ERNDIM
Quantitative Schemes
Cystine in White Blood Cells

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 Cystine in White Blood Cells is the monitoring of the analytical quality of the quantitative assay of cystine in white blood cells in the management and diagnosis of patients with cystinosis. For details see www.erndimqa.nl

2. *Participants*

A total of 36 datasets have been submitted and 1 laboratory did not submit any data at all.

3. *Design*

The Scheme has been designed, planned and coordinated by Daniel Herrera as scientific advisor and Dr. R.M. Schoeman as scheme organiser (on behalf of the MCA Laboratory), all appointed by and according to the procedure of the ERNDIM Board. The design includes special attention to sample composition and to the layout of the reports. As a subcontractor of ERNDIM, the MCA Laboratory prepares and distributes 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 two sets of lyophilised samples: one set containing 8 samples protein pellets and the other 8 samples supernatants of lysed white blood cells spiked with cystine. As can be seen from table 1, the weighed amounts of protein and cystine were identical in pairs of samples. The nature, source and added amounts of the analytes are summarised in table 1.

[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 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.

Table 1. Pair identification, source and amount of added analytes.

Analyte	Source	Added Quantities Protein (mg/vial)+Cystine (nmol/vial)			
		Sample Pair 2025. 01 - 08	Sample Pair 2025. 02 - 05	Sample Pair 2025. 03 - 06	Sample Pair 2025. 04 - 07
Protein	Sigma P8119	0.4	2.5	1.0	1.4
Cystine	Sigma 49603	0.6	0.125	0.35	3.625

Reports

All data-transfer, the submission of data as well as request and viewing of reports take place 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 on the eight 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 delay of 14 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 ERNDIM website is the different levels of detail of results which allows individual laboratories the choice of fully detailed and/or summarised reports. The "Analyte in Detail" is the most detailed report and shows results of a specific analyte in a specific sample. A more condensed report is the "Current Report" which summarises the performance of all analytes in a specific sample. The Annual Report summarizes all results giving an indication of overall performance for all analytes in all 8 samples. Depending on the responsibilities within the laboratory participants can choose to inspect the annual report (QC managers) or all (or part of) detailed reports (scientific staff).

4. Discussion of Results in the Annual Report 2025

In this section the results of the annual report 2025 are summarised in terms of accuracy, precision, linearity, recovery, inter-laboratory co-efficient of variation (CV) and relations between these parameters. Please keep at hand your annual report from the website when you follow the various aspects below and keep in mind that we only discuss the results of "all labs". It is up to you to inspect and interpret the results of your own laboratory.

4.1 Accuracy

A first approach to evaluating your performance in terms of accuracy is comparison of your mean values in the eight samples with those of all labs. This is shown in the columns "your lab" and "all labs" under the heading "Accuracy". For example, for protein the mean of all labs is 1.370 mg/vial, with which you can compare the mean of your lab.

It is important to recognise that using ERNDIM Quantitative EQA material to establish bias is potentially a limitation. The bias of the method has been determined by comparing results to a derivation of the ERNDIM all laboratory trimmed mean, not 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 parameter for the analytical performance of a laboratory and is addressed in the scheme's design. Samples provided in pairs can be regarded as duplicates from which CVs can be calculated. The column "Precision" in the annual report shows your CVs in comparison to the mean value for all labs.
The mean CV for protein is 7.3% and for cystine (nmol/aliquot) is 10.6%.

4.3 Linearity

Linearity over the whole relevant analytical range is another important parameter for analytical quality and is also examined within the schemes. A comparison of the weighed quantities on the x-axis and your measured quantities on the y-axis allows calculation of the coefficient of regression (**r**). The column "Linearity" in the annual report shows your **r** values in comparison to the median **r** values for all labs. Ideally the **r** value is close to 1.000 and this is indeed observed with a value of 0.998 for cystine (nmol/aliquot) and 0.994 for protein.

4.4 Recovery

A second approach to describe accuracy is the percentage recovery of added analyte. In this approach the amounts of weighed quantities added to the samples are the assumed target values after adjustment for blank values. The correlation between weighed amounts (on the x-axis) and your measured quantities (on the y-axis) has been calculated. The slope of the resulting relationship ("a" in y = ax + b) in this formula multiplied by 100% is your recovery of the added amounts. The outcome for your lab in comparison to the median outcome of all labs is shown in the column "Recovery". It can be seen that the mean recovery of cystine (nmol/aliquot) is 97% and of protein is 96%.

4.5 Interlab CV

For comparison for diagnosis and monitoring of treatment for one patient in different hospitals and for use of shared reference values it is essential to have a high degree of harmonization between results of 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. We see an interlab CV of 18.1% for protein, 21.8% for cystine (nmol/aliquot) and of 35.8% for cystine (nmol ½ cys/mg protein) and unfortunately we have not seen any improvement.

4.6 Interrelationships between results

Cystine (nmol ½ cys/mg protein) is a ratio of the assays of cystine (nmol/aliquot) and protein (mg/pellet). The precision will be the cumulated precision of both assays.

4.7 Report in correct numbers

As we have indicated in previous reports it is important to report in the correct units. Although we feel that nearly all labs do that now, some strange results of individual labs might be traced back to “clerical errors.” So, if you have a deviating result, please check if you reported your result in the correct units.

4.8 Your performance: Flags

To easily judge performance of individual laboratories the annual report of an individual laboratory may include flags (in different colours) 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) receive a green flag. Thus, a green flag indicates satisfactory performance for analysis of that analyte. Criteria for flags can be found in the general information on the website (on this website under general information; interactive website, explanation annual report).

4.9 Poor Performance Policy

A wide dispersion in the overall performance of individual laboratories is evident. Table 2 shows the percentage of flags observed. 73% of the laboratories have no flag at all and thus have attained excellent overall performance. In contrast, at the other extreme there are also 9% of laboratories with more than 25% flags. Intensive discussion within the Scientific Advisory Board (SAB) resulted in a 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 in order to solve any particular analytical problems and 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%	9%	9%
25%	9%	18%
20 – 25%	0%	18%
15 – 20%	3%	21%
10 – 15%	0%	21%
5 – 10%	6%	27%
0 – 5%	0%	27%
0%	73%	100%

4.10 Certificates

As for other schemes the performance as it is indicated by the red/green flags in the individual 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 has to be backed up by the individual annual report in the case of internal or external auditing.

4.11 Additional Specific Remarks of the Scientific Advisor

A minimum of 10 points and no critical errors were required to achieve satisfactory performance in the interpretative aspects of the CWBC scheme. No laboratories (other than non-submitters) scored less than 12 points, and one laboratory was given critical errors for distribution 2025.01. A summary of the results of the interpretative component of the scheme for 2025 is presented below.

Distribution 2025.01. Clinical information: Patient referred from optician for possible cystinosis

Accepted answer: Consistent with Cystinosis

The median cystine concentration (all laboratories) for this distribution was 2.70 nmol ½ cystine / mg protein. The age of the patient was not provided for this distribution, however, the high concentration of cystine should prompt all laboratories to consider cystinosis as the most likely diagnosis considering the reason for testing and regardless of the method of white cell isolation used in the laboratory (granulocytes versus mixed-leucocytes).

97 % of the laboratories submitting an interpretation agreed that the concentration of white cell cystine was consistent with cystinosis. One laboratory suggested carrier status as the most likely scenario; however, this was due to the laboratory measuring the protein concentration for this distribution 3 times over the expected value. This laboratory was granted a critical error.

Distribution 2025.02. Clinical information: 6-month-old male with Fanconi syndrome

Accepted answer: Not consistent with cystinosis.

The median cystine concentration (all laboratories) for this distribution was 0.10 nmol ½ cystine / mg protein. 100 % of the participants agreed that the concentration for this distribution was not consistent with cystinosis. A few laboratories (using granulocytes) reported that although the white cell cystine level was within the normal range (0.04 - 0.16 nmol 1/2 cystine/mg protein), it was just below the heterozygote range (0.14-0.57) (Wilmer et al (2011) Pediatr Nephrol) and requested a repeat sample for confirmation and complete genetic analysis of the cystinosin (CTNS) gene. Most of the laboratories concluded that cystinosis could be excluded or it was highly unlikely and suggested to investigate for other causes of Fanconi syndrome.

No critical errors were assigned to laboratories in this distribution. It is encouraging to see that low concentrations of cystine are measured accurately by all the laboratories.

Distribution 2025.03. Clinical information: Known cystinosis patient on treatment

Accepted answer: Within therapeutic range.

The median cystine concentration (all laboratories) for this distribution was 0.676 nmol ½ cystine / mg protein. 97 % of laboratories agreed that the cystine value was withing the expected therapeutic range. There are different therapeutic ranges quoted by the laboratories depending on the white cell isolation protocol used, being the most common expected values, less than 1.0 nmol ½ cystine / mg protein for laboratories measuring cystine in mixed leucocytes (Belldina et al. (2003) Br J Clin Pharmacol 56:520) and less than 2.0 nmol ½ cystine / mg protein for laboratories using granulocytes. It is essential to share the protocol used for white cell isolation in the laboratory with clinical teams, so a realistic therapeutic range is aimed by clinicians.

No critical errors were assigned to laboratories in this distribution.

Distribution 2025.04. Clinical information: 1 year old, sibling recently diagnosed with nephropathic cystinosis

Accepted answer: Consistent with cystinosis.

The median cystine concentration (all laboratories) for this distribution was 5.12 nmol ½ cystine / mg protein. 100% of the participants agreed that the concentration for this distribution was consistent with cystinosis. The laboratories agreed that this is a typical presentation for classical nephropathic cystinosis that requires urgent referral to the metabolic and renal clinical teams and confirmation by DNA sequencing of CTNS gene. Overall excellent performance of the laboratories in this distribution.

Distribution 2024.05. Clinical information: 25-year-old with photophobia

Accepted answer: Not consistent with cystinosis.

The median cystine concentration (all laboratories) for this distribution was 0.10 nmol ½ cystine / mg protein. 100 % of the participants agreed that the concentration for this distribution was not suggestive of ocular cystinosis. It is encouraging to see that low concentrations of cystine are measured accurately and no unnecessary follow up is requested by laboratories.

Distribution 2025.06 Clinical information: Both parents known to be carriers of pathogenic cystinosin variants

Accepted answer: “Not consistent with cystinosis” or “Consistent with carrier status” or “Consistent with cystinosis”

The median cystine concentration (all laboratories) for this distribution was 0.650 nmol ½ cystine / mg protein. This mildly elevated concentrations are difficult to interpret however the consensus was that this clinical scenario was consistent with carrier status. Some laboratories recommended performing CTNS gene analysis as moderate increase of cystine in white blood cells can be compatible with carrier status or with homozygous or compound heterozygous status for mildly pathogenic cystinosin variants. There is overlap of concentrations between carriers and affected cystinosis patients and the biochemistry testing can be informative but at this concentration will require genetic analysis for confirmation.

No critical errors were assigned to laboratories in this distribution.

Distribution 2025.07. Clinical information: On cysteamine

Accepted answer: Above therapeutic range.

The median cystine concentration (all laboratories) for this distribution was 4.89 nmol ½ cystine / mg protein. 100% of laboratories agreed that the cystine value was significantly above therapeutic range. Assuming the sample was collected at the correct time the laboratories suggested check adherence to medication and the need for the dosage to be readjusted after confirming the initial result with a repeat sample. Overall excellent performance of the laboratories in this distribution.

Distribution 2025.08. Clinical information: 4-year-old with proteinuria of unknown cause

Accepted answer: Consistent with Cystinosis

The median cystine concentration (all laboratories) for this distribution was 2.71 nmol ½ cystine / mg protein. The high concentration of cystine should prompt all laboratories to consider cystinosis as the most likely diagnosis regardless of the method of white cell isolation used in the laboratory (granulocytes versus mixed leucocytes).

100 % of the laboratories submitting an interpretation agreed that the concentration of white cell cystine was consistent with cystinosis. The laboratories recommended urgent referral to the metabolic and renal clinical teams and confirmation by DNA sequencing of CTNS gene. Overall excellent performance of the laboratories in this distribution.

5. *Summary*

We feel that the scheme is well-established. The average performance of the laboratories is satisfactory but of course the performance of some individual laboratories requires improvement. The elevated Inter-laboratory CVs demonstrates lack of standardization which requires improvement. We would like to emphasize the need for all laboratories to use internal quality control. At its simplest, this can be made from pooling surplus supernatants from assayed samples however the scheme organizer is marketing IQC material that can be purchased through MCA laboratories (mca.finance@skbwinterswijk.nl). This material for protein and cystine analysis has been manufactured at clinically relevant assigned concentrations that can be easily used by laboratories to monitor assay performance.

We would also note that a comments box is provided for all distributions if you wish to justify your interpretation or would suggest any further testing in a specific scenario. These comments may be considered when assigning critical errors.

6. *Preview of the Scheme in 2026*

The design of the 2026 scheme is mostly the same as in 2025. Laboratories are expected to participate in 6 out of 8 distributions with a score of at least 12 points out of 16 (2 points for correct interpretation, 0 points for incorrect interpretation), and no critical errors to attain satisfactory performance. We have increased the score to 12 points for next year to make it more challenging for laboratories and to make it comparable to the performance criteria of other interpretative schemes. The interpretation component will be scored and reflected in your yearly certificate.

7. *Questions, Comments and Suggestions*

If you have any questions, comments or suggestions please address to the scientific advisor of the Scheme Mr. D. Herrera, deputy scientific advisor Mr. R. Bramley or the scheme organizer 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/

Leeds, 10th February 2026

Daniel Herrera

Mr Daniel Herrera
Scientific Advisor

Please note:
This annual report is intended for participants of the ERNDIM Cystine in White Blood Cells 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	10th February 2026	• 2025 annual report published

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