ERNDIM

Quality Assurance in Laboratory Testing for IEM

AUGUST 2025

NEWSLETTER

TABLE OF CONTENTS

ERNDiM NEWSLETTER

MESSAGE FROM THE CHAIR

Dear Colleagues,

In this newsletter, we will present an update of current ERNDIM activities. In 2025, ERNDIM has experienced a moderate growth both in numbers of participants and activities. Last year we had 17 EQA schemes, with 2213 scheme registrations from 417 participants in 62 countries. In part, this growth is explained by the introduction of new schemes, such as Special Assays in Dried Blood Spots (SADB) and Amino Acids Interpretation (AAI) schemes. In 2024, we launched a new pilot scheme for lipid analysis (LIS—Lipid in Serum scheme), which includes new biomarkers and others that will be moved in the future from the Special Assays in Serum scheme. **Together, these reinforce the importance of external quality assurance and start to participate in ERNDIM schemes.**

As well as providing grants for both scheme participation and visits of individual scientists to centres of expertise, ERNDIM is expanding its educational activities. In 2025, we will be hosting the 2025 ERNDIM Workshop in Madrid, Spain. We have organised previous participant meetings when the international ICIEM meetings were outside Europe. Unfortunately, the last ERNDIM Workshop in 2021 was held online due to the COVID-19 pandemic.

We sincerely hope that you can join us in person in Madrid. Please see Page 4 for further details.

ERNDIM continues to co-organise in-person training events with SSIEM, which have taken place in Freiburg, Jerusalem, Manchester, and Amsterdam in a similar format to the pre-pandemic years. In 2024, we started a new format of scientific meetings. This consists of on-line workshops hosted by scientific advisors, focused on technical aspects of their respective schemes, mainly directed to laboratory professionals. In 2024, we hosted a Quantitative Amino Acids scheme (QTAS) workshop with 223 registrations, and an Acylcarnitines in Serum scheme (ACS) workshop with 125 registrations. We have recently hosted a further two on-line workshops following the same format, on Purines and Pyrimidines in Urine (PPU) and Quantitative Organic Acid (QTOU).

In 2024, for the first time, we also held an on-line Qualitative Organic Acids in Urine scheme (QLOU) workshop (hosted by Judit Garcia-Villoria, Joachim Janda and Camilla Scott). The workshop, with 166 registrations, was focused on the clinical samples from their respective 2023 schemes. The plan is to continue these as annual workshops. We also intend on having a similar meeting for the Acylcarnitines in Dried Blood Spots (ACDB) schemes.

In 2023, together with the Latin-American Society of Inborn Errors of Metabolism and Newborn Screening (SLEIMPN), we organized a webinar for participants in Latin America to increase awareness of ERNDIM. We presented three different schemes and general aspects of ERNDIM (hosted by Pedro Ruiz-Sala, Cristiano Rizzo, Rafa Artuch and Judit Garcia-Villoria).

High-quality EQA schemes are only feasible with the input of experts from the field, and the Executive Committee gratefully acknowledges our Scientific Advisors for their enthusiastic involvement in scheme organisation.

Best wishes,
Rafa Artuch
On behalf of the ERNDIM Executive Committee

ERNDIM SYMPOSIUM MADRID, OCTOBER 2025

The 2025 ERNDIM Workshop will take place 9-10 October 2025, in Madrid, Spain. ERNDIM provides a stimulating program for all its participants to learn about the latest news and innovations in the field of diagnosis and treatment of Inborn Errors of Metabolism. This year's program includes sessions on lysosomal metabolism, novel lipid biomarkers, rare organic acidurias and oral abstract sessions on new diagnostic methods and metabolites, and challenging cases.

Following each session, we will have a live Q&A session, in which your active participation is welcome. In addition, we will organise live, interactive workshops on Organic acids, Amino acids, and lysosomal enzymes.

We have organized previous participant meetings when the international ICIEM meetings were outside Europe. Unfortunately, the last ERNDIM Workshop in 2021 was held online due to the COVID-19 pandemic. We sincerely hope that you can join us in person in Madrid.

For further information, and to register, please visit
www.geyseco.es/ERNDIM2025

APPEAL FOR DONATED SAMPLES

ERNDIM Qualitative schemes are dependent on the availability of real patient samples. Participants are encouraged to contact ERNDIM if they are able to donate samples which may be suitable for any of the Qualitative schemes run by ERNDIM. If the sample is suitable and is used in a scheme, the donating laboratory will receive a 20% discount on their participation in the scheme, during the scheme year following use of the donated sample.

If you are able to collect a clinical sample that could be used as an EQA sample for one of ERNDIM's qualitative schemes, please contact the Administration Office, who will send you the ERNDIM consent form and details of how and where to send the samples. To thank our young donors, we're happy to provide a special certificate of appreciation upon request for any children who contribute a sample. These certificates are also available in multiple languages.

Sample requirement details and a consent form can be found on the EQA schemes tab of the ERNDIM website under "Sample Donations". Please contact admin@erndim.org before sending any samples and please do not send any samples to the Administration Office.

If you have any questions, please contact the Administration Office (admin@erndim.org).

ADMIN OFFICE CHANGES

Since our last Newsletter in 2020, the ERNDIM Administration Office has undergone several significant changes. During the Covid-19 lockdowns in the UK, the Administration Team adapted to a fully remote working model. In 2021, we embraced a hybrid working arrangement, blending remote and office-based work to maintain flexibility and efficiency.

In August 2021, the office relocated from St Mary's Hospital to Manchester Science Park. More recently, in 2025, we moved again to a new Business Park in Salford Exchange Quay. Throughout these changes, ERNDIM continues to share office space with EMQN (European Molecular Quality Network), while both organizations remain independent EQA providers.

We are also delighted to announce the expansion of our ERNDIM Admin team. In 2023 and 2025, two new Scientific Administrators joined us, boosting our capacity to deliver outstanding support to our schemes and participants. The team now consists of six dedicated members: an Executive Administrator, three Scientific Administrators, and two part-time Administration Assistants.

This strengthened team structure enables us to enhance our administrative services and respond to your inquiries more efficiently, ensuring continued excellence in supporting the ERNDIM community.

Celebrating 30 Years of ERNDIM: An Anniversary Meeting in Sitges

In April 2024, ERNDIM marked an inspiring milestone with its 30th Anniversary meeting held in the beautiful coastal town of Sitges, Barcelona. This special gathering brought together past and present contributors from around the globe to celebrate three decades of advancing the diagnosis of metabolic diseases and supporting laboratories worldwide.

The event was a unique opportunity to reflect on ERNDIM's remarkable journey—from its early days to its ongoing commitment to excellence in quality assurance and collaborative research. Attendees were honoured to welcome three of the founding fathers—Brian Fowler, Jim Bonham, and Leo Spaapen—whose vision and dedication have shaped ERNDIM into the respected organisation it is today.

Over the course of the meeting, thought-provoking presentations highlighted ERNDIM's history, current achievements, and future ambitions. Topics ranged from the success of external quality assessment schemes and diagnostic proficiency testing to the latest advancements in mass spectrometry and metabolomics. A heartfelt patient group presentation underscored the real-world impact of ERNDIM's work, emphasizing the vital connection between laboratory excellence and patient care.

The meeting's vibrant atmosphere reflected the passion and collaboration that define ERNDIM's community. As we celebrated 30 years of progress, we also looked ahead to continued innovation and support for laboratories dedicated to improving metabolic disease diagnosis worldwide.

This anniversary marks not just a moment of pride, but a renewed commitment to the future. Stay tuned for more updates and initiatives throughout 2025 as ERNDIM continues to lead the way in enhancing global laboratory standards.

MetabERN UPDATE

About MetabERN

The Clinical/Research Network named "European Reference Network on Rare Hereditary Metabolic Diseases", (acronym "MetabERN"), has been established thanks to the Cross-border Health Care directive and is being funded within the framework of the Third Programme for the Union's action in the field of Health. MetabERN represents the first comprehensive, pan-metabolic, pan-European, patient-orientated platform, aimed to transform how care is provided to patients with inherited metabolic diseases (IMDs) in Europe.

The main goal of this initiative is to ensure coordinated action in creating the widest possible collaboration among paediatric and adult metabolic physicians and patient associations at EU level, facilitating patient access to specialists with expertise in the metabolic field and to foster research activity. MetabERN manages a number of projects, to be found on the website http://metab.ern-net.eu/. The following examples may be of interest to ERNDIM's members:

The shared initiative by MetabERN, ERNDIM, and Orphanet:

In the metabolic field, there is a big demand for updated information on diagnosis and diagnostics. MetabERN would like to make a detailed directory of diagnostic laboratories of high standards in combination with information on all the different inborn errors of metabolism. Orphanet (supported by grants from the European Commission) is an existing database on rare diseases, including the IEM. ERNDIM, for its part, has the overview of the metabolic diagnostic laboratories in Europe. A collaboration and united forces between ERNDIM and Orphanet under the auspices of MetabERN will be able to provide just such a detailed directory. Currently, efforts are being made to obtain the necessary approvals from ERNDIMS members to share data with MetabERN and Orphanet.

Unified European Registry for Inherited Metabolic Disorders, U-IMD:

The number of participating centres is today 29. The number of all registered patients is 3484. The overall aim of this project is to promote health for children, adolescents and adults affected by rare Inherited Metabolic Disorders. The project has three major activities:

1. Establishing the U-IMD patient registry as a tool of MetabERN.
2. Upgrading already existing IMD registries to the standard of U-IMD. The starting point has been the registry of the International Working Group on Neurotransmitter Related Disorders (iNTD).
3. Developing a standard for minimal core data sets shared by the MetabERN and the European Rare Kidney Disease Reference Network (ERKNet).

https://u-imd-registry.org/index.php?id=about

4ReconIMD, Reconstruction and Computational Modelling for Inherited Metabolic Diseases

Overall Recon4IMD objective: "To accelerate the diagnosis of patients at risk of an IMD by computational modelling of genetic risk, enzyme structure, and metabolic networks, personalised using genomic, proteomic and metabolomic data." This ambitious project in personalized medicine aims to unify most types of "omics" data from patients with inborn metabolic diseases. Computational models are developed to integrate all these different biological data collected from metabolic centres across Europe.

https://www.recon4imd.org/

European Reference Network | MetabERN
European Reference Network for Hereditary Metabolic Disorders

MALCOLM HERON, 1942 – 2023

The smooth running and effectiveness of many professional societies and organisations is underpinned by the careful and reliable organisation of their finances. When in the mid-1990s, ERNDIM began to emerge as an important provider of proficiency and EQA schemes for the inherited metabolic disease community at an international scale, ensuring that the finances were well-organised became key.

Thankfully, we had the help of Malcolm Heron. He began an association with ERNDIM shortly after his retirement from the Civil Service in the UK where he had worked for many years as a senior accountant, and we were very fortunate to gain his support. He quickly recognized the importance of ERNDIM and was tireless in his pursuit of payment from the various organisations that subscribed to the programmes offered, by 1996 this included more than 160 participants from 30 countries.

Malcolm spent many hours on the phone, and in the days before email was as well established, corresponding by letter, with a large network of Finance departments in hospitals and universities throughout Europe and elsewhere. He patiently, but persistently, reminded and encouraged those arranging payment to ensure that the funds arrived in a timely way. He always remained good-natured and understanding, but was remarkably effective in ensuring the financial health of ERNDIM for many years as it grew.

However, Malcolm was much more than a good bookkeeper, he had taken both ERNDIM and SSIEM to his heart. He would leave no problem unresolved and frequently went to great lengths to support participants and as we became fortunate enough to develop our own 'ERNDIM Administration Office', he was happy to support and encourage Sara and the team as they took over the reins.

Together with his wife Marion, he travelled widely attending SSIEM symposia in Australia, Japan, and Europe, representing both ERNDIM and SSIEM at these events and helping deal with queries as they arose. He formed lasting friendships around the world as a result, and his friends in the IMD community were never far from his thoughts.

Outside the Society he had a great love of music and choral singing in particular, and was very active, as a Treasurer, of course, in his local Church. When prompted at social events, he could be persuaded, with a bit of encouragement, to offer a rendition of various songs in his deep baritone voice —perhaps the most memorable being a North England Folk Song, The Lambton Worm sung, with gusto, in the dialect of Malcolm's home county, Durham.

In the days and weeks before his death, I had the privilege to visit Malcolm and each time he enquired after and spoke fondly of friends and colleagues in both ERNDIM and SSIEM. Perhaps we are not always aware of the importance of these relationships as they help form some of the fabric of our lives, but Malcolm never took these for granted and cherished those with whom he had met and worked.

He died at home with his family around him, on 2nd August 2023 after a period of steadily deteriorating health. Malcolm was a supportive friend, a kind and generous hearted man, always willing to help if he could, he will be missed by many, and his life will be remembered and celebrated by all who knew him well.

James R Bonham

Report from the ESHG-Eurogentest committee

The Quality Sub Committee (QSC) was a subcommittee of EuroGentest and EuroGentest is itself a subcommittee of the European Society of Human Genetics (ESHG). EuroGentest was structured with a committee and four subcommittees. This structure was difficult to maintain due to excessive overlap between responsibilities and tasks different from other ESHG committees. Last year, Geert Matthijs, the Chair of Eurogentest, proposed to limit to a single EuroGentest Committee making the most of the available manpower, clear coordination of tasks, easy communication; committee members will take the lead of the projects and groups ad hoc will be created for such projects. The Board of ESHG approved this proposal. The detailed remit and composition of the group is outlined on the ESHG website: https://www.eshg.org/egt

Eurogentest organized an online seminar on April 1st, 2025, which covered:

- An IVDR update and the current state of European genetic laboratories, based on the results of the ESHG-IVDR survey,
- Clinical and technical quality assurance challenges, using rapid exome sequencing in neonatal intensive care,
- An overview of the current status of professional recognition in genetics (EBMG),
- Specific EuroGentest projects aimed at promoting best practices in our field.

The recording of this webinar is available on the ESHG website.

For the coming years, EuroGentest plans to focus on the following projects:

- **Collection of external quality assessment data:** harmonisation of the definition among external quality assessment (EQA) providers is necessary: for this purpose, having representatives from all of them and recruiting them will be the first focus of this workgroup. The second objective will be to define how to act on performance: given that the ESHG is a professional body, and all national societies are part of it, this issue could and should be addressed.
- **IVDR-related activities:** the In Vitro Diagnostic Regulation (IVDR) presents a major challenge to genetic diagnostic laboratories, especially on the use of in-house developed tests when no CE-IVD kit is commercially available for the same diagnostic application. A Task Force on IVDR aims to share information with diagnostic laboratories, as well as to make clear to the community and regulatory authorities that there are certain concerns for genetics in relation to the implementation of the IVDR. ESHG has joined BioMed Alliance, a group of European medical societies active in lobbying at the European level. The European Commission has taken actions to ensure the availability of in vitro diagnostics and will assess the impact of the legislation on devices responding to special needs (referred to as the 'orphan devices') and on the development of innovative devices in Europe. The Commission has also indicated that special attention shall be given to costs and administrative burden stemming from the implementation of IVDR.
- **Harmonization in genetic counselling:** it presents a complex challenge, particularly as aspects of quality in clinical practice are often more difficult to evaluate and enforce than in laboratory settings. Consequently, developing comprehensive guidelines can be daunting. One practical solution to initiate this process is the creation of a well-structured questionnaire for national societies. This would facilitate the collection of data on current practices across different regions. In close collaboration with the European Board of Medical Genetics (EBMG), the aim is to update previous reports and publish findings regarding the current state of genetic counselling in Europe.
- **Update to the guidelines for diagnosis of FMR1-associated disorders (fragile X syndrome):** A working group has been created to update the guidelines for molecular testing and genetic reporting of fragile X syndrome (FXS). The available document dates back to 2014, and the technique that is mostly used to test the FMR1 expansion has now changed to be based on triplet repeat PCR.
- **Reporting of genome-wide diagnostic tests in the prenatal setting:** the plan is to produce recommendations on reporting genome-wide diagnostic tests in prenatal settings. This will be a joint endeavour with the International Society for Prenatal Diagnosis (ISPD) and with the Policy and Ethics Committee (PEC) of ESHG. Given that ISPD is a global society, the aim will be to develop a globally applicable guideline. The work may also incorporate recommendations on the types of tests to apply and the related indications.

ERNDIM is fully involved in the first project, although the challenge is to make the voice of biochemical genetics heard in a group dominated by molecular genetics. An "EQA provider poor performance questionnaire" was proposed by Weronika Gutowska-Ding from EMQN and amended by Eurogentest members, including myself. It has been sent to EQA providers and answers are pending.

Report by Christine Vianey-Saban

A new EQA Scheme: Amino Acid Interpretation (AAI) scheme

Interpretation of laboratory results is key to arriving at a correct diagnosis, particularly in highly specialized areas such as inherited metabolic disorders (IMD). Quantitative amino acids' is one of the tests with the highest workload for IMD laboratories, and it is essential that not only the correct results are provided, but also an appropriate interpretation. Therefore, the Amino Acid Interpretation (AAI) scheme was launched as a pilot scheme in 2016 by Brian Fowler based on the scheme developed by Mary Anne Preece in the UK. This external quality assessment (EQA) is unique for ERNDIM in not requiring biological samples. It provides metabolic biochemistry laboratory experts with the opportunity to interpret amino acid profiles based on already obtained results. This allows for both the continuous evaluation of metabolic biochemistry experts and their training through educational cases.

Each year, six amino acid profiles are provided. These include characteristic profiles of classical metabolic diseases, which should be recognizable by metabolic biochemistry laboratory experts, as well as more atypical profiles or profiles of very rare metabolic diseases that not all laboratories may have encountered. This is particularly important because, thanks to next-generation sequencing, new metabolic diseases, or atypical biochemical and clinical profiles of already known metabolic diseases are discovered each year.

Since 2023, the AAI scheme has been established as a full scheme, and the concept of critical error was introduced. More than 120 laboratories participated in its first year as a full scheme. Laboratories achieved performance rates ranging from 82% to 98% from the six cases presented, with more than 30% of laboratories achieving the maximum score. The cases with the lowest performance, as expected, were the adenosine kinase deficiency and the glutaminase deficiency, with their rarity explaining the performance. Five laboratories had critical errors, which were defined by the inability to diagnose a treatable disease. In 2024, over 140 laboratories participated, with 94% achieving a performance rate exceeding 80%. Only one laboratory had a critical error due to overlooking the possibility of aminoacidopathy.

As such, we believe that the introduction of the ERNDIM AAI scheme is a major contribution to the quality of metabolic biochemistry laboratories and provides a model for other metabolite groups within ERNDIM. We look forward to working with participants to improve the quality of this scheme.

Scheme assessors (alphabetical): Olivier Braissant, Rachel Carling, Brian Fowler (retired), Alistair Horman, Daniela Karall, Mary Anne Preece (retired), Anke Schumann

Authors: Apolline Imbard (deputy scientific advisor), Sabine Scholl-Bürgi (scientific advisor)

Special Assays in DBS Updates

The ERNDIM Special Assays in Dried Blood Spots (DBS) scheme was established in 2022 following a successful two-year pilot. The scheme provides External Quality Assessment (EQA) for eleven analytes, including amino acids, free carnitine, succinyl acetone, and NTBC. While intra-laboratory reproducibility was found to be acceptable, there was room for improvement in standardization and recovery, especially for succinylacetone.

The scheme has undergone modifications to align with other ERNDIM schemes and the fee increase justified by the anticipated improvement in service to customers. Since 2022, eight EQA samples have been distributed annually and participant results from these samples have been used to evaluate performance. During the 2022 to 2024 scheme years, additional non-scoring samples were also sent out. The results from these samples were used internally by ERNDIM and did not factor into participation evaluations. As of 2025, the distribution of non-scoring samples has been discontinued, maintaining a consistent total of eight EQA samples.
Overall, the ERNDIM Special Assays in Dried Blood Spots scheme is committed to providing high-quality EQA services and contributing to the standardization and improvement of DBS testing.

Rachel Carling (scientific advisor)

A new pilot scheme: Lipid Assays in Serum (LIS)

In 2024, ERNDIM launched a new pilot scheme, Lipid Assays in Serum (LIS), which includes several lipids currently included in the Special Assays in Serum (SAS) scheme, and some new additions. The analytes currently included are listed in the table below.

Currently, the SAS scheme includes a large number of analytes, which makes it difficult to add new analytes of interest due to issues surrounding solubility and analyte interactions. The ERNDIM Scientific Advisory Board agreed that removing a group of analytes from the SAS scheme would provide the opportunity to increase the range of analytes covered by our EQA schemes.

In this instance, it was agreed that lipids provide a convenient group of analytes to remove, with the potential to add additional lipids to the new EQA scheme.

In recent years, several new lipid markers were implemented for diagnostic use, including biomarkers for sphingolipidoses, peroxisomal disorders, and sterol biogenesis disorders, making this an interesting group for a separate EQA scheme. For the pilot, laboratories which currently participate in the more specialised lipids in the SAS scheme were invited to join. 56 laboratories are currently registered and actively participating in the scheme.

While the LIS scheme is in the pilot phase no analytes will be removed from the SAS scheme.

To validate the new scheme, it is running as a pilot for a second year in 2025. Following review of participant submissions and feedback, the Scientific Advisory Board will then make a decision regarding moving to a full scheme in 2026.

Dr. Susanna Goorden
and Dr. Marie van Dijk
Scientific Advisors for Lipids in Serum

Metabolite	Disorder	Group of disorders	SAS/new
Lysosphingolipids			
Lyso-sphingomyelin (Lyso-SM)	Niemann Pick Disease type A/B (NPA/B)	Sphingolipidoses	SAS
Lyso-globotriaosylceramide (Lyso-Gb3)	Fabry Disease	Sphingolipidoses	SAS
Glucosylsphingosine	Gaucher Disease	Sphingolipidoses	SAS
N-palmitoyl-O-phosphocholineserine (PPCS); (previously known as Lysosphingomyelin-509)	Niemann Pick Disease type C (NPC) and Niemann Pick Disease type A/B (NPA/B)	Sphingolipidoses	New
Lyso-monosialoganglioside 1 (Lyso-GM1)	GM1 gangliosidosis	Sphingolipidoses	New
Lyso-monosialoganglioside 2 (Lyso-GM2)	GM2 gangliosidoses (Tay Sachs and Sandhoff disease)	Sphingolipidoses	New
Oxysterols			
Cholestane-3β,5α,6β-triol	Niemann Pick Disease type C (NPC)	Sphingolipidoses	SAS
7-ketocholesterol (7-KC)	Niemann Pick Disease type C (NPC)	Sphingolipidoses	SAS
Lysophospatidylcholines			
C26:0-lysophospatidylcholine (C26:0-lysoPC)	X-linked adrenoleukodystrophy (X-ALD), D-bifunctional protein (DBP) deficiency, peroxisomal acyl-CoA type 1 (ACOX1) deficiency and Zellweger Spectrum Disorders (ZSD)	Peroxisomal disorders	SAS
Sterols			
Cholestanol	Cerebrotendinous Xanthomatotic (CTX)	Sterol biogenesis disorders	SAS
7-dehydrocholesterol (7-DHC)	Smith Lemli Opitz Syndrome (SLO)	Sterol biogenesis disorders	SAS
Desmosterol	Desmosterolosis	Sterol biogenesis disorders	New
Lathosterol	Lathosterolosis	Sterol biogenesis disorders	New
Sitosterol	Sitosterolemia	Sterol transport disorders	New
Ubiquinones			
Coenzyme Q10 (Ubiquinone)	Primary and secondary Coenzyme Q10 deficiencies	Mitochondrial disorders	SAS

Calls to the Community

We invite members of the community to review the following requests from ERNDIM participants. If you are able to offer advice, share resources, or lend your expertise, please reach out to the administration office at **admin@erndim.org**. Your input and collaboration are greatly appreciated.

1. Daniel Herrera (Scientific Advisor of CWBC) is **planning a case series publication on ocular cystinosis.** Any laboratory involved with at least one case of ocular cystinosis diagnosed biochemically and confirmed by genetic analysis, and wants to be involved in this publication, please contact the admin office.

2. For participants in the CDG scheme who use isoelectric focusing (IEF) with antibody, one of our members is **seeking recommendations for effective antibodies**, as their current option is proving too weak. If you have experience with reliable antibodies for this application, please contact the admin office.

3. For participants of the SAS scheme using **an enzymatic assay for measuring free carnitine**, we have a participant who is struggling to source Carnitine acetyltransferase, and would like to know what suppliers others in the community are using.

ERNDIM 2025 SYMPOSIUM

Thursday 9th
Friday 10th

October 2025

Madrid SPAIN

Crowne Plaza Madrid
Centre Retiro

ERNDiM

GEYSECO.es
GESTIÓN DE CONGRESOS Y SOCIEDADES