Results ERNDIM QC scheme for CDG screening 2013

Nijmegen,
Original report issued: 02-2014
Amended report issued: 06-2014

Please find below the results of the 2013 ERNDIM scheme for CDG screening. Within ERNDIM, we are currently discussing to harmonize the reporting schedule of all schemes, which has caused some delay in reporting for the CDG scheme. For 2014, we will at least provide a summary of the results and the original diagnoses soon after the second reporting period.

To ensure future rounds of this CDG scheme, I would to ask you if you could provide patient material, preferably plasma/serum without additives. Please, send samples (~3.0 ml) to my address below, including information about age, sex, and a brief clinical description on first visit of the patient. In this way, we could again deliver 6 samples beyond 2014 and offer 50 µl samples for laboratories that perform CE or HPLC.

In case of any questions, please do not hesitate to contact us.

With kind regards, also on behalf of Cas Weykamp,

Dr. Dirk J. Lefeber
Clinical Biochemical Geneticist
830- Laboratory of Genetic, Endocrine and Metabolic Disease
Radboud University Nijmegen Medical Centre
Geert Grooteplein 10
6525 GA Nijmegen
The Netherlands
tel: +31 24 3614567 / 3953
fax: +31 24 3668754
Dirk.Lefeber@Radboudumc.nl

QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

ERNDIM Administration Office
Manchester Centre for Genomic Medicine
6th Floor, St Mary's Hospital, Oxford Road,
Manchester M13 9WL, United Kingdom.
Tel: +44 161 276 6741
Fax: +44 161 850 1145
Email: admin@erndim.org

Scientific Advisor
Dr Dirk Lefeber
830- Laboratory of Genetic, Endocrine and Metabolic Disease
Radboud University Nijmegen Medical Centre
Geert Grooteplein 10
6525 GA Nijmegen, The Netherlands
Tel: +31 24 3614567 / 3953
Fax: +31 24 3668754
Email: Dirk.Lefeber@Radboudumc.nl

Scheme Organiser
Dr. C.W. Weykamp
Queen Beatrix Hospital
MCA Laboratory
P.O. Box 9005
NL – 7100 GG Winterswijk
The Netherlands
Tel:
Fax:
Email: c.w.weykamp@skbwinterswijk.nl

Congenital Disorders of Glycosylation
Annual Report 2013
Date of issue: February 2014
Amended report issued: June 2014

1. **Scheme Design**
   The scheme has been designed and planned by the Scientific Advisor (SA) and Scheme Organiser (SO, subcontractor on behalf of SKML), both appointed by and according to procedures laid down by the ERNDIM Board.

2. **Samples**
   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 offered a 50 µl sample volume. All samples are obtained following local ethical and consent guidelines.

3. **Shipment**
   The seven samples were sent out to the 60 registered laboratories in one parcel on 12th February 2013. Twenty-one laboratories requested and were sent the larger sample volume.

4. **Receipt of results**
   Returns were submitted by email to the SA. The Returns for the first round (samples CDG025, CDG026, CDG027, and CDG028) and second round (samples CDG029, CDG030 and CDG031) were received from 49 laboratories (83%) by the due date.

   There were seven laboratories who failed to make a return on either submission round. Five of these also did not submit any results in 2012. Three laboratories reported on the first round only and three laboratories reported on the second round only.

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: For normal profiles in general 2 points. For abnormal profiles, comments should be made on the possibility of secondary causes in view 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 seven samples is 28, while a maximum of 16 and 12 points are available for labs that only submitted results for the first or second round respectively. The agreed level for satisfactory performance is 20 points. Laboratories that participate only in one circulation are treated as partial-submitters and can achieve satisfactory performance with 12 points, if results were submitted for the first round only or 10 points if results were submitted for the second round only.

   For the 2014 scheme onwards another criterion for satisfactory performance will be 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.

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 52 reporting laboratories, isofocusing was the method employed most often (34), followed by HPLC (9), CE (5), mass spectrometry (2) and western blot (2).

The shipped samples were from CDG patients, from controls and of patients with established excessive intake of alcohol. The final results of the eight samples with respect to CDG are summarized in Table 1 below.

Table 1: Samples in the 2013 scheme

Sample	Clinical information (sex, age, phenotype)	Diagnosis
CDG 025	M, 2 yrs, psychomotor retardation, epilepsy	Control
CDG 026	F, 1 yr, muscle weakness, CK increase, epilepsy	DPM2-CDG
CDG 027	M, 42 yrs, hepatopathy	Alcohol abuse
CDG 028	M, 12 yrs, hypotonia, hepatomegaly, hypoglycemia	Transferrin polymorphism
CDG 029	F, 8 yrs, gastro-enteritis, increased liver enzymes, anemia	Control
CDG 030	F, 8 months, hypotonia, epilepsy, deafness and strabismus	PMM2-CDG
CDG 031	F, 55 yrs, movement disorder	Alcohol abuse

ERNDIM CDG025
A normal profile was identified by all centres.

ERNDIM CDG026
The vast majority of labs reported an abnormal type I profile of transferrin. The clinical information includes a description of increased CK. Together with muscle weakness, this is seen in only a limited number of CDG-I subtypes and allows direct studies of specific subtypes. In the defects of the dolichol-P-mannose synthase complex (DPM genes DPM1, DPM2, DPM3), increased CK has been reported. Also in MPDU1-CDG (CDG-If), increased CK has been reported. Recognition of this feature is important, since it greatly facilitates identification of the causative gene defect. Some labs mentioned to look for DPM synthase defects. Also PGM1-CDG was mentioned as possible cause. Indeed, CK elevations are known for PGM1-CDG. Some PGM1 deficient cases can present with a CDG-I like profile, however mostly accompanied by a slight increase of monosialotransferrin.

ERNDIM CDG027
A CDG type I profile was observed and reported by almost all centers. In view of the age of the patient and non-specific symptoms, ~80% of the laboratories suggested the possibility of alcohol abuse as cause for the abnormal transferrin glycosylation profile.

Most centres commented on the possibility of alcohol abuse as a cause for type I profiles, in agreement with age. Possible the clinical description of hepatopathy fits with alcohol abuse or both are independent. In our experience, liver disease in general is more associated with mild type II profiles. In a few cases, trisialotransferrin was also slightly increased (please check normal ranges!), possibly suggesting type II or related to liver disease.

ERNDIM CDG028
This sample was of a non-CDG patient, but with a polymorphism in the transferrin protein. The polymorphism did not interfere with known glycosylation isoforms of transferrin and was recognized by almost all laboratories.

ERNDIM CDG029
A normal profile was identified by all centres.

ERNDIM CDG030
A type I abnormality was found for this sample by the majority of centers. Secondary causes for a CDG-I profile could still be relevant, but the clinical symptoms fit very well with a CDG-I defect. The presentation

of deafness has been found more frequently for RFT1-CDG, as mentioned specifically by some labs. Direct RFT1 sequencing or LLO analysis could be suggested to test for RFT1-CDG. Deafness can also occur in other CDG-I subtypes (and in the general population), which is an argument to start diagnostics with the most common subtype PMM2-CDG. In this case, measurement of PMM activity showed a deficiency, which was confirmed by mutations in the PMM2 gene.

ERNDIM CDG031
A CDG type I profile was observed and reported by almost all centers. In view of the age of the patient, alcohol abuse should be considered as secondary cause for abnormal type I CDG profiles. ~80% of the laboratories suggested the possibility of alcohol abuse as cause for the abnormal transferrin glycosylation profile.

Table 2: Proficiency per sample

Sample	No of returns	Technical Aspects (%)	Diagnostic Suggestions (%)	Total (%)
CDG025	49	100%	100%	100%
CDG026	49	97%	55%	76%
CDG027	49	91%	81%	86%
CDG028	49	98%	94%	96%
CDG029	49	99%	98%	98%
CDG030	49	98%	91%	94%
CDG031	49	97%	80%	88%

Table 3: Detailed scores for submitting laboratories

2013	**Technical, item C**								**Advice, item D**								
Sample ID	**025**	**026**	**027**	**028**	**029**	**030**	**031**	**Total**	**025**	**026**	**027**	**028**	**029**	**030**	**031**	**Total**	**Total score**
Average score	2	1,94	1,85	1,96	1,98	1,96	1,94		2	1,10	1,65	1,88	1,96	1,82	1,59		**max 28**
1	2	1	1	1	1	1	1	8	2	0	0	0	0	0	0	2	**10**
2	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
3	2	2	2	2	2	2	2	14	2	1	2	2	2	2	1	12	**26**
4	2	2	2	2	2	2	2	14	2	2	2	2	2	2	1	13	**27**
5	2	2	2	2	2	2	2	14	2	2	2	2	2	2	2	14	**28**
6	2	2	2	2	2	2	2	14	2	1	2	2	2	2	1	12	**26**
7					2	2	2	6					2	1	2	5	**11**
8	2	2	2	2	2	2	2	14	2	1	1	2	2	2	2	12	**26**
9	2	2	2	2	2	2	2	14	2	1	2	2	2	2	1	12	**26**
10	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
11	2	2	2	2	2	2	2	14	2	1	2	2	2	2	1	12	**26**
12	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
13	2	2	1	2	2	2	2	13	2	1	0	2	2	2	1	10	**23**
14	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
15	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
16	2	2	2	2	2	2	2	14	2	1	2	0	2	2	2	11	**25**
17	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**

Table 3: Detailed scores for submitting laboratories (continued)

2013	Technical, item C								Advice, item D								
Sample ID	**025**	**026**	**027**	**028**	**029**	**030**	**031**	**Total**	**025**	**026**	**027**	**028**	**029**	**030**	**031**	**Total**	**Total score**
Average score	2	1,94	1,85	1,96	1,98	1,96	1,94		2	1,10	1,65	1,88	1,96	1,82	1,59		**max 28**
18	2	2	1	2	2	2	2	13	2	2	2	2	2	2	2	14	**27**
19	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
20	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
21	2	2		2	2	2	2	12	2	1		2	2	2	2	11	**23**
22	2	2	2	2	2	2	2	14	2	2	2	2	2	2	2	14	**28**
23	2	2	2	2	2	2	2	14	2	1	1	2	2	2	2	12	**26**
24	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
25	2	0	0	2	2	2	2	10	2	0	0	2	2	2	1	9	**19**
26	2	2	2	2	2	2	2	14	2	1	1	0	2	1	1	8	**22**
27	2	2	2	2	2	2	2	14	2	1	1	2	2	2	2	12	**26**
28	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
29	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
30	2	2	2	2	2	2	2	14	2	2	2	2	2	2	2	14	**28**
31	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
32	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
33	2	2	2	2				8	2	1	2	2				7	**15**
34	2	2	2	2	2	2	2	14	2	1	1	2	2	1	0	9	**23**
35	2	2	2	2	2	2	2	14	2	2	2	2	2	2	2	14	**28**
36	2	2	2	2	2	1	2	13	2	1	2	2	2	1	2	12	**25**
37	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
38	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
39					2	2	0	4					2	2	0	4	**8**
40	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
41	2	2	2	2	2	2	2	14	2	2	2	2	2	1	2	13	**27**
42	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
43	2	2	0	2	2	2	2	12	2	1	0	2	2	2	1	10	**22**
44					2	2	2	6					2	1	1	4	**10**
45	2	2	2	2	2	2	2	14	2	1	1	2	2	1	1	10	**24**
46	2	2	2	2	2	2	2	14	2	2	1	2	2	2	0	11	**25**
47	2	2	2	2				8	2	1	1	2				6	**14**
48	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
49	2	2	2	2				8	2	1	2	2				7	**15**
50	2	2	2	2	2	2	2	14	2	1	2	2	2	2	2	13	**27**
51	2	2	2	2	2	2	2	14	2	0	2	2	2	2	2	12	**26**
52	2	2	2	1	2	2	2	13	2	1	1	2	2	2	1	11	**24**

Dirk Lefeber
Scientific Advisor

Cas Weykamp
Scheme Organiser