Participants were able to view the cases and submit their results using the ERNDIM Formdesk web site.

Scoring system

As for the previous circulation, each of the three aspects, analytical findings, diagnosis and further tests, were scored equally with a maximum of two points for each category. Where appropriate, half point scores were also used. Plasma amino acid concentrations together with the laboratories reference ranges were provided.

Case 2021-4

Methionine adenosyl-tranferase deficiency I/III.
The results provided were from an asymptomatic girl, born after 40 gestational weeks. Newborn screening was positive with elevated methionine concentration. The sample was taken at age one month. Homocysteine-concentration was slightly (40.8 µmol/l) and methionine-concentration was grossly (1087 µmol/l) elevated. Cystine concentration was not decreased. The diagnosis was confirmed by mutation analysis showing homozygous for mutation in *MAT1A*-gene.

Correct findings / abnormalities
Elevated methionine (1 point) and homocysteine concentration (1 points) were considered necessary for full points. Mention that cystine concentration was not decreased was scored with 1 point. Maximum attainable score was 2 points.

Correct Diagnosis
The correct diagnosis was methionine adenosyl-transferase deficiency (MAT) I/III and was scored with 2 points. The differential diagnosis cystathionine beta-synthase(CBS) deficiency was scored with 1 point. Maximum attainable score was 2 points.

Further tests
Molecular genetic studies for MAT I/III was scored with 2 points. Molecular genetic studies for cystathionine beta-synthase deficiency was scored with 1 point. Testing for S-adenosylmethionine (SAM) or S-adenosylhomocysteine (SAH) was scored with 1 point. Maximum attainable score was 2 points.

Comments on overall performance
Performance was good with 90% overall proficiency.

Reference
Chien et al. (2015) Mudd's disease (MAT I/III deficiency): a survey of data for MAT1 homozygotes and compound heterozygotes. Orphanet J Rare Dis 10:99.

Best interpretation (scored with 2 points each)

- **Findings.** Increased homocysteine, extremely large increase in methionine, normal phenylalanine and insignificant increase in tyrosine, small increase in cystine and insignificant increases in other amino acids.
- **Diagnosis.** MAT1/III deficiency. Other conditions associated with increased methionine are symptomatic. Methionine of this magnitude in CBS deficiency would be on betaine treatment and treated from birth. **Further tests.** Plasma S-adenosylmethionine (where available). DNA mutation analysis of relevant genes i.e. MAT1/III, (GNMT, SAHH, ADK, CBS)**.**

Version Number (& Date)	Amendments
Version 1.0, 24 Nov 2021	Report published
Version 2.0, 04 May 2022	Page 5: figure updated to include lab 1-48 (previously it just included labs 2-48)

Case 2021-5

Glucose transporter type 1 deficiency syndrome (Glut1-DS) under modified Atkins diet (MAD).
The results provided were from 9-years-old girl with glucose transporter type 1 deficiency syndrome treated with modified Atkins diet (ketosis with elevated ß-hydroxybutyric acid concentration (3.447 mmol)). The patient has a heterocygous mutation in *SLC2A1*-gene.

Correct findings / abnormalities
Mention elevated isoleucine, leucine and valine were scored each with 1 point. Maximum attainable score was 2 points.

Correct Diagnosis
The correct diagnosis ketosis due to ketogenic diet in a patient with Glut1-DS was scored with 2 points. (Mild) MSUD under therapy was scored with 1 point. Maximum attainable score was 2 points.

Further tests
Clinical investigation and medical history, amino acids (with alloisoleucine), ketone bodies in plasma and organic acids in urine were scored each with 1 point. Maximum attainable score was 2 points.

Comments on overall performance
Performance was good with 85% overall proficiency.

Best interpretation (scored with 2 points each)

- **Findings.** Slightly increased branched chain amino acids, valine > leucine (therefore MSUD unlikely).
- **Diagnosis.** Results suggest ketosis, but may be dietary. Is patient on ketogenic diet (e.g. Glut1-DS)? Has MSUD been excluded?
- **Further tests.** Check for alloisoleucine to exclude MSUD. CSF glucose and plasma acylcarnitines if Glut1-DS have not previously been excluded. Contact requestor for dietary information.

Ornithine aminotransferase deficiency (OAT deficiency)
The results provided were from a 16-years old male adolescent receiving a dietary treatment. Symptoms were myopia, a delayed bone-age and a short stature. The parents of our patient were consanguineous. Ornithine concentration was 4-times over the upper reference (878 µmol/l). The diagnosis was confirmed by homozygous mutation in *OAT* gene.

Correct findings / abnormalities
Elevated ornithine-concentration (2 points). Maximum attainable score was 2 points.

Correct Diagnosis
The correct diagnosis was ornithine aminotransferase (OAT) deficiency and was scored with 2 points. The differential diagnosis Hyperornithinemia-Hyperammonemia-Homocitrullinuria (Triple-H/HHH) syndrome was scored with 1 point. Maximum attainable score was 2 points.

Further tests
Molecular genetic studies for OAT deficiency was scored with 1 point. Lab-tests for orotic acid, ammonia, homocitrulline and creatine was scored with 1 point. Ophthalmologic examination was scored with 1 point. Maximum attainable score was 2 points.

Comments on overall performance
Performance was good with 94% overall proficiency.

Reference
Michel M et al. (2015) Gyrate Atrophy in 2 Siblings – Ophthalmological Findings and a New Mutation. Klin Paediatr 227:296-8

Best interpretation (scored with 2 points each)

- **Findings.** Gross increase in ornithine, slight increase in arginine and low lysine concentration.
- **Diagnosis**. OAT deficiency because of increase of ornithine (gln and cit normal) and clinical presentation affecting eye vision (though only partly characterized). HHH is a differential diagnosis though unlikely.
- **Further tests.** Ensure that diagnostic work up was already performed: perform molecular analysis of *OAT* gene, urinary amino acid to exclude any increase of homocitrulline. Ensure that the dietary treatment is correct.

Comments on the whole of the second circulation results 2021

- As mentioned above abnormalities, diagnosis and further tests were each scored with maximum 2 points.
- Each of the four evaluators scored all results independently and where three or four of their scores were in agreement, this was taken as final. In cases where the scores were not in agreement, further close evaluation based on agreed scoring criteria was used to determine on the final score.

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: 24.11.2021

The scientific evaluators

Sabine Scholl-Bürgi, Rachel Carling, Mary Anne Preece and Brian Fowler

Part. No.	2021.04 abnormalities	2021.04 diagnosis	2021.04 recommendations	2021.04 Sum	2021.05 abnormalities	2021.05 diagnosis	2021.05 recommendations	2021.05 Sum	2021.06 abnormalities	2021.06 diagnosis	2021.06 recommendations	2021.06 Sum	Sum 2021.04-2021.06
1	1,0	2,0	2,0	5,0	2,0	2,0	2,0	6,0	2,0	2,0	1,0	5,0	16,0
2	2,0	1,0	1,0	4,0	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	14,0
3	2,0	1,0	1,0	4,0	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	14,0
4	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	18,0
5	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	18,0
6	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	18,0
7	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	2,0	2,0	2,0	6,0	17,0
8	2,0	2,0	1,0	5,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	17,0
9	2,0	1,0	1,0	4,0	2,0	1,0	2,0	5,0	2,0	2,0	2,0	6,0	15,0
10	2,0	2,0	2,0	6,0	2,0	0,0	1,0	3,0	2,0	2,0	1,0	5,0	14,0
11	1,0	2,0	2,0	5,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	17,0
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24	1,0	2,0	2,0	5,0	2,0	2,0	2,0	6,0	2,0	2,0	2,0	6,0	17,0
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33	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	2,0	2,0	1,0	5,0	16,0
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39	2,0	2,0	2,0	6,0	2,0	2,0	1,0	5,0	2,0	2,0	2,0	6,0	17,0
40	2,0	2,0	2,0	6,0	0,0	2,0	0,0	2,0	2,0	2,0	2,0	6,0	14,0
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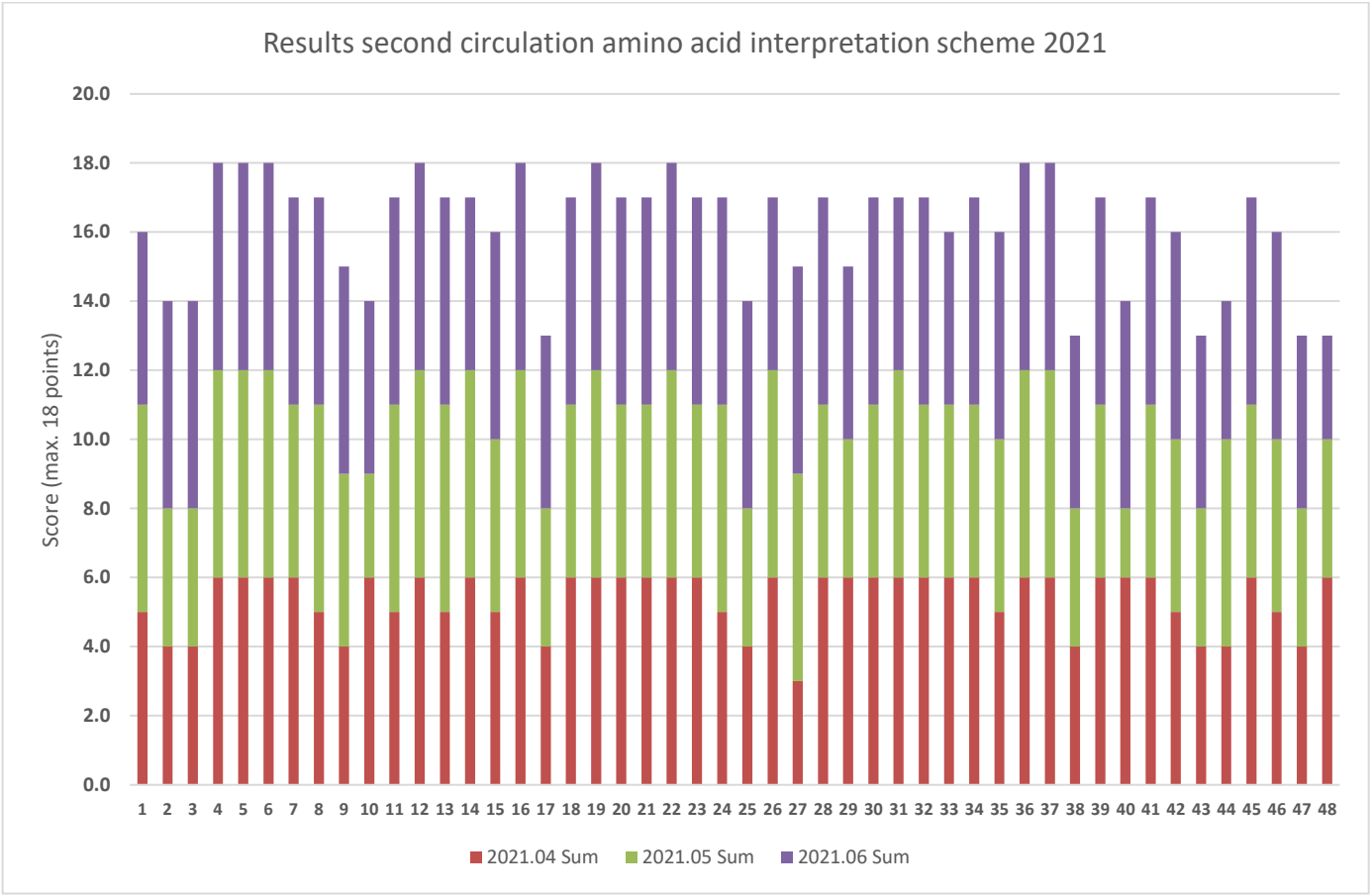
43	1,0	2,0	1,0	4,0	2,0	1,0	1,0	4,0	2,0	2,0	1,0	5,0	13,0
44	2,0	1,0	1,0	4,0	2,0	2,0	2,0	6,0	2,0	0,0	2,0	4,0	14,0
45	2,0	2,0	2,0	6,0	2,0	1,0	2,0	5,0	2,0	2,0	2,0	6,0	17,0
46	2,0	1,0	2,0	5,0	2,0	1,0	2,0	5,0	2,0	2,0	2,0	6,0	16,0
47	2,0	1,0	1,0	4,0	2,0	1,0	1,0	4,0	2,0	2,0	1,0	5,0	13,0
48	2,0	2,0	2,0	6,0	2,0	1,0	1,0	4,0	2,0	0,0	1,0	3,0	13,0
total	**90**	**86**	**82**	**258**	**94**	**70**	**81**	**245**	**96**	**92**	**84**	**272**	**775**
% prof.	**94%**	**90%**	**85%**	**90%**	**98%**	**73%**	**84%**	**85%**	**100%**	**96%**	**88%**	**94%**	**90%**


Results second circulation amino acid interpretation scheme 2021
Score (max. 18 points)
20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48
2021.04 Sum
2021.05 Sum
2021.06 Sum