Cognitive Amino Acids Pilot Scheme

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- background
- logistics
- example circulation
- review after 4 circulations
- questionnaire to users
- conclusions - and discussion

Background

- interpretation of biochemical results key to arrive at diagnosis
- UK NEQAS interpretive comments scheme
  - routine clinical chemistry
  - assesses the post-analytical aspects of the clinical testing process
  - educational scheme, aimed at individuals, 1 case per month
  - could a similar scheme work for metabolic analytes?

- several ERNDIM schemes do already include interpretation
  - organic acids, acyl carnitines, DPT etc – use authentic samples
- amino acids
  - one of highest workload tests
  - good quantitative scheme (accuracy, linearity, precision)
  - but no interpretive aspect
  - 269 participants so cannot use authentic samples
    - 1mL vial per circulation ~ 600ml blood

Cognitive amino acids scheme

- UK (Steve Krywawych) ran a scheme with UK NEQAS
  - 11 labs
  - folded in 2011 due to logistical problems
- proposal put to ERNDIM for a pilot scheme
- accepted and commenced 2017
  - each circulation to comprise 3 sets of amino acid results
  - use real results from patient samples
  - returns from participants to include
    - abnormalities
    - diagnosis
    - further tests
- scored by 4 scientific evaluators

Logistics

- on line entry and evaluation was planned but was not possible
- first circulation by email
- subsequent circulations used the ERNDIM Formdesk portal

Circulation 1 (2017)

- 2017-1 Classical homocystinuria
  - plasma amino acid results + chromatogram
- 2017-2 Lysinuric protein intolerance
  - plasma amino acids + selected urinary levels
- 2017-3 Non ketotic hyperglycinaemia
  - plasma and urine amino acids provided

Circulation 2 (2018)

- 2018-1 Ornithine transcarbamylase deficiency
  - plasma amino acids
- 2018-2 Citrin deficiency
  - plasma amino acids
- 2018-3 Glycogen storage disease type 1
  - plasma and urine amino acids + routine chemistry results

Circulation 3 (2018)

- 2018-4 Argininaemia
  - plasma, urine and CSF amino acids
- 2018-5 Propionic aciduria
  - plasma and urine amino acids
- 2018-6 Tyrosinaemia type 3
  - plasma amino acids

Circulation 4 (2019)

- 2019-1 Ornithine transcarbamylase deficiency on treatment
  - plasma amino acids
- 2019-2 Pyruvate dehydrogenase deficiency
  - plasma amino acids
- 2019-3 Hyperlysinaemia
  - plasma amino acids

Participants

- initially Austria, Germany, Switzerland and UK
  - 33 labs invited, 2 declined
  - 26 submissions received
- participation extended to France
  - 54 participants
  - 46, 42 & 45 submissions received

Scoring

Circulation	abnormalities	diagnosis	further tests	TOTAL
2017-1	2	2		4
2018-1	2	1	1	4
2018-2	2	2	2	6
2019-1	2	2	2	6

Scoring

Circulation	abnormalities	diagnosis	further tests	TOTAL
2017-1	2	2		4
2018-1	2	1	1	4
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2019-1	2	2	2	6

- scoring was difficult
  - no single right answer
  - marking scheme never covers all responses!

An example data set (2018-5)

Clinical information

Sex/Age	10 days-old boy
Pregnancy	two seizures of the mother, eeg normal
Birth	uneventful
Family History	normal
Previous history	n/a
Initial symptoms	became somnolent
Follow-up	normal
Treatment	symptomatic

- ammonia 134 µmol/L (ref range 24-48)

	Plasma		Urine	
	µmol/L	Ref range	µmol/mmol creat	Ref range
taurine	42	10-95	91	8-226
threonine	82	33-128	30	20-138
serine	181	24-178	227	80-282
glutamate	82	6-93	3	0-30
glutamine	683	20-550	122	52-205
proline	290	52-277	114	21-213
glycine	490	70-430	1661	283-1097
alanine	409	99-380	241	75-244
citrulline	18	0-29	9	0-11
valine	103	57-262	9	3-26
methionine	15	3-41	4	7-27
isoleucine	41	26-53	4	0-6
leucine	94	46-109	15	3-25
tyrosine	57	11-112	20	6-55
phenylalanine	37	23-110	13	4-32
ornithine	62	10-151	3	0-19
lysine	144	45-240	27	22-171
histidine	48	25-114	41	80-295
arginine	77	0-85	5	0-14

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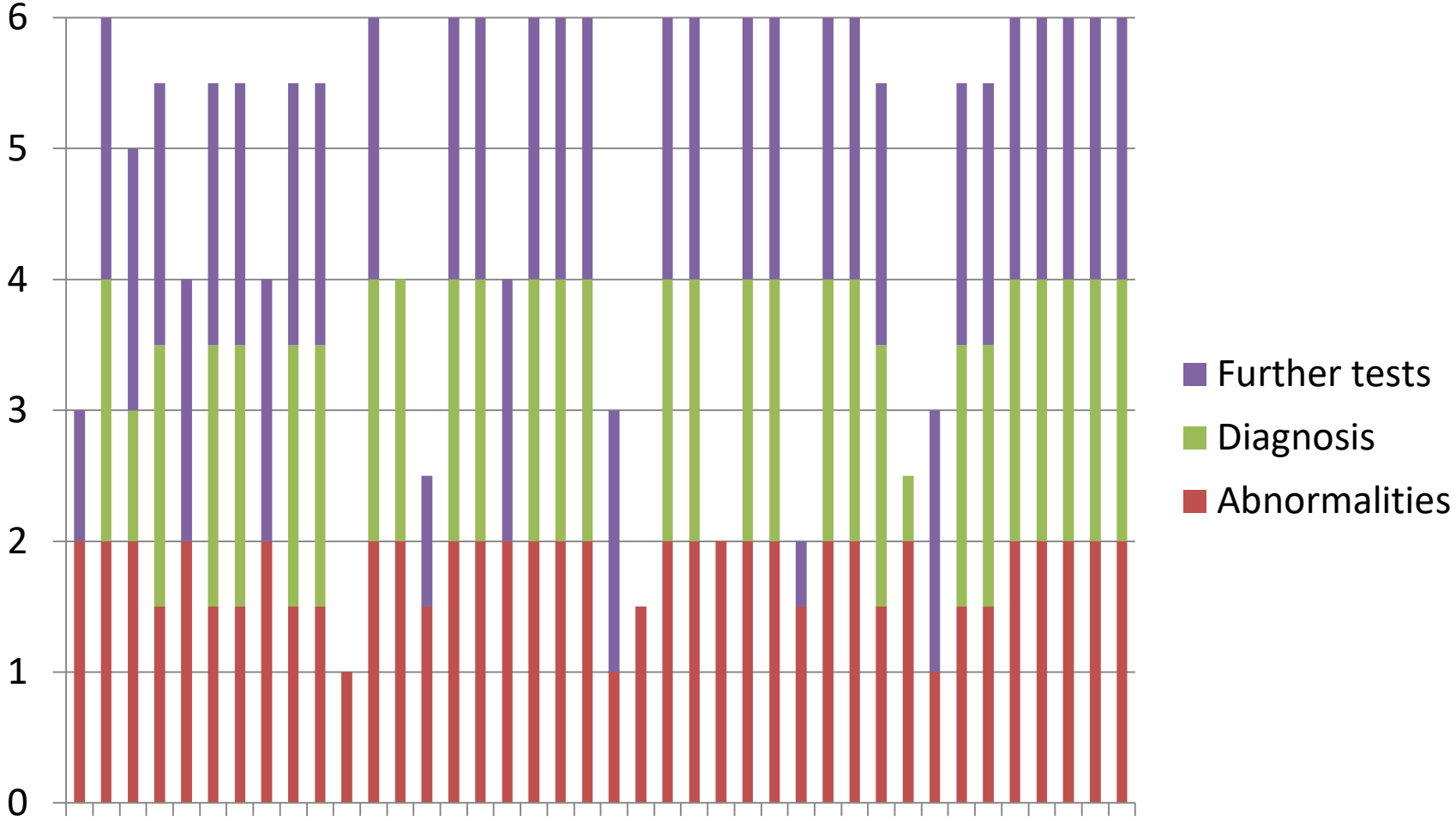
Marking scheme

- Findings (maximum 2 points)
  - increased plasma glutamine 0.5 points
  - milder increase of glycine and alanine 0.5 points
  - moderate increase of urine glycine 0.5 points
  - mild hyperammonaemia 0.5 points
- Diagnosis (maximum 2 points)
  - organic acidaemia 2.0 points
  - ketotic hyperglycinaemia 2.0 points
  - propionic acidaemia 2.0 points
  - methylmalonic acidaemia 2.0 points
- Further tests (maximum 2 points)
  - organic acids/acyl carnitines 2 points
  - repeat plasma ammonia 0.5 points
  - full blood count 0.5 points

- scored by all evaluators independently
- discrepant scoring reviewed ➔ final score

Summary of scores for sample 2018-5



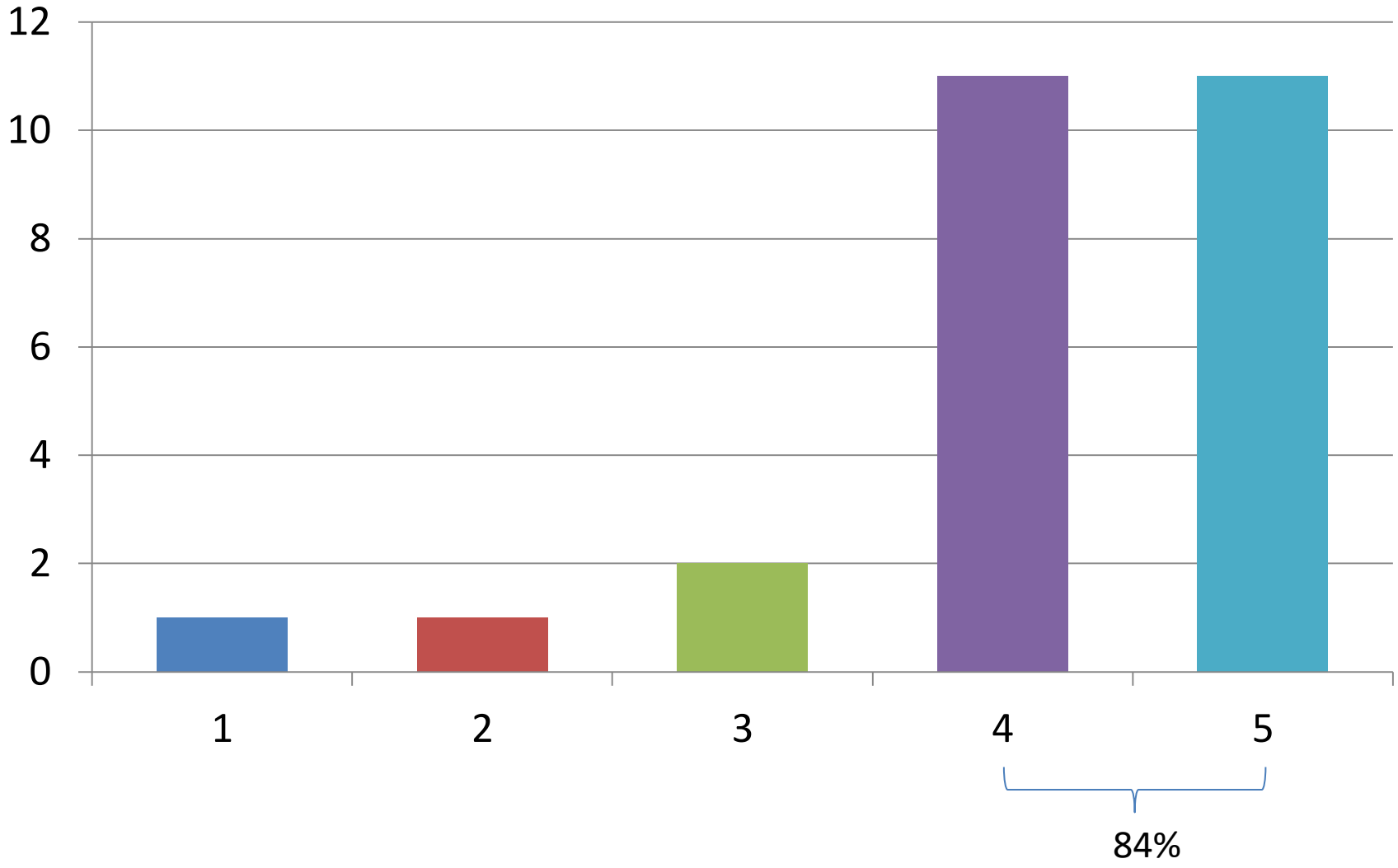
Assessor's meeting July 2019 review of the pilot

- only used IEC results so far, but others (HPLC, TMS) could be included
- need to do more work on marking scheme
- certain aspects need clarification
  - is it an amino acid scheme or does it go wider?
  - include certain/tentative diagnosis as in other ERNDIM schemes
  - should non-diagnostic results be included
    - eg liver disease, specimen deterioration, treatment monitoring
- if the scheme were rolled out would need
  - improved logistics for assessors and participants
  - may need multiple centres with up to 60 participants cf DPT, OAS etc
  - but UK NEQAS scheme has over 300 participants and no marking scheme!
- participant questionnaire

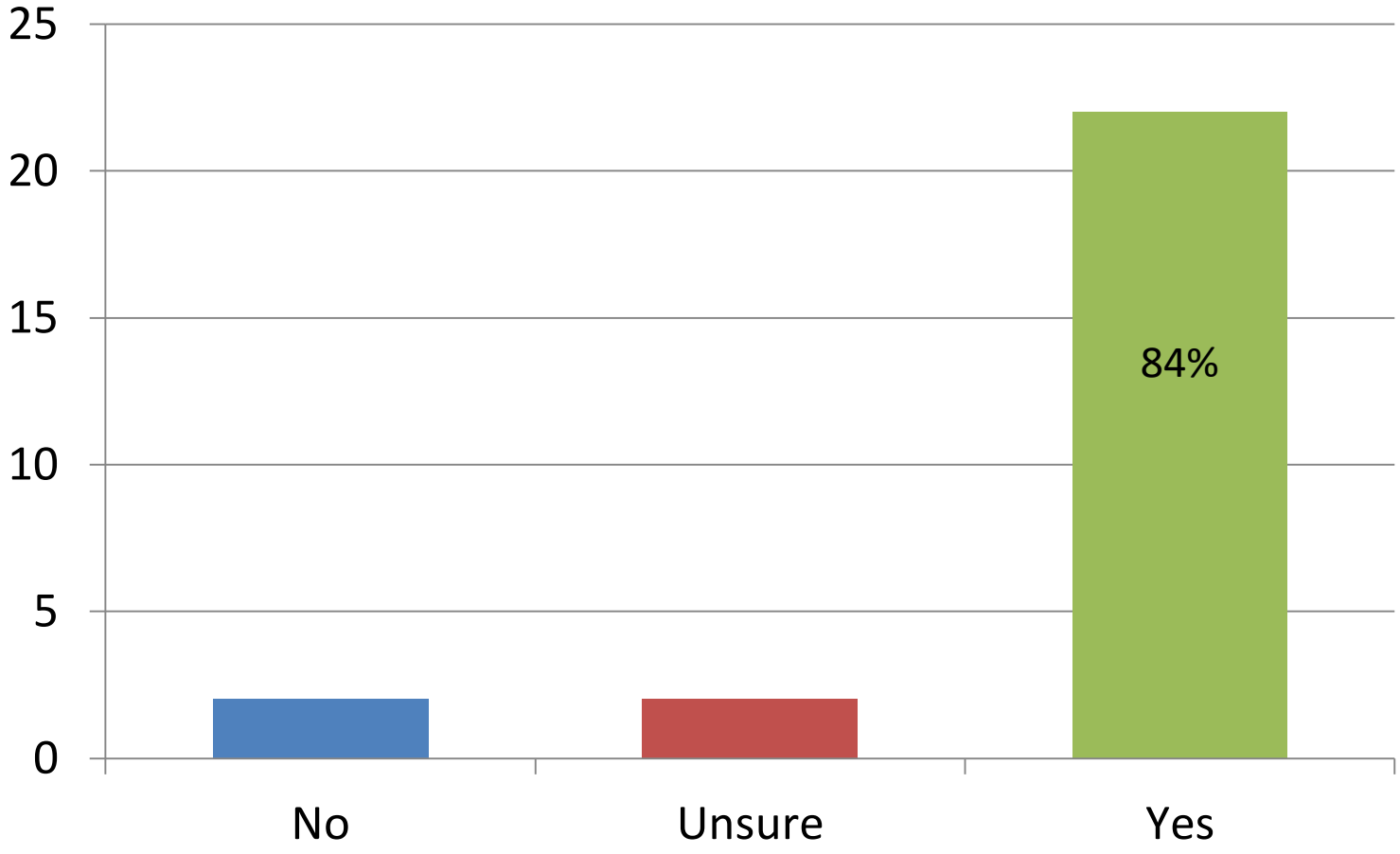
Questionnaire

- sent to primary and secondary contacts at 45 participating centres
- anonymous
- 26 responses

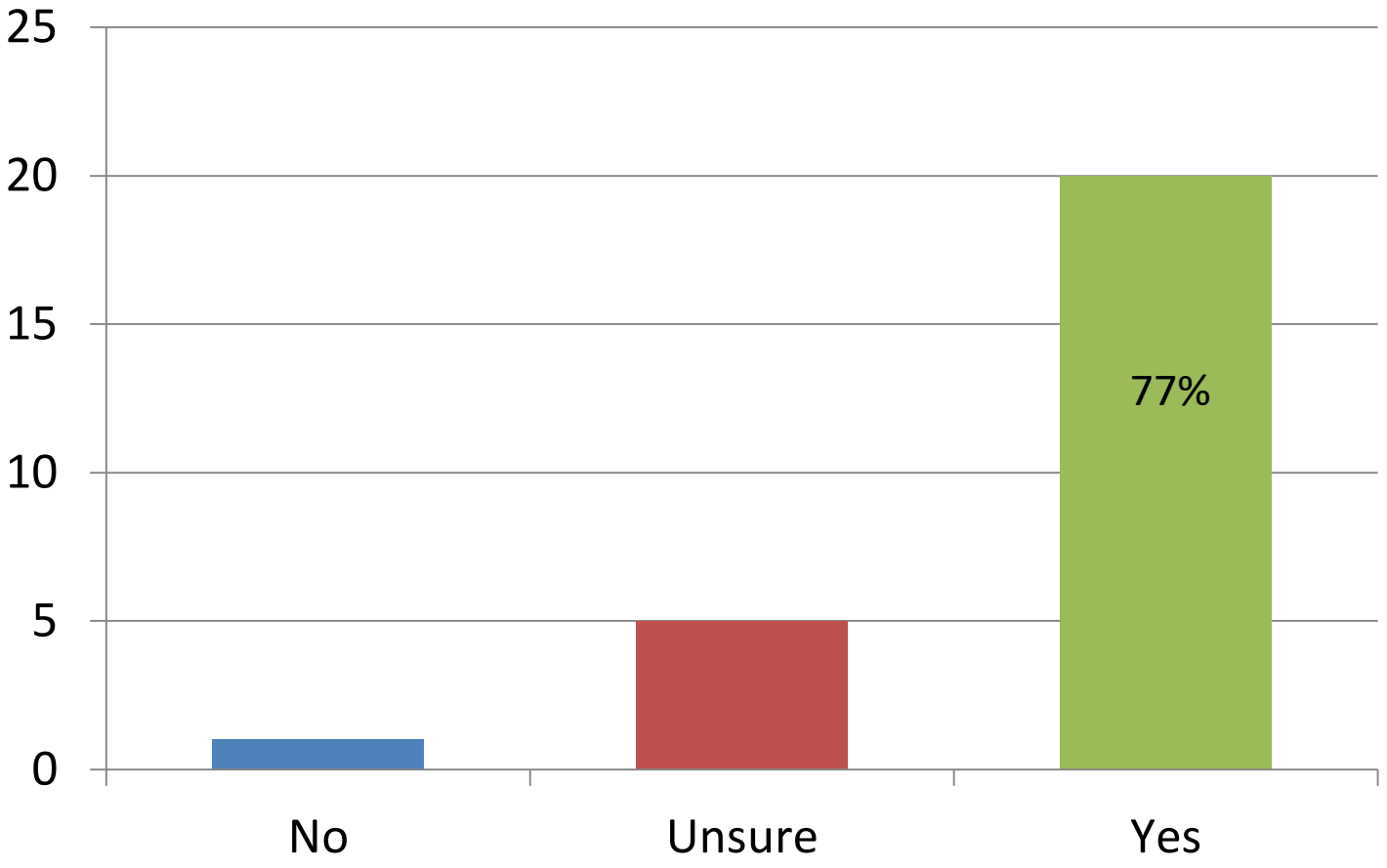
Q1. How useful have you found the Cognitive Amino Acid pilot scheme? (1-5, 5 being the best score)



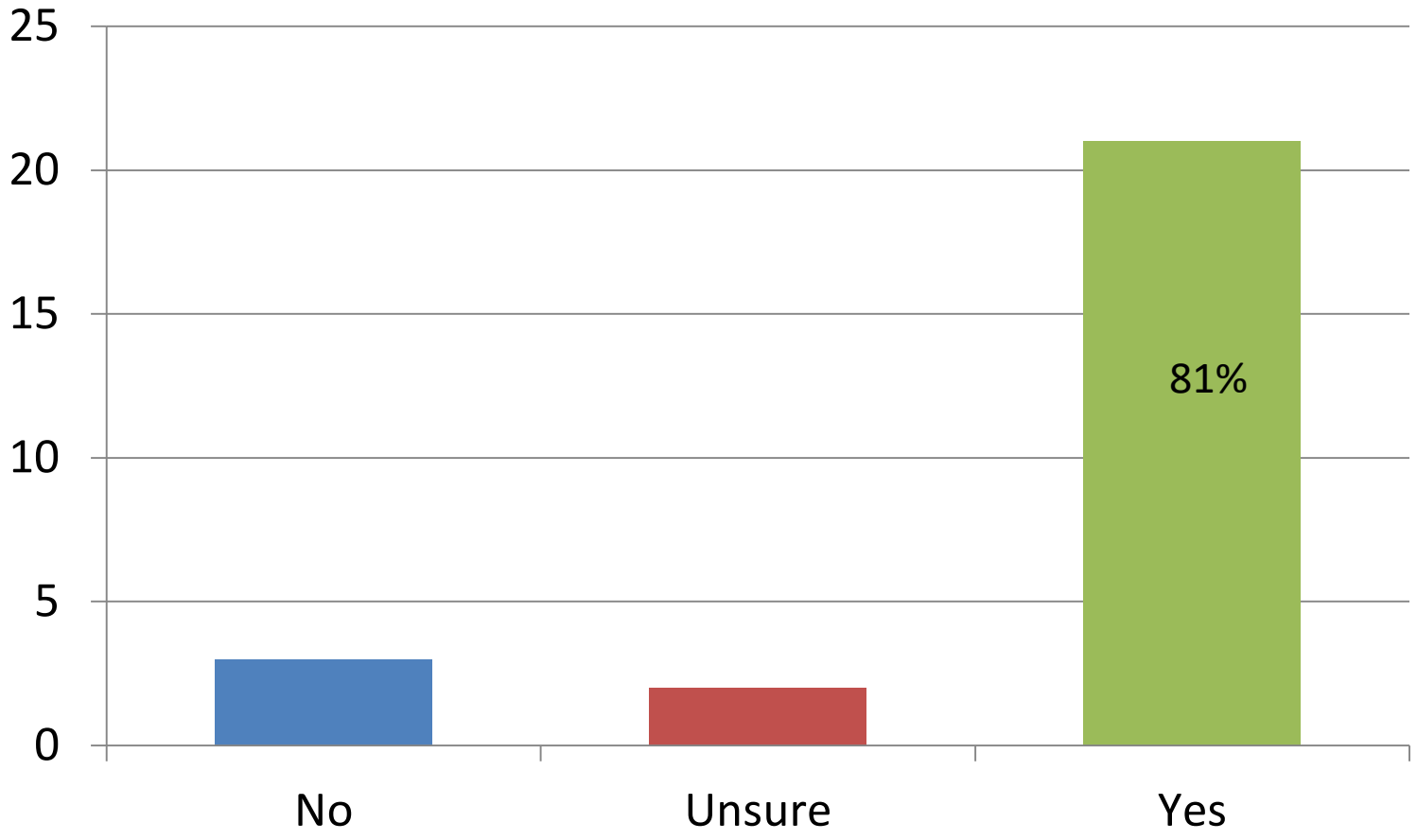
Q2. Do you think that ERNDIM should introduce the Cognitive Amino Acid scheme as a full scheme permanently?



Q3. Do you think that the reports from each distribution are adequate?



Q4. Would it be useful if the report contained examples of "high scoring" and "low scoring" comments?



Q5. Have you got any other suggestions as to how ERNDIM could improve the scheme?

Please provide examples (11 responses).

- Aims/scope of the scheme unclear
  - some cases broader than expected
  - ?have real situation cases with all analytical data
- Reference ranges very variable
- Interesting to see secondary amino acid abnormalities, but cannot expect a definitive diagnosis
- Scoring
- Technical ERNDIM issues
- This scheme is not useful or necessary

Conclusions after 4 circulations

- most responding participants find the scheme useful and would like it to continue
  - valuable exposure to rare diagnostic patient results
  - promotes discussion and learning
    - increasing workload
    - pass on knowledge
    - expanding field
  - potential to include other analytes
- but
  - only a snap-shot of real life
  - no interaction or clinical discussion (no different from other ERNDIM schemes)
- no mention of money!

Acknowledgements

- Thanks to ERNDIM for hosting pilot scheme
- Thanks to my co-assessors
  - Brian Fowler
  - Rachel Carling
  - Sabine Scholl-Bürgi

What next?

- Report to ERNDIM SAB

- Open to discussion