ERNDIM
Quantitative Schemes
Purines and Pyrimidines (urine)

ANNUAL REPORT 2025

Scheme Organiser	Scientific Advisor	Website for reporting results	Administration office
R.M. Schoeman, PhD Streekziekenhuis Koningin Beatrix MCA Laboratory Beatrixpark 1 7101 BN Winterswijk The Netherlands e-mail: mca.office@skbwinterswijk.nl	J. Bierau, PhD Erasmus Medical Centre Department Clinical Genetics P.O. Box 2040 3000 CA Rotterdam Netherlands e-mail: admin@erndim.org **Deputy Scientific Advisor** L.K.M. Steinbusch, PhD Maastricht University Medical Centre Department Clinical Genetics P.O. Box 5800 6202 AZ Maastricht Netherlands e-mail: admin@erndim.org	Ms I. de Graaf Streekziekenhuis Koningin Beatrix MCA Laboratory Beatrixpark 1 7101 BN Winterswijk The Netherlands e-mail: i.degraaf@skbwinterswijk.nl	ERNDIM Administration Office c/o EMQN CIC Office, Third Floor, ICE Building 3 Exchange Quay, Salford, M5 3ED United Kingdom e-mail: admin@erndim.org

Published: Rotterdam-Winterswijk, 5th February 2026[1]

1. *Purpose*

The purpose of the ERNDIM External Quality Assurance Scheme for Quantitative Purines and Pyrimidines in Urine is to monitor the analytical quality of the quantitative assay for a range of analytes in urine in laboratories that provide screening and diagnosis of patients with inherited metabolic disorders. For details, see www.erndim.org /www.ERNDIMQA.nl.

2. *Participants*

A total of 54 datasets have been submitted. No annual report could be generated for two laboratories because no results were submitted.

3. *Design*

The scheme has been designed, planned and coordinated by the scientific advisor, Dr Jörgen Bierau, and by Dr R. M. Schoeman, as scheme organiser (on behalf of the MCA Laboratory), both appointed by and in accordance with the procedure 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 sub-contractor of ERNDIM, the MCA Laboratory prepares and distributes the EQA samples and provides a website for online submission of results and access to scheme reports.

[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.

Samples

Each year, eight lyophilised urine samples, comprising four identical pairs, are distributed to participants. All samples are prepared from the same native urine sample and were enriched with varying amounts of the analytes. Thus, the final concentration of each sample is the physiological concentration (for many purines and pyrimidines practically zero) plus the spiked amount. The compounds, their source and the amounts added are listed in the table below. Thus, the final concentration of each sample is the remaining physiological concentration plus the spiked amount. Samples have been tested for stability and homogeneity according to ISO 13528, and are stable for the duration of the scheme's submission calendar when stored under defined conditions.

Analyte	Source	Added quantities in µmol/liter			
		Sample pair 2025. 01 & 07	Sample pair 2025. 02 & 08	Sample pair 2025. 03 & 05	Sample pair 2025. 04 & 06
3-Ureidoisobutyric acid	Sigma 74005	34.9	0.0	49.9	10.0
3-Ureidopropionic acid	Sigma 94295	300.0	49.7	0.0	149.1
5-OH methyluracil	Sigma 852589	49.6	15.4	0.0	35.9
Adenine	Sigma A8751	0.0	49.6	25.5	100.6
Adenosine	Sigma A9251	10.9	74.6	50.0	0.0
AICAriboside	Sigma A9978	26.1	0.0	50.3	10.2
Cytidine	Sigma C122106	74.0	25.1	0.0	49.7
Deoxy-adenosine	Sigma D7400	74.9	25.3	0.0	49.7
Deoxy-guanosine	Sigma D7145	0.0	24.7	15.3	50.3
Deoxy-inosine	Sigma D5287	26.0	100.3	50.1	0.0
Deoxy-uridine	Sigma D5412	35.2	0.0	76.7	9.6
Dihydro-thymine	TRC D449440	0.0	75.9	24.7	149.9
Dihydro-uracil	Sigma D7628	26.0	149.6	74.6	0.0
Guanosine	Sigma G6752	49.8	0.0	102.1	100.4
Hypoxanthine	Sigma H9377	200.1	25.0	0.0	100.0
Inosine	Sigma I4125	0.0	99.7	25.4	150.5
Orotic Acid	Sigma O2875	0.0	75.1	25.0	125.2
Pseudo-uridine	Berry &Ass.11080	49.8	0.0	99.6	24.9
Succinyladenosine	Bio Connect S688825	10.1	29.8	20.3	0.0
Thymidine	Sigma T9250	100.2	25.3	0.0	50.4
Thymine	Sigma T0376	0.0	75.2	52.1	150.4
Uracil	Sigma U0750	49.9	249.4	99.8	0.0
Uridine	Sigma U3750	74.5	0.0	150.3	24.8
Xanthine	Sigma X4002	199.8	49.6	0.0	100.7

Reports

All data transfer, data submission, and report requests and views proceed 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 accessible to you with your username and password. The anonymised mean results of all labs are accessible to all participants. The statistics for the respective reports are explained in the website's general information section.

Short-term reports on the individual specimens are available two weeks after the submission deadline and provide up-to-date information on analytical performance. Although it is technically possible to produce reports immediately, there is a 14-day delay to allow the scientific advisor to review 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 different levels of detail in the results, which allow individual laboratories to choose fully detailed and/or summarised reports. The most detailed report that can be requested from the website is the "Analyte in Detail," which shows results for a specific analyte in a specific sample (216 such Analyte-in-Detail reports can be requested in the 2025 cycle for the added analytes, as well as an additional 16 for creatinine and uric acid). A more condensed report is the "Cycle Review", which summarises the performance of all analytes in a specific sample (16 such Cycle-Review-Reports can be requested in 2025). The most comprehensive report is the Annual Report, which summarises the performance of all analytes in each of the four pairs of samples. One such Annual Report can be requested in 2025.

4. Discussion of Results in the 2025 Annual Report

In this section, the results of the annual report 2025 are summarised in terms of accuracy, precision, linearity, recovery, inter-laboratory coefficient of variation (CV), and the relationships among these parameters. Please keep your annual report from the Interactive Website at hand as 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 accuracy is to compare the mean outcome of the eight samples from your lab with the mean outcome from all labs. This is done in the first column of the annual report. For example, the mean across all laboratories for adenine is 43.1 µmol/litre.

It is important to recognise that using ERNDIM Quantitative EQA material to establish bias is potentially a limitation. The method's bias has been determined by comparing results to a derivation of the ERNDIM all-laboratory trimmed mean rather than a true target value. As the materials produced by the scheme are not reference materials, the bias determined is not a measure of absolute accuracy and is simply a measure of performance relative to other laboratories.

4.2 Precision

Reproducibility is an important quality parameter in the laboratory and is considered in the design of schemes. Samples are prepared in pairs, and each pair can be regarded as duplicates from which CVs can be calculated (intra-laboratory CV as an indicator of reproducibility). The outcome for your lab in comparison to the median of all labs is shown in column "Precision" of the Annual Report. The all laboratory mean imprecision ranges from 4.4% for thymine to 10.0% for succinyl adenosine. The overall intra-laboratory CV is 6.9%.

4.3 Linearity

Linearity over the 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. The outcome for your lab in comparison to the median of all labs is in the column "Linearity" of the annual report. The regression coefficient ranges from 0.966 for 5-OH-methyluracil to 0.998 for dihydrothymine, hypoxanthine, inosine, thymine, and uracil.

4.4 Recovery

A second approach to describe accuracy is the percentage recovery of the added analyte. In this approach, recovery is measured relative to the weighed amount of analyte used to enrich the sample. The correlation between the weighed quantities added to the samples (on the x-axis) and your measured quantities (on the y-axis) has been calculated. The slope of the correlation multiplied by 100% is your recovery of the added amounts. The outcome for your laboratory in comparison to the median outcome of all laboratories is shown in the column “Recovery” in the Annual Report. The all laboratory mean recovery ranges from 91% for 5-OH-methyluracil to 107% for guanosine. The overall recovery is 97%.

4.5 Inter-lab CV

For comparison of outcomes for a single patient across different hospitals, and for the use of shared reference intervals and/or consensus target treatment ranges (less relevant for purines and pyrimidines), it is important to achieve a high degree of inter-laboratory harmonisation. Part of the schemes’ design is to monitor this by calculating the inter-laboratory CV. This, along with the number of laboratories that submitted results, is shown in the column “Data all Labs” in the Annual Report. Most laboratories submitted results for xanthine (50), whereas only 17 laboratories measured cytidine. The inter-laboratory CV ranges from 8.79% for xanthine to 21.1% for succinyl adenosine. The mean inter-laboratory CV for all analytes is 13.1%.

4.6 Cross Sectional Relations

The various parameters described above often have an interrelation: more than one parameter contributes to good or poor analytical performance.

For example, for xanthine, all parameters indicate good performance: precision (CV = 6.2%), linearity (r = 0.996), recovery (97%) and inter-lab variation (inter-lab CV 8.79%) with the majority of laboratories (n=50 datasets) submitting results.

4.7 Your performance: Flags

To easily assess individual laboratory performance, each laboratory's annual report may include flags for poor performance in accuracy, precision, linearity, and recovery. Analytes with satisfactory performance for at least three of the four parameters (thus no or only one flag) receive a green flag. Thus, a green flag indicates satisfactory performance for the analysis of that particular analyte. Criteria for flags can be found in the general information on the website (under general information, interactive website; explanation of the annual report).

4.8 Poor Performance Policy

It is evident that there is considerable variation in the overall performance of individual laboratories. Table 2 shows the percentage of flags observed. 17% of the laboratories have no flag at all and thus have attained excellent overall performance. In contrast, at the other extreme, 2% of laboratories have more than 25% red flags. However, it should be noted that not all laboratories return results for all analytes. Intensive discussion within the Scientific Advisory Board (SAB) resulted in a harmonised scoring scheme for the quantitative schemes that has been in place for more than ten years; likewise, there has been agreement on 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 Quantitative 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 against these levels of satisfactory performance and issue a letter of advice to those

laboratories that do not achieve satisfactory performance. The letter is intended to initiate dialogue between the EQA scheme organiser and the participating laboratory to address specific analytical problems and improve lab performance, in pursuit of our overall aim to enhance the 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 of 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%	2%	2%
25%	0%	2%
20 – 25%	2%	4%
15 – 20%	6%	10%
10 – 15%	11%	21%
5 – 10%	29%	50%
0 – 5%	33%	83%
0%	17%	100%

4.9 Certificates

Overall performance (as indicated by red/green flags in each laboratory's annual report) is summarised in the annual participation certificate. The certificate lists the total number of special assays 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 note that the certificate should be viewed in conjunction with the individual annual report for internal or external auditing.

4.10 Additional Specific Remarks of the Scientific Advisor

We aim to include as many purines and pyrimidines as possible; however, this is limited by availability, cost, and solubility. For this reason, certain analytes are included at low concentration levels or are not included at all.

The inclusion of 2,8-dihydroxyadenine proved to be impossible, as it was not feasible to prepare a stable solution from the solid compound.

Orotidine was removed from this year's scheme after the manufacturer informed us that the available stock was not authentic ("true") orotidine.

It was decided to exclude 3-ureidoisobutyric acid from the annual report due to unexplained discrepancies between the amounts added and the mean across all participants.

5. Summary

The ERNDIM External Quality Assurance Scheme for Quantitative Purines and Pyrimidines in Urine monitors the analytical performance of laboratories involved in the screening and diagnosis of patients with inherited metabolic disorders. During the first 10 years of the scheme, the inter-laboratory CV decreased significantly. In recent years, it has gradually stabilised at 20%, and this year it has even gone down to 13.1%. This demonstrates the educational relevance of the scheme.

Notwithstanding the overall success of the scheme, each participant should carefully evaluate, adjust, and revalidate any analytical method that does not perform satisfactorily. Satisfactory performance is defined as precision CV <10% and linearity with r>0.99. If these criteria cannot be achieved, an alternative analytical method should be considered.

This Annual Report addresses analytical performance in terms of accuracy, precision, linearity, recovery and inter-laboratory CV. All parameters (intra-laboratory CV, linearity, recovery, inter-laboratory CV and the number of participating laboratories) are comparable to those observed in 2024.

6. *Preview 2026 Scheme*

The design of the scheme in 2026 will be the same as that of the 2025 scheme. Orotidine will be reintroduced.

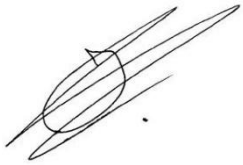
We aim to distribute educational samples from patients with 2,8-dihydroxyadeninuria (Adenine Phosphoribosyl Transferase (APRT) deficiency), Adenylosuccinate lyase (ADSL) deficiency and AICAribosiduria (ATIC deficiency). We expect to be able to distribute liquid urine samples of patients with 2,8-dihydroxyadeninuria – both treated and untreated with allopurinol – in 2027.
To prepare, test, and distribute lyophilised samples, we require at least 300 mL of urine with a creatinine concentration of >1 mM. Please contact the scientific advisor if you are willing to contribute a suitable sample. In cases of APRT deficiency, it is essential that the sample be collected before treatment with allopurinol, as this medication effectively inhibits xanthine oxidase, thereby preventing the formation of 2,8-dihydroxyadenine.
At present, it is also unclear whether the solubility of 2,8-dihydroxyadenine in lyophilised urine differs from that of the pure solid compound. It may therefore be necessary, for these specific disorders, to distribute liquid samples rather than lyophilised samples. We welcome any suitable samples, as well as suggestions and practical advice.

7. Questions, Suggestions and Complaints

If you have any questions, comments or suggestions, please address them to the scientific advisor of the scheme, Dr Jörgen Bierau and/or to the scheme organiser, Dr R.M. Schoeman (mca.office@skbwinterswijk.nl).

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/

Rotterdam, 28 January 2026



Dr. J. Bierau
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM Purines & Pyrimidines in Urine scheme. The content may not be used for any publication without permission of the scheme advisor.

The fact that your laboratory takes part in ERNDIM schemes is not confidential. However, the raw data and performance scores are confidential and will be shared only within ERNDIM to evaluate your laboratory's 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

END