Congenital Disorders of Glycosylation (CDG)

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Note: This annual report is intended for participants of the ERNDIM CDG EQA scheme. The contents should not be used for any publication without permission of the Scientific Advisor.

The fact that your laboratory participates in ERNDIM schemes 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. 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 (https://cscq.hcuge.ch/cscq/ERNDIM/Initial/Initial.php) is hosted and maintained by CSCQ (Swiss Centre for Quality Control)., both on behalf of ERNDIM.

2. Samples

Samples were selected by the Scientific Advisor and tested for suitability in the Scientific Advisor's laboratory (Unidade Bioquimica Genetica, Centro de Genetica Medica Jacinto de Magalhães, Centro Hospitalar Universitário do Porto. Portugal). 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 2021 scheme, 3 samples were provided by the Scientific Advisor and 3 by the MCA Laboratory. 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 16th February 2021. Twenty-four laboratories requested a total of 31 extra sample sets and were sent the larger sample volume.

[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.**

4. Receipt of results

Results were submitted to an online results website (cscq.hcuge.ch/cscq/ERNDIM/) which is hosted and maintained by CSCQ. The submission deadlines for the first round (samples CDG-PP-2021-A, -B and -C) and second round (samples CDG-PP-2021-D, -E and -F) were 24th May 2021 and 4th October 2021 respectively. Overall, 62/67 (93%) registered participants submitted results for the 2021 scheme: 61 (91%) laboratories submitted results on time for both submission rounds. One lab (1.5%) only submitted results for the first round. While a separate five laboratories (7.5%) failed to make a return on either submission round; of these two 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 2022 scheme onwards labs that only submit results for one submission rounds will be classed as partial submitters, see section 7 (Preview of the 2022 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 2021 CDG scheme, 3 critical errors were identified. These were agreed at the meeting of the Scientific Advisory Board on 25th and 26th November 2021.

a. Appeals

If your laboratory has been assigned poor performance in the 2021 scheme and you wish to appeal against this classification, please use the link given in the Performance Support letter you received to submit your appeal request. The online form should be completed with full details of the reason for your appeal and submitted within one month of receiving your Performance Support Letter. Please note that only appeals submitted using the online response form will be considered.

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 2021 scheme

Sample	Clinical information (age, sex, phenotype)	Diagnosis
CDG-PP-2021-A	F, 40 yrs, increased transaminases, gGT	Alcohol abuse
CDG-PP-2021-B	M, 8 yrs, intellectual disability, macrocephaly, hypertelorism, truncal obesity	MAN1B1-CDG
CDG-PP-2021-C	M, 4 yrs, intellectual disability, epilepsy	Normal sample
CDG-PP-2021-D	F, 20yrs, type 1 diabetes, severe scoliosis and membranoproliferative glomerulonephritis	SLC37A4-CDG
CDG-PP-2021-E	M, 21yrs, growth deficiency, minor neurological involvement, minor facial dysmorphism	SLC35A2-CDG
CDG-PP-2021-F	F, 10 yrs, cataract, dysmorphic features, hepatomegaly	Normal sample

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 laboratories that reported their method (62/67), Isofocusing was the method employed most often (22/62), followed by CE (17/62), HPLC (12/62), Mass Spectrometry (6/62) and Other (5/62).

Table 2: Scoring of samples in the 2021 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG-PP-2021-A	62	94%	96%	95%
CDG-PP-2021-B	62	97%	98%	97%
CDG-PP-2021-C	62	100%	100%	100%
CDG-PP-2021-D	61	95%	97%	96%
CDG-PP-2021-E	61	95%	97%	96%
CDG-PP-2021-F	61	99%	99%	99%

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

Total Score	No of labs
<60%	0
60 – 69.9%	1
70 – 79.9%	3
80 – 89.9%	3
90 – 99.9%	4
100%	51
Total	**62**

The full anonymised results for all labs that submitted results are given in APPENDIX 1 on page 5 of this report.

CDG-PP-2021-A: 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 that could also fit very well with an adult case of PMM2-CDG or MPI-CDG, since several case reports have been published with near-normal transferrin glycosylation and abnormal liver enzymes. It is unclear if the clinical condition of the current individual was related to the alcohol abuse or was unrelated. The Total Proficiency score was of 95%, representing a stabilized result when compared with former year's score.

A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the Scientific Advisory Board (SAB).

CDG-PP-2021-B: MAN1B1-CDG

A type 2 profile was identified by nearly all laboratories and interpreted as abnormal by nearly all as well, resulting in a total proficiency score of 97%. 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 MAN1B1-CDG. Therefore, in case of interpretation of a profile as CDG-II, a neuraminidase treatment should be performed to exclude transferrin polymorphism. Identification of the profile as abnormal and indicating MAN1B1-CDG/CDG II as a possible diagnosis and suggestion for NGS/WES should be included for full scoring.

A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the SAB.

CDG-PP-2021-C: Control

All laboratories reported this sample as normal resulting in a proficiency score of 100%.

CDG-PP-2021-D: SLC37A4-CDG

A type 2 profile was identified by nearly all laboratories and interpreted as abnormal by nearly all as well, resulting in a proficiency score of 96%. The first step would be to confirm an eventual protein polymorphism using neuraminidase treatment on the suspected sample or collecting serum sample from the parents for transferrin IEF pattern confirmation. If a transferrin polymorphism is excluded, diagnostic should proceed by glycan analysis and a molecular genetics approach based on NGS panel technology for CDG.

Nevertheless, a PubMed search linked the clinical phenotype with the paper "SLC37A4-CDG: Second patient" Wilson MP et al. JIMD Rep. 2021 Jan 6;58(1):122-128, so probably a direct Sanger sequencing could also be the first approach.

CDG-PP-2021-E: SLC35A2-CDG

A type 2 profile was identified by nearly all laboratories and interpreted as abnormal by nearly all as well, resulting in a proficiency score of 96%. The first step would be to confirm an eventual protein polymorphism using neuraminidase treatment on the suspected sample or collecting serum sample from the parents for transferrin

IEF pattern confirmation. If a transferrin polymorphism is excluded, diagnostic should proceed by glycan analysis and a molecular genetics approach based on NGS panel technology for CDG.

Although an atypical male patient in a x-linked disorder, recent papers with male SLC35A2-CDG refers to similar clinical phenotype (Vals MA et al. Clinical, neuroradiological, and biochemical features of SLC35A2-CDG patients. J Inherit Metab Dis. 2019 May;42(3):553-564. doi: 10.1002/jimd.12055), so a direct Sanger sequencing could also be the first approach.

A normal profile interpretation of this sample, without additional Diagnostic Suggestions, was considered a critical error by the SAB.

CDG-PP-20121-F: Control
Nearly all laboratories reported this sample as normal resulting in a proficiency score of 99%.

7. **Preview of the 2022 scheme**
To bring this scheme into line with the other ERNDIM qualitative schemes, **for the 2022 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**. **This information has been included in the 2022 CDG scheme instructions.**

We had planned to introduce this for the 2021 scheme however this information was mistakenly not included in the 2021 scheme instructions, so we have delayed the introduction of this policy to the 2022 scheme.

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.

Dr Dulce Quelhas
Scientific Advisor

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

2021	Technical, item C							Advice, item D							
Sample ID	A	B	C	D	E	F		A	B	C	D	E	F		
Average score / Lab ID	1.87	1.94	2.00	1.90	1.89	1.98	Total	1.92	1.95	2.00	1.93	1.92	1.98	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	0	1	9	2	2	2	2	0	1	9	18
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	2	2	2	2	2	12	2	2	2	2	2	2	12	24
7	2	2	2	1	0	2	9	2	2	2	2	2	2	12	21
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	1	2	2	2	2	2	11	1	2	2	2	2	2	11	22
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	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	0	0	2	2	2	2	8	0	0	2	2	2	2	8	16
20	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
21	2	2	2	0	2	2	10	2	2	2	1	2	2	11	21
22	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
23	2	0	2	2	0	2	8	2	1	2	2	0	2	9	17
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	2	12	24
27	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
28	1	2	2	2	2	2	11	2	2	2	2	2	2	12	23
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	2	2	2	12	2	2	2	2	2	2	12	24
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	2	2	2	2	2	12	2	2	2	2	2	2	12	24
37	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
38	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
39	2	2	2	1	2	2	11	2	2	2	1	2	2	11	22
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

2021	Technical, item C							Advice, item D							
Sample ID	A	B	C	D	E	F		A	B	C	D	E	F		
Average score / Lab ID	1.87	1.94	2.00	1.90	1.89	1.98	Total	1.92	1.95	2.00	1.93	1.92	1.98	Total	Total score (max 24)
44	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
45	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
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	2	2	2	2	2	2	12	2	2	2	2	2	2	12	24
53	2	2	2				6	2	2	2				6	12
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	2	2	2	2	2	12	24
56	0	2	2	2	2	2	10	0	2	2	2	2	2	10	20
57	1	2	2	0	2	2	9	2	2	2	0	2	2	10	19
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	2	2	2	2	2	12	2	2	2	2	2	2	12	24
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

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

Version Number	Published	Amendments
1	30 May 2022	• 2021 annual report published
2	21 September 2022	• Page 3, Table 2: proficiencies for sample 2021-E updated as result of changes to scores for lab 18 • Page 3, Table 3: updated as result of changes to scores for lab 18 • Page 5, Appendix 1: Scores for lab 18 for sample 2021-E corrected

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