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Second Round Interim Report 2022 (DOC5149)

Version Number¹: 01

Date of issue: 26th October 2022

ERNDIM Code:**Please Note:**

- This report is intended for participants of the ERNDIM AAI Pilot 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 pilot 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 2022 second round results was 30th May 2022. Participants were able to view the cases and submit their results using the ERNDIM Formdesk website. 105 laboratories registered for the 2022 AAI pilot scheme but only 91 labs (88%) submitted results for the second 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 amino acid concentrations together with the laboratories reference ranges were provided.

The tables (Table 1-3) show scoring to which the evaluators agreed previously. Scoring 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 8) for details of the changes made since the last version of this document.

3. Results of samples and evaluation of reporting

3.1. Case 2022-4: BCAT (branched-chain amino acid transaminase) deficiency.

3.1.1. Sample Details

The results provided were from a 2-year-old girl with developmental delay. For further details please see Kneer et al. Expanding the genetic and phenotypic spectrum of branched-chain amino acid transferase 2 deficiency. *J Inher Metab Dis.* 2019 Sep;42(5):809-17 (subject 2).

3.1.2. Scoring details

Table 1: Scoring details for case 2022-4.

	Interpretation		Score (points)
Findings, abnormalities [A, maximum 2 points]	Elevated	Val > leu > ile	2
	Elevated	Val, leu, ile	1
Diagnosis [D, maximum 2 points]	BCAT deficiency		2
	Ketosis		1
	Valine metabolism disorder		1
	MSUD		0
Further tests (if molecular genetics recommended, specify the gene) [R, maximum 2 points]	Molecular genetic testing of <i>BCAT2</i> gene		2
	Amino acids in plasma (repeat), including alloisoleucine		1
	Organic acids urine		1
	Ketone bodies		1

Scores for participating laboratories are in APPENDIX 1 on page 6.

3.1.3. Comments on overall performance

Overall proficiency was 68%. Especially, the diagnosis (D, proficiency 51%) and subsequently the recommendation for further tests (R, proficiency 84%) was difficult to make because BCAT deficiency is very rare and the amino acid pattern is similar to that of “more common” maple syrup disease. Therefore, this case may also lead to a better diagnosis in the future.

3.1.4. Best interpretation (scored with 2 points each)

- **Findings:** Increased valine, leucine, isoleucine, with valine >> leucine
- **Diagnosis:** Possible branched chain aminotransferase (BCAT) deficiency. Maple syrup urine disease unlikely but not excluded.
- **Further tests:** Urine organic acids, plasma alloisoleucine, molecular genetic analysis (*BCAT2*, *BCKDHA*, *BCKDHB* and *DBT*), refer to metabolic team.

3.2. Case 2022-5: No specific inborn disorder of metabolism

3.2.1. Sample details

The results were from a sample from a 19-day old girl who had as an in-patient new-born screening methionine and homocysteine above cut off value. Venous plasma was deproteinised promptly upon receipt. Patient had congenital heart disease with some liver dysfunction and low vitamin B₁₂ concentration (192 ng/L (259-823)) normal folate (7.2 µg/L (3.5-14.5)) and increased homocysteine.

3.2.2. Scoring details

Table 2: Scoring details for case 2022-5.

	Interpretation		Score (points)
Findings, abnormalities [A, maximum 2 points]	Elevated	Homocysteine	2
	Normal	Met	1
Diagnosis [D, maximum 2 points]	No metabolic disorder		1
	Vitamin B ₁₂ deficiency		1
	Folate deficiency/ <i>MTHFR</i> polymorphism		1
Further tests (if molecular genetics recommended, specify the gene) [R, maximum 2 points]	Vitamin B ₁₂ concentration		1
	Folate concentration		1
	Repeat homocysteine		1
	MMA (plasma or urine)		1
	Urine organic acids (MMA)		1

Scores for participating laboratories are in APPENDIX 1 on page 6.

3.2.3. Comments on overall performance

Performance was 72% for overall proficiency. Performance for diagnosis and further testing was particularly low.

This case was difficult because the patient does not have a metabolic disorder but only low vitamin B₁₂ concentration. This was for the participants difficult to discuss AND for the evaluators to score.

3.2.4. Best interpretation (scored with 2 points each)

- **Findings:** Elevated total homocysteine, methionine high normal.
- **Diagnosis:** Hyperhomocysteinemia probably due to low maternal folate and vitamin B₁₂ concentrations.
- **Further tests:** Request vitamin B₁₂ and folate and urine organic acids including a methylmalonic acid quantitation. Consider *MTHFR* genotyping.

3.3. Case 2021-4: Ethylmalonic encephalopathy

3.3.1. Sample details

The sample was from a 6-month-old male who developed after an infection (gastroenteritis) sepsis-like disease with petechial efflorescence. The diagnosis of an infection could not be confirmed. He had persistent lactataemia, muscular hypotonia and a halt in physical and mental development.

3.3.2. Scoring details

Table 3: Scoring details for case 2022-6.

	Interpretation		Score (points)
Findings, abnormalities [A, maximum 2 points]	Elevated	proline	1
	Elevated	alanine	1
	Elevated	alanine/lysine	1
Diagnosis [D, maximum 2 points]	Mitochondrial disorder		2
	Ethylmalonic encephalopathy		2
Further tests (if molecular genetics recommended, specify the gene) [R, maximum 2 points]	organic acids urine		2
	acylcarnitine profile		2
	genetic testing mitochondrial disorder		2
	genetic testing <i>ETHE1</i>		2

Scores for participating laboratories are in APPENDIX 1 on page 6.

3.3.3. Comments on overall performance

Overall proficiency was 92%.

3.3.4. Best interpretation (scored with 2 points each)

- **Findings:** Strongly raised alanine and moderately raised proline. Alanine/lysine ratio > 3 suggests true hyperalaninaemia.
- **Diagnosis:** Alanine and proline likely elevated secondary to lactic acidosis. Clinical history and results may suggest *ETHE1* deficiency or other mitochondrial disease.
- **Further tests:** Molecular genetic analysis of *ETHE1*. Functional analysis of respiratory chain complexes.

3.4. Comments on the whole of the first circulation results 2022

- The amino acid interpretation scheme is a pilot scheme with 105 participants.
- We tried to include cases where changes in amino acid concentrations can be primary or secondary to the underlying inborn disorder of metabolism.
- Therefore, the amino acid concentrations of two patients with very rare and unusual inborn errors of metabolism and one patient with a vitamin deficiency were selected.
- The overall performance was in all three cases below 80% (80% was considered to be a good result).

Table 4: Overall scores for the second circulation in the amino acid interpretation scheme

	2022.04				2022.05				2022.06				2022.04 - .06
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Totals
Total Points	127	93	153	373	180	101	115	395	180	162	159	501	1269
% proficiency	70%	51%	84%	68%	99%	55%	63%	72%	99%	89%	87%	92%	77%

Key

A = Findings, abnormalities

D = Diagnosis

R = Recommendations for further testing

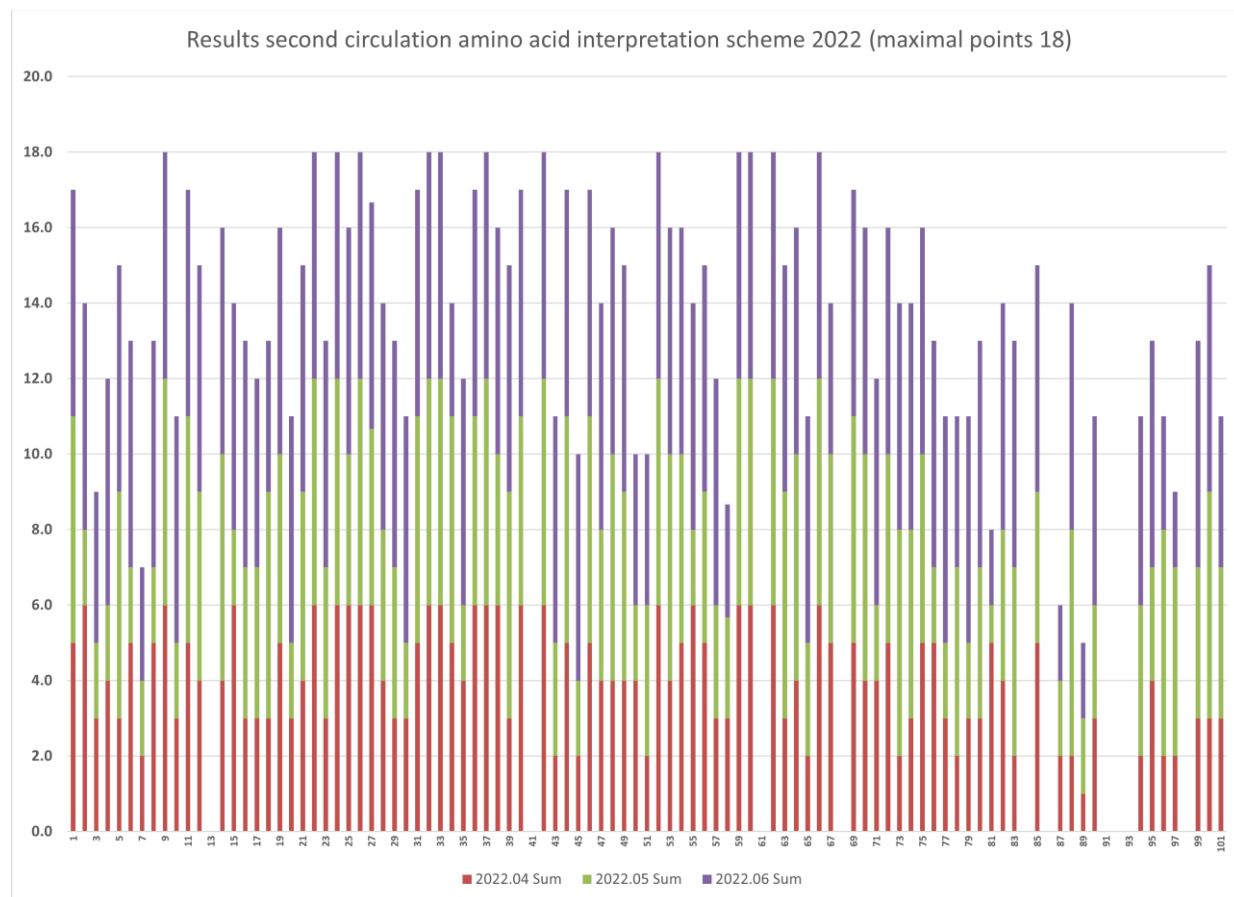


Figure 1: Detailed scores for the second circulation in the amino acid interpretation scheme

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: 26.10.2022

The Scientific Evaluators

Sabine Scholl-Bürgi, Scientific Advisor

Scheme Assessors: Brian Fowler, Rachel Carling, Mary Anne Preece, Daniela Karall, Apolline Imbard and Olivier Braissant

APPENDIX 1. Detailed scores for submitting laboratories**Key**

A = Findings, abnormalities

D = Diagnosis

R = Recommendations for further testing

Please note that only laboratories that submitted results for the second round are included in the table below.

Anon. lab number	2022.04				2022.05				2022.06				2022.04 - .06
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
1	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
2	2.0	2.0	2.0	6.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	14.0
3	2.0	0.0	1.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	0.0	4.0	9.0
4	2.0	0.0	2.0	4.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	12.0
5	1.0	0.0	2.0	3.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	15.0
6	1.0	2.0	2.0	5.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	13.0
7	1.0	0.0	1.0	2.0	2.0	0.0	0.0	2.0	2.0	1.0	0.0	3.0	7.0
8	1.0	2.0	2.0	5.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	13.0
9	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
10	1.0	0.0	2.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	11.0
11	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	17.0
12	1.0	1.0	2.0	4.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	15.0
14	1.0	1.0	2.0	4.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	16.0
15	2.0	2.0	2.0	6.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	14.0
16	1.0	0.0	2.0	3.0	2.0	0.0	2.0	4.0	2.0	2.0	2.0	6.0	13.0
17	1.0	0.0	2.0	3.0	2.0	1.0	1.0	4.0	2.0	2.0	1.0	5.0	12.0
18	1.0	0.0	2.0	3.0	2.0	2.0	2.0	6.0	2.0	0.0	2.0	4.0	13.0
19	2.0	2.0	1.0	5.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	16.0
20	1.0	0.0	2.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	11.0
21	1.0	2.0	1.0	4.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	15.0
22	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
23	1.0	0.0	2.0	3.0	2.0	0.0	2.0	4.0	2.0	2.0	2.0	6.0	13.0
24	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
25	2.0	2.0	2.0	6.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	16.0
26	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
27	2.0	2.0	2.0	6.0	2.0	1.0	1.7	4.7	2.0	2.0	2.0	6.0	16.7
28	1.0	2.0	1.0	4.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	14.0
29	1.0	0.0	2.0	3.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	13.0
30	1.0	0.0	2.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	11.0
31	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	17.0
32	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
33	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
34	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	2.0	1.0	0.0	3.0	14.0
35	2.0	1.0	1.0	4.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	12.0
36	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
37	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
38	2.0	2.0	2.0	6.0	2.0	0.0	2.0	4.0	2.0	2.0	2.0	6.0	16.0

Anon. lab number	2022.04				2022.05				2022.06				2022.04 - .06
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
39	1.0	0.0	2.0	3.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	15.0
40	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
42	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
43	1.0	0.0	1.0	2.0	2.0	1.0	0.0	3.0	2.0	2.0	2.0	6.0	11.0
44	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	17.0
45	1.0	0.0	1.0	2.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	10.0
46	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
47	1.0	1.0	2.0	4.0	2.0	0.0	2.0	4.0	2.0	2.0	2.0	6.0	14.0
48	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	16.0
49	1.0	1.0	2.0	4.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	15.0
50	2.0	0.0	2.0	4.0	2.0	0.0	0.0	2.0	2.0	2.0	0.0	4.0	10.0
51	1.0	0.0	1.0	2.0	2.0	0.0	2.0	4.0	2.0	2.0	0.0	4.0	10.0
52	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
53	1.0	1.0	2.0	4.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	16.0
54	1.0	2.0	2.0	5.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	16.0
55	2.0	2.0	2.0	6.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	14.0
56	1.0	2.0	2.0	5.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	15.0
57	1.0	2.0	0.0	3.0	2.0	1.0	0.0	3.0	2.0	2.0	2.0	6.0	12.0
58	1.0	0.0	2.0	3.0	1.7	0.0	1.0	2.7	2.0	1.0	0.0	3.0	8.7
59	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
60	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
62	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
63	1.0	0.0	2.0	3.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	15.0
64	1.0	1.0	2.0	4.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	16.0
65	1.0	0.0	1.0	2.0	2.0	1.0	0.0	3.0	2.0	2.0	2.0	6.0	11.0
66	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
67	2.0	1.0	2.0	5.0	2.0	1.0	2.0	5.0	2.0	0.0	2.0	4.0	14.0
69	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
70	1.0	1.0	2.0	4.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	16.0
71	2.0	0.0	2.0	4.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	12.0
72	1.0	2.0	2.0	5.0	2.0	2.0	1.0	5.0	2.0	2.0	2.0	6.0	16.0
73	1.0	0.0	1.0	2.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	14.0
74	1.0	0.0	2.0	3.0	2.0	1.0	2.0	5.0	2.0	2.0	2.0	6.0	14.0
75	1.0	2.0	2.0	5.0	2.0	2.0	1.0	5.0	2.0	2.0	2.0	6.0	16.0
76	1.0	2.0	2.0	5.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	13.0
77	1.0	0.0	2.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	11.0
78	2.0	0.0	0.0	2.0	2.0	2.0	1.0	5.0	2.0	2.0	0.0	4.0	11.0
79	1.0	0.0	2.0	3.0	2.0	0.0	0.0	2.0	2.0	2.0	2.0	6.0	11.0
80	1.0	0.0	2.0	3.0	2.0	2.0	0.0	4.0	2.0	2.0	2.0	6.0	13.0
81	1.0	2.0	2.0	5.0	0.0	0.0	1.0	1.0	0.0	0.0	2.0	2.0	8.0
82	2.0	2.0	0.0	4.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	14.0
83	1.0	0.0	1.0	2.0	2.0	2.0	1.0	5.0	2.0	2.0	2.0	6.0	13.0
85	1.0	2.0	2.0	5.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	15.0
87	1.0	0.0	1.0	2.0	2.0	0.0	0.0	2.0	2.0	0.0	0.0	2.0	6.0
88	1.0	0.0	1.0	2.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	14.0

Anon. lab number	2022.04				2022.05				2022.06				2022.04 - .06
	A	D	R	Sum	A	D	R	Sum	A	D	R	Sum	Total Score
89	1.0	0.0	0.0	1.0	2.0	0.0	0.0	2.0	2.0	0.0	0.0	2.0	5.0
90	1.0	1.0	1.0	3.0	2.0	0.0	1.0	3.0	2.0	1.0	2.0	5.0	11.0
94	1.0	0.0	1.0	2.0	2.0	0.0	2.0	4.0	2.0	1.0	2.0	5.0	11.0
95	2.0	1.0	1.0	4.0	2.0	1.0	0.0	3.0	2.0	2.0	2.0	6.0	13.0
96	1.0	0.0	1.0	2.0	2.0	2.0	2.0	6.0	2.0	1.0	0.0	3.0	11.0
97	1.0	0.0	1.0	2.0	2.0	1.0	2.0	5.0	2.0	0.0	0.0	2.0	9.0
99	1.0	0.0	2.0	3.0	2.0	1.0	1.0	4.0	2.0	2.0	2.0	6.0	13.0
100	1.0	0.0	2.0	3.0	2.0	2.0	2.0	6.0	2.0	2.0	2.0	6.0	15.0
101	1.0	1.0	1.0	3.0	2.0	1.0	1.0	4.0	2.0	0.0	2.0	4.0	11.0

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

Version Number	Published	Amendments
1	26 October 2022	<ul style="list-style-type: none"> 2022 second round report published

END OF REPORT