ERNDiM
Quality Assurance in Laboratory Testing for IEM

Amino Acids Interpretation (AAI) Scheme

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2026 First Round Interim Report *(DOC5136)*

Version Number[1]: 01
Date of issue: 21st July 2026

Please Note:

- This interim report is intended for participants of the ERNDIM AAI scheme. The contents should not be used for any publication without permission of the Scientific Advisor.
- **This is an interim report and it includes provisional scores only**. All scores are subject to change following moderation at the Scientific Advisory Board meeting in autumn of this year. For final scores and performance data the ERNDIM AAI Annual Report should be referred to.
- The fact that your laboratory participates in this scheme is not confidential, however, the raw data and performance scores are confidential and will only be shared within ERNDIM for the purpose of evaluating your laboratories performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the ERNDIM Privacy Policy on www.erndim.org.

1. Results Submission

The deadline for submission of the 2026 first round results was 26th May 2026. Participants were able to view the cases and submit their results using the ERNDIM Formdesk website.

148 laboratories registered for the 2026 AAI scheme, of these 146 labs (98.6%) submitted results for the first round.

2. Scoring System

As for the previous circulations, each of the three aspects, analytical findings, diagnosis, and further tests, were scored equally with a maximum of two points for each category. Plasma, CSF and/or urine amino acid concentrations together with the laboratories reference ranges were provided.

The scoring was carried out in accordance with a pre-determined scheme. It was done by two blinded evaluators each (the evaluators were blinded to both, the ERN number and to the scores of the second evaluator). If the scores were not concordant the scheme advisor scored in addition. Further close evaluation based on agreed/revised scoring criteria was used to determine on the final score.

[1] **If this Report is not Version 1 for this scheme year, go to APPENDIX 2 (page 10) for details of the changes made since the last version of this document.**

3. Results of samples and evaluation of reporting

3.1. Case 2026-1: Non-Ketotic Hyperglycinemia (NKH).

3.1.1. Sample Details

The results of the amino acid analysis are from a 3-day-old male infant who had to be intubated due to seizures and subsequent respiratory failure. The mother had already noticed that the child had frequent bouts of hiccups during pregnancy. Otherwise, the pregnancy was uneventful. The child was born at 41 weeks' gestation and, following birth, exhibited irritability, muscular hypotonia and weak sucking. Treatment consisted of sodium benzoate and dextromethorphan. Molecular genetic analysis revealed a homozygous mutation in the *GLCD* gene.

3.1.2. Analytical findings (maximum 2 points)

Analysis of the amino acids in plasma and cerebrospinal fluid revealed significantly elevated concentrations of glycine in both specimens. Furthermore, the cerebrospinal fluid-to-plasma ratio for glycine was significantly elevated (0.167); the reference range is less than 0.02. All participants reported significantly higher glycine concentrations.

3.1.3. Diagnosis (maximum 2 points)

A diagnosis of NKH a as the primary or alternative diagnosis was awarded two points, all participants reported NKH as the primary diagnosis or, at the very least, as a differential diagnosis (146/146 = 100%).

3.1.4. Further tests (maximum 2 points)

One point should be awarded for genetic testing, one point for repeat metabolite analysis and one point for enzyme analysis when recommending further tests. However, this diagnostic approach no longer reflects everyday clinical practice. On the one hand, repeat metabolite testing involving a repeat lumbar puncture would not be indicated; on the other hand, enzyme analysis is only offered in a few laboratories and is therefore likely to be reserved for cases with unclear genetic findings. For this reason, the mention of molecular genetic analysis, including the correct gene or diagnosis, was awarded two points.

3.1.5. Comments on overall performance

In this scheme, overall proficiency was the first time 100%. However, both the clinical symptoms and the laboratory results were very clear.

3.2. Case 2026-2: PNPO (=pyridox(am)ine 5-P oxidase).

3.2.1. Sample details

The results of the plasma amino acid analysis were obtained from a male infant on the first day of life; those from the cerebrospinal fluid were obtained on the third day of life. The infant had experienced foetal distress (the pH was 7.1, lactate 2.8 mmol/L) and abnormal movements suggestive of cerebral seizures. He was therefore given phenobarbital. The family history is noteworthy, as a sibling died at the age of 5 weeks following uncontrollable seizures. Molecular genetic analysis revealed a homozygous mutation in the *PNPO* gene.

3.2.2. Analytical findings (maximum 2 points)

Plasma and cerebrospinal fluid amino acid concentrations were provided; however, the samples were not collected on the same day. Some amino acid concentrations were found to be elevated; particularly noteworthy among these were those of alanine and proline (as markers of metabolic stress) and glycine and threonine (as markers of a PNPO deficiency)

Participants were awarded two points if they named all four amino acids. Participants who mentioned fewer than the four amino acids were awarded one point (additionally, mention of threonine and glycine was required for one point). This was the case for 59 participants. A further 9 participants did not receive any points, as they reported only one amino acid as being elevated.

3.2.3. Diagnosis (maximum 2 points)

131 participants identified the correct diagnosis as the primary or differential diagnosis and were therefore awarded two points. Thirteen participants did not specify the diagnosis of a vitamin B6-dependent inherited metabolic disorder. However, they mentioned other metabolic disorders such as non-ketotic hyperglycinemia or organoaciduria, which are associated with elevated glycine concentrations. These participants were awarded one point. Two participants scored zero points because they either did not identify the pre-determined differential diagnoses or considered the results to be too non-specific.

3.2.4. Further tests (maximum 2 points)

The evaluation of the recommended parameters was divided into two test sets. Test set 1 comprised the following parameters: urine α-aminoadipic semialdehyde (AASA), PNPO activity, blood/CSF pyridoxal phosphate, CSF neurotransmitters, Δ1-piperidine-6-carboxylate, genetics: *PNPO, ALDH7A1, SLC6A9, PLPBP.*

Two points were awarded if at least two tests from Test set 1 were recommended (107 participants). One point was awarded if only one test from Test set 1 was mentioned, regardless of whether other tests (Test set 2) were recommended (such as NKH enzyme assay, pipecolic acid, organic acids, urine amino acids, blood acylcarnitines), that was the case for 25 participants.

3.2.5. Comments on overall performance

Overall proficiency stood at 83%, with diagnostic competence being the highest at 94%. In particular, the clinical symptoms were very striking in this case, as was the combination of elevated threonine and glycine levels. As there is, in principle, a treatment option for this metabolic disorder, early diagnosis is important. We hope therefore that, when faced with a real patient presenting with these symptoms and findings, participants will include metabolic disorders of vitamin B6 metabolism in their differential diagnosis.

3.3. Case 2026-3: Methylmalonic aciduria

3.3.1. Sample details

The results of the plasma amino acid analysis were recorded on the fifth day of life in a female infant. The pregnancy and delivery were uneventful. The family medical history was unknown at the time of admission to hospital.

The girl had lost 19% of her weight since birth (which is always an indication of an underlying condition). She also had muscular hypotonia and an abnormal breathing pattern, suggesting metabolic acidosis.

The laboratory tests revealed metabolic acidosis. Sodium and chloride levels were provided so that participants could calculate the anion gap (anion gap = sodium – (chloride + bicarbonate)). The anion gap was elevated at 24 mmol/L (154 – (120 + 10); reference range up to 16 mmol/L). This already provides an indication of the aetiology of the acidosis (such as organoaciduria, for example).

Hyperammonaemia was also observed. However, the glutamine concentration is relatively low given this significantly elevated ammonia concentration. This, together with the elevated glycine concentration, could also be an indication of organoaciduria.

The concentrations of other amino acids were also elevated. This could be due to the infant's critical condition inclusive the ketosis (which may lead to an elevation of BCAAs).

3.3.2. Analytical findings (maximum 2 points)

For the analytical findings, one point was awarded for each of the following assessments:

- elevated ala, gly, pro, thr, lys, ser, tyr
- elevated ile, leu, val
- only slightly elevated gln (despite NH3↑)

The concentration of alloisoleucine was not specified.

A total of 143 participants received two points. Many participants explained their assessment, which was good.

3.3.3. Diagnosis (maximum 2 points)

120 participants identified the correct diagnosis (group) as the primary or differential diagnosis and were therefore awarded two points. 20 participants did not mention organoacidurias in the diagnosis part. They were awarded one mark because they mentioned important differential diagnoses such as UCD or MSUD. The proficiency for this part was 89%.

3.3.4. Further tests (maximum 2 points)

Although this is a diagnostic scheme, many participants also recommended emergency treatment. Whilst this is not assessed, it is nonetheless very important.

However, only the recommendations for further tests were assessed; one point was awarded for each of the following investigations:

- acylcarnitine profile in DBS, plasma, serum (n = 108)
- organic acids in urine (incl. orotic acid) (n = 142)
- genetic testing (MUT, PCC, UCD) (n = 84)
- vitamin B12, homocysteine (n = 13)

116 participants scored 2 points, and 28 scored 1 point. The proficiency was therefore 89%.

3.3.5. Comments on overall performance

Overall proficiency stood at 92%. In this case, the other laboratory parameters (i.e. the acid-base balance and the ammonia concentration) were particularly noteworthy.

Together with the results of the amino acid analysis, it was possible to narrow down the differential diagnoses and reach a definitive diagnosis through further investigations.

It was very positive that most of the participants were aware that this was an absolute emergency situation.

3.4. Comments on the whole of the first circulation results 2026

We hope that we have once again succeeded in presenting three interesting and instructive cases to the participants this round. The aim should be to describe the laboratory changes, the diagnosis and the further recommendations in such a way that it is also easy to understand for the doctors looking after the patient.

In this first three cases, it was also important to take into account the clinical symptoms and other relevant laboratory tests.

The overall competence was good with 92%. The expertise at NKH was particularly good, scoring 100% (see Figure 1).

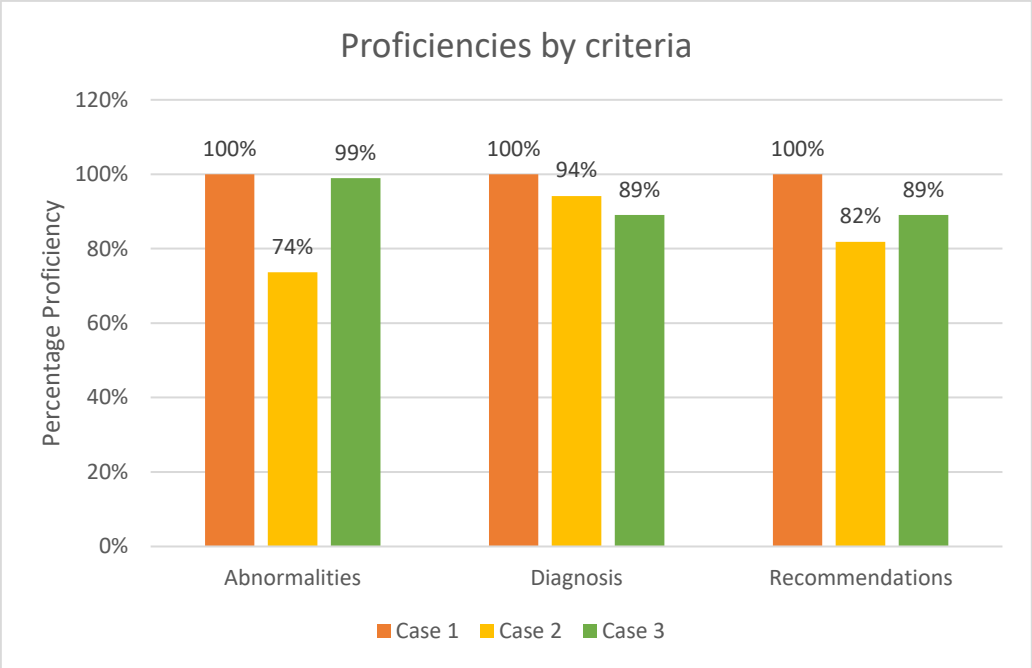

Figure 1: Proficiencies by criteria.

The common methods used by the participants for amino acid analysis are LC-MS/MS with a share of 51% and HPLC with ninhydrin detection (1/2 Int. Std.) with a share of 29%.

Table 1: Laboratory methods for the analysis of amino acids used by the participants (146/148 participants completed this question)

Method	No of responses
LC-MS/MS	75
Ion-exchange chrom Ninhydrin 1/2 Int. Std	42
Reverse phase HPLC/UPLC with non-MS detection	12
LC-MS	8
Ion-exchange chrom Ninhydrin 0 Int. Std	7
LC-HRMS	1
GC-FID and/or Reverse phase HPLC with Fluorimetric detection	1
Total	**146**

Table 2: Overall scores for the first circulation in the 2026 Amino Acid Interpretation scheme

	2026.01				2026.02				2026.03				2026.01 - .03
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Totals
Total Points	292	292	292	876	215	275	239	729	289	260	260	809	2414
% proficiency	100%	100%	100%	100%	74%	94%	82%	83%	99%	89%	89%	92%	92%

Key

A = Findings, abnormalities

D = Diagnosis

R = Recommendations for further testing

We encourage participants to send us comments and suggestions regarding this scheme and do not hesitate to contact us if you question any of our scoring.

Date: 20th July 2026

The Scientific Evaluators

Sabine Scholl-Bürgi, Scientific Advisor
Scheme Assessors: Apolline Imbard (Deputy Scientific Advisor), Olivier Braissant, Rachel Carling, Alistair Horman, Daniela Karall, and Anke Schumann

APPENDIX 1. Detailed scores for submitting laboratories

Key

A = Findings, Abnormalities

D = Diagnosis

R = Recommendations for further testing

DNS = did not submit any results

	2026.01				2026.02				2026.03				2026.01 - .03
Anon. lab number	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
1	2	2	2	6	2	2	2	6	2	2	2	6	18
2	2	2	2	6	1	1	0	2	2	2	2	6	14
3	2	2	2	6	1	2	2	5	2	2	2	6	17
4	2	2	2	6	2	2	2	6	2	2	2	6	18
5	2	2	2	6	1	2	2	5	2	2	2	6	17
6	2	2	2	6	2	2	2	6	2	1	1	4	16
7	2	2	2	6	1	2	2	5	2	2	2	6	17
8	2	2	2	6	2	2	2	6	2	2	1	5	17
9	2	2	2	6	1	2	1	4	2	2	1	5	15
10	2	2	2	6	2	2	2	6	2	2	2	6	18
11	2	2	2	6	1	2	2	5	2	2	2	6	17
12	2	2	2	6	1	2	1	4	2	1	1	4	14
13	2	2	2	6	1	2	1	4	1	2	2	5	15
14	2	2	2	6	1	2	2	5	2	2	2	6	17
15	2	2	2	6	2	2	2	6	2	2	2	6	18
16	2	2	2	6	2	2	1	5	2	2	0	4	15
17	2	2	2	6	1	2	2	5	2	2	2	6	17
18	2	2	2	6	2	2	2	6	2	2	2	6	18
19	2	2	2	6	2	2	2	6	2	2	2	6	18
20	2	2	2	6	2	2	2	6	2	2	2	6	18
21	2	2	2	6	2	1	0	3	2	2	2	6	15
22	2	2	2	6	1	1	0	2	2	2	1	5	13
23	2	2	2	6	2	1	0	3	2	1	1	4	13
24	2	2	2	6	2	2	2	6	2	2	2	6	18
25	2	2	2	6	2	2	2	6	2	2	2	6	18
26	2	2	2	6	2	2	2	6	2	2	2	6	18
27	2	2	2	6	2	2	2	6	2	1	1	4	16
28	2	2	2	6	1	2	2	5	2	1	1	4	15
29	2	2	2	6	0	1	0	1	2	2	2	6	13
30	2	2	2	6	2	2	1	5	2	2	2	6	17
31	2	2	2	6	2	2	1	5	2	2	2	6	17
32	2	2	2	6	1	2	1	4	2	2	2	6	16
33	2	2	2	6	1	2	2	5	2	2	1	5	16
34	2	2	2	6	2	2	2	6	2	0	2	4	16
35	2	2	2	6	2	2	1	5	2	2	2	6	17
36	2	2	2	6	1	2	2	5	2	0	1	3	14
37	2	2	2	6	1	2	2	5	2	2	2	6	17
38	2	2	2	6	1	2	2	5	2	1	1	4	15

	2026.01				2026.02				2026.03				2026.01 - .03
Anon. lab number	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
39	2	2	2	6	2	1	0	3	2	2	2	6	15
40	2	2	2	6	2	2	2	6	2	2	2	6	18
41	2	2	2	6	2	2	2	6	2	2	2	6	18
42	2	2	2	6	2	2	2	6	2	2	2	6	18
43													DNS
44	2	2	2	6	2	2	2	6	2	2	2	6	18
45	2	2	2	6	2	2	2	6	2	2	2	6	18
46	2	2	2	6	1	2	2	5	2	2	2	6	17
47	2	2	2	6	2	2	2	6	1	2	2	5	17
48	2	2	2	6	1	2	2	5	2	2	2	6	17
49	2	2	2	6	0	2	2	4	2	2	2	6	16
50	2	2	2	6	1	2	2	5	2	2	1	5	16
51	2	2	2	6	2	2	2	6	2	1	1	4	16
52	2	2	2	6	2	2	2	6	2	2	2	6	18
53	2	2	2	6	1	2	2	5	2	2	2	6	17
54	2	2	2	6	0	2	2	4	2	2	2	6	16
55	2	2	2	6	2	2	1	5	2	2	2	6	17
56	2	2	2	6	1	2	2	5	2	0	2	4	15
57	2	2	2	6	2	2	2	6	2	2	2	6	18
58	2	2	2	6	1	2	2	5	2	1	1	4	15
59	2	2	2	6	2	2	2	6	2	2	2	6	18
60	2	2	2	6	2	2	2	6	2	2	2	6	18
61	2	2	2	6	2	2	2	6	2	2	2	6	18
62	2	2	2	6	1	2	2	5	2	1	2	5	16
63	2	2	2	6	2	2	2	6	2	2	2	6	18
64	2	2	2	6	2	2	2	6	2	2	2	6	18
65	2	2	2	6	1	2	2	5	2	2	2	6	17
66	2	2	2	6	2	2	2	6	2	2	2	6	18
67	2	2	2	6	1	2	2	5	2	1	2	5	16
68	2	2	2	6	1	2	2	5	2	2	2	6	17
69	2	2	2	6	2	2	2	6	2	2	2	6	18
70													DNS
71	2	2	2	6	1	2	2	5	2	1	1	4	15
72	2	2	2	6	2	2	2	6	2	2	2	6	18
73	2	2	2	6	1	2	1	4	2	2	2	6	16
74	2	2	2	6	2	2	1	5	2	2	2	6	17
75	2	2	2	6	2	2	2	6	2	2	2	6	18
76	2	2	2	6	1	2	1	4	2	2	2	6	16
77	2	2	2	6	1	2	2	5	2	2	1	5	16
78	2	2	2	6	2	2	2	6	2	2	2	6	18
79	2	2	2	6	1	2	2	5	2	2	2	6	17
80	2	2	2	6	2	2	2	6	2	2	2	6	18
81	2	2	2	6	2	1	0	3	2	1	0	3	12
82	2	2	2	6	2	2	1	5	2	1	1	4	15
83	2	2	2	6	1	2	1	4	2	2	2	6	16

	2026.01				2026.02				2026.03				2026.01 - .03
Anon. lab number	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
84	2	2	2	6	2	2	2	6	2	2	1	5	17
85	2	2	2	6	2	2	1	5	2	2	2	6	17
86	2	2	2	6	1	2	2	5	2	2	2	6	17
87	2	2	2	6	2	2	2	6	2	2	2	6	18
88	2	2	2	6	1	2	2	5	2	2	2	6	17
89	2	2	2	6	2	2	2	6	2	2	2	6	18
90	2	2	2	6	1	2	1	4	2	2	2	6	16
91	2	2	2	6	2	0	0	2	2	1	1	4	12
92	2	2	2	6	1	2	2	5	2	2	2	6	17
93	2	2	2	6	1	2	2	5	2	2	2	6	17
94	2	2	2	6	2	1	0	3	2	2	2	6	15
95	2	2	2	6	0	1	0	1	2	1	1	4	11
96	2	2	2	6	2	2	2	6	2	2	1	5	17
97	2	2	2	6	1	2	2	5	2	1	1	4	15
98	2	2	2	6	1	2	1	4	2	2	2	6	16
99	2	2	2	6	2	2	2	6	2	2	2	6	18
100	2	2	2	6	1	2	1	4	2	2	2	6	16
101	2	2	2	6	2	2	1	5	2	2	2	6	17
102	2	2	2	6	1	2	2	5	2	2	2	6	17
103	2	2	2	6	2	1	0	3	2	2	2	6	15
104	2	2	2	6	2	2	2	6	2	2	2	6	18
105	2	2	2	6	1	2	2	5	2	2	2	6	17
106	2	2	2	6	1	2	2	5	2	2	1	5	16
107	2	2	2	6	2	2	2	6	2	2	2	6	18
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109	2	2	2	6	2	2	1	5	2	0	1	3	14
110	2	2	2	6	2	2	2	6	2	2	2	6	18
111	2	2	2	6	1	2	2	5	2	2	2	6	17
112	2	2	2	6	2	2	2	6	2	2	2	6	18
113	2	2	2	6	1	2	2	5	2	2	2	6	17
114	2	2	2	6	2	2	2	6	2	2	2	6	18
115	2	2	2	6	1	2	2	5	2	1	2	5	16
116	2	2	2	6	0	2	2	4	2	2	2	6	16
117	2	2	2	6	2	2	2	6	2	2	2	6	18
118	2	2	2	6	1	2	2	5	2	2	2	6	17
119	2	2	2	6	1	1	0	2	2	2	2	6	14
120	2	2	2	6	2	2	2	6	2	2	2	6	18
121	2	2	2	6	2	2	2	6	2	2	2	6	18
122	2	2	2	6	1	2	2	5	2	2	2	6	17
123	2	2	2	6	0	2	1	3	2	2	2	6	15
124	2	2	2	6	2	2	2	6	2	2	2	6	18
125	2	2	2	6	0	1	0	1	2	2	2	6	13
126	2	2	2	6	2	2	2	6	2	2	2	6	18
127	2	2	2	6	2	2	2	6	2	2	2	6	18
128	2	2	2	6	1	2	2	5	2	2	2	6	17

Anon. lab number	2026.01				2026.02				2026.03				2026.01 - .03
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
129	2	2	2	6	2	2	1	5	2	2	2	6	17
130	2	2	2	6	1	2	2	5	2	2	2	6	17
131	2	2	2	6	1	2	2	5	2	2	2	6	17
132	2	2	2	6	2	2	2	6	2	2	2	6	18
133	2	2	2	6	2	2	2	6	2	2	2	6	18
134	2	2	2	6	2	2	2	6	2	1	2	5	17
135	2	2	2	6	1	2	2	5	2	2	2	6	17
136	2	2	2	6	2	2	2	6	2	2	2	6	18
137	2	2	2	6	1	1	1	3	2	2	2	6	15
138	2	2	2	6	2	2	2	6	2	2	2	6	18
139	2	2	2	6	2	2	1	5	2	0	1	3	14
140	2	2	2	6	0	0	0	0	2	1	1	4	10
141	2	2	2	6	0	2	2	4	2	2	2	6	16
142	2	2	2	6	2	2	2	6	2	0	1	3	15
143	2	2	2	6	2	2	2	6	2	2	2	6	18
144	2	2	2	6	1	2	2	5	2	2	2	6	17
145	2	2	2	6	1	2	2	5	2	2	2	6	17
146	2	2	2	6	1	2	2	5	2	2	2	6	17
147	2	2	2	6	2	2	2	6	2	2	2	6	18
148	2	2	2	6	1	2	1	4	1	1	1	3	13

APPENDIX 2. Change log (changes since the last version)

Version Number	Published	Amendments
1	21 July 2026	• 2026 first round interim report published

END OF REPORT