Congenital Disorders of Glycosylation (CDG)

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Annual Report 2025

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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 2025 scheme, 3 samples were provided by the Scientific Advisor, 1 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). Samples are stable for the duration of the scheme's submission calendar when stored under defined conditions.

[1] **If this Annual Report is not Version 1 for this scheme year, go to Appendix 2 (page 7) 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 57 registered laboratories in one parcel on 4th February 2025. Twenty-eight laboratories requested a total of 43 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-2025-A, -B and -C) and second round (samples CDG-PP-2025-D, -E and -F) were the 26th May 2025 and the 8th September 2025, respectively. From the 57 laboratories registered for the 2025 CDG scheme, 49 labs submitted results for both submission rounds. Six laboratories (10.5%) only submitted results for one submission round, and 2 laboraties (3.5%) did not submit for either summission 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 2025 CDG scheme, three critical errors were identified. All critical errors for the 2025 ERNDIM schemes were agreed at the meeting of the Scientific Advisory Board on 27th and 28th November 2025.

Further information regarding the Framework for Assessment and Education in Qualitative Schemes can be found under the Participant Information tab on the ERNDIM registration website (www.eqa.erndim.org).

   a. **Appeals**
   If your laboratory has been assigned poor performance in the 2025 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 a control individual, and from an individual with a transferrin variant. The final results of the six samples with respect to CDG are summarised in Table 1 below.

Table 1: Samples in the 2025 scheme

Sample ID	Clinical information	Sex	Patient Age	Diagnoses
CDG-PP-2025-A	Hips lipodystrophy, terminal nystagmus, without autonomous walking.	F	17 years	PMM2-CDG
CDG-PP-2025-B	Inverted nipples, epilepsy, liver dysfunction.	F	4 years	Normal serum

Sample ID	Clinical information	Sex	Patient Age	Diagnoses
CDG-PP-2025-C	Mild intellectual disability, hearing impairment, epilepsy.	M	30 years	RFT1-CDG
CDG-PP-2025-D	Cerebellar hypoplasia, dysmorphic features, nystagmus.	F	4 years	PMM2-CDG
CDG-PP-2025-E	Autistic behaviour spectrum.	M	7 years	Transferrin variant
CDG-PP-2025-F	Muscular hypotonia, intellectual disability, scoliosis.	F	11 years	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.

Considering both the first and second rounds, 55 of the 57 laboratories reported their analytical method. Among these, isofocusing remained the most frequently employed technique (17/55), closely followed by HPLC (14/55) and CE (13/55), with mass spectrometry (10/55) and other methods (1/55) used less frequently.

Table 2: Scoring of samples in the 2025 scheme

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG-PP-2025-A	53	100	91.5	95.8
CDG-PP-2025-B	53	96.2	95.3	95.8
CDG-PP-2025-C	53	97.2	92.5	94.8
CDG-PP-2025-D	51	98.0	90.2	94.1
CDG-PP-2025-E	51	91.2	88.2	89.7
CDG-PP-2025-F	51	97.1	85.3	91.2

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

Total Score	No of labs
<50%	0
50 - 59.9%	0
60 – 69.9%	3
70 – 79.9%	2
80 – 89.9%	6
90 – 99.9%	12
100%	26
Total	**49**

The full anonymised results for all labs are given in Appendix 1 on page 6 of this report.

CDG-PP-2025-A: Type 1 – PMM2-CDG

A type I transferrin glycoform profile was identified and interpreted as abnormal by all laboratories, resulting in a total proficiency score of 95.8%. The pattern corresponded to a classical type I profile, without major differences between the analytical methods used.

The clinical information provided is compatible with PMM2-CDG, the most frequent CDG-I subtype. Therefore, when a type I profile is observed in this context, PMM2-CDG should be considered as the most likely diagnosis. The high total score reflects not only the correct identification of the abnormal type I profile but also the provision of appropriate diagnostic recommendations, which were mainly focused on genetic studies and enzymatic analysis of the phosphomannomutase activity in leukocytes. Correct identification of the profile as abnormal and the suggestion of PMM2-CDG as a possible diagnosis were required for full scoring.

CDG-PP-2025-B: Normal sample

A normal transferrin glycoform profile was identified and interpreted as normal by almost all laboratories, resulting in a total proficiency score of 95.8%.

CDG-PP-2025-C: Type 1 – RFT1-CDG

A type I abnormal transferrin glycoform profile was reported by almost all laboratories, resulting in a total proficiency score of 94.8%. The profile was clearly abnormal, and no relevant differences were observed between the different

analytical methods. The elevated total score demonstrates both the accurate recognition of the abnormal type I profile and the inclusion of appropriate diagnostic recommendations, which were mainly focused on genetic studies.

Around 38% (20/53) of participants suggested RFT1-CDG as a potential diagnosis, mainly based on the presence of hearing impairment in the clinical presentation.

One participant using mass spectrometry committed a critical error by failing to identify the abnormal sample and reporting it as normal.

CDG-PP-2025-D: Type 1 – PMM2-CDG

A type I transferrin glycoform profile was identified and interpreted as abnormal by most laboratories, resulting in a total proficiency score of 94.1%. The pattern corresponded to a classical type I profile, without major differences between the analytical methods used.

The clinical information provided is compatible with PMM2-CDG, the most frequent CDG-I subtype. Therefore, when a type I profile is observed in this context, PMM2-CDG should be considered as the most likely diagnosis. The high total score reflects not only the correct identification of the abnormal type I profile but also the provision of appropriate diagnostic recommendations, which were mainly focused on genetic studies and enzymatic analysis of phosphomannomutase activity in leukocytes. Correct identification of the type I abnormal profile, together with the suggestion of PMM2-CDG as a possible diagnosis and the recommendation of appropriate genetic studies, was required for full scoring.

In this sample, a participant applying isofocusing did not recognize the abnormal type I pattern and therefore reported the result as normal, constituting a critical error.

CDG-PP-2025-E: Transferrin variant

Most laboratories using IEF or CE reported an abnormal transferrin glycoform profile, either directly suggesting a protein polymorphism or describing it as an abnormal type II pattern, resulting in a total proficiency score of 89.7%. The polymorphism was detectable only by IEF or CE, but not by HPLC, Western blot, or mass spectrometry.

For laboratories reporting an abnormal profile, recommending neuraminidase treatment as a confirmatory step was required for full scoring. Two laboratories using CE and one participant using IEF reported a normal profile, misinterpreting the transferrin glycoform pattern, while one participant incorrectly assigned the sample as type I CDG.

Although the presence of a transferrin polymorphism is clinically benign, it can complicate the interpretation of the glycoform profile and should always be ruled out before considering a pathological cause (see Figure 1).

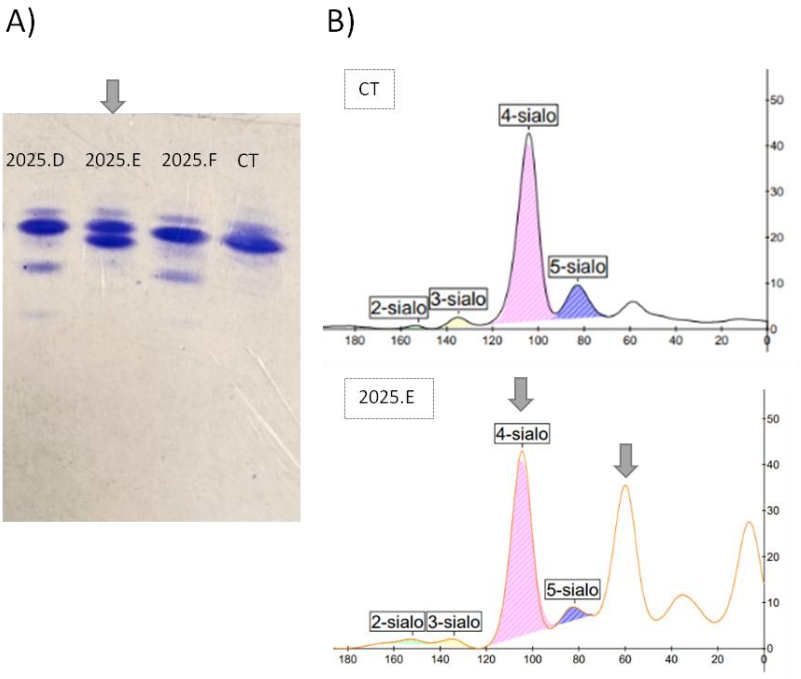

Figure 1.

A) Isoelectric focusing (IEF) analysis of transferrin in samples **2025.D**, **2025.E** (showing a transferrin variant), **2025.F**, and a control (**CT**) individual.

B) Capillary electrophoresis (CE) electropherograms from a control (**CT**) individual (top) and sample **2025.E** (bottom). Arrows indicate the tetrasialotransferrin peaks corresponding to the wild-type transferrin (left) and the variant transferrin (right).

CDG-PP-2025-F: Type 1 – PMM2-CDG

A type I transferrin glycoform profile was detected and classified as abnormal by almost all laboratories, resulting in a total proficiency score of 91.2%. The profile exhibited the typical characteristics of a classical type I pattern, and comparable results were obtained across the different analytical methods employed.

The clinical presentation was compatible with PMM2-CDG, the most common subtype of CDG-I. In such cases, the observation of a type I profile should prompt consideration of PMM2-CDG as a primary diagnostic possibility. The high total score indicates that most laboratories not only recognised the abnormal pattern but also provided suitable diagnostic recommendations, primarily focused on genetic testing and assessment of phosphomannomutase activity in leukocytes. Accurate interpretation of the abnormal profile, together with the suggestion of PMM2-CDG as a possible diagnosis and the inclusion of appropriate diagnostic guidance, was required for full scoring.

A critical error was identified for one participant using CE, who interpreted the profile as normal despite the presence of an abnormal pattern.

7. Comment on the 2025 scheme

Overall, the outcome of the 2025 CDG scheme was very good. The overall proficiency of participating laboratories was high and comparable to that observed in previous scheme years. Both analytical and interpretative performances were consistent across most samples. Sample E showed a slightly lower proficiency score compared to the other samples, mainly due to difficulties encountered by some laboratories in the interpretation of abnormal transferrin glycoform profiles caused by transferrin variants. This highlights the importance of correct recognition of this type of profile, when applicable, particularly for laboratories with less experience or those that have recently changed analytical methodology. It is therefore essential that each laboratory is familiar with the appearance of transferrin variant profiles as detected by its own analytical method.

8. Preview of the 2026 scheme

During 2026, 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.

9. Questions, Suggestions and Complaints

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

Most complaints received by ERNDIM consist of minor misunderstandings or problems with samples, which can usually be resolved via direct contact with the ERNDIM administrative staff. If you wish to file a formal complaint, please email your complaint with details of your issue to admin@erndim.org or contact us through our website at https://www.erndim.org/contact-us/

10. 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. Please note, the use of this data for training artificial intelligence systems is strictly prohibited.

Date of report: 5th Feb 2026

Name and signature:

Dr Dulce Quelhas
Scientific Advisor

Dr Blai Morales Romero
Deputy Scientific Advisor

APPENDIX 1. Detailed scores for submitting laboratories

CE = Critical Error

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		
	2.00	1.92	1.94	1.96	1.82	1.94	Total	1.83	1.91	1.85	1.80	1.76	1.71	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	2	2	**12**	**24**	
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	1	2	**11**	**23**	
5							**0**							**0**	**0**	
6	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
7	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
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9	2	2	2	2	2	2	**12**	2	2	2	1	2	1	**10**	**22**	
10	2	0	2	2	1	2	**9**	1	0	2	1	2	1	**7**	**16**	
11	2	2	2	2	2	2	**12**	2	2	1	2	2	2	**11**	**23**	
12	2	2	2	2	2	2	**12**	1	2	2	1	1	1	**8**	**20**	
13	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
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26	2	2	0	2	2	2	**10**	1	2	0	1	2	1	**7**	**17**	Sample C
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39	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
40	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	

Sample ID / Average score / Lab ID	Technical							Advice							Total score (Max 24)	CE
	A	B	C	D	E	F		A	B	C	D	E	F			
	2.00	1.92	1.94	1.96	1.82	1.94	Total	1.83	1.91	1.85	1.80	1.76	1.71	Total		
41	2	2	2	2	0	2	**10**	1	1	2	2	0	2	**8**	**18**	
42	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
43	2	2	2	2	2	2	**12**	1	2	2	2	2	2	**11**	**23**	
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46				2	2	2	**6**				1	2	2	**5**	**11**	
47	2	2	1				**5**	2	2	1				**5**	**10**	
48	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
49							**0**							**0**	**0**	
50	2	2	2	2	0	0	**8**	1	2	2	2	0	0	**7**	**15**	Sample F
51	2	2	2	2	2	2	**12**	2	2	2	2	2	2	**12**	**24**	
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54				2	2	2	**6**				2	2	1	**5**	**11**	
55	2	2	2	0	2	1	**9**	1	2	1	0	1	1	**6**	**15**	Sample D
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**	

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

Version Number	Published	Amendments
1	06 February 2026	• 2025 annual report published

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