Congenital Disorders of Glycosylation

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Annual Report 2020

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1. Scheme Design

The scheme has been designed and planned by the Scientific Advisor (SA) and Scheme Organisers (SO, listed at the top of this page), both appointed by and according to procedures laid down by the ERNDIM Board.

a. Sub-contracted activities:
The samples were aliquoted and dispatched by MCA Laboratory, Netherlands, while the results website (cscq.hcuge.ch/cscq/ERNDIM/) is hosted and maintained by CSCQ, both on behalf of ERNDIM.

2. Samples

Samples were selected by the Scientific Advisor and tested for suitability in the Scientific Advisor's laboratory (Translational Metabolic Laboratory, Radboud University Medical Centre, Nijmegen, Netherlands). Preparation and dispatch of the EQA samples was done by the relevant Scheme organiser (MCA Laboratory, Winterswijk, Netherlands). All EQA materials are lyophilised plasma or serum samples (25 µl). Laboratories that need a larger sample volume due to their analysis method (e.g. HPLC) were sent extra sample sets for a reduced scheme price.

For the 2020 scheme, 5 samples were provided by the Scientific Advisor and one by Dulce Quelhas, Porto, Portugal. All samples were obtained following local ethical and consent guidelines.

To be able to continue this scheme we need a steady supply of new patient samples. If you have one or more samples available and are willing to donate these to the scheme, please contact us at admin@erndim.org. Laboratories which donate samples that are used in the scheme are eligible for a 20% discount on the CDG scheme fee in the following year.

3. Shipment

The six samples were sent out to the 69 registered laboratories in one parcel on 11th February 2020. Twenty-five laboratories requested a total of 30 extra sample sets and were sent the larger sample volume.

4. Receipt of results

Results were submitted to an online results website (cscq.hcuge.ch/cscq/ERNDIM/) which is hosted and maintained by CSCQ (Swiss Centre for Quality Control, Chêne-Bourg, Switzerland). The submission deadlines for the first round (samples CDG 2020.01 - CDG 2020.03) and second round were 1st June 2020 and 28th September 2020 respectively. Overall 65/69 (94%) registered participants submitted results for the 2020 scheme: 59 (86%) laboratories submitted results on time for both submission rounds; an additional two labs (2.9%) submitted their results for one of the submission rounds after the submission deadline. Four labs (5.8%) only submitted results for the first round, and one of these submitted their results after the submission deadline.

[1] **If this Annual Report is not Version 1 for this scheme year, go to APPENDIX 2 (page 6) for details of the changes made since the last version of this document.**

While a separate four laboratories (5.8%) failed to make a return on either submission round; one of these was an Educational Participant and one withdrew from the scheme.

5. Scoring scheme

In agreement with ERNDIM rules, we applied a scoring system of 2+2:

Item C: technical aspects: 1 point for identification of an abnormal profile and 1 point for correct identification of the profile as type I or II.

Item D: diagnostic suggestions: This section should be filled for scoring. Just referring to a specialised lab is insufficient. If required, advice can be obtained from a reference laboratory or in collaboration with a clinical colleague. For normal profiles 2 points are scored. For abnormal profiles, comments should be made on the possibility of the presence of a secondary cause in light of the clinical indication. In addition, the right suggestions should be made for the next step in the diagnostic process that eventually will lead to the genetic defect. Scoring for this part is not so straightforward, but we tried to keep it as consistent as possible. The maximum score achievable with full submission for all samples is 24, while a maximum of 12 points are available for labs that only submitted results for the first or second round. The level for satisfactory performance is 17 points. Laboratories that participate only in one circulation can achieve satisfactory performance with 8 points, however for the 2021 scheme onwards labs that only submit results for one submission rounds will be classed as partial submitters, see section 7 (Preview of the 2021 scheme) for further details. For the 2014 scheme onwards, another criterion for satisfactory performance is the absence of any “critical error”, which is defined as an error resulting from seriously misleading analytical findings and/or interpretations with serious clinical consequences for the patient. For the 2020 CDG scheme, 3 critical errors were identified. These were agreed at the meeting of the Scientific Advisory Board on 19th and 20th November 2020.

a. Appeals

If your laboratory has been assigned poor performance in the 2020 scheme and you wish to appeal against this classification please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter.

6. Results of samples and evaluation of reporting

The shipped samples were from (CDG) patients and from controls and from a confirmed individual with alcohol abuse. The final results of the six samples with respect to CDG are summarized in Table 1 below.

Table 1: Samples in the 2020 scheme

Sample	Clinical information (age, sex, phenotype)	Diagnosis
2020.01	M, 11 yrs, mental retardation, coagulopathy	PMM2-CDG
2020.02	M, 48 years, ataxia	Control
2020.03	F, 5 yrs, strabismus, deafness, epilepsy	Control
2020.04	M, 8 yrs, frequent infections, liver fibrosis	Control
2020.05	M, 64 yrs, unsolved hepatitis,	Alcohol abuse
2020.06	F, 4 yrs, diarrhoea, hepatomegaly, protein-losing enteropathy	MPI-CDG

All submitted results are treated as confidential information and are only shared with ERNDIM approved persons for the purposes of evaluation and reporting. For the purposes of evaluation, the Scientific Advisor’s centre is not included in the following results.

For the laboratories that reported their method (51/64), CE was the method employed most often (19/51), followed by HPLC (15/51), Isofocusing (13/51), Mass Spectrometry (2/51) and Other (2/51).

Table 2: Scoring of samples in the 2020 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG2020.01	65	95%	96%	95%
CDG2020.02	66	95%	99%	97%
CDG2020.03	64	96%	96%	96%
CDG2020.04	61	99%	99%	99%
CDG2020.05	61	97%	98%	97%
CDG2020.06	61	100%	100%	100%

Table 3: Distribution of scores (for labs that submitted sufficient results for performance to be assessed)

Total Score	No of labs
<60%	2
60 – 69.9%	0
70 – 79.9%	2
80 – 89.9%	3
90 – 99.9%	6
100%	52
Total	**65**

The full anonymised results for all labs registered for the scheme are given in APPENDIX 1 on page 5 of this report.

ERNDIM CDG 2020.01: PMM2-CDG
A type 1 profile was identified by nearly all laboratories and interpreted as abnormal by nearly all as well, resulting in a proficiency score of 95%. The pattern was a classical type one pattern and no major differences were noticed when comparing the performance of different methods.

The clinical symptoms are however rather suggestive for PMM2-CDG. Therefore, in case of interpretation of a profile as CDG-I, a diagnosis of PMM2-CDG should be advised in this situation. Identification of the profile as abnormal and indicating PMM2-CDG as a possible diagnosis should be included for full scoring. Proficiency score: 95%.

ERNDIM CDG 2020.02: Control
Nearly all laboratories reported this sample as normal. resulting in a proficiency score of 97%.

ERNDIM CDG 2020.03: Control
Nearly all laboratories reported this sample as normal. resulting in a proficiency score of 96%.

ERNDIM CDG 2020.04: Control
Nearly all laboratories reported this sample as normal. resulting in a proficiency score of 99%.

ERNDIM CDG 2020.05: alcohol abuse
Many laboratories reported this sample as abnormal and indicated a mild type I profile. However, in some cases (due to mild sialic acid loss), a CDG-II and mixed profile was indicated. This sample is from an individual with chronic alcohol use. This is known as a secondary cause for (mild) CDG-I profiles. The clinical indication of an adult patient with ataxia could also fit very well with an adult case of PMM2-CDG, since several case reports have been published with near-normal transferrin glycosylation and an isolated clinical presentation of ataxia. It is unclear if the clinical condition of the current individual was related to the alcohol abuse or was unrelated. No indication for PMM2-CDG was found. Proficiency score: 97%, representing an improvement when compared with last year's score.

ERNDIM CDG 20120.06: MPI-CDG
A type 1 profile was identified by all laboratories and interpreted as abnormal, resulting in a proficiency score of 100%.
Although there are an increasing number of CDGs without neurological involvement, having taken into account the limited patient clinical information together with a type 1 transferrin IEF pattern, it is suggestive of MPI-CDG. The laboratory investigation could be initiated with phosphomannose isomerase and phosphomannomutase enzyme activity determination, but it is also a suitable option to go directly for *MPI* and *PMM2* gene sequencing. Noteworthy is the recommendation to exclude secondary causes, including other IEM like HFI and galactosemia.

7. Preview of the 2021 scheme

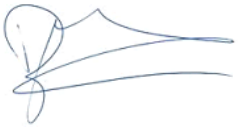
To bring this scheme into line with the other ERNDIM qualitative schemes, **for the 2021 scheme onwards participants that submit results for 3 or fewer samples in a scheme year will be classed as partial submitters and their performance will not be evaluated**. Partial submitters receive a formal Non-submitter letter notifying them of this status and their certificate of participation shows them as not submitting results for the relevant scheme. As the number of participants in the CDG scheme are limited due to the nature of the EQA samples, ERNDIM reserves the right to exclude participants that are classed as partial/non-submitters for 2 out of 3 registered years (i.e. persistent partial and non-submitters) from the scheme.

8. Questions, Comments and Suggestions

If you have any questions, comments or suggestions in addition to specific user comments please contact the ERNDIM Administration Office (admin@erndim.org).

9. Confidentiality Statement

This annual report is intended for participants of the ERNDIM Congenital Disorders of Glycosylation scheme. The contents of this report or data derived from the use or analysis of ERNDIM EQA materials must not be used in written publications or oral presentations unless the explicit prior consent of ERNDIM has been granted.



Prof Dirk Lefeber
Scientific Advisor

Dr Dulce Quelhas
Deputy Scientific Advisor

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

2020	Technical, item C							Advice, item D							
Sample ID	.01	.02	.03	.04	.05	.06		.01	.02	.03	.04	.05	.06		
Average score / Lab ID	1.89	1.89	1.92	1.98	1.92	2.00	Total	1.92	1.97	1.92	1.98	1.93	2.00	Total	Total score (max 24)
1	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
2	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
3	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
4	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23
5	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
6	2	2	2				6	2	2	2				6	12
7	0	2	0	2	2	2	8	1	2	1	2	2	2	10	18
8	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
9	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
10	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
11	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
12	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
13	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
14	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
15	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
16	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
17	2	2	2	2	0	2	10	2	2	2	2	1	2	11	21
18	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
19	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
20	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23
21	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
22	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
23	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23
24	2	2	2	2	0	2	10	2	2	2	2	0	2	10	20
25	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
26	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
27	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
28	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
29	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
30	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
31	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
32	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
33	2	2	2				6	2	2	2				6	12
34	1	2	2	2	2	2	11	2	2	2	2	2	2	12	23
35	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
36	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23
37	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
38	2	2	1				5	2	2					4	9
39	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24

2020	Technical, item C							Advice, item D							
Sample ID	.01	.02	.03	.04	.05	.06		.01	.02	.03	.04	.05	.06		
Average score / Lab ID	1.89	1.89	1.92	1.98	1.92	2.00	Total	1.92	1.97	1.92	1.98	1.93	2.00	Total	Total score (max 24)
40	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
41	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
42	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
43	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
44	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
45	2	2	2				6	2	2	2				6	12
46	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
47	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
48	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
49	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
50	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
51	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
52	0	0	2	2	2	2	8	0	0	0	2	2	2	6	14
53	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
54	2	2		2	2	2	10	2	2		2	2	2	10	20
55	0	2	0	1	2	2	7	0	2	0	1	2	2	7	14
56	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
57	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
58	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
59	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
60	2	1	2	2	2	2	11	2	2	2	2	2	2	12	23
61	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
62	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
63	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
64	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
65	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
66*		2			2		4							0	4

* = This lab did not submit enough results for their performance to be assessed and is included in the table for information only

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

Version Number	Published	Amendments
1	11 June 2021	• 2021 annual report published
2	21 September 2022	• Page 2, Table 2: proficiencies for sample 2020.05 updated as result of changes to scores for lab 21 • Page 3, Table 3: updated as result of changes to scores for lab 21 • Page 5, Appendix 1: Scores for lab 21 for sample 2020.05 corrected

END OF REPORT