Congenital Disorders of Glycosylation (CDG)

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Please 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 2023 scheme, 1 sample was provided by the Scientific Advisor, 3 by the MCA Laboratory and 2 by Dr. Rafael Artuch (Laboratorio de Bioquímica, Hospital Sant Joan de Déu, Barcelona, Spain). All samples were obtained following local ethical and consent guidelines.

Details regarding stability of samples were provided in the scheme instructions, which are available to download from the Participant Information tab of the ERNDIM Registration Website (www.eqa.erndim.org).

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.

[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.**

3. **Shipment**
The six samples were sent to the 55 registered laboratories in one parcel on 7th February 2023. Twenty-five laboratories requested a total of 36 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. The submission deadlines for the first round (samples CDG-PP-2023-A, -B and -C) and second round (samples CDG-PP-2023-D, -E and -F) were 15th May 2023 and 18th September 2023 respectively. Overall, 54/55 (98%) registered participants submitted results for the 2023 scheme: 50 (91%) laboratories submitted results on time for both submission rounds, with a further 2 laboratories (3.6%) submitting results after the deadline for the first submission round. Two separate labs (3.6%) only submitted results for one round each. While a one laboratory (1/55, 1.8%) failed to make a return on either submission round.

5. **Scoring scheme**
In agreement with ERNDIM rules, we applied a scoring system of 2+2:

Technical aspects: 1 point for identifying an abnormal profile and 1 point for correctly identifying the profile as type I or II.

Diagnostic suggestions: This section should be filled in 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 correct suggestions should be made for the next step in the diagnostic process, which eventually will lead to the identification of 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 submit results for the first or second round. The level for satisfactory performance is 17 points. In instances where the SAB agrees that a sample will be classed as an Educational Sample, the scores associated with the sample will be not included in the performance evaluation of the participating laboratories' overall scheme.

Labs that only submit results for 3 or fewer samples in a scheme year are classified as partial submitters and their performance is not evaluated. This information is included in the CDG scheme instructions. 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.

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 2023 CDG scheme, no critical errors were identified. All critical errors for the 2023 ERNDIM schemes were agreed at the meeting of the Scientific Advisory Board on 30th November and 1st December 2023.

   a. **Appeals**
   If your laboratory has been assigned poor performance in the 2023 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, from controls, and from a confirmed individual with alcohol abuse. The final results of the six samples with respect to CDG are summarised in Table 1 below.

Table 1: Samples in the 2023 scheme

Sample ID	Clinical information	Sex	Patient Age	Diagnoses
CDG-2023-A	Hepatic fibrosis, gamma-glutamyl transferase (GGT)	F	21 years	Alcohol Abuse sample
CDG-2023-B	Polycystic kidney disease, hyperinsulinemic hypoglycemia	M	2 years	Control
CDG-2023-C	Mild intellectual disability, pigmentary retinopathy and slurred speech.	F	17 years	PMM2-CDG
CDG-2023-D	Axial hypotonia, mild-moderate intellectual disability, Abnormalities in coagulation	F	15 years	PMM2-CDG
CDG-2023-E	Seizure, Axial hypotonia	F	3 years	Control
CDG-2023-F	Global developmental delay, autism spectrum disorder, bruising susceptibility	M	4 years	Transferrin variant

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 (53/53), Isofocusing was the most employed method (17/53), followed by HPLC (13/53), CE (11/53), Mass Spectrometry (7/53) and Other (5/53).

Table 2: Scoring of samples in the 2023 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG-2023-A	53	96.2	88.7	92.5
CDG-2023-B	53	98.1	69.8	84.0
CDG-2023-C	53	98.1	98.1	98.1
CDG-2023-D	53	97.2	96.2	96.7
CDG-2023-E	53	98.1	98.1	98.1
CDG-2023-F	53	83.0	81.1	82.1

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

Total Score	No of labs
<60%	1
60 – 69.9%	2
70 – 79.9%	5
80 – 89.9%	6
90 – 99.9%	14
100%	24
Total	**52**

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

CDG-PP-2023-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 also 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 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 **92%,** representing a stabilised result compared to the former year's score.

CDG-PP-2023-B: Control
Most laboratories reported this sample as normal, resulting in a Technical proficiency score of **98,1%.** Although, this sample was from a PMM2-CDG patient with Polycystic kidney disease with hyperinsulinaemic hypoglycaemia (HIPKD). It is a recently described disease caused by a single nucleotide variant, c.-167G>T, in the promoter region of *PMM2* (encoding phosphomannomutase 2), either in homozygosity or compound heterozygosity with a pathogenic coding variant in *trans*. A relevant number of participants suggested the correct diagnosis, taking into account the highly suggestive clinical phenotype.

CDG-PP-2023-C: PMM2-CDG
A type 1 profile was identified and interpreted as abnormal by most laboratories, resulting in a proficiency score of **98.1%.** The pattern was a classical type 1 pattern, and no significant differences were noticed when comparing the performance of different methods. The clinical symptoms are, however, somewhat suggestive of PMM2-CDG. Identifying the profile as abnormal and indicating PMM2-CDG as a possible diagnosis was necessary for total scoring.

CDG-PP-2023-D: PMM2-CDG
A type 1 profile was identified and interpreted as abnormal by most laboratories, resulting in a proficiency score of 96.7%. The pattern was a classical type I pattern, and no significant differences were noticed when comparing the performance of different methods.

The clinical symptoms are, however, somewhat suggestive of PMM2-CDG. Therefore, in case of interpretation of a profile as CDG-I, a diagnosis of PMM2-CDG should be advised in this situation. The total scoring should include the identification of the profile as abnormal and the indicating of PMM2-CDG as a possible diagnosis.

CDG-PP-2023-E: Control
Almost all laboratories reported this sample as normal, resulting in a proficiency score of 98.1%.

A high number of participants (14/53) did not submit additional Diagnostic Suggestions. Nevertheless, this has not been taken into account for the final evaluation.

CDG-PP-2023-F: Transferrin polymorphic variant

Most labs using IEF or CE reported an abnormal profile of transferrin, either directly suggesting a protein polymorphism or an abnormal type II profile, resulting in a total proficiency score of 82.1%. **It is important to note that polymorphism was only visible by IEF, HPLC, WB, and CE and not by mass spectrometry.** Several laboratories performed neuraminidase incubation to confirm a polymorphism. The presence of a polymorphism is clinically without any complication, but this could complicate the interpretation of the profile type.

7. Preview of the 2024 scheme

a. Scientific Advisory team

In 2024, CDG scheme scientific advisory team will change, as Dirk Lefeber is stepping down and Blai Morales is taking his position. The ERNDIM wants to publicly thank all the expertise and dedication to the CDG scheme over the years Dirk has assumed the Scientific advisor position. We also want to welcome Blai to his new position.

b. Scoring for the 2025 scheme

For the **2025** scheme the scoring system for normal samples will change to reflect real life working practice, so that 2 points will only be scored if a comment is included warning the clinician that the **transferrin glycoform profiling** does not exclude **all CDG**.

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 ERNDIM Congenital Disorders of Glycosylation scheme participants. 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 explicit prior consent of ERNDIM has been granted.

Dr Dulce Quelhas
Scientific Advisor

Blai Morales Romero
Deputy Scientific Advisor

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

Sample ID / Average score / Lab ID	Technical							Advice							Total score (Max 24)
	A	B	C	D	E	F	Total	A	B	C	D	E	F	Total	
	1.92	1.96	1.96	1.94	1.96	1.66		1.77	1.40	1.96	1.92	1.96	1.62		
1	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
2	2	2	2	1	0	2	**9**	2	2	0	2	2	0	**8**	**17**
3	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
4	2	2	2	1	0	2	**9**	2	2	2	2	2	1	**11**	**20**
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	2	2	2	**12**	1	2	2	2	2	2	**11**	**23**
8	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
9	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
10	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
11	2	2	2	2	2	2	**12**	2	2	0	2	2	1	**9**	**21**
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	1	0	2	**9**	2	2	0	2	2	0	**8**	**17**
15	2	2	2	1	2	2	**11**	2	2	2	2	2	2	**12**	**23**
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	1	2	**11**	2	2	2	2	2	2	**12**	**23**
19	2	2	2	2	0	0	**8**	-	-	-	-	-	-	**-**	**Partial Submitter**
20	2	2	2	2	2	2	**12**	2	2	2	2	2	0	**10**	**22**
21	2	0	2	1	2	2	**9**	2	0	0	2	0	1	**5**	**14**
22	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
23	2	2	2	2	**2**	2	**12**	2	2	2	2	2	2	**12**	**24**
24	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
25	2	2	2	1	2	2	**11**	2	2	2	2	2	2	**12**	**23**
26	2	2	2	1	0	2	**9**	2	2	1	2	2	1	**10**	**19**
27	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
28	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
29	2	2	2	1	0	2	**9**	2	2	2	2	2	2	**12**	**21**
30	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
31	2	2	2	1	2	2	**11**	2	2	1	2	2	1	**10**	**21**
32	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
33	-	-	-	-	-	-	**-**	-	-	-	-	-	-	**-**	**Non-submitter**
34	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
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**	0	2	2	2	**10**	0	2	1	0	2	1	**6**	**16**
38	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**

Sample ID / Lab ID	Technical							Advice							Total score (Max 24)
	A	B	C	D	E	F	Total	A	B	C	D	E	F	Total	
Average score	1.92	1.96	1.96	1.94	1.96	1.66		1.77	1.40	1.96	1.92	1.96	1.62		
39	0	**2**	2	2	2	2	**10**	2	2	2	2	2	2	**12**	**22**
40	-	-	-	-	-	-	**-**	2	2	2	2	2	2	**12**	**Partial Submitter**
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	0	2	2	1	**0**	2	**7**	2	2	2	2	2	2	**12**	**19**
44	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
45	2	2	2	2	0	2	**10**	2	2	0	0	2	0	**6**	**16**
46	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**
47	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
48	2	2	2	2	1	2	**11**	2	2	2	2	2	2	**12**	**23**
49	2	2	2	1	2	2	**11**	2	2	1	2	2	0	**9**	**20**
50	2	2	2	2	0	2	**10**	2	2	2	2	2	2	**12**	**22**
51	2	2	2	1	1	2	**10**	2	2	0	2	2	0	**8**	**18**
52	2	2	2	2	1	2	**11**	2	2	2	2	2	2	**12**	**23**
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	2	0	2	2	0	**8**	**20**

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

Version Number	Published	Amendments
1	12th June 2024	• 2023 annual report published

END OF REPORT