QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

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Congenital Disorders of Glycosylation
Final Report 2019

Date of issue: 15 May 2020[1]

Amended report issued: 06 July 2020[2]

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 (35 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 2019 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 67 registered laboratories in one parcel on 12th February 2019. Twenty-three laboratories requested a total of 32 extra sample sets and were sent the larger sample volume.

4. Receipt of results

For the first time 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 returns for the first round (samples CDG 2019.01 - CDG 2019.03) and second round (samples CDG 2019.04 - CDG 2019.06) were received by the due date from 61 (91%) laboratories for both submission rounds. An additional one (1.5%) lab submitted their results for the second round after the submission deadline. Two labs only submitted results for the first round while 2 different labs only submitted results for the second round. There were three laboratories who failed to make a return on either submission round.

Version Number (& Date)	Amendments
[1] version 1 (15 May 2020)	• 2019 Annual Report published
[2] version 2 (06 July 2020)	• Page 1, section 2 – updated with text on origin of samples and discounts for sample donations • Page 2, tables 2 & 3 – updated to reflect change to scoring for sample 2019.04 • Page 4, table 4 – scores for sample 2019.04 added for lab 17

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. 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 2019 CDG scheme, no critical errors were identified. This has been agreed at the meeting of the Scientific Advisory Board on 21st and 22nd November 2019.

6. Results of samples and evaluation of reporting

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 (49/64), CE was the method employed most often (17/49), followed by Isofocusing (15/49), HPLC (14/49), Mass Spectrometry (1/49) and Other (2).

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 2019 scheme

Sample	Clinical information (age, sex, phenotype)	Diagnosis
2019.01	F, 2 years, encephalopathic epilepsy	Control
2019.02	M, 9 years, increased transaminases, low blood sugars, exercise intolerance, cardiomyopathy	PGM1 on galactose
2019.03	F, 6 years, cataract, mental retardation, skeletal abnormalities	Control
2019.04	M, 16 years, intellectual disability, hypotonia and low coagulation factors	ALG6-CDG
2019.05	F, 1 year, hepatomegaly, skeletal dysplasia	Control
2019.06	M, 48 years, ataxia	Alcohol abuse

Table 2: Scoring of samples in the 2019 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG2019.01	61	98%	98%	98%
CDG2019.02	61	96%	84%	90%
CDG2019.03	60	100%	100%	100%
CDG2019.04	61	96%	81%	89%
CDG2019.05	62	100%	100%	100%
CDG2019.06	62	90%	77%	84%

Table 3: Distribution of scores (for labs that submitted results)

Total Score	No of labs
<60%	0
60 – 69.9%	2
70 – 79.9%	4
80 – 89.9%	6
90 – 99.9%	28
100%	24
Total	**64**

The full anonymised results for all labs registered for the scheme are given in Table 4 on pages 4-5 at the end of this report.

ERNDIM CDG 2019.01: Control
A normal profile was identified by nearly all laboratories and interpreted as normal by nearly all as well, resulting in a proficiency score of 98%.

ERNDIM CDG 2019.02: PGM1-CDG on galactose
Nearly all laboratories reported this sample as abnormal. PGM1-CDG is characterised as a mixed CDG-I/II profile. Nevertheless, some samples look more similar to a CDG-I profile and mild CDG-II aspects might be missed. Therefore, some laboratories reported as CDG-I profile, especially when using western blot or low resolution mass spectrometry, which focus on CDG-I abnormalities. The clinical symptoms are however rather suggestive for PGM1-CDG. Therefore, even in case of interpretation of a profile as CDG-I, a diagnosis of PGM1-CDG should be advised in this situation. Identification of the profile as abnormal and indicating PGM1-CDG as possible diagnosis should be included for full scoring. Proficiency score: 90 (which is much improved as compared to a similar sample in the 2018 round, 72%.

ERNDIM CDG 2019.03: Control
All centres reported a normal profile, resulting in a proficiency score of 100%.

ERNDIM CDG 2019.04: ALG6-CDG
The vast majority of labs reported this sample as an abnormal CDG-I profile. The clinical symptoms are not directly suggestive of a certain CDG-I subtype. Therefore, general indications for further diagnostics provide a full score. This could include CDG enzyme analysis, gene sequencing (targeted panels or whole exome) or analysis of lipid linked oligosaccharides. Proficiency score: 88%.

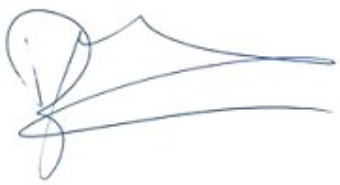
ERNDIM CDG 2019.05: control
All centres reported a normal profile, resulting in a proficiency score of 100%.

ERNDIM CDG 2019.06: 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 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: 84%.

7. **Preview of the 2020 scheme**
   The format of the scheme will remain the same, including website reporting as introduced during the 2019 scheme. The URL is **https://cscq.hcuge.ch/cscq/ERNDIM/** and details were included in the 2020 CDG scheme instructions.

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.



Dirk Lefeber
Scientific Advisor

Table 4: Detailed scores for submitting laboratories

2019	Technical, item C							Advice, item D							
Sample ID	.01	.02	.03	.04	.05	.06		.01	.02	.03	.04	.05	.06		
Average score / Lab ID	1,97	1,92	2,00	1,98	2,00	1,79	Total	1,97	1,67	2,00	1,70	2,00	1,55	Total	Total score (max 24)
1	2	2	2	2	2	1	11	2	1	2	1	2	1	9	20
2	2	2	2	2	2	1	11	2	1	2	1	2	1	9	20
3	2	2	2	2	2	1	11	2	2	2	2	2	1	11	22
4	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
5	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
6	2	1	2	2	2	2	11	2	0	2	2	2	1	9	20
7	2	2	2	2	2	2	12	2	2	2	1	2	1	10	22
8	2	2	2	2	2	2	12	2	1	2	1	2	2	10	22
9															
10	2	2	2	2	2	1	11	2	2	2	2	2	1	11	22
11	2	2	2	2	2	2	12	1	2	2	2	2	2	11	23
12	2	2	2	2	2	2	12	2	1	2	1	2	2	10	22
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	2	2	12	2	2	2	2	2	2	12	24
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	1	11	23
20															
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	1	11	23
23				2	2	2	6				2	2	1	5	11
24	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
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	1	11	23
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	1	2	1	10	22
29	2	2	2	2	2	0	10	2	1	2	2	2	0	9	19
30	2	1	2		2	2	9	2	0	2		2	2	8	17
31	2	2	2	2	2	2	12	2	2	2	1	2	2	11	23
32	1	2	2	2	2	2	11	1	2	2	2	2	2	11	22
33	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
34	2	2	2	2	2	2	12	2	2	2		2	2	10	22
35	2	2	2	2	2	1	11	2	2	2	2	2	1	11	22
36	2	1	2	2	2	2	11	2	1	2	2	2	2	11	22
37	2	2	2	2	2	2	12	2	2	2	2	2	1	11	23
38	2	2		2	2	2	10	2	2		2	2	1	9	19
39	2	1	2	2	2	2	11	2	1	2	2	2	0	9	20
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	1	11	23
43	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24

2019	Technical, item C							Advice, item D							
Sample ID	**.01**	**.02**	**.03**	**.04**	**.05**	**.06**		**.01**	**.02**	**.03**	**.04**	**.05**	**.06**		
Average score / **Lab ID**	1,97	1,92	2,00	1,98	2,00	1,79	**Total**	1,97	1,67	2,00	1,70	2,00	1,55	**Total**	**Total score (max 24)**
44	2	1	2	2	2	0	**9**	2	0	2	0	2	0	**6**	**15**
45	2	2	2	2	2	1	**11**	2	2	2	2	2	2	**12**	**23**
46	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
47	2	2	2				**6**	2	2	2				**6**	**12**
48	2	2	2		2	2	**10**	2	1	2		2	2	**9**	**19**
49	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
50	2	2	2	2	2	0	**10**	2	0	2	0	2	0	**6**	**16**
51	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
52	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
53	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
54	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
55	2	2	2	2	2	2	**12**	2	1	2	2	2	2	**11**	**23**
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	1	**11**	**23**
58	2	2	2	2	2	2	**12**	2	1	2	2	2	1	**10**	**22**
59				2	2	2	**6**				0	2	1	**3**	**9**
60	2	2	2	2	2	2	**12**	2	2	2	1	2	2	**11**	**23**
61	2	2	2	2	2	2	**12**	2	2	2	1	2	2	**11**	**23**
62		2			2	2	**6**		1			2	2	**5**	**11**
63	2	2	2				**6**	2	1	2				**5**	**11**
64	2		2	2	2	1	**9**	2		2	1	2	1	**8**	**17**
65	2	2	2	2	2	2	**12**	2	2	2	2	2	1	**11**	**23**
66															
67	1	2	2	1	2	2	**10**	2	2	2	1	2	2	**11**	**21**

END OF REPORT