European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism

ERNDIM

QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

SPRING 2016

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Message from the Chair

Dr George Ruijter, Chair, Executive Committee

Dr Mick Henderson has chaired ERNDIM for the past 7 years and as of January 2016, I have succeeded him in this position.

During the time Mick was Chair, ERNDIM has been transformed to a much more professional organisation. The major hallmarks of this transformation include the formation of an administrative office, now led by Dr Sara Gardner.

The Board of Trustees has also been made more independent from the Scientific Advisory Board and the Executive Committee so, as Mick explains it can function as a 'critical friend' Finally, much work has been done towards ERNDIM becoming accredited.

Naturally, these accomplishments are the joint success of the ERNDIM team as a whole, but Mick's calm reiteration of the steps he felt were necessary to bring ERNDIM to the next level has had an invaluable impact on the changes made in our organisation. Mick - thank you for your past and future effort.

As the new Chair of the ERNDIM, I will briefly introduce myself. I am a Biochemical Geneticist in the Erasmus Medical Centre in Rotterdam, The Netherlands. I joined the ERNDIM team of Scientific Advisors in 2008, when Dr Marinus Duran introduced me to the organisation of the Netherlands Diagnostic Proficiency Testing (DPT) scheme. In addition to organising the DPT Netherlands scheme, I also started a pilot scheme for Urine mucopolysaccharides in 2010, which became a full ERNDIM scheme in 2012.

News in ERNDIM usually originates from meetings of the Scientific Advisory Board, the group that discusses details of the core business of ERNDIM: providing External Quality Assurance schemes.

We are planning to start pilots for a few new schemes over the next year. One is a cognitive amino acid scheme which will be in addition to the existing, very successful quantitative amino acid scheme. Another proposed pilot is a separate quantitative acylcarnitines scheme which will replace the presence of more and more acylcarnitines in the Special Assays Serum scheme. More details are provided in this newsletter (page 5).

Also, our subcontractor SKML (Dr Cas Weykamp and his team), which organises the Quantitative schemes is working on improvements to the results website for the quantitative schemes so that more detail will be provided about performance in the annual report. This will be introduced in 2016/2017 and we will send full details nearer its release.

Very best wishes for 2016

George Ruijter

On behalf of the ERNDIM Executive Committee

Progress towards Accreditation

We are still making steady progress towards applying for accreditation. In the past year we have:

- Harmonised all EQA scheme annual reports so they comply with the requirements of ISO 17043
- Made the Certificates of Participation accessible from www.erndimqa.nl
- Produced the ERNDIM Participant's Guide which includes information on all aspects of participating in ERNDIM's EQA schemes & is accessible from the Registration Website (see page 8)
- Begun the process of formalising our relationships with our subcontractors
- Expanded Educational

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Performance Assessment

Critical Error

In 2014 we introduced 'Critical Error' in the evaluation of the qualitative schemes. A critical error is an error that would be unacceptable to the majority of labs and would have a serious adverse effect on patient management.

A confirmed critical error will mean automatic classification as a poor performer, so all proposed critical errors will need to be ratified by the Scientific Advisory Board (SAB) at the Spring meeting.

Participants with a confirmed critical error will be sent a Performance Support letter in the same way as labs that score poorly in a scheme are sent a letter.

EQA Scheme	Poor performance in 2014 schemes due to:	
	Critical Errors only	Poor score (inc labs with critical error & poor score)
Acylcarnitnes in DBS	3/98	0/98
CDG	1/52	1/52
Lysosomal enzymes in fibroblasts	0/68	4/68
Diagnostic Proficiency Testing	12/98	7/98
Urine MPS	4/89	3/89
	20/405	15/405

Poor performance in the 2014 Qualitative schemes

The introduction of critical error has had a clear impact on the overall performance of the 2014 qualitative schemes (see table above). The number of confirmed critical errors in the 2014 qualitative schemes was 20 with the majority (12) being in the Diagnostic Proficiency schemes. Poor performance has increased from 3.7% (15/405), based on inadequate scores, to 8.6% (35/405) based on poor scores and critical error.

By introducing the concept of critical error we hope to identify serious mistakes in diagnostics, with the aim to stimulate quality improvement.

"By introducing the concept of critical error we hope to identify serious mistakes in diagnostics"

Accreditation Progress

(Continued from page 1)

Participations to the Quantitative schemes

- Expanded the Administration Office with the recruitment of a new Administration Assistant
- Formalised over 30 new polices and procedures
- Co-opted Mick Henderson, formerly Chair of ERNDIM, to the Executive Committee as Quality Lead. He will liaise with the Admin Office and the Executive Committee overseeing the progress towards accreditation.

Participation Costs

ERNDIM is rapidly maturing into a professional organisation and is faced with the costs for accreditation, continuity and proper staffing of the Manchester Administrative Office. The Executive Committee works hard to keep the costs for participation as low as possible. However, even with gratefully received support from SSIEM, increases in the scheme fees are inevitable. Usually the participation fees for the ERNDIM schemes are annually increased by a modest percentage to keep up with inflation.

In 2016, additional increases were made to the DPT, Urine MPS and Special Assays in serum schemes. For the DPT and Urine MPS schemes the increases were necessary to cover the costs of the subscriptions to the CSCQ results website for those schemes. These costs were relayed to the schemes requiring that system only. The additional increase in the cost of the Special Assays in serum scheme was due to the addition of rather expensive carnitines esters to that particular scheme.

CSCQ Results Website

The CSCQ Results website continues to work well. Both the DPT and Urine MPS schemes now use the CSCQ Results website for online submission of results.

This year we are also hoping to move the CDG and Qualitative Organic Acids scheme to the CSCQ results website with our long term plan being to move the Acylcarnitines scheme in 2017/18.

We are very grateful for support from SSIEM in funding the development of these CSCQ website extensions which will allow a more rapid transition to online results submission for these schemes than would otherwise have been possible.

If you have any queries or concerns please contact CSCQ;
Xavier.albe@hcuge.ch

Uncertainty of measurement in Biochemical Genetics

In April 2016 the British Inherited Metabolic Disease Group (BIMDG, www.bimdg.org.uk) and MetBioNet (www.metbio.net) are organising a workshop on "Uncertainty in laboratory reports – does it affect patients?". The workshop will bring together clinical staff, metabolic physicians and dietitians and laboratory scientists to learn from one another in a workshop forum using the experience of ERNDIM schemes in a number of areas.

It is clear that all laboratory measurements carry an associated degree of uncertainty resulting from:

- Pre-analytic factors such as sample collection and transport
- Biological variation including diurnal variation and diet
- Analytical factors including the accuracy and imprecision of the assay used
- Post analytic aspects including the interpretation of qualitative data and the reference range assumed when interpreting quantitative results

While these factors are generally well understood by laboratory staff they are often less well understood by the clinicians who use the laboratory data.

The use of serial measurement to monitor and assess dietary compliance in patients with metabolic disease is a practical example where relatively minor changes in the result obtained can be over interpreted as requiring a modified dietary regime. In fact, significant changes may result from poor sample quality (particularly with dried blood spot samples) or the inherent imprecision of the assay.

Similarly, the accuracy and reliability of diagnostic testing is not always 100%, even when performed by experienced specialist centres, particularly when confronted with samples of limited volume displaying considerable phenotypic heterogeneity. This contributes, alongside clinical awareness, to the prolonged diagnostic odyssey experienced by some patients with rare disorders.

ISO15189 demands that laboratories are responsible for ensuring that test results are fit for their clinical purpose by setting and maintaining the quality of their analytical methods, and that the methods used are appropriate for the given clinical application. The principles of estimating uncertainty of measurement contribute to ensuring test outputs are fit for their clinical purpose by:

- Defining what an analytical method measures
- Meeting a defined analytical goal
- Indicating the confidence that can be placed in a test result
- Contributing to defining, monitoring and indicating where a test procedure may be improved.

Laboratories are also responsible for engaging with users to ensure that the requesting doctors and other clinical users understand the relevance of uncertainty of measurement in a clinically meaningful way to fully discharge their accreditation and clinical governance responsibilities.

Over the years ERNDIM has accumulated significant, clinically relevant data, in relation to laboratory variation in biochemical genetics that can guide laboratory based staff and clinicians to provide these services more effectively. It is hoped that the BIMDB & MetBioNet workshop in April will allow us to gain a greater shared insight into the significance of this variation in clinical practice that will benefit our patients.

"It is clear that all laboratory measurements carry an associated degree of uncertainty "

Chromatogram Library

We're developing a chromatogram library which will be publicly accessible from www.erndim.org. The library will catalogue the resources available in the qualitative scheme annual reports and our contributions to the SSIEM academy.

To establish this we have had the help of a Swiss work experience student financed locally and working between Manchester and Sheffield Children's hospitals for a 6 month period.

So far over 136 different disorders (organic acid, amino acid, oligosaccharides, purines & pyrimidines and miscellaneous disorders) have been catalogued. Searchable key metabolites will be identified for each disorder. We expect to almost complete the library by the end of March 2016 and hope to launch it online soon afterwards.

To complement the directory we also want to create a tutorial outlining how best to approach an unidentified spectrum.

Once missing disorders have been added we plan to invite participants to submit interesting cases for possible inclusion.

We hope this library will prove to be a useful addition to available resources for the interpretation of lab results for diagnosis of inborn errors of metabolism and that users will help to maintain its dynamic nature by contributing further cases.

Plea for samples

ERNDIM's Qualitative EQA schemes use real clinical samples as EQA materials. Obtaining suitable samples of sufficient volume can prove very difficult. One scheme which finds sample supply challenging is the Acylcarnitines in dried blood spots scheme which provides genuine clinically derived samples for assay and interpretation. The scheme relies on voluntary donations from patients; either permission to take "extra" blood when a sample is taken for clinical purposes, or permission to use "spare" blood if there is any left over after diagnostic or monitoring analyses are completed. Patients are frequently happy to help, but in a busy clinic or acute situation the clinical team may not remember to ask!

Retrospective permission to use "spare" blood may be easier to obtain, but then the laboratory needs to consider the possibility and not discard the excess until the patient/family have been approached for permission.

These difficulties mean that we always have a shortage of informative samples for distribution, particularly samples from untreated patients.
If any participants could provide samples in the future it would help enormously. We require 3-4ml of lithium heparin anti-coagulated whole blood or 65-70 30-50µl blood spots on Whatman (Schleicher & Schuell) 903 or Perkin Elmer/Ahlstrom 226 paper to provide sufficient material for one circulation. Samples for use in the scheme should be accompanied by a short clinical history, definitive diagnosis, and confirmation that informed consent/local ethical approval (as required in the referring centre) for use of the sample has been obtained. Please contact the ERNDIM office (erndim@cmft.nhs.uk) and/or one of the acylcarnitine scheme organisers (Qual.bloodspot@med.uni-heidelberg.de or chas.turner@kcl.ac.uk) if you think you may be able to supply a suitable sample.

"ERNDIM's Qualitative EQA schemes use real clinical samples as EQA materials"

Participant Survey 2015

We would like to thank everyone who responded to the Participant Survey in June 2015. We received responses from 252 participants from 219 centres in 52 countries; a very healthy response rate of over 52%!

The results from the annual survey help us to continue to improve the quality and efficiency of the ERNDIM schemes and also the service that we offer you so your input is very important to us.

A full report on the Survey Results is on the website but briefly 8 out of 12 of the schemes had the same overall scores as last year with 2 schemes (Acylcarnitines in DBS & Lysosomal Enzymes in fibroblasts) having slightly improved scores. The best scores for individual aspects were for 'Frequency of samples', Appropriateness of analyte concentration' and 'Adequacy of the report' while the most improved score of the whole survey was for Cystine in WBC (Sample volume).

The responses to the questions which assess the overall performance of ERNDIM were very positive with the overwhelming majority of respondents rating the quality of services provided by ERNDIM as 'excellent' or 'good', and having 'complete' or 'a lot' of confidence that ERNDIM can deliver the service required by participants.

We also asked if you would be interested in participating in a Quantitative acylcarnitines in serum scheme and over 200 centres answered 'Yes'! Plans for this scheme are now being developed—see 'Future pilot schemes' on page 5.

Laboratory Directory

The directory has been moved to a new server at the University of Basel which streamlines administrator access and we now have expert backup from a local company, BySite.

It is a dynamic website which allows update of laboratory information and selection of assays from a drop down menu. It presently includes >150 labs and we issue a plea to all laboratories to check if they are present in the directory and if so to update their information. If a particular assay is not present in the drop down menu it can be added to the list just by contacting us.

Finally please let us know if you need to be reminded of a password and new labs can join directly through the website.

Current Pilot Schemes & Studies

Three pilot schemes ran in 2015:

- Neurotransmitters in CSF (Prof Simon Heales, London; started in 2014)
- Pterins in urine and pterins/ DHPR in DBS (Prof Nenad Blau, Heidelberg; started in 2014)
- Keratan Sulfate (Dr George Ruijter, Rotterdam; new pilot for 2015)

In addition a pilot study on the addition of LysoGb3 to the Special Assays in Serum scheme began.

Keratan sulphate pilot

New developments in biochemical testing for Mucopolysaccharidoses have resulted in a pilot scheme for quantitative analysis of keratan sulfate which began in 2015. BioMarin has kindly agreed to sponsor this pilot study. Participation is limited to a small number of labs that had available the novel quantitative keratan sulfate assay, but we will inform ERNDIM participants if wider participation is possible in the future.

LysoGb3 in the Special Assays Serum

Fabry disease is an X-linked lysosomal storage disease (LSD) caused by the deficiency of lysosomal alpha-Galactosidase A. There are two marker metabolites for Fabry disease: **Gb3** (globotriaosylceramide) in urine or **lyso Gb3** (deacylated Gb3) in plasma.

Gb3 is the main glycosphingolipid which accumulates when there is a deficiency of alpha-Galactosidase A, and is useful for the diagnosis and assessment of the disease burden. It is increased at diagnosis in plasma (males only) and urine (males & females). Urinary Gb3 levels decline in male patients after initiation of enzyme replacement therapy. Lyso Gb3 is elevated in plasma in males and normal or mildly elevated in females. This metabolite can be determined by HPLC-MS/MS, UPLC-ESI-MS/MS and HPLC-fluorescence.

After long discussions with expert groups in Amsterdam, London and the USA the SAB decided to start with **lyso Gb3 in serum**, since its use has increased in recent years, it is also stable and much more soluble in water than Gb3.

However the long term addition of the required amount of lyso Gb3 would have meant a substantial increase in the scheme price. Fortunately, Genzyme has offered to support the purchase of lyso-Gb3 enabling the inclusion of this metabolite in the Special Assays Serum scheme.

In return ERNDIM will share summary data with Genzyme but will not disclose any details or results of individual participants.

"New developments in biochemical testing for Mucopolysaccharidoses have resulted in a pilot scheme for quantitative analysis of keratan sulfate "

Future Pilot Schemes

Cognitive Amino Acids

We recognise that one of the gaps in our service is testing of participants' interpretative prowess in the case of our quantitative schemes. Thus quantitative schemes only test accuracy and precision of analysis unlike other schemes such as the qualitative organic acids, CDG, acylcarnitines, DPT and mucopolysaccharides schemes that contain an interpretation component. We hope to plug this gap by providing a new scheme in which sets of amino acid results would be provided with brief clinical information. Participants would interpret the results as if from a patient and return the results via a web based report. We propose to limit the scheme to amino acids in the first instance as previously trialled in the UK, and run this on a pilot scale.

The aim is to have 300 participants when the scheme is a full EQA scheme but initially we will invite labs from the UK, Southern Germany, Austria, Switzerland, to participate in the pilot. Four assessors for the scheme have been nominated: Mary Anne Preece (UK), Rachel Carling (UK), Brian Fowler (Switzerland) & Sabine Scholl-Bürgi (Austria).

We propose to circulate 3 sets of results 4 times per year. Participants would be asked to respond using a structured report, similar to the DPT scheme report format, and using the same CSCQ web-based system.

We are presently designing templates to allow modification of the present CSCQ website and we hope to introduce the pilot scheme in autumn 2016.

DPT Pacific Rim/South Asia

In the 2015 Newsletter we announced plans for a new DPT centre for the South Asia/Pacific Rim region. The number of participations are growing in that region and it is anticipated that there will be considerable need for more EQA resources and support in coming years. Kevin Carpenter and Veronica Wiley (both in Sydney, Australia) have kindly offered to host and run such a scheme and to base it in Australia. While the expansion of the DPT scheme has been approved in principle by the ERNDIM Board of Trustees detailed discussions about the practicalities are just beginning. This will be a significant step for ERNDIM and it is important that all aspects of expanding the DPT scheme are considered before the new centre launches.

If you have any comments or would like more information please contact the ERNDIM office.

Acylcarnitines in serum

We were very pleased that so many of you said you would be interested in participating in this scheme (Participant Survey 2015, page 4) and discussions on how best to implement this scheme are underway.

ESHG EuroGentest Quality Subcommittee

The ESHG Genetic Services Quality Committee (GSQC) is now titled the EuroGentest Quality Subcommittee (QSC) which sits within the newly organised EuroGentest structure of the ESHG.

The QSC met initially on June 6th 2015 in Glasgow at the annual meeting of the ESHG to discuss its future role and decided to initially focus on several quality issues including: EQA and poor performance within the diagnostic laboratory community, establishment of quality assessment for genetic counselling and quality issues in relation to newborn screening of inborn errors of metabolism. Further progress on these issues was discussed in a telephone conference on 30th October and meetings in 2016 are planned for January 15th and May 21st.

Also at the 2015 ESHG, Viktor Kozich, Jim Bonham and Brian Fowler participated as moderators of a session on "Newborn screening: pretest information, selection of disorders and pilot studies, analytical performance, counselling issues" within a workshop on "Prenatal and newborn screening – what could and should we learn from each other?"

ERNDIM provided grants of 500€ each to support the attendance at the workshop of five ERNDIM participants.

Training Support Grants

"ERNDIM offers a small number of Training Support Grants each year"

As part of our aim to help improve standards in biochemical genetic testing ERNDIM offers a small number of Training Support Grants each year.

This grant is designed for trainees, in a permanent laboratory position, to gain experience and knowledge in a European ERNDIM approved laboratory in order to develop or introduce new methods to their own laboratory.

Funds can be applied for to cover the travel and accommodation costs incurred by such visits and a maximum of 6 grants will be awarded each year, subject to the approval of the ERNDIM Executive Committee. Full application criteria are given in the application form which can be found on the ERNDIM website under Training\Grants.

In 2015 we awarded 3 training support grants:

- Dr Pandey from Kathmandu Medical College & Teaching Hospital in Nepal visited Prof Fingerhut's Neonatal Screening Laboratory in Zurich as part of an ongoing collaboration for a pilot study on Newborn screening for metabolic disorders in Nepal.
- Dr Fodra from the National Institutes of Health in Manila, Philippines visited Dr Wibrand's laboratory in Copenhagen to learn about testing for lysosomal storage disorders.
- Dr Kift from St James Hospital in Leeds, UK visited Dr Bierau's laboratory in Maastricht to gain experience on the analysis and interpretation of purines and pyrimidines by UPLC-MS/MS.

You can read reports on all these visits on the website under Training\Travel Grant Reports.

National Quality Assurance Advisory Panel (UK)

ERNDIM has been asked to report poor performance of UK labs to the National Quality Assurance Advisory Panel (NQAAP) for Chemical Pathology, a sub-committee of the UK's Royal College of Pathology. The SAB have discussed the issues surrounding this and agreed that we will provide NQAAP with the requested information as it is acting on behalf of the UK government and all UK labs should already be reporting any cases of poor performance to the UK accreditation body.

The data shared will be a summary of the performance of all UK labs in the individual ERNDIM EQA schemes unless a lab is a persistent poor performer in which case NQAAP may require ERNDIM to pass on more information so that they can contact the lab directly.

We will contact all UK labs with more details later this year before any data is shared.

But it is already the case in the UK that the principal PATHOLOGY EQA provider, NEQAS, already shares data with NEQAAP, so all labs with be familiar with this process. The terms and conditions of ERNDIM participation will also be updated to reflect this change to our procedures.

Be assured that if ERNDIM receives similar requests from agencies in other countries we will initiate a dialogue with the laboratories affected before taking any action.

ERNDIM Management Committees

Executive Committee

After 7 years as Chair, Mick Henderson has stepped from the role and will instead be co-opted to the Exec as Quality Lead so that he can continue to be involved in the work towards ERNDIM's accreditation application. During Mick's time as Chair ERNDIM has seen many changes including setting up the Administration office and changes to the Board of Trustees. We would like to thank Mick for all his hard work over the last 7 years. We would like to welcome George Ruijter as the new Chair of the Exec. As George explains in his first Chair's update (page 1) he has been involved with ERNDIM since 2008 and is currently the Scientific Advisor for the DPT Netherlands and the Urine MPS scheme as well as running the Keratan Sulfate pilot scheme.

Board of Trustees

We would like to thank Mick Henderson and Marjolein van der Burgt who have both stepped down as Trustees after 12 & 2 years respectively.

Joining the Board of Trustees from 1st January are George Ruijter and Mrs Hiie Taks. As mentioned above George is the new Chair of the Executive Committee while Mrs Taks is a member of the Estonian patient society for galactosemia and PKU.

Full details of the members of the Board of Trustees, the Executive Committee and the Scientific Advisory Board are on the website (About\ Organisation and Key Persons).

SSIEM Academy

SSIEM ACADEMY 2015

ERNDIM collaborated with ETAC to organise the two day training meeting that was held in London on the 20th and 21st April.

The course was heavily oversubscribed; 112 applications were received and 39 scientists and 39 clinicians attended.

The topics of the Academy were Congenital Disorders of Glycosylation, Glycogen Storage Disorders, Mitochondrial Diseases and Neurotransmitters.

The joint clinical and lab workshops proved very popular and the feedback was positive with all 76 returned evaluation forms agreeing or strongly agreeing that "The programme was relevant to current practice" and that "The academy was relevant to my educational needs".

SSIEM ACADEMY 2016

The topic for the 2016 Academy (18th-19th April 2016) will be Amino acids, Hyperammonemia, Urea cycle defects and Metabolic liver disease.

Registration was in November 2015 and all available places were filled as 123 applications were received for the 80 places.

Information on future Academies will be posted on the ERNDIM website under News & Events.

"all evaluation forms agreed that the academy was relevant to my educational needs".

Participants' Meeting 2016

In 2016 the annual Participants' meeting will be held on the morning of the first day of the SSIEM conference in Rome, Tuesday 6th September.

As well as sessions open to all conference attendees the meeting also includes meetings for just the DPT scheme participants.

The DPT scheme is the ultimate External Quality Assurance challenge for laboratories active in IEM diagnostics. For each of the samples distributed discussion includes: diagnosis, analytical results, interpretation and, particularly focusses on problems both in analytical methods and interpretation. The purpose of the meeting is educational and participants' individual results and scores are not discussed. Your active participation in this meeting is very valuable and much appreciated. We look forward to seeing all the DPT participants at the 2016 meeting.

The full programme will be circulated nearer the time and will be available from the ERNDIM website. Details of the workshop will also be included in the SSIEM Conference programme.

Website update (www.erndim.org)

Documents added in the last year

- Newsletters
  - Newsletter 2016

Meetings & Reports

- Meetings
  - Presentations, ERNDIM meeting, Lyon, Sept. 2015
  - Posters by EQA scheme Scientific Advisors, SSIEM, Lyon, Sept. 2015
- Reports
  - Report on the 2015 Participant Survey
  - 2014 EQA scheme annual reports

Training & Education

- Travel Grant Reports
  - Travel Grant Reports by Dr Pandey, Dr Fodra & Dr Kift

Registration Website (www.erndim.org/qa)

We've added a Participant Information tab which is only accessible if you log into the Registration Website:

- General Information
  - ERNDIM participants' Guide
  - ERNDIM Registration Website manual
  - Educational Participation Application forms
- EQA Schemes

Scheme specific information will be uploaded here, for example in 2015 we uploaded the instructions and report forms for the Acylcarnitines Heidelberg scheme.

ERNDIM
QUALITY ASSURANCE IN LABORATORY TESTING FOR IEM

"Working towards a consensus between Biochemical Genetics Centres on reliable and standardised procedures for diagnosis, treatment and monitoring of inherited metabolic diseases"

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