ERNDiM
Quality Assurance in Laboratory Testing for IEM

ERNDIM Quantitative Schemes Pterins in Urine

ANNUAL REPORT 2025

Scheme Organiser	Scientific Advisor	Website for reporting results	Administration office
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1. *Purpose*

The purpose of the ERNDIM External Quality Assurance Scheme for Pterins in Urine is the monitoring of the analytical quality of the assay of pterins in laboratories involved in the screening and diagnosis of patients with inherited metabolic disorders. The scheme consists of a quantitative assay of pterins in urine and will be discussed in this report. For details, see www.erndim.org / www.ERNDIMQA.nl

2. *Participants*

A total of 29 datasets have been submitted.

3. *Design*

The Scheme has been designed, planned and coordinated by Dr. Alessio Cremonesi as scientific advisor and Dr. R.M. Schoeman as scheme organiser (on behalf of the MCA Laboratory), both appointed by and according and in line with the procedures of the ERNDIM Board. The design includes samples and reports to provide information with a balance between short-term and long-term reports and between detailed and aggregated information. As a subcontractor of ERNDIM, the MCA Laboratory prepares and distributes the EQA samples to the scheme participants and provides a website for on-line submission of results and access to scheme reports.

Samples

The scheme consisted of 8 lyophilised samples, all prepared from the same basic urine, but with various amounts of added analytes. The analytes included are biopterin and neopterin and results are expressed in both µmol/L and mmol/mol creatinine. The samples were identical two by two: the pairs, the biochemical and (mimicked) clinical characteristics are in Table 1 below. Samples have been tested for stability and homogeneity according to ISO 13528. 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 1 for details of the changes made since the last version of this document.

Table 1. Samples

Sample Pair	Biochemical Characteristics	Clinical Characteristics
1 and 8	Neopterin normal Biopterin normal	A healthy person / A non-BH4 deficiency
2 and 7	Neopterin increased Biopterin decreased	A 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency
3 and 6	Neopterin slightly increased Biopterin slightly decreased Primapterin increased	A pterin-4a-carbinolamine dehydratase (PCD) deficiency
4 and 5	Neopterin increased Biopterin decreased	A 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency

Reports

All data-transfer, the submission of data as well as request and viewing of reports proceeded via the interactive website www.erndimqa.nl which can also be reached through the ERNDIM website (www.erndim.org). The results of your laboratory are confidential and only accessible to you (with your name and password). The anonymised mean results of all labs are accessible to all participants. Statistics of the respective reports are explained in the general information section of the website.

An important characteristic of the website is that it supplies short-term and long-term reports. **Short-term reports** are associated with the eight individual specimens, for each of which there has been a specific deadline in the year 2025. Three weeks after the respective deadline participants could request their reports and as such had eight times up-to-date information on their analytical performance. Although it is technically possible to produce reports immediately, there is a delay of 21 days to enable the scientific advisor to inspect the results and add comments to the report when appropriate. The **annual long-term report** is based on the design-anchored connection between samples, which enables a range of analytical parameters (accuracy, precision, linearity, recovery, and inter-lab dispersion) to be reported once the annual cycle has been completed.

A second important characteristic of the website is the wide range in aggregation of results, which permits labs to make an individual choice for detailed and/or aggregated reports. The most detailed report, which can be requested from the website, is the "Analyte in Detail", which shows results of a specific analyte in a specific sample (56 such Analyte-in-Detail-reports can be requested in the year 2025 cycle). A more condensed report is the "Current Report" (Called "Cycle Review" on the website), which summarises the performance of all analytes in a specific sample (8 such Current Reports can be requested in 2025). The highest degree of aggregation has the Annual Report, which summarises the performance of all analytes of all 8 samples (1 such Annual-Report can be requested in 2025). Depending on their position in the laboratory, one can choose to have a glance at only the annual report (managers) or at all 56 detailed reports (technicians).

4. Discussion of Results in the Annual Report 2025

In this part, the results as seen in the annual report 2025 will be discussed. Subsequently we will focus on accuracy, recovery, precision, linearity, interlab CV and cross-sectional relations. Please keep at hand your annual report from the Interactive Website when you read the "guided tour" below and keep in mind that we only discuss the results of "all labs": it is up to you to inspect and interpret the specific results of your laboratory.

4.1 Accuracy

A first approach to describe the accuracy is comparison of your mean outcome in the eight samples with the mean of all labs. This is shown in the columns "your lab" and "all labs" under the heading "Accuracy", respectively. E.g., for neopterin the mean of all labs is 70.3 µmol/L with which you can compare the mean of your lab.

4.2 Precision

Reproducibility is an important parameter for quality in the laboratory and is encountered in the schemes' design. Samples come in pairs, which can be regarded as duplicates from which CV's can be calculated (Intra Laboratory CV as indicator for reproducibility). Outcome for your lab in comparison to the median of all labs is shown in the column "Precision" of the Annual Report. Precision ranges from 4.1% for creatinine to 18.3% for biopterin (mmol/mol creatinine). The overall intralab CV is 12.7%.

4.3 Linearity

Linearity over the whole relevant analytical range is another important parameter for analytical quality. Again, this is encountered in the schemes' design. With weighed quantities on the x-axis and your measured quantities on the y-axis the coefficient of regression (-r-) has been calculated. Outcome for your lab in comparison to the median of all labs is in the column "Linearity" of the annual report. The coefficient of regression ranges from 0.981 for creatinine to 0.999 for biopterin (µmol/L).

4.4 Recovery

A second approach to describe accuracy is the percentage recovery of added analyte. In this approach, it is assumed that the recovery of the weighed quantities is the target value. The correlation between weighed quantities as added to the samples (on the x-axis) and your measured quantities (on the y-axis) have been calculated. The slope of the correlation multiplied by 100 is your recovery (%) of the added amounts. Outcome for your lab in comparison to median outcome of all labs is shown in the column "Recovery" in the annual report. For all labs the recovery ranges from 98% for primapterin (mmol/mol creatinine) to 102% for biopterin (µmol/L). The overall recovery is 100%.

4.5 Interlab CV

For comparison of outcome for one patient in different hospitals and for use of shared reference values it is relevant to have a high degree of harmonization between results of various laboratories. Part of the schemes' design is to monitor this by calculating the Interlaboratory CV. This, along with the number of laboratories who submitted results, is shown in the column "Data All labs" in the Annual Report. Most laboratories submitted results for creatinine) (32). The Interlab CV ranges from 5.94% for creatinine to 58.0% for primapterin (mmol/mol creatinine). The mean Interlab CV for all analytes is 32.5%.

4.6 Cross Sectional Relations

The various parameters as described above often have an interrelation: often more than one parameter directs towards good or bad analytical control.
This pattern, clearly seen in the other ERNDIM schemes is less prominent in the pterins scheme.

4.7 Your laboratory performance: Flags

In order to easily judge performance of individual laboratories, the annual report of an individual laboratory may include flags in case of poor performance for accuracy, precision, linearity and recovery. Analytes with satisfactory performance for at least three of the four parameters (thus no or only one flag or no result) receive a green flag. Thus, a green flag indicates satisfactory performance for analysis of that particular analyte while a flag indicates that your laboratory has failed to attain satisfactory

performance. Criteria for red flags can be found in the general information on the website (general information; interactive website, explanation annual report).

4.8 Poor Performance Policy

A wide dispersion in the overall performance of individual laboratories is evident. Table 2 shows the percentage of flags observed. 43% of the laboratories have no flag at all and thus have attained excellent overall performance. In contrast, at the other extreme there are also 14% of laboratories with 25% flags. Intensive discussion within the Scientific Advisory Board (SAB) resulted in a harmonised scoring scheme that has been in place for the quantitative schemes for more than ten years; Likewise, there has been agreement as to what constitutes satisfactory performance. Both parameters are checked annually and if necessary re-evaluated. For further information, please refer to the Framework for Assessment and Education for Hybrid Schemes on our website (https://eqa.erndim.org/information/view/14).The ERNDIM Board has decided that the Scientific Advisor will judge the performance of the individual laboratories based on these levels of satisfactory performance and issue a letter of advice of failure to achieve satisfactory performance to those laboratories, which do not achieve satisfactory performance. The letter is intended to instigate dialogue between the EQA scheme organiser and the participating laboratory to solve any analytical problems to improve quality of performance of labs in the pursuit of our overall aim to improve quality of diagnostic services in this field.

If your laboratory is assigned poor performance and you wish to appeal against this classification, please email the ERNDIM Administration Office (admin@erndim.org), with full details of the reason for your appeal, within one month receiving your Performance Support Letter. Details of how to appeal poor performance are included in the Performance Support Letter sent to poor performing laboratories.

Table 2. Percentage Flags

% Red Flags seen in Annual Report	Percentage Labs in this Category	Cumulative Percentage of Labs
>25%	0%	0%
25%	14%	14%
>20 – <25%	0%	14%
>15 – ≤20%	14%	29%
>10 – ≤15%	11%	39%
>5 – ≤10%	14%	54%
>0 – ≤5%	4%	57%
0%	43%	100%

4.9 Interpretation

In this scheme, we also requested the interpretation with respect to metabolic conditions. Table 3 shows the interpretation frequency for the respective sample pairs. The correct interpretation is marked in green.

Table 3. Interpretation.

Description	Pair 1-8	Pair 2-7	Pair 3-6	Pair 4-5
A healthy person	19 – 25	0 – 0	0 – 0	0 – 0
A Pterin-4a-carbinolamine dehydratase (PCD) deficiency	0 – 0	1 – 0	22 – 26	1 – 0
A 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency	0 – 0	26 – 28	5 – 2	26 – 27
A GTP cyclohydrolase (GTPCH) deficiency	1 – 0	0 – 0	0 – 0	0 – 0
A phenylalanine hydroxylase (PAH) deficiency	1 – 0	0 – 0	0 – 0	0 – 0
A non-BH4 deficiency	6 – 3	0 – 0	1 – 0	0 – 0

4.10 Additional Specific Remarks of the Scientific Advisor

It is important to bear in mind that for a correct interpretation of the scheme not only the analytical results but also the provided phenylalanine concentrations must be used. In addition, we recommend to carefully check the chromatographic separation between primapterin and biopterin so that quantitative results for the former analyte are only provided when a clear peak is present in the sample.

5. *Certificates*

Starting from 2017 the pterins are included on the certificates. Overall performance (as indicated by red/green flags in each laboratories annual report) is summarised in the annual participation certificate. The certificate lists the total number of analytes in the scheme, the number for which results have been submitted, and the number for which satisfactory performance has been achieved. It is important to bear in mind that the certificate shoulld be viewed in conjunction with the individual annual report in the case of internal or external auditing.

6. *Preview Scheme 2026*

Laboratories will be expected to participate in at least 6 out of 8 distributions. Please note that this year the minimum score required to attain satisfactory performance has been raised from 10 to 12 points. Accordingly, laboratories must achieve at least 12 points out of 16 (2 points for correct interpretation, 0 points for incorrect interpretation) with no critical errors in order to attain satisfactory performance.

7. Questions, Remarks, Suggestions

If you have any questions, remarks or suggestions please address to the Scientific Advisor Dr. Alessio Cremonesi or the scheme organiser Dr. R.M. Schoeman.

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

An external quality assessment is available for the DHPR activity in DBS at www.sciensano.be. Laboratories which are interested in this assessment can contact Dr. Nathalie Vandevelde (Nathalie.Vandevelde@sciensano.be).

Zürich, 20.01.2026

Dr. Alessio Cremonesi
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM Pterins in urine scheme. The contents should not be used for any publication without permission of the scheme advisor.

The fact that your laboratory participates in ERNDIM schemes is not confidential. However, the raw data and performance scores are confidential and will be shared within ERNDIM for the purpose of evaluating your laboratory performance, unless ERNDIM is required to disclose performance data by a relevant government agency. For details, please see the terms and conditions in the ERNDIM Privacy Policy on www.erndim.org.

APPENDIX 1. Change log (changes since the last version)

Version Number	Published	Amendments
1	5th February 2026	• 2025 annual report published

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