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 2024 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).

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[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.**

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 to the 55 registered laboratories in one parcel on 7th February 2024. Twenty-five laboratories requested a total of 40 extra sample sets and were sent a 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-2024-A, -B and -C) and second round (samples CDG-PP-2024-D, -E and -F) were the 13th May 2024 and the 9th September 2024, respectively. One laboratory (1/55, 1.8%) withdrew from the scheme, the remaining 54 labs submitted results for both submission rounds. One laboratory (1.9%) submitted results after the deadline for the first submission round. One lab was registered as an Educational Participant.

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 2024 CDG scheme, two critical errors were identified. All critical errors for the 2024 ERNDIM schemes were agreed at the meeting of the Scientific Advisory Board on 28th and 29th November 2024.

   a. **Appeals**
   If your laboratory has been assigned poor performance in the 2024 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 2024 scheme

Sample ID	Clinical information	Sex	Patient Age	Diagnoses
CDG-PP-2024-A	Hepatomegaly, intellectual disability, epilepsy	M	8 years	Normal profile
CDG-PP-2024-B	Strabismus, axial hypotonia, deep venous thrombosis	F	10 years	Type 1 - PMM2-CDG
CDG-PP-2024-C	Nephrotic syndrome, hypertrophic cardiomyopathy, osteoporosis	M	5 years	Transferrin variant

Sample ID	Clinical information	Sex	Patient Age	Diagnoses
CDG-PP-2024-D	Delayed speech and language development, seizure, intellectual disability	M	3 years	Normal profile
CDG-PP-2024-E	Hypoalbuminemia, elevated hepatic transaminases, ataxia	F	40 years	Type 1 - alcohol abuse
CDG-PP-2024-F	Hepatic fibrosis, kyphoscoliosis, peripheral neuropathy	F	15 years	Type 1 - PMM2-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 laboratories that reported their method (54/54), Isofocusing was the method employed most often (17/54), followed by HPLC (13/54), CE (13/54), Mass Spectrometry (8/54) and Other (3/54).

Table 2: Scoring of samples in the 2024 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG-PP-2024-A	54	97.2	97.2	97.2
CDG-PP-2024-B	54	95.4	89.8	92.6
CDG-PP-2024-C	54	92.6	88.0	90.3
CDG-PP-2024-D	54	91.7	93.5	92.6
CDG-PP-2024-E	54	98.1	78.7	88.4
CDG-PP-2024-F	54	96.3	85.2	90.7

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

Total Score	No of labs
<50%	0
50 - 59.9%	5
60 – 69.9%	0
70 – 79.9%	3
80 – 89.9%	4
90 – 99.9%	13
100%	29
Total	**54**

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

CDG-PP-2024-A: Control sample

Almost all laboratories reported this sample as normal, resulting in a proficiency score of 97.2%.

CDG-PP-2024-B: Type 1 – PMM2-CDG

All labs reported this sample as abnormal and nearly all centers correctly assigned this profile as type I profile. The profile was rather mild with elevation of disialotransferrin and some participants reported a slight elevation of asialotransferrin as well. The age and clinical presentation could hint in the direction of PMM2-CDG. The advice for further diagnostics should include the option of PMM2-CDG as most frequent CDG-I subtype.

CDG-PP-2024-C: Transferrin 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 90.3%. It is important to note that the polymorphism was only detected by IEF or CE, and not by HPLC, WB, and 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.

CDG-PP-2024-D: Control

A normal profile was identified and interpreted as normal by most labs, resulting in a proficiency score of 92.6%.

CDG-PP-2024-E: Alcohol abuse

Most labs reported this sample as abnormal and correctly classified the profile as type I due to increased asialo- and disialo-transferrin (Trf). Additionally, most labs suggested alcohol abuse as a probable secondary cause, resulting in a proficiency score of 88.4%.

The sample was obtained from an adult patient with excessive alcohol intake, a condition typically associated with an abnormal type I pattern. However, some labs also observed a slight increase in monosialo- and trisialo-Trf, leading them to classify the profile as type II or mixed type I/II. This finding may be attributed to associated liver disease, which can produce mild type II profiles. Given the patient's age and clinical history, the possibility of a secondary cause for the altered profile is highly likely and should be mentioned.

CDG-PP-2024-F: PMM2-CDG

A type 1 profile was identified and interpreted as abnormal by most labs, resulting in a proficiency score of 90.7%. The pattern exhibited a classical type I profile, with no significant differences observed across different analytical methods.

However, the clinical symptoms are somewhat suggestive of PMM2-CDG. Therefore, when interpreting a type I profile, a diagnosis of PMM2-CDG should be considered in this context. Correct identification of the profile as abnormal, along with indicating PMM2-CDG as a potential diagnosis, should be included for complete scoring.

Two critical errors were noted in this sample, involving two participants who failed to recognise an abnormal type I pattern and incorrectly reported the sample as normal.

7. Preview of the 2025 scheme

During 2025, a new reporting system is expected to be available on the CSCQ website, allowing direct download of reports in the same way as other qualitative ERNDIM schemes.

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

Dr. Blai Morales Romero
Deputy Scientific Advisor

APPENDIX 1. Detailed scores for submitting laboratories

Your laboratory's anonymised lab number in the table below is: **4**

***** CE = Critical Error

Sample ID	Technical							Advice							Total score (Max 24)	CE*
	A	B	C	D	E	F		A	B	C	D	E	F			
Average score / Lab ID	1.94	1.91	1.85	1.83	1.96	1.93	Total	1.94	1.80	1.76	1.87	1.57	1.70	Total		
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	1	2	**11**	**23**	
3	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
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	0	2	2	**10**	2	2	2	1	0	1	**8**	**18**	
8	2	2	2	2	2	2	**12**	2	2	2	2	0	2	**10**	**22**	
9	0	2	1	2	2	2	**9**	0	2	0	2	0	0	**4**	**13**	
10	2	2	2	2	2	2	**12**	2	2	2	2	0	1	**9**	**21**	
11	2	2	1	2	2	2	**11**	2	1	1	2	2	1	**9**	**20**	
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	0	2	**10**	**22**	
18	2	2	2	2	2	2	**12**	2	2	2	2	2	1	**11**	**23**	
19	2	2	2	2	2	2	**12**	2	1	1	2	2	1	**9**	**21**	
20	2	1	2	2	2	2	**11**	2	1	2	2	2	2	**11**	**22**	
21	2	1	2	2	2	2	**11**	2	2	2	2	2	1	**11**	**22**	
22	2	1	2	0	2	2	**9**	2	1	1	0	0	0	**4**	**13**	
23	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
24	2	2	1	2	0	2	**9**	2	2	2	2	0	2	**10**	**19**	
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	1	2	2	2	2	**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	2	2	2	**12**	**24**	
29	2	2	2	2	2	2	**12**	2	1	2	2	2	1	**10**	**22**	
30	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
31	2	1	2	2	2	2	**11**	2	0	2	2	2	2	**10**	**21**	
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	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	1	2	2	2	**11**	**23**	

Sample ID / Average score / Lab ID	Technical							Advice							Total score (Max 24)	CE*
	A	B	C	D	E	F	Total	A	B	C	D	E	F	Total		
Average score	1.94	1.91	1.85	1.83	1.96	1.93		1.94	1.80	1.76	1.87	1.57	1.70			
37	2	2	0	0	2	2	**8**	2	1	0	0	2	1	**6**	**14**	
38	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
39	2	2	0	2	2	0	**8**	2	1	0	2	1	0	**6**	**14**	**CE**
40							**0**							**0**	**Withdrawn**	
41	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
42	2	2	2	0	2	0	**8**	2	1	1	1	0	0	**5**	**13**	**CE**
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	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	1	1	2	2	2	**10**	2	2	0	2	0	2	**8**	**18**	
49	2	2	2	1	2	2	**11**	2	2	2	1	2	2	**11**	**22**	
50	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
51	1	2	2	2	2	2	**11**	1	2	2	2	2	2	**11**	**22**	
52	2	2	2	2	2	2	**12**	2	2	2	2	1	2	**11**	**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	0	2	**10**	**22**	
55	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	20th Feb 2025	• 2024 annual report published

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