The Eurogentest Project and ERNDIM

Interim Report on Biochemical Genetic Testing in Europe: deficits and needs and EQA

- Background
- Developments in Biochemical Genetic Testing in Europe: the role of ERNDIM
- The Eurogentest Project and the role of ERNDIM
- Report of the first Eurogentest Best Practice meeting of National Representatives of EU25 held on December 2nd, 2005 in Basel.
- Conclusions and recommendations on deficits and needs
- Feedback, discussions and action based on the recommendations (second Eurogentest Best Practice meeting of National Representatives of EU25 held on October 5-6, 2006 in Prague)

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11.04.2007

Biochemical Genetic Testing in Europe: deficits and needs and EQA

Background

Developments in Biochemical Genetic Testing in Europe: the role of ERNDIM

General introduction

The difficulty and complexity of Biochemical Genetic Testing for inherited metabolic diseases (IMD) has increased in parallel to the explosion of the number of recognised disorders. At the end of the 1940s a few amino acid disorders could be detected with simple paper chromatography whereas today hundreds of different disorders can be identified such as amino acid, organic acid, lipid, carbohydrate, mucopolysaccharide, purine and pyrimidine metabolism defects and disorders of post-translational modification such as glycosylation. The scope of Biochemical Genetic Testing has expanded in parallel with technological advances such as quantitative ion-exchange chromatography, gas chromatography coupled with mass spectrometry, high performance liquid chromatography and tandem mass spectrometry alongside classical techniques of macromolecule identification, enzymology and molecular genetic analysis. A small number of these disorders can be detected by newborn screening. Most however need to be searched for by selective screening based on clinical suspicion.

During the last decade tandem mass spectrometry together with automated sample processing and sophisticated data handling has facilitated the detection of many more inherited disorders than previously possible.

Thus some neonatal screening laboratories throughout the world now screen for additional fatty acid oxidation disorders, organic acidurias and amino acidaemias.

Quality control and Biochemical Genetic Testing.

Previously validation of methods used for diagnosis and treatment monitoring in the IMD was mainly achieved by comparison of data between control and patient groups in a single centre and results published after peer review. Now agreed thresholds of metabolite levels after treatment, multi-centre studies, increased mobility of patients between countries and agreed critical cut off values in newborn screening by tandem MS all demand satisfactory quality assurance including external quality control to guarantee comparability of results between different centres. It is necessary to raise the levels of accuracy, precision, reproducibility and harmonisation of Biochemical Genetic Testing to those obtained in other disciplines of laboratory medicine such as clinical chemistry. At the same time it must be emphasised that the complexity of Biochemical Genetic Testing often requires highly specialised techniques and equipment with interpretation of the results by experienced personnel. Also the types of laboratories involved vary from university departments working mainly in research to clinical chemistry laboratories in hospitals.

Improving the standard of Biochemical Genetic Testing in Europe: the ERNDIM Foundation

It is generally accepted that quality control for Biochemical Genetic Testing must be implemented on an international basis due to the small number of participating laboratories in any individual country.

Therefore quality control of Biochemical Genetic Testing has been addressed on a European wide basis by ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism) since its founding in 1994. Its EQA schemes are operated according to accepted norms on a European wide scale. ERNDIM aims to develop a consensus between European Biochemical Genetics Centres on reliable and standardised procedures for diagnosis, treatment and monitoring of inherited metabolic diseases. It also promotes education through meetings and provision of relevant documentation such as recommended operating procedures and annual reports of EQA schemes on the internet. ERNDIM aims to be financially self sufficient through minimal administration costs and efficient subscription collection.

Today ERNDIM offers 9 different schemes including quantitative organic acids, quantitative amino acids, special assays in plasma and urine, proficiency testing for organic acids, purines & pyrimidines, white cell cystine, acyl carnitines and diagnostic proficiency testing. Schemes are operated according to guidelines summarised by Sciacovelli et al. (2001) and are harmonized with respect to numbers and frequency of samples and direct submission of results and receipt of reports by internet. Schemes are provided by SKML (Stichting Kwaliteitsbewaking Medische Laboratoriumdiagnostiek, Dutch Foundation for Quality Assessment in Clinical Laboratories) or academic centres working closely with a Scientific Advisory Board and administered by the ERNDIM executive committee, which represents the ERNDIM Foundation Board.

Future issues within ERNDIM

There is clear evidence of improvement in performance in Biochemical Genetic Testing since ERNDIM started but much improvement is still necessary. Scoring and assessment of performance needs to be harmonised in order to define good performance and to link this to certificates of participation.

New schemes need to be introduced for new groups of analytes but only on a sound scientific and economic basis. New schemes under consideration include neurotransmitters and other analytes in cerebrospinal fluid and lysosomal enzymes.

In addition the accreditation of the QA schemes themselves as well as participating labs must be achieved.

Formal training for clinical biochemists in Biochemical Genetic Testing, similar to that existing for paediatricians needs to be established.

A new European Directory of Biochemical Genetic Testing laboratories needs to be developed and should include information on EQA participation and accreditation status of participating labs.

The Eurogentest Project and the role of ERNDIM

The Eurogentest project aims to promote the proper utilisation and management of genetic services; harmonisation of accreditation and certification of genetic testing laboratories; establishment of procedures and guidelines for the validation of methods and technologies. ERNDIM represents Biochemical Genetic Testing within the project and is currently engaged in the following activities.

- harmonisation of existing and new schemes for EQA in Biochemical Genetic Testing and increase of coverage to the whole of the 25 EU countries.
- evaluation of the present state of participation in EQA schemes in EU25 to identify needs for improvement and expansion by either expansion of capacity of existing schemes addition of new ones
- provision of a comprehensive directory of Biochemical Genetic Testing laboratories, emphasising participation in ERNDIM and other EQA schemes, and linked to other directories within Eurogentest.
- development and dissemination of guidelines for best practice for internal and external quality through meetings with national representatives of EU25 workshops.
- development of measures to determine satisfactory performance and links to laboratory accreditation.
- development of i) standard analytical guidelines to cover all groups of analytes relevant to IMD and ii) standard reporting procedures.

Some of these aspects were addressed at the first Best Practice meeting of National Representatives of EU25 held on **December 2nd, 2005 in Basel.**

Report of the first Eurogentest Best Practice meeting of National Representatives of EU25

The aim of the meeting was to review best practice in Biochemical Genetic Testing including quality assurance (QA). Needs and deficits in Europe were identified and moves towards producing guidelines for Biochemical Genetic Testing and QA were initiated.

Best practice in Biochemical Genetic Testing

Lectures on the state of the art of Biochemical Genetic Testing were presented for the following aspects:

QA for Biochemical Genetic Testing in general: *Leo Spaapen, Maastricht*

Best practice for analysis and QA for various groups of metabolites

- amino acids: *Leo Spaapen, Maastrict (for Brian Fowler, Basel)*
- organic acids: *Jim Bonham, Sheffield*
- acyl carnitines: *Charles Turner, London*
- purines and pyrimidines: *Jorgen Bierau, Maastricht*
- diagnostic proficiency schemes: *Christine Saban, Lyon*
- general aspects of diagnostic guidelines: *Jim Bonham, Sheffield*

(Presentations are available as Powerpoint files, http://www.erndim.unibas.ch/, "Meetings and Reports")

Biochemical Genetic Testing in the EU: strengths and weaknesses

Prior to the meeting all participants were requested to complete a questionnaire surveying strengths and weaknesses of Biochemical Genetic Testing in the individual countries. Questions included:

the population size
the number of births / year
the disorders tested for and number of centres for newborn screening
the number of diagnostic laboratories performing Biochemical Genetic Testing
limitations to testing e.g. restricted funding
the spectrum of disorders covered
whether labs participate in external quality control
whether labs are accredited
whether any national training programmes are in place
whether succession planning for staff is in place
the number of medical centres for IEM
whether there are any IEM(s) with unusual incidence in individual countries.

It must be recognised that due to different recording systems and sometimes lack of structured provision of services the information provided cannot be completely accurate. Nevertheless the information afforded by the questionnaires served as a valuable basis for work during the meeting. Questionnaires were completed by 24 National Representatives from the EC countries. A National representative from Malta had not been identified then but has since been recruited.
The questionnaire information is summarised as follows:

Population size

The very wide variation in population within the total population of 457 million (383 million EU15 and 74 million new member countries) renders design of guidelines for individual countries extremely difficult.

Thus 3 countries have a population < 1 million, 5 countries 1-5 million, 6 between 5– 10 million, 5 between 10 – 20 million, 2 between 20 – 50 million and 4 > 50 million.

Number of births / year

The number of births / year ranges from 4120 to 725'900 with an average of approx. 180’000

Newborn Screening: disorders tested for and number of centres

The highest number of disorders are tested for in Austria, Portugal and Germany, with a number of 27, 15 and 12, respectively.

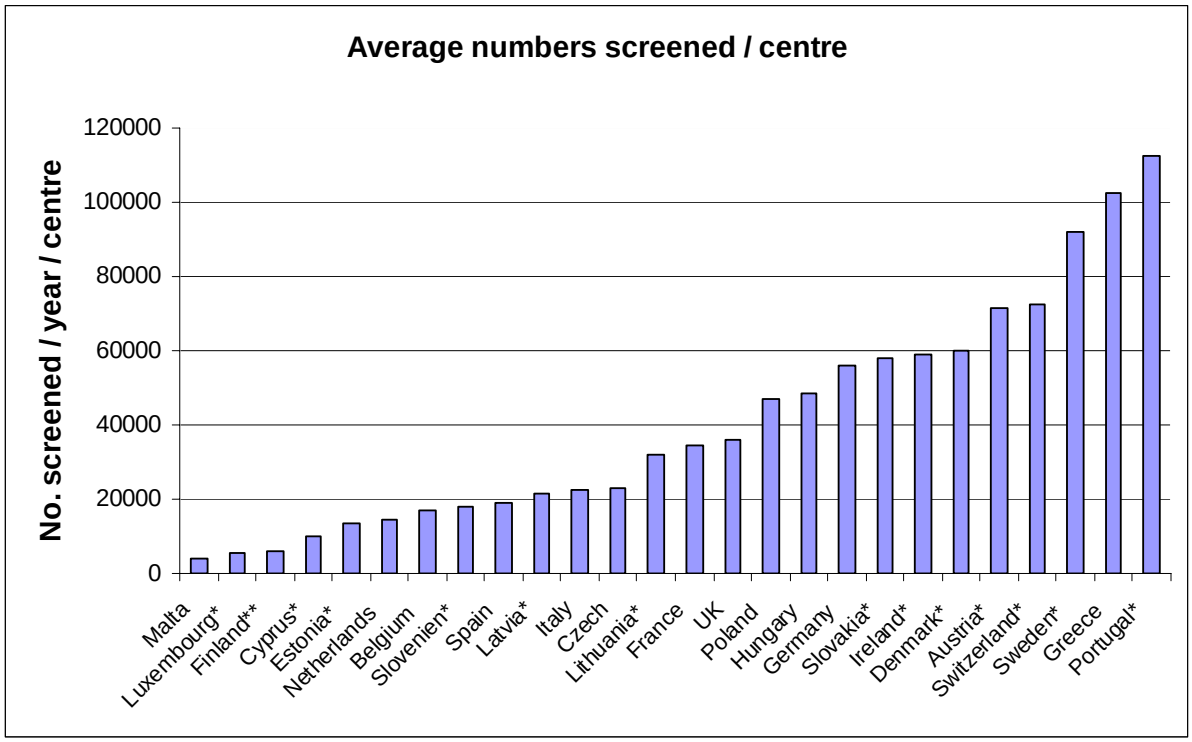
In other countries the number of disorders tested is between 1 and 6 with slightly more disorders tested in the old EC countries in comparison to the new EC members. Finland screens only for hypothyroidism and Malta for only haemoglobinopathies and hypothyroidism.

In all 254 EC countries there are 150 Centres for Newborn Screening. 128 centres are in the old and 22 in the new member countries.

The number of centres for screening related to population is shown in Figure 1.

It must be noted that for those countries with more than one centre the values shown are only averages and there may be a large variation in numbers screened in each centre.

Figure 1

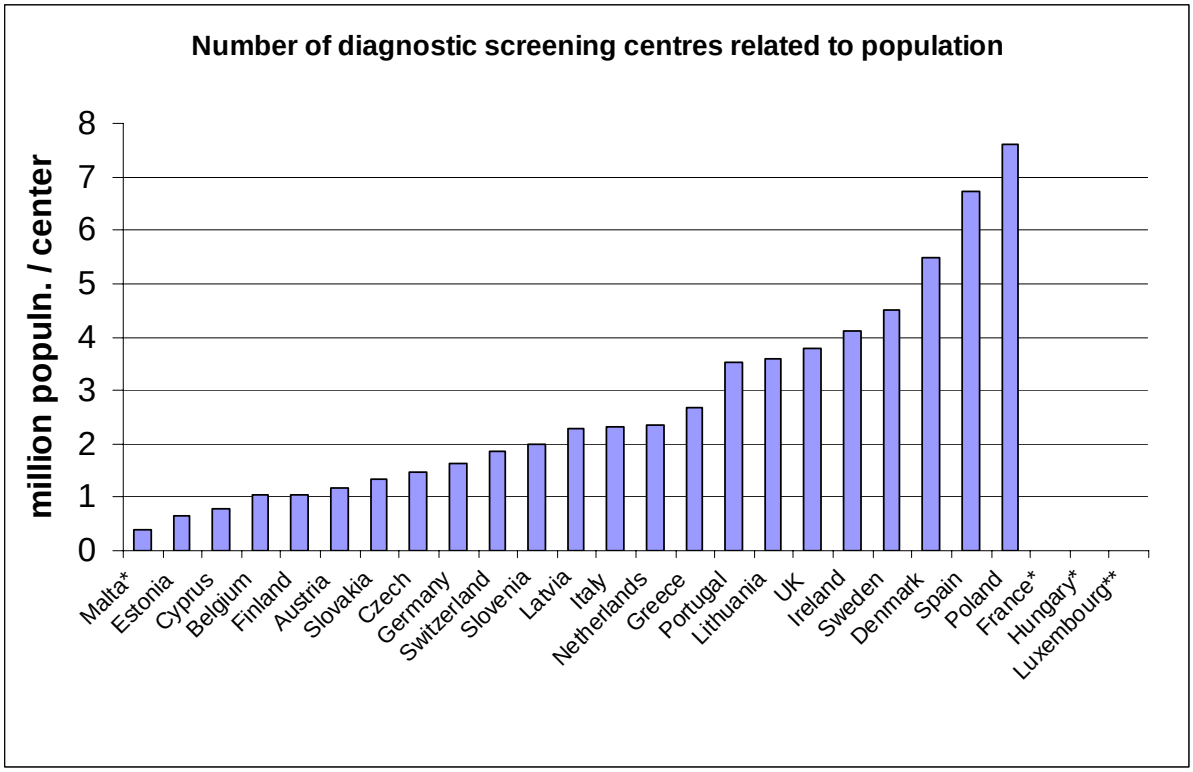


* countries with one centre, ** only Hypothyroidism

Number of Diagnostic laboratories performing Biochemical Genetic Testing

In total 160 diagnostic labs are known which perform Biochemical Genetic Testing, 137 labs in the old member and 23 in the new member countries (excluding France for which data is unavailable).
On average, one Biochemical Genetic Testing laboratory covers a population of 2.8 million. The number of centres related to population for individual countries is shown in Figure 2.

Figure 2



* not available, ** no centre

Number of medical centres for IEM

Overall there are 153 medical centres known to be active in the field of IEM, 131 are in the old EC countries and 22 are in the new member countries. The average size of population per one centre is 2.9 million in old member 3.4 million in new member countries.

Limitations to Biochemical Genetic Testing

Several main reasons were given as the reason for limitation of Biochemical Genetic Testing

- Funding restrictions are the principal limitation in 18 countries
- Lack of specialised staff in IEM is a factor in 9 countries
- the size of population size sets the limit for 5 countries
- lack of QC schemes for some tests available

Funding problems seem to be a factor both in old and new EC countries with funding limitations reported in 8 of 10 from new member and 12 of 13 from old member countries.

The spectrum of disorders covered and estimated case numbers

To answer this question data was sought in the form of this table

Spectrum of tests available	**Nationally**	**Internat.**	**Estimate* number test /year**	**Estimate* number cases /year**
Amino acids	22/25	5/25		
Organic acids	19/25	7/25		
Carbohydrate Metabolism	18/25	9/25		
Fatty acid oxidation	16/25	11/25		
Respiratory Chain	14/25	7/25		
Mucopoly-saccharidoses	20/25	7/25		
Sphingo-lipidoses	14/25	9/25		
Purines, Pyrimidines	15/25	10/25		
Peroxisomal Disorders	16/25	9/25		
Creatine synthesis disorders	9/25	12/25		
Congenital disorders of Glycosylation	14/25	9/25		

Testing for amino acids, organic acids, carbohydrates and mucopolysaccharides is available in most countries (18-23/25) National availability for other tests is less complete with, for example, creatine synthesis disorders testing only available in 9 countries. Most large countries provide all tests nationally while smaller countries clearly need to obtain some types of Biochemical Genetic Testing abroad.
Regarding sample load and cases found it is clear from results obtained in this survey as well as previous experience that it is extremely difficult to obtain comprehensive, accurate data on this question, particularly the numbers of cases detected. Problems relate to undesirability to share data and confusion between new cases and already diagnosed ones but the main deficit is usually a lack of a complete diagnostic register. No data was given by 6 countries and for these and even for those countries for which estimates were provided it is necessary to carry out more research to obtain meaningful estimates of case loads on a European-wide basis.

Participation in External Quality Control

In general laboratories from most countries perform a full or partial program of EQA although within a country participation may be incomplete. Thus 16 countries report participation of all labs and 8 report participation of some labs (ie. Belgium, Czech Republic, France, Finland, Germany, Poland, Slovakia and Spain). Overall there is no major difference between old and new member countries. This observation emphasises that there is still a need to expand EQA.

Accreditation
In most countries there are no accredited laboratories. In 10 countries all or some laboratories are accredited. In the U.K. 15 of the 16 labs are accredited by CPA. The types of accreditation are not always the same with accreditation of tests in Estonia, of prenatal diagnosis (metabolites in amniotic fluid and molecular biology) but only for a particular person and not the lab in France.

Training
Training programmes both in old and new member countries appear to be poorly developed. Thus 4 out of 14 and 4 out of 10 have a training programme in old and new member countries, respectively.
This is clearly an important limitation to Biochemical Genetic Testing as mentioned above.

Succession planning
Planning for the succession of staff is in place in just 9 countries but even in those countries it is not always complete.

The occurrence of particular IEMs with unusual incidence
An unusually high or low incidence of a particular inherited IEM may influence the type of Biochemical Genetic Testing in a country.
An unusual incidence of an IEM was reported in 11 out of 25 countries as follows:

- Austria: MPS IVB, CDG, propionic acidaemia, glutaric aciduria
- Cyprus: one village has a carrier frequency for GM1 gangliosidosis of 1:12 and Sandhoff disease has a carrier frequency is 1:7 in Maronite community (<1% of the population)
- Estonia: very low incidence of MCAD deficiency of 1:193 000
- Finland: lysinuric protein intolerance, hyperornithinemia with gyrate atrophy, aspartylglucosaminuria, Salla disease, very low incidence of PKU (zero among original Finns)
- Greece: Sanfilippo typeB
- Ireland: PKU, Galactosaemia, GA1, ? Resp. chain defects, Cystic fibrosis
- Malta: gangliosidosis
- Netherlands: several very rare diseases e.g. Cog-7 deficiency
- Poland: low incidence of MCAD, high incidence of LCHAD, high prevalence of the 841delCT mutation of the SURF1 gene
- Slovakia: alkcaptonuria with the world-wide highest incidence of 1 in 19000, Smith-Lemli-Opitz syndrome with asuggested incidence of 1 in 20000,
- Slovenia: low number of galactosemia patients

Conclusions and recommendations on deficits and needs

Strengths and weaknesses in individual countries were focused on in

a) short presentations by each National Representative
b) a presentation on "needs assessment and review of IMD services in the UK" by Anne Green, Birmingham
c) interactive work in five groups, the conclusions of which were presented *in plenum*.

The five groups were constituted as follows

1	2	3	4	5
Anne Green UK	Leo -Spaapen The Netherlands	Elisabeth Holme Sweden	Christine Saban France	Ernst Christensen Denmark
Jim Bonham, UK	Ounap Katrin Estonia	Francois Baudouin Belgium	Claus-Dieter Langhans Germany	Mojca Zerjav-Tansek, Slovenia
Kari Pulkki, Finland	Gradowska Wanda Poland	Pospisilova Eva Czech Republic	Antonia Ribes Spain	Helen Michelakakis, Greece
Charles Turner, UK	Silva M.M. Portugal	Hoffmann J-P Luxembourg	Jurgita Songailiene Lithuania	Amelie Morrone, Italy
Darina Behulova, Slovakia	Walsh Richard Ireland	Vevere Parsala Latvia	Schuler Agnes Hungary	
Olaf Bodamer, Austria				
Anthi Drousiotou, Cyprus				

The conclusions from the groups together are as follows

1. The need for **networking** within a country and between countries, particularly for smaller countries. Clustering of laboratory tests, sharing of samples and backup arrangements are needed. This could be geographically based but also shared language would be useful.
2. The need for **rationalising tests** if workloads are very low.
3. The small number of patients with individual disorders in the small EU 25 countries e.g. Estonia and Poland causes **difficulty in gaining experience** in recognition and diagnostic proficiency.
4. A **test repertoire**, i.e. a minimum set of tests for centres needs to be defined
5. **Funding** of services for diagnostic investigations and Quality Assurance is a problem in many countries (e.g Poland, Estonia, Portugal and Ireland). Reimbursement of fees for follow-up is an issue for Austria
6. Generally inherited metabolic diseases and therefore Biochemical Genetic Testing have a **low position on the political agenda** and there is a need to increase awareness.

7. There is **concern about privatisation** and it is suggested that the potential role of accreditation and use of standards might be used to defend/combat this.
8. The **unavailability of training programmes** for clinical and biochemical diagnostics (Poland, Estonia, Portugal and Ireland) and a general lack of interested people for the field of IEM to guarantee continuity of IEM-patient care in the future.
9. There is an obligation for laboratories to **provide training** to support the European initiative, particularly for the most well developed ones.
10. There is a lack of **accreditation** of laboratories in most countries.
11. There is lack of an **umbrella organization** in several individual countries with some notable exceptions.
12. There is a lack of **communication** between labs and among clinicians taking care of patients in some countries leading to lack of overview of facilities in some countries (e.g. France, Germany).
13. There is the need for national **databases** (register) of diagnoses, which should subsequently link into international ones. These could be modelled on those already started, e.g. in the UK (metbio.net) and Spain (REDEMETH).
14. A weakness in some countries, e.g. Spain can be territorial differences in the level of services different local screening programmes within a single country

Recommendations to overcome deficits, especially focused on the EUGT project

1. Define basic standards / minimum core requirements / test repertoires in relation to size of country. This could be based on a minimum number of samples, requests / tests per annum, taking into account the need for quality markers, e.g. turnaround time and the importance of gate keeping for specimens sent away.
2. Identification of clusters of countries/sharing where workloads are very low. Exchange visits and / or workshops for the particular groups of countries should be promoted by the Eurogentest project.
3. Training initiatives for implementing new tests identified and potential role of Eurogentest to support and fund such initiatives. Eurogentest could promote initiatives for trainees to train in the more developed countries with some funding to support the training institution.
4. Reference laboratories should be identified at both the national and international level with proposals for how should they be financed.
5. Stimulation of accreditation of laboratories by a scoping exercise to evaluate present situation throughout Europe and then working to pull together the best / minimum recommendations.
6. The EQA schemes themselves need to achieve accreditation.
7. A survey of the scope of Metabolic Physician and Biochemist Training across Europe should be initiated.
8. An Initiative similar to that taking place in the UK to scope the size of the problem, perhaps initially to collect data on number of patients with certain IMD disorders across Europe.
9. Expansion of EQA so that quality assessment materials is made easily available including the provision of cell banks for biological material from patients.
10. Establishment of National registers of diagnosed cases. EUGT/ERNDIM should work together with existing national organisations such as those in the UK, Germany, Spain and Italy. In the absence of a national structure we should initiate a European wide action to help remedy this deficit.
11. Best Practice guidelines for methodology, minimum services and QA should be produced by ERNDIM/EUGT to provide the basis for local justification of increased budgets. The advised recommendations and issues should be a Directive of the European Commission.

Recommendations to overcome deficits

Progress and Feedback and discussion on recommendations by National Representatives at meeting held in Prague, October 5-6, 2006.

1. ***Define basic standards / minimum core requirements / test repertoires in relation to size of country***
   This recommendation is difficult to fulfil due to the need for speedy access to certain tests, cross country barriers, payment issues (e.g. insurance companies often won't pay for tests carried out abroad) and reluctance to give up or share provision of certain testing. A useful approach might be to define on a general level what is needed then marry this to existing and future services. Nevertheless the need for smaller countries to become parts of networks is accepted at least for certain groups of analytes.

2. ***Identification of clusters of countries/sharing where workloads are very low. Exchange visits and / or workshops***
   This is agreed as necessary but as for point one is not easy to translate into practice. Both points 1 and 2 need to be sorted out in the next best practice meeting of National Representatives.
   It must be noted that geographical proximity is not always a criteria for clustering of centres and may be better arranged along spokes or with existing partners.

3. ***Training initiatives for implementing new tests***
   Initiatives for training in reference labs in more developed countries
   These measures can be developed by 1) organisation of a series of international training courses for groups of countries with geographical proximity 2) provision of small grants for training of individuals in a reference laboratory. Such grants have already been established by ERNDIM and one has already been awarded to allow a person from the Centre for Medical Genetics, Vilnius University Hospital, Lithuania to visit the Dept. of Biochemical Genetics, Academic Hospital, Maastricht. (see ERNDIM web-site for report)

4. ***National and international reference laboratories for training should be identified***
   The need for such laboratories is accepted but they need to be carefully defined with agreed formal criteria. ERNDIM should have a main role in identification of these labs.

5. ***Stimulation of accreditation of laboratories by scoping present status***
   Accreditation status of laboratories will be shown for those listed in the ERNDIM laboratory directory. Also Biochemical Genetic Testing labs took part in the accreditation survey of WP1.2. Moves to include all Biochemical Genetic Testing labs in the WP1.2 directory are being considered. National representatives strongly favour this activity but emphasise that standards for accreditation must be applicable for Biochemical Genetic Testing laboratories.
   Also it was brought to attention that for some countries certification is the first step to accreditation

6. ***Accreditation of the EQA schemes themselves***
   ERNDIM EQA scheme organisers are fully involved in the WP1.9 initiative on Quality management of EQA schemes. Measures to implement recommendations resulting from the WP1.9 forum meeting of February 2-3, 2007 will be discussed at the next ERNDIM Scientific Advisory Board and Executive Committee meetings.

7. ***A survey of the scope of Metabolic Physician and Biochemist Training***
   This item should be carried out through the national Representatives and National Societies. Also a section on this topic will be mounted on the ERNDIM web-site. Discussions have also begun with the SSIEM aimed at a joint initiative on training for biochemists similar to that operating under the SSIEM Education and Training Advisory Committee (ETAC) for physicians.

8. ***An Initiative similar to that taking place in the UK to scope the number of patients with certain IMD disorders across Europe***
   It is recognised that this may not be as easy to carry out in all countries as it was in the U.K. Nevertheless ERNDIM should liaise with National Societies and parent associations to try to achieve this. It must be noted however that not all EU countries have national societies, only 10 are listed on the SSIEM web-site and there is room here for direct initiatives from ERNDIM.
   Confidentiality and data protection issues must be resolved.

9. ***Establishment of National registers of diagnosed cases***
   - through existing national organisations
   - through European wide action
   National Societies and Parent groups should be approached to help in this activity.
   Data protection issues need to be carefully considered.

10. ***Expansion of EQA and improved availability of quality assessment materials including cell banks for biological material***

ERNDIM has established a fund to allow laboratories from countries with limited resources to participate in our EQA schemes free of charge.

The idea of a sample bank for EQA samples is seen as ambitious but would be of great benefit and is broadly welcomed.

11. **Best Practice guidelines for methodology, minimum services and QA**

Such guidelines are seen as highly valuable and the planned programme for producing these within the ERNDIM SAB and Trust Board is welcomed. Concerns that "intellectual property" rights issues may inhibit sharing of best practice guidelines were raised but this should not be an issue once they are published.

12. ***The advised recommendations and issues should be a Directive of the European Commission.***

This would be an enormous step requiring action at government level and might be too ambitious. Nevertheless exploratory enquiries should be made since some form of official recognition of recommendations for Biochemical Genetic Testing in the EU would be very valuable in supporting national initiatives.

Other points- National Representatives are encouraged to inform their own National Societies of EUGT activities.

Information for the ERNDIM / EUGT database on Biochemical Genetic Testing services is not always readily available and may have to be obtained from either the National Representative or the National Society or both working together.

It is agreed that National Representatives should be informed of laboratories which participate in ERNDIM schemes from (just) their own country.