosine	16 *	30 - 120
Tryptophan	24 *	30 - 80
Histidine	57	30 - 150
Glutamate	55	35 - 130

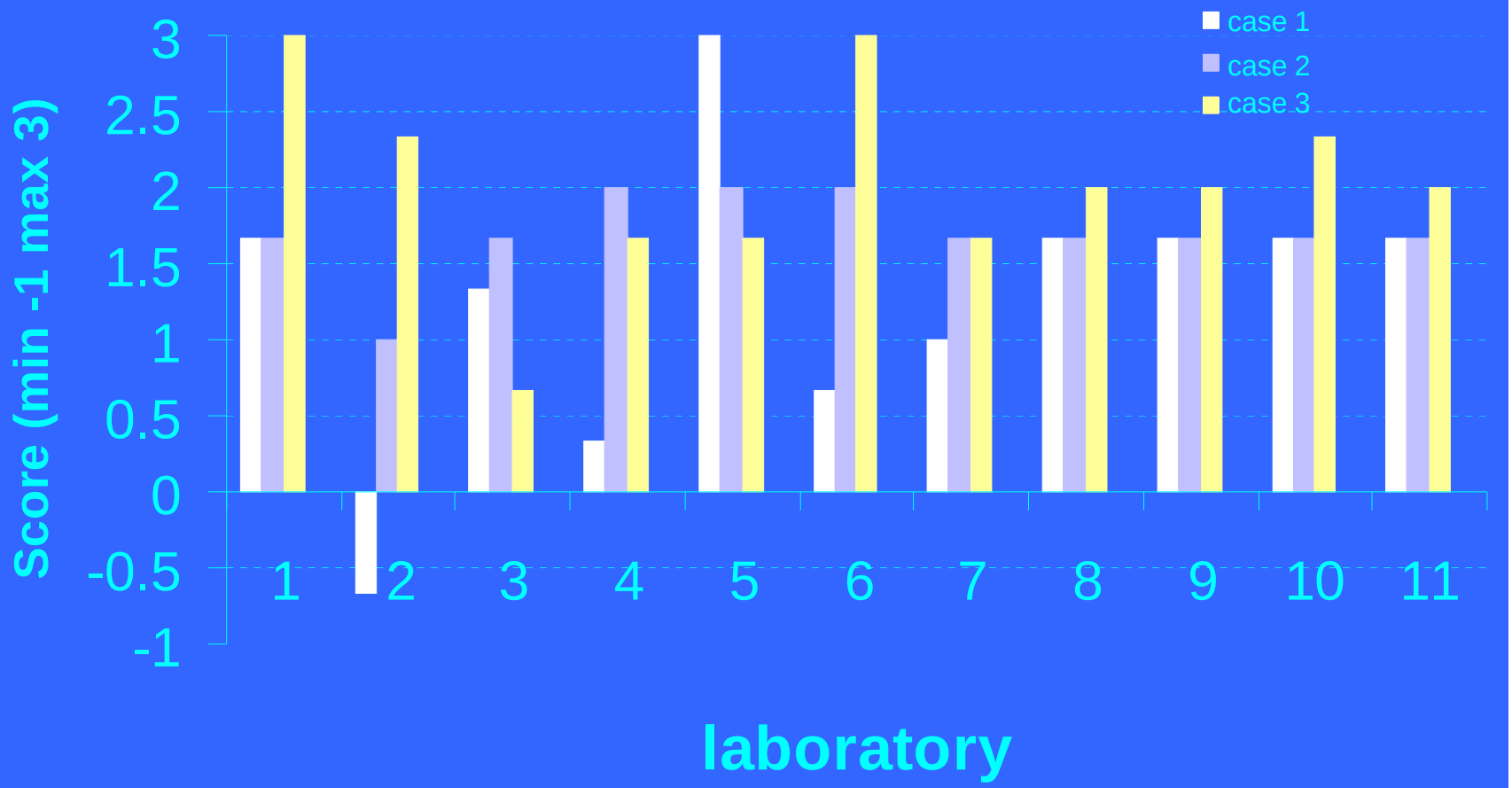
Case 2 - 7m, acidosis, decreased consciousness
fructose-1,6-bisphosphatase deficiency

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	346 *	100 - 290
Serine	124	90 - 290
Threonine	91	70 - 220
Proline	382 *	85 - 290
Leucine	86	65 - 220
Isoleucine	63	26 - 100
Valine	220	90 - 300
Alanine	721 *	150 - 450
Glutamine	614	480 - 800
Arginine	90	40 - 120
Ornithine	51	25 - 120
Lysine	176	100 - 300
Methionine	17	10 - 60
Taurine	92	40 - 140
Phenylalanine	39	35 - 100
Tyrosine	39	30 - 120
Tryptophan	40	30 - 80
Histidine	74	30 - 150
Glutamate	113	35 - 130

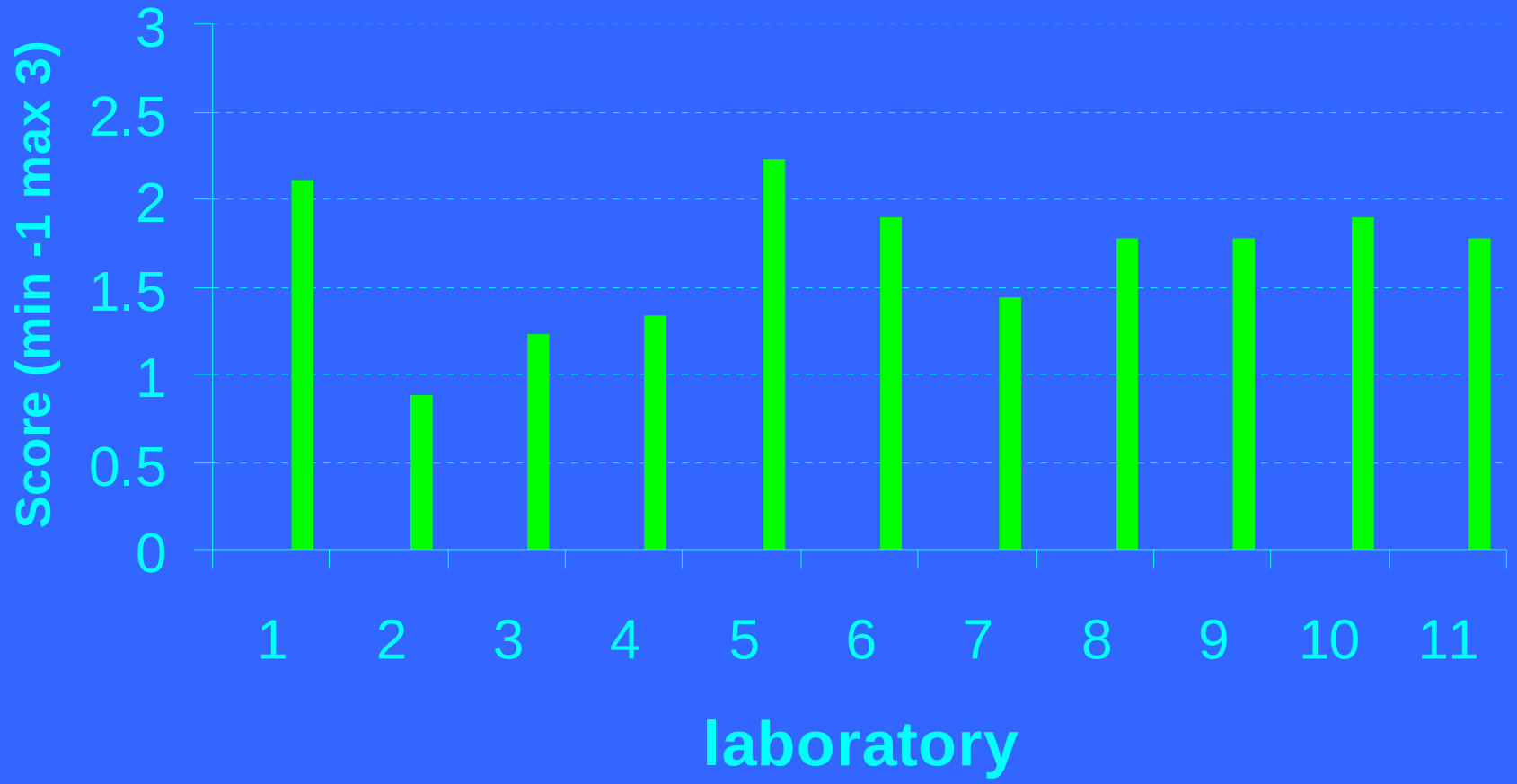
Case 3 - 7m, acidosis, decreased consciousness meningitis

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	84 *	100 - 290
Serine	30 *	90 - 290
Threonine	29 *	70 - 220
Proline	43 *	85 - 290
Leucine	83	65 - 220
Isoleucine	39	26 - 100
Valine	140	90 - 300
Alanine	84 *	150 - 450
Glutamine	337 *	480 - 800
Arginine	24 *	40 - 120
Ornithine	31	25 - 120
Lysine	57 *	100 - 300
Methionine	8 *	10 - 60
Taurine	46	40 - 140
Phenylalanine	66	35 - 100
Tyrosine	23 *	30 - 120
Tryptophan	5 *	30 - 80
Histidine	58	30 - 150
Glutamate	55	35 - 130

Individual case results for the interpretative amino acid QA scheme



Average results for the interpretative amino acid QA scheme



Cases 1, 2 and 3

- distributed by email
- marked by email
- discussions with NEQAS
- to pilot web based scheme for cases 4, 5 & 6
- teething problems
  - relevant personnel did not know cases were open
  - deadline extended…

Case 4 – 1y, regression, raised lactate 4 mmol/L

HHH syndrome (hyperornithinaemia, homocitrullinuria, hyperammonaemia)

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	148	100 - 290
Serine	76 *	90 - 290
Threonine	53 *	70 - 220
Proline	158	85 - 290
Leucine	103	65 - 220
Isoleucine	51	26 - 100
Valine	182	90 - 300
Alanine	251	150 - 450
Glutamine	538	480 - 800
Arginine	31 *	40 - 120
Ornithine	950 *	25 - 120
Citrulline	34	16 - 32
Lysine	306 *	100 - 300
Methionine	35	10 - 60
Taurine	19 *	40 - 140
Phenylalanine	46	35 - 100
Tyrosine	52	30 - 120
Tryptophan	41	30 - 80
Histidine	76	30 - 150
Glutamate	55	35 - 130

Case 5 – 21d, episodes of vomiting
Homocystinuria due to MTHFR deficiency

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	457 *	100 - 290
Serine	328 *	90 - 290
Threonine	238 *	70 - 220
Proline	290	85 - 290
Leucine	151	65 - 220
Isoleucine	62	26 - 100
Valine	205	90 - 300
Alanine	503 *	150 - 450
Glutamine	446	480 - 800
Arginine	71	40 - 120
Ornithine	222 *	25 - 120
Citrulline	11	10 - 35
Lysine	316 *	100 - 300
Methionine	12	10 - 60
Taurine	190 *	40 - 140
Phenylalanine	90	35 - 100
Tyrosine	87	30 - 120
Tryptophan	35	30 - 80
Histidine	145	30 - 150
Glutamate	338 *	35 - 130
Total homocysteine	228 *	5 - 15

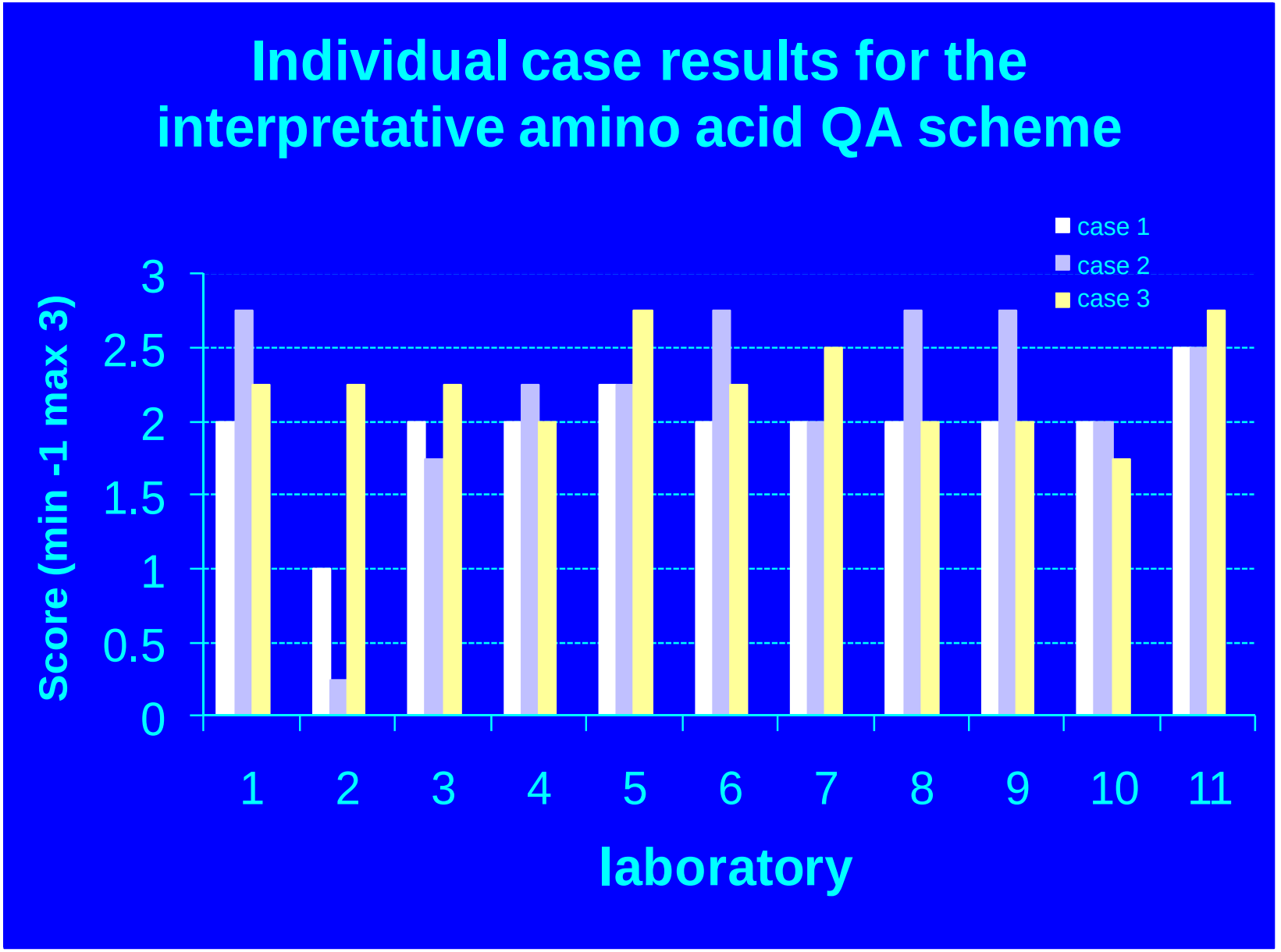
Case 6

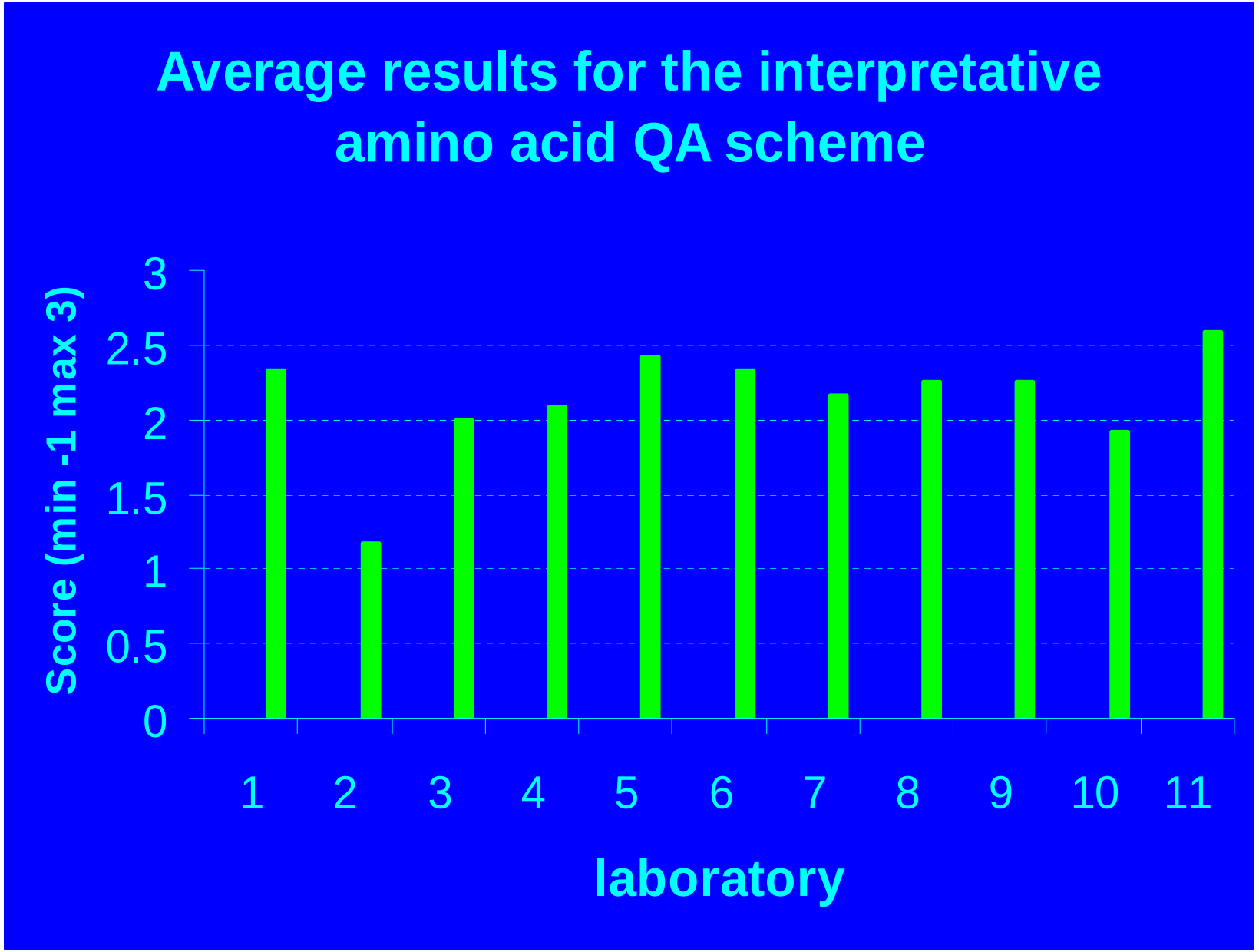
- age 4 years
- normal development
- recently sib presented with persistent unexplained hyperammonaemia in neonatal period
- father has unexplained progressive visual loss due partly to a retinopathy and partly to cataracts

Case 6 – hyperornithinaemia due to ornithine aminotransferase deficiency

Plasma Amino Acid	Value μmol/L	Reference interval μmol/L
Glycine	80 *	100 - 290
Serine	64 *	90 - 290
Threonine	38 *	70 - 220
Proline	74 *	85 - 290
Leucine	132	65 - 220
Isoleucine	78	26 - 100
Valine	258	90 - 300
Alanine	132 *	150 - 450
Glutamine	327 *	480 - 800
Arginine	49 *	40 - 120
Ornithine	847 *	25 - 120
Citrulline	14	10 - 35
Lysine	63 *	100 - 300
Methionine	9 *	10 - 60
Taurine	51	40 - 140
Phenylalanine	55	35 - 100
Tyrosine	41	30 - 120
Tryptophan	40	30 - 80
Histidine	68	30 - 150
Glutamate	43	35 - 130
Total homocysteine	5	5 - 15

Individual case results for the interpretative amino acid QA scheme




Average results for the interpretative amino acid QA scheme
Score (min -1 max 3)
3
2.5
2
1.5
1
0.5
0
1
2
3
4
5
6
7
8
9
10
11
laboratory

Outstanding issues and questions (from Steve's slides)

- include known diagnosis (cf consensus)
- diagnostic/monitoring
- amino acid type tabulated (cysteine, homocysteine, ASA, citrulline)
- amino acid order
- reference interval
- plasma/CSF
- time interval scoring result only a guide
- cases on web – training material
- requirement for new cases
- other (extending scheme to other participants)

Cognitive amino acid scheme my comments

- restart scheme
  - score samples 7, 8 & 9
    - ?need to re-input comments
  - circulate more cases
  - need timetable
  - email labs when cases are open for comment
  - inform assessors when cases ready to score
  - email labs when scoring and outcome available
- results from patients with very rare diagnoses
  - include in scheme for education purposes

Cognitive amino acid scheme

- advantages
  - exposure to rare diagnostic patient results
  - promotes discussion and learning (cognitive)
  - potential to include other analytes
  - participant number small enough to enable comparison of all comments
- disadvantages
  - snap-shot of real life
  - no interaction, clinical discussion

Conclusions

Cognitive/interpretative quality schemes

- enormous potential in highly specialist area
- promote adherence to guidelines
- promote best practice for reporting
- only way to quality assure qualitative tests
- invest in the future
  - pass on knowledge
  - expanding field
  - exposure to rare disorders