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**Summary  
Document**

Clinical Molecular Genetics  
External Quality Assessment

European scheme providers' meeting  
Frankfurt am Main, Germany  
10<sup>th</sup> November 2005

March 2006



EuroGentest



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The views expressed in this document are those of the meeting participants and do not necessarily reflect the policies of the institutions or companies they are affiliated to.

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## Clinical Molecular Genetics

### European External Quality Assessment providers meeting

#### An exploration of opportunities for harmonisation and collaboration between EQA schemes.

The discussion meeting took place on Thursday November 10<sup>th</sup> 2005 at the Intercity Hotel Frankfurt am Main, Germany.

<b>Programme</b>	
08:30 – 09:00	Welcome coffee (banquet foyer)
09:00 – 09:15	<b>Clemens Müller-Reible</b> (Würzburg), welcome, presentation of EuroGentest and the aims of work package 1.3 (“External Quality Assessment for Molecular Genetic Testing”)
Brief presentations of the different EQA schemes:	
09:15 – 09:30	<b>Rob Elles</b> (Manchester), European Molecular Genetics Quality Network (EMQN), Manchester, UK
09:30 – 09:45	<b>Christine Mannhalter</b> (Vienna), Austrian association for Quality Assurance and Standardization of medical-diagnostic tests (ÖQUASTA), Vienna, Austria
09:45 – 10:00	<b>Pierre-Alain Morandi</b> (Chêne-Bourg), Swiss Centre for Quality Control (CSCQ), Chêne-Bourg, Switzerland
10:00 – 10:15	<b>Simon Ramsden</b> (Manchester), United Kingdom National External Quality Assessment Service (UKNEQAS) for Molecular Genetics, Manchester, UK
10:15 – 10:30	<b>Ralf-Rüdiger Flörke</b> (Düsseldorf), Institute for Standardization and Documentation in the Medical Laboratory (INSTAND), Düsseldorf, Germany
10:30 – 10:45	<b>Els Dequeker</b> (Leuven), Cystic Fibrosis Network, Leuven, Belgium
10:45 – 11:00	<b>Clemens Müller-Reible</b> (Würzburg), Professional Association of German Human Geneticists (BVDH), Munich, Germany
11:00 – 11:30	Coffee break (banquet foyer)
11:30 – 11:45	<b>Piet Meijer</b> (Leiden), European Concerted Action on Thrombosis (ECAT) Foundation, Leiden, Netherlands
11:45 – 12:00	<b>Manuela Simoni</b> (Münster), European Academy of Andrology (EAA), Department of Clinical Pathophysiology University of Florence, Italy
12:00 – 12:15	<b>Mario Pazzagli</b> (Florence), Coordinator of the EU project EQUAL, Multi-National External Quality Assay (EQA) Programmes in Clinical Molecular Diagnostics
12:15 – 12:30	<b>Michael Neumaier</b> (Mannheim), German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Reference Institute for Bioanalytics (RfB), Bonn, Germany
12:30 – 12:45	<b>David Perry</b> (Cambridge), UKNEQAS for Blood Coagulation, Haemophilia Genetics, Sheffield, UK
12:45 – 13:00	<b>Ian Jennings</b> (Sheffield), UKNEQAS for Blood Coagulation, Thrombophilia Genetics, Sheffield, UK
13:00 – 13:15	<b>Marco Salvatore</b> (Rome), Istituto Superiore di sanità (ISS) Rome, Italy
13:15 – 14:15	Lunch (restaurant)
14:15 – 14:30	<b>Simon Patton</b> (Manchester, EMQN) A repository and database of available EQA materials
14:30 – 14:45	<b>Rob Elles</b> (Manchester) OECD guidelines for quality assurance in molecular genetic testing
14:45 – 17:00	Discussion on aspects of harmonisation and opportunities possible future collaboration

## Meeting Participants

Participant	Institution
Parviz Ahmad-Nejad	German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Reference Institute for Bioanalytics (RfB), Bonn, Germany
Sandi Deans	United Kingdom National External Quality Assessment Service (UKNEQAS) for Molecular Genetics, Manchester, UK
Els Dequeker	Cystic Fibrosis Network, Leuven, Belgium, EuroGentest unit 1 leader
Alexandra Dorn-Beineke	German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Reference Institute for Bioanalytics (RfB), Bonn, Germany
Rob Elles	European Molecular Genetics Quality Network (EMQN), Manchester, UK EuroGentest WP1.3 leader
Ralf-Rüdiger Flörke	Institute for Standardization and Documentation in the Medical Laboratory (INSTAND reg. ass.), Düsseldorf, Germany
Ian Jennings	UKNEQAS for Blood Coagulation, Thrombophilia Genetics, Sheffield, UK
Uta Malburg	EuroGentest project officer, Würzburg, Germany
Christine Mannhalter	Austrian association for Quality Assurance and Standardization of medical-diagnostic tests (ÖQUASTA), Vienna, Austria
Piet Meijer	European Concerted Action on Thrombosis (ECAT) Foundation, Leiden, Netherlands
Pierre-Alain Morandi	Swiss Centre for Quality Control (CSCQ), Chêne-Bourg, Switzerland
Clemens Müller-Reible	Professional Association of German Human Geneticists (BVDH), EuroGentest WP1.3 co-leader
Michael Neumaier	German Society for Clinical Chemistry and Laboratory Medicine (DGKL), Reference Institute for Bioanalytics (RfB), Bonn, Germany
Simon Patton	European Molecular Genetics Quality Network (EMQN), Manchester, UK
Mario Pazzagli	Coordinator of the EU project EQUAL, Multi-National External Quality Assay (EQA) Programmes in Clinical Molecular Diagnostics
David Perry	UKNEQAS for Blood Coagulation, Haemophilia Genetics, Sheffield, UK
Simon Ramsden	United Kingdom National External Quality Assessment Service (UKNEQAS) for Molecular Genetics, Manchester, UK
Marco Salvatore	Istituto Superiore di sanità (ISS), Rome, Italy
Manuela Simoni	European Academy of Andrology (EAA), Münster, Germany
Kate Vickers	EuroGentest project officer, Manchester, UK

## Introduction

External Quality Assessment (EQA) schemes are available to laboratories offering clinical molecular genetic tests through national and international schemes. The availability and format of EQA schemes varies across Europe and they exist for a relatively small number of the genetic testing services available.

Representatives of fourteen molecular EQA scheme providers from across Europe attended a meeting in Frankfurt in November 2005 to exchange information and discuss possibilities for collaboration and harmonisation. This was the first meeting of its kind and was organised and funded by the EuroGentest Network of Excellence.

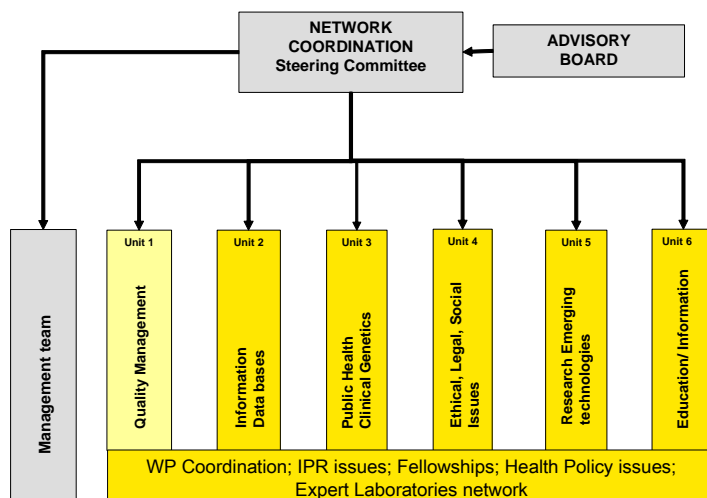
The main aims of the meeting were:

- To compare existing activities (structure and scope of schemes).
- To examine further needs and requirements of laboratories for EQA.
- To explore possibilities for collaboration and harmonisation amongst EQA providers.
- To explore possibilities for mutual recognition.

This document provides a summary of the presentations outlining each of the EQA schemes represented at the meeting and a summary of the discussion that took place. Appendix I provides contact information for molecular genetics EQA schemes available in Europe. Updates to this information will be placed on the EuroGentest (Unit 1) website ([www.eurogentest.org](http://www.eurogentest.org)). In addition, details of a repository for EQA materials collected by EMQN, in collaboration with EuroGentest and UKNEQAS that are available to European EQA scheme providers, are given in Appendix II.

EuroGentest is a European Commission funded network of excellence (NoE) focussed on genetic testing and the delivery of genetic services. It was established following a Joint Research Centre report to the Commission detailing deficits in quality assurance in molecular genetic testing in 2003. EuroGentest aims to document the “state of the art” across Europe and explore ways to harmonise systems and improve quality (Ibarreta et al. 2003 EUR20977 EN [www.jrc.es](http://www.jrc.es)). The scope of EuroGentest includes the complete life cycle of a genetic test from technological and scientific innovation through implementation to service, aspects of public health and access to services and ethical, legal and social issues. Significant effort is directed towards quality assurance of laboratory genetic services. External tracking of laboratory performance (External Quality Assessment) as measured by peer comparison is a key component of quality assurance.

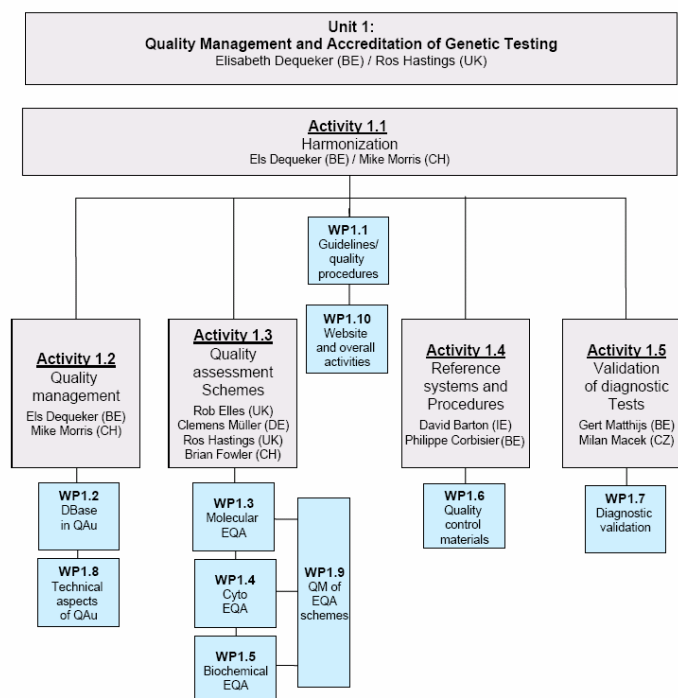
### Network of Excellence: “EUROGENTEST”



The Frankfurt meeting demonstrated that despite differences in origin and approach a level of commonality between European EQA schemes already exists. Most schemes began within the last ten years, had evolved similar mechanisms of scientific oversight and contact with the user community. The more recently established schemes had not developed governance structures that formally linked them to official or professional bodies. A minority had achieved accreditation or certification as EQA providers. Most of the schemes have a regional or European user base and normally accept participants from across Europe. At the operational level there was also convergence. Most schemes distributed genomic DNA samples to participants rather than the source biological material. The majority of schemes scored laboratories on the correct identification of a qualitatively defined genotype relevant to a disease specific service. Half of the schemes asked expert panels to score the clinical interpretation of genotypes against published guidelines. More recently some schemes addressed the need to challenge individual steps in the analytical process through technical EQA.

In the absence of a harmonised system for defining and recording error rates it was not possible to compare the error rates in genotyping. However, where schemes were able to quote error rates they varied from 1 – 28%. Most EQA schemes did not have formal criteria for defining single occurrences of poor performance or persistent (repeated) poor performance. However, schemes had similar, mostly informal systems to offer support, advice and education to laboratories registering errors in EQA programmes.

### Structure of EuroGentest Unit 1.



The EuroGentest Unit 1 EQA workgroup hope that the Frankfurt meeting will lead to follow-on action to help European EQA providers develop their schemes, meet the needs of their users and increase levels of participation. Further discussions may follow leading towards mutual recognition by governments, regulators and professional bodies of EQA participation as an important educational tool, a measure of laboratory proficiency and a contribution to retaining the public confidence in molecular genetic testing.

## Summary of EQA schemes

### European Molecular Genetics Quality Network (EMQN)



**Co-ordinator:** Dr Rob Elles

**Executive Administrator:** Dr Simon Patton

**Host Institution:**

National Genetics Reference Laboratory

St Mary's Hospital

Hathersage Road

Manchester M13 0JH, UK

**Tel:** +44 161 276 6741

**Fax:** +44 161 276 6606

**Web address:** [www.emqn.org](http://www.emqn.org)

#### Structure of organisation

- In 1998 the European Molecular Genetics Quality Network (EMQN) began a pilot project to offer EQA to laboratories in Europe. From January 1999 to March 2002, EMQN was supported by a European Commission grant under the Standards Measurement and Testing programme (contract number SMT4-CT98-7515). Since April 2002, the network has been supported by subscription.
- The management group comprises key experts and representatives of EU national EQA schemes UK, Finland, Italy, Germany, France, Belgium (CF), and an executive administrator.
- EMQN also has 28 national partners from EU and non-EU countries
- Participants and contacts (>850 on database, >400 registered)
- EMQN has applied for certification under ISO9001

#### EQA Schemes offered

In 2005 EMQN in collaboration with other partners offered 16 EQA schemes, the majority of these test the ability of a laboratory to provide an accurate diagnostic report for a clinical problem involving a particular gene target or service area.

#### EQA schemes offered in 2005 through EMQN

Breast Cancer (familial)	Huntington Disease
Charcot Marie Tooth	Phenylketonuria
Cystic Fibrosis (In collaboration with European Thematic Network for Cystic Fibrosis)	Prader Willi/Angelman Syndrome
Duchenne Muscular Dystrophy	Retinoblastoma
Fragile X disease	Spino Cerebellar Ataxia
Freidreich Ataxia	Y-chromosome microdeletions (In collaboration with European Academy of Andrology)
Haemochromatosis	Porphyria's (Pilot scheme)
Hereditary Non Polyposis Colon Cancer	DNA Sequencing

#### Cost of participation

Registration with EMQN costs €50 per year and participation in each EQA scheme costs €200.

A reduced fees scheme is available upon application for public sector laboratories in developing countries.

#### EQA scheme structure

##### Material

DNA (in solution) is provided to laboratories. The genotype of the material has been previously validated by at least two centres using two different methodologies. Mock clinical and referral information is provided. Usually each scheme comprises three clinical cases.

##### Distribution

Yearly concurrent distribution of all schemes (usually in September of each year).

##### Reporting and Interpretation of results

Results are reported in the laboratory's usual reporting format and since 2005 are submitted via the website to the scheme organiser. Reports are accepted in English and the scheme organiser's national language.

Reports are scored according to the following criteria:

- Accuracy and consistency
- Clear 'take home' message
- Methods referenced
- Authorised/audit trail
- Key points mentioned

Interpretation of results is evaluated in most cases, reporting policies differ between schemes, however, significant evidence of improvement in reporting has been observed.

### Performance trends

The large number of participants allows for a first overview of performance trends. Every type of error has occurred in every phase of the analytical process as well as in report writing. Errors that would have led to a misdiagnosis were classified as 'diagnostic errors' while minor flaws in report content or layout etc. were marked but regarded as 'non-diagnostic'. In the initial phase, EQA schemes mostly involved a small number of nominated expert laboratories with a high performance standard. As a general trend, error rates increased when schemes were opened to a wider group of laboratories.

Occasionally, an EQA scheme has identified systematic technical problems. As an example, in 2003 the EQA scheme for BRCA gene testing has revealed a lack of specificity of a single primer in the BRCA1 gene. Use of this primer led to erroneous results in 10 laboratories, thus inflating the overall error rate for this year. The mutation in question was sent out again in the following year and all laboratories had successfully revised their primers.

Mean error rates for all schemes since 1997

Year	Number of participants	Genotyping errors
1997	26	1.28%
1998	50	0.93%
1999	73	2.08%
2000	149	3.10%
2001	198	2.18%
2002	260	2.04%
2003	432	7.13%
2004	623	3.03%
<b>Mean</b>		<b>2.72%</b>

### Outcomes of poor performance

All laboratories receive a report detailing their individual performance in each scheme. Laboratories may challenge the marks awarded in an appeal. Laboratories that make a genotype error leading to a score of zero are contacted to discuss the cause of the problem. They are also offered technical advice and additional follow-up samples to genotype. There are no formal procedures to deal with persistent poor performance.

**UKNEQAS for molecular genetics**

**Steering Committee Chairperson:** Dr David Robinson  
**Scheme Organiser:** Sandi Deans (Zandra.Deans@nuth.nhs.uk)

**Host Institution:**  
 UKNEQAS for Molecular Genetics  
 Institute of Human Genetics  
 International Centre for Life  
 Newcastle upon Tyne  
 UK

**Web address:** <http://www.ukneqas-molgen.org.uk>

**Structure of organisation**

- The scheme organiser is advised by a steering committee of ten senior molecular geneticists from the UK, Ireland and the Netherlands, the scheme organiser and representatives of Clinical Genetics, Cytogenetics and Industry and the national advisory panel.
- Schemes are open to all public and private laboratories in the UK, the Netherlands and Ireland.

**Accreditation status**

The UKNEQAS for Molecular Genetics was granted unconditional accreditation by Clinical Pathology Accreditation in January 2001. Since which time the scheme has successfully undergone a second cycle inspection.

**EQA Schemes offered**

A rolling programme relevant to eight diseases is offered each year.  
 Diseases services covered since 1997 include:

Myotonic dystrophy	Spinal muscular atrophy
Duchenne and Becker muscular dystrophies	Mitochondrial diseases
Cystic fibrosis	Spinal cerebellar ataxias
Prader Willi and Angelman syndromes	Familial breast and ovarian cancer
Fragile X syndrome	Huntington disease
Hereditary and motor sensory neuropathy and hereditary neuropathy with liability to pressure palsies	Hereditary non-polyposis colon cancer
Familial adenomatous polyposis	Friedreich ataxia

**Cost of participation**

Each disease service specific scheme costs £250.

**EQA scheme structure****Material**

DNA (in solution), genotype validated by two centres and two methodologies. Mock clinical and referral information is provided. Usually each scheme comprises three clinical cases.

**Distribution**

One annual distribution of samples, sent on two dates six weeks apart, with one date for reports to be returned by.

**Reporting and Interpretation of results**

Full clinical reports are assessed by the steering committee and second markers, based on strict marking criteria set for each disease scheme. Reports on individual laboratory performance are returned to the participants. This often provides the stimulus for meetings to discuss best practice. However, UKNEQAS does not organise best practise meetings itself.

**Poor performance**

Poor performance is determined for each disease service specific scheme. Laboratory reports returned to the scheme organiser as part of the EQA are assigned a numerical score for genotyping and a separate score for interpretation. Criteria to determine poor performance are set by the steering group as a numerical threshold value. Laboratories scoring below this value are advised that they have performed poorly for that exercise. For UK laboratories non participation in a scheme where a service is offered is also considered as poor performance.

**Persistent Poor Performance** is defined as either poor performance for an EQA exercise in **three** out of any **six** consecutive EQA rounds or poor performance in any **two** consecutive rounds of EQA. Poor performers are asked to complete additional EQA exercises. Persistent poor performers within the UK National Health Service are referred to the UK National External Quality Assessment Panel. There is an annual review of scores. Concerns are fed back to the UK Clinical Molecular Genetics Society (CMGS).

## UK NEQAS for Blood Coagulation EQA for Molecular Genetic Testing in the Diagnosis of Familial Thrombophilia



**Scheme director:** Professor Isobel Walker

**Co-ordinator:** Ian Jennings (deputy scheme manager) [i.jennings@coageqa.org.uk](mailto:i.jennings@coageqa.org.uk)

**Host Institution:**

Rutledge Mews  
3 Southbourne Road  
Sheffield  
UK

**Tel:** +44 114 267 3300

**Fax:** +44 114 267 3309

**Web address:** [www.ukneqasbc.org](http://www.ukneqasbc.org)

### Structure of organisation

- UK NEQAS for Blood Coagulation was originally founded in 1967. The familial thrombophilia scheme started in 1996 and is administered by the UKNEQAS for Blood Coagulation EQA programme.
- The Scheme Director reports to a steering committee, and also the UK National Quality Assurance Advisory Panel.
- UK NEQAS for Blood Coagulation EQA programmes are open to all healthcare laboratories and commercial organisations, whether they are based within or outside the UK.
- On average 80 participants join the scheme many countries, including Croatia, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Portugal, South Africa, Sweden and UK.

### EQA Schemes offered

Molecular genetics testing for Factor V Leiden and Prothrombin mutations.

### Cost of participation

Details of participation fees are available from the scheme office.

### EQA scheme structure

#### Material

Citrated whole blood is distributed. Laboratories are asked to score the genotype of the samples provided.

#### Distribution

Three distributions of samples per year. A minimum of two samples are distributed per survey.

### Performance trends

Errors in diagnosis are recorded by 1-4% of centres participating in each survey. Both transcription errors and analytical errors have been observed. More than 26 000 Factor V Leiden assays are performed per year in the UK alone. Errors in diagnosis may have far reaching clinical implications emphasising the importance of EQA.

### Outcomes of poor performance

Any one incorrect diagnosis is considered as an unsatisfactory performance. Incorrect diagnosis in any two surveys over a five year period will result in a letter from the scheme director offering support.

## UK NEQAS for Blood Coagulation Haemophilia genetics



**Co-ordinator:** David J Perry (david.perry@addenbrookes.nhs.uk)

**Host Institution:**

UKNEQAS for blood coagulation  
Rutledge Mews  
3 Southbourne Road  
Sheffield  
S10 2QN  
UK

**Tel:** +44 114 267 3300

**Fax:** +44 114 267 3309

**Web address:** www.ukneqasbc.org

### Structure of organisation

A pilot scheme ran in 1998-2000 and was re-established in 2003. The scheme is part of the UK NEQAS for blood coagulation. A Special Advisory Group on Haemophilia Molecular Genetics was established in 2003 as part of UK NEQAS Blood Coagulation. Currently ten UK labs participate in the scheme, however there are plans to open the scheme to international participants.

### EQA Schemes offered

Haemophilia molecular genetics, to date the scheme has only covers Haemophilia A, but this is planned to be expanded in 2006 to include Haemophilia B and possibly Von Willebrand disease.

### Cost of participation

€370 per year.

### EQA scheme structure

#### Material

Whole blood samples or DNA from immortalised cell lines either in solution or lyophilised are distributed. Clinical information and theoretical questions are included with the samples.

#### Distribution

Two distributions of three samples per year.

### Reporting and Interpretation of results

Reporting formats are assessed relative to Clinical Molecular Genetics Society (CMGS) Guidelines ([www.cmgs.org/bpg/guidelines](http://www.cmgs.org/bpg/guidelines)). Both presentation and interpretation of reports are scored. Participants are assessed for an unambiguous report format and against an agreed standard format for mutation nomenclature, linkage/haplotype and inversion mutation nomenclature. Participants are asked to provide a full interpretation of genetic test results and are asked to take account of the clinical question supplied with the EQA case, for example the ethnic background if relevant.

### Performance trends

In 2003/2004 15 labs registered for the scheme. Only eight laboratories submitted reports, four of which were below the standard expected by assessors. Errors included: clerical errors, ambiguous reports, failure to answer the clinical question and inadequate interpretation of the data.

### Outcomes of poor performance

Poor performance is defined as a failure in any exercise. It is considered that an error in haemophilia genetic testing is potentially catastrophic. Laboratories failing an exercise are notified. At present persistent poor performance has not occurred. However, in the event of persistent poor performance, a letter from the Director of the scheme would be sent with the offer of input and support from the advisory group.

## European Concerted Action on Thrombosis (ECAT)

**Director:** Dr. Piet Meijer (p.meijer@ecat.nl)

**Host Institution:**

ECAT Foundation  
P.O. Box 2215  
2301 CE Leiden  
Netherlands

**Web address:** www.ecat.nl



**Structure of organisation**

The objective of the ECAT Foundation is to provide an international External Quality Assessment Programme (EQAP) for laboratories working in the field of haemostasis and thrombosis.

The scheme was started in 2000 and is run in collaboration with the DGKC (German Society for Clinical Chemistry), which is responsible for the distribution and quality of the samples in the molecular biology modules. The scheme has 54 participants from Europe and Australia.

**EQA Schemes offered**

Molecular Biology schemes are offered for three modules of linked tests:

Module A: Factor V, Prothrombin, Factor XIII, MTHFR, Glycoprotein IIb/IIIa, PAI-1

Module B: HFE, Apo E, Apo B100, Alpha-1-Proteinase Inhibitor, ACE I/D, CETP

Module C: UGT-1A, TPMT, CYP2D6

**Cost of participation**

€ 80 for one module; € 100 for two modules; €140 for three modules.

**EQA scheme structure**

**Material**

DNA from patients. Laboratories are asked to score the genotype of the samples provided.

**Distribution**

Two distributions are offered per year.

**Reporting and Interpretation of results**

Results are returned in a tabular reporting form and can be returned via internet, fax or postal service. The deadline is usually 4 to 5 weeks after dispatch of the samples. In order to improve the availability of reports, use of internet is strongly recommended.

**Outcomes of poor performance**

Not defined

## The EAA/EMQN EQA for microdeletions of the Y chromosome

**Scheme Organiser:** Prof Dr Manuela Simoni  
**Executive Administrator:** Dr Simon Patton (EMQN)  
**Host Institution:** see EMQN



**Web address:** [www.emqn.org](http://www.emqn.org)

### Structure of organisation

- 1997-1999 run by EAA
- From 2000 run in conjunction with EMQN
- Approx 90 participants from 24 different countries.

### EQA Schemes offered

Microdeletions of the Y chromosome

**Cost of participation:** €200 (plus €50 registration with EMQN)

### EQA scheme structure

#### Material

DNA from cell lines

#### Distribution

Once per year by EMQN

### Reporting and Interpretation of results

Reports marked by three assessors, who are molecular geneticists or specialist andrologists. Reports are marked according to the EAA/EMQN best practise guidelines that were issued in 2004 and were published in Simoni et al (2004) International Journal of Andrology, **27**: 240-249.

### Performance trends

In 2004 267 cases were analysed. Three diagnostic errors and 14 non-diagnostic errors were made. 83.3% of labs scored full marks in 2004.

### Outcomes of poor performance

All laboratories receive a report detailing their individual performance in each scheme. Laboratories may challenge the marks awarded in an appeal. Laboratories that make a genotype error leading to a score of zero are contacted to discuss the cause of the problem. They are also offered technical advice and additional follow-up samples to genotype. There are no formal procedures to deal with persistent poor performance.

## **EQUAL Multi-National External Quality Assay (EQA) programmes in Clinical Molecular Diagnostics based on Performance and Interpretation of PCR assay methods.**



**Co-ordinator:** Mario Pazzagli (equal@unifi.it)

**Host Institution:**

Department of Clinical Physiopathology  
Clinical Biochemistry Unit  
University of Florence  
Italy

**Web address:** <http://www.ec-4.org/equal>

**Structure of organisation**

- Eight partners from across Europe.
- 380 labs participated in the three EQUAL EQA schemes (200 for the Equal-qual, 120 for the Equal-quant and 60 for the Equal Seq).

**EQA Schemes offered**

EQUAL-qual monitoring of performance of qualitative PCR based assays  
EQUAL-quant monitoring performance of the 5'-nuclease quantitative PCR based assay  
EQUAL-seq monitoring DNA sequence based assays

**Cost of participation**

- There was no cost for participation, partners provided their services voluntarily, the scheme supported under the FP6 European Commission Research Programme.

**EQA scheme structure**

**Material**

DNA from patients, cell lines and plasmids. No clinical information was included with the samples. Theoretical questions were asked of the participants.

**Distribution**

The three EQA schemes were sent once to each participant, those participants who attended a training course subsequently received a second round of EQA.

**Reporting and Interpretation of results**

Reports were returned in various formats according to each scheme. Analytical performance was marked in each scheme, Interpretation was only marked in the DNA sequencing scheme.

**Performance trends**

For some evaluations performance was assessed against a standard sample. For others the consensus mean value was used. As a guideline the United States CSLI document MM14 was used.

**Outcomes of poor performance**

Result values were classified arbitrarily from excellent to poor. Participants with a poor performance were invited to participate in six training courses organized in different countries in Europe (for details see [www.ec-4.org/equal](http://www.ec-4.org/equal)).

## The Italian External Quality Assessment in Molecular Genetics (IEQA)

**Co-ordinator:** Domenica Taruscio (taruscio@iss.it)

**Contacts:** Marco Salvatore, Vincenzo Falbo

**Host Institution:**

Istituto Superiore di Sanità

viale Regina Elena, 299

00161 Rome

Italy

**Web address:** <http://www.cnmr.iss.it>



### Structure of organisation

- The scheme started in 2001 and is financially supported by the Italian Ministry of Health (two consecutive Research Projects).
- Italian public laboratories have been enrolled, covering all Italian regions; they have been grouped in 6 inter-regional Working Units (WUs).
- Decisions are discussed by a Steering Committee, which includes the WU co-ordinators (interregional and ISS units) and reference experts.
- On average, 32 laboratories participated in the scheme for cystic fibrosis; 14 for beta thalassemia; 21 for Fragile-X syndrome and 6 for adenomatous polyposis coli (APC) gene.
- According to the Italian Society of Human Genetics census performed 2002, the total number of molecular genetic (public and private) laboratories in Italy is 147. Therefore about 2/3 of labs are not involved in IEQA.

### EQA Schemes offered

Cystic fibrosis	Fragile-X syndrome
Beta thalassemia	Adenomatous polyposis coli (APC) gene.

### Cost of participation

- Participation is voluntary and free

### EQA scheme structure

#### Material

DNA samples are derived from patients and cell lines. Clinical information is included with samples.

#### Distribution

One distribution of six validated DNA samples per year per disease.

### Reporting and Interpretation of results

Laboratories submit the results of the analysis including, raw data, interpretation of results and written reports. There are National Guidelines on genetic testing; in addition, criteria have been established by the Steering group of the IEQA, who evaluate the reports. Each laboratory receives comments about the quality of their results (including raw data, interpretation of results and written reports).

### Performance trends

Average genotyping errors (%)

	2001	2002	2003	2004
Cystic Fibrosis	11	10	3	5
Beta Thalassemia	n/a	n/a	6	n/a
Adenomatous polyposis coli (APC)	n/a	28	14	28
Fragile X	9	14	28	n/a

### Outcomes of poor performance

In case of poor performance suggestions are sent to laboratories to improve the analysis. An annual meeting of participating laboratories is organised to illustrate and discuss results. During the first two EQA trials lack of accuracy in many reports was detected, therefore in 2003 a standard report form for molecular genetic testing was sent to laboratories.

**BVDH (Professional Association of German Human Geneticists).**

**Co-ordinator:** Prof. Dr. Clemens R. Müller Reible

**Executive Administrator:** Christine Scholz

**Host Institution:**

BVDH Berufsverband Deutscher Humangenetiker e.V.G

Geschäftsstelle

Inselkammerstr. 4

82008 München-Unterhaching, Germany.

Tel.: +49- 89 /55 02 78-55

Fax: +49- 89 /55 02 78-56

**Web address:** <http://www.bvdh.de/> or <http://www.hgqn.org/> (EQA scheme database)

**Structure of organisation**

A steering group decides on the structure and on the introduction of new schemes. The participant registers at the website. Scheme providers validate and circulate the EQA samples and questions and evaluate reports. The BVDH office handles finances, the archive and statistics. There were 270 participants in 2004.

**EQA schemes offered in 2005 through BVDH**

Adrenogenital syndrome (AGS)	HNPCC
Cystic fibrosis (CF) in collaboration with CF-Network	Huntington disease (HD)
Charcot-Marie-Tooth (CMT) in collaboration with EMQN	Multiple endocrine neoplasias (MEN)
Duchenne muscular dystrophy	Myotonic dystrophy, type 1 (DM1)
Fragile X syndrome (FRAX)	Prader-Willi-/Angelman syndrome (PWAS)
Friedreich ataxia (FRDA)	Spino-cerebellar ataxias (SCA)
Haemochromatosis (HFE)	

**Cost of participation**

40 € per scheme for members of BVDH and 60 € for non-members.

**EQA scheme structure**

- Disease-oriented (the most prevalent diseases)
- Method-oriented (the most frequently used methods)
- Analytical performance (genotype)
- Biological and clinical interpretation (written report)
- Formal aspects (turn-around time, layout etc.)
- Annual meetings of scheme participants to discuss results and problems

**Material**

DNA (in solution), genotype validated by two centres and two methodologies.

Mock clinical and referral information is provided.

**Distribution**

Once a year. Usually each scheme comprises three cases.

**Reporting and Interpretation of results**

Results are reported in the laboratory's usual reporting format and are returned to the scheme organiser.

Reports are scored according to the following criteria:

- Accuracy and consistency
- Clear 'take home' message
- Methods referenced
- Authorised/audit trail

Interpretation of results is evaluated in all cases, reporting policies differ between schemes, however, significant evidence of improvement in reporting has been observed.

**Outcomes of poor performance**

All laboratories receive a report detailing their performance in each scheme. Laboratories may appeal against the marks awarded. Laboratories that made genotyping errors are offered technical advice. There are no formal procedures to deal with consistent poor performance.

**DGKL (German Society for Clinical Chemistry and Laboratory Medicine), RfB (Reference Institute for Bioanalytics).**



**Co-ordinator:** Prof. Dr. Michael Neumaier (Mannheim)

**Executive Administrator:** Dr. Rolf Kruse (RfB)

**Host Institution:**

Referenzinstitut für Bioanalytik (RfB)

Im Mühlenbach 52a

53127 Bonn

Germany

**Tel:** +49-228-21 50 25

**Fax:** +49-228-21 15 29

**Web address:** <http://www.dgkl-rfb.de/>

**Structure of organisation**

The Reference Institute for Bioanalytics (RfB) is a reference institution acting as notified body by appointment of the German Chamber of Physicians (Bundesärztekammer) according to the Guidelines for Quality Assessment in Clinical Chemistry and Laboratory Medicine (RiliBÄK). The body of the RfB is the German Society for Clinical Chemistry and Laboratory Medicine (Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DKGL). The RfB is connected to international standardisation activities and, in particular, is represented by members of its scientific committee in numerous national and international committees (IFCC, DIN/CEN/ISO, <http://www.e-c4.org/>).

**EQA schemes offered in 2006 through DGKL and RfB**

Factor V	Set A
Factor II (Prothrombin 20210)	
Factor XIII	
MTHFR	
Glycoprotein II b III a (GPIIbIIIa)	
PAI 1 (Plasminogen-Activator Inhibitor 1)	
ApoE	Set B
ApoB100	
Alpha1-AT ( $\alpha$ 1-Proteinase-Inhibitor)	
ACE I/D	
CETP (Cholesterol Ester Transfer Protein)	
HFE	
TPMT (Thiopurine-S-Methyltransferase)	Set C
CYP2D6 (Cytochrome p450 2D6)	
UGT-1A	

**Cost of participation**

1 set €40.00, 2 sets €55.00, 3 sets €70.00

**EQA scheme structure**

**Material**

DNA (in solution). There is no clinical information provided with the samples.

**Distribution**

Two schemes are distributed each year.

**Reporting and Interpretation of results**

Participants are asked to provide genotype information. Survey results are either transmitted electronically via the DGKL website or as hardcopy to the RfB.

There are no marks/points given to evaluate the participants' performance. Participant's performance is documented in evaluation forms, and also by a certificate of participation. Results are commented on by the coordinator.

**Outcomes of poor performance**

Poor performance is addressed by a comment in the evaluation. Training courses are offered. In some cases written communication with the participant to help troubleshooting takes place. Persistent poor performance has not been observed. Approximately 92-95 % of the reports are free from genotyping errors.



## INSTAND reg. ass. (Institute for Standardization and Documentation in the Medical Laboratory).

**Co-ordinators:** Dr. Ralf-Rüdiger Flörke, Prof. Dr. Grosse-Wilde,  
Dr. F. Heinemann, Dr. G. Kappert, Prof. Dr. Friedrich Maly

**Host Institution:**

Institution für Standardisierung und Dokumentation im medizinischen Laboratorium e.V. (INSTAND)

Ubier Straße 20

40223 Düsseldorf

Germany

**Tel:** +49 211-33 82 621 / -251

**Fax:** +49 221-33 82 603

**Web address:** <http://www.instand-ev.de/>

### Structure of organisation

There are two steering groups, an inner steering group comprising one or two scheme organisers and a secondary steering group consisting of all INSTAND scheme organisers. These groups discuss new schemes and general issues.

### EQA schemes offered in 2006 through INSTAND

<b>Molecular genetics I</b> (2 samples each, 0.5 ml human blood - 25 € /Survey)	
Factor V-Leiden-Mutation	
Prothrombin 20210	
732 MTHFR C677T	
<b>Molecular genetics II</b> (cDNA, 3 samples each - 16.00 € /Survey)	
Factor V-Leiden-Mutation	Set 1 (total 60 € for each EQA survey)
Fibrinogen receptor HPA 1a/1b	
Collagen receptor C807T	
MTHFR C677T	
PAI-1 4G/5G	
Prothrombin 20210	
alpha1-antitrypsin (PiM, PiS, PiZ)	Set 2 (total 60 € for each EQA survey)
HFE (H63D, C282Y)	
Apolipoprotein E (E2, E3, E4)	
Copper binding protein: ATP7B (H1069Q)	
UDP-glucuronyltransferase1 (TATA-box)	
<b>Molecular genetics III – V</b> (3 sets of 3 samples each, lyophilized with 500ng DNA per sample - Each set 60€ /Survey; 40€ per additional set)	
F XIII Val34Leu	Set 1
GPIA C807T	
HPA-1 T393C	
HPA-5 G1648A	
MTHFR A1298C	
HFE C282Y	Set 2
HFE H63D	
HFE S65C	
ApoE E2 E3 E4	
ApoB 100	
a1-AT PiS	
a1-AT PiZ	
CFTR Delta F508	Set 3
LCT T-13910C	
UGT1A6 A541G	
BCHE atypical variation	
BCHE K variation	
GH-R del exon 3	

**Cost of participation**

Participation in EQA schemes costs between 16 €/survey and 60 € /set of 5-7 diseases.

**EQA scheme structure****Material**

Molecular genetics I: human blood; molecular genetics II: DNA (in solution), isolated from leukocytes, Molecular genetics III-IV: DNA (freeze-dried), isolated from cell culture material. No clinical information is provided with the samples.

**Distribution**

Distribution between one and three schemes per year.

**Reporting and Interpretation of results**

Genotype only is requested and participants report in a tabular reporting form. Reports are scored according to defined criteria.

**Performance trends (only for Molecular Genetics I)**

	<b>2004</b>	<b>2005</b>
<b>Average genotype errors</b>	11	21
<b>Average genotype error (%)</b>	1.9	3.0

**Outcomes of poor performance**

In cases of poor performance the participant does not receive a certificate from INSTAND. There are no formal procedures to deal with persistent poor performance as this situation has not been observed to date.

## Cystic Fibrosis Network

**Co-ordinator:** Prof. Dr. Els Dequeker

**Host Institution:**

University of Leuven - Department of Human Genetics  
Herestraat 49, Box 602  
B-3000 Leuven  
Belgium

**Tel:** +32 16 34 58 81

**Fax:** +32 16 34 59 97

**Web address:** <http://www.cfnetwork.be/>



### Structure of organisation

Since 1996, annual external quality assessment schemes have been organised under the heading of the CF network. The European Cystic Fibrosis Network was a successful project under the 4<sup>th</sup> and 5<sup>th</sup> framework programmes from the European Union. Since 2004 the CF network has been supported by companies. The network also works in close collaboration with BVDH, the CF diagnostic working group in France, EMQN and Unit 1 of EuroGentest. More than 200 laboratories participated in this scheme from 34 countries, including US and Australia.

### Cost of participation

Participation in the scheme is free, however, since 2005 shipping costs are charged to participants: 40 € for EU countries, 75 € for non EU countries. No shipping costs are charged to participants in developing countries.

### EQA scheme structure

**Material**

DNA in solution (6 samples/scheme) with clinical information.

**Distribution**

Distribution of one scheme per year.

### Reporting and Interpretation of results

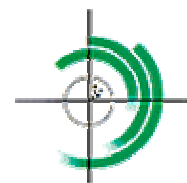
Written reports and raw data are submitted by regular mail or electronic and genotype results and information on the screened mutation and used technologies (methods) are recorded on an on-line datasheet. Marks are awarded for genotype results. Raw data and interpretation of the written report are also assessed.

### Outcomes of poor performance

Each participant receives a general report summarising the results from all laboratories in addition to an individual report. In the event of poor performance an individual report is issued commenting on the errors made. If persistent poor performance is observed the participant is reminded in the individual report that errors have occurred previously. A certificate is given to the laboratories without genotype mistakes and no interpretation errors.

## CSCQ (Swiss Centre for Quality Control)

**Co-ordinator:** Pierre-Alain Morandi  
**Executive Administrator:** Dr André Deom  
**Host Institution:**  
 Schweizerisches Zentrum für Qualitätskontrolle (CSCQ)  
 Chemin du Petite-Bel-Air 2  
 CH-1225 Chêne-Bourg  
 Switzerland  
**Tel:** +41 (22) 305 52 36  
**Fax:** +41 (22) 305 52 38  
**Web address:** <http://www.cscq.ch/index.htm>



### Structure of organisation

CSCQ is a non-profit organisation which offers external proficiency testing programmes to Swiss and non-Swiss medical laboratories. The institution is accredited for all surveys (ISO 17020, ISO guide 43, ILAC G13) and certified according to ISO 9001. The CSCQ is recognised by the Swiss authorities. The Swiss Society of Medical Genetics is a member of the CSCQ committee.

### EQA Schemes offered

**Table 1. EQA schemes offered in 2006 through CSCQ**

In co-operation with QUALAB (Swiss commission for quality control in the medical laboratory).	
Haemochromatosis	Programme BC
Factor II	Programme HC
Factor V	

### Cost of participation

Participation in EQA schemes costs between 90 € (programme BC) and 147 € (programme HC). Participants are obliged to become a member of CSCQ and have to pay a membership fee that is graduated according to frequency of participation per year and European and non-European members.

### EQA scheme structure

#### Material

DNA (in solution), no clinical information is provided with the samples.

#### Distribution

Between two and three schemes per year.

### Reporting and Interpretation of results

Laboratories are requested to provide genotype information. Participants submit results electronically via the CSCQ website. There are no marks/points given to evaluate the participants' performance.

### Outcomes of poor performance

Participants receive a report that includes an individual comment concerning the errors. In the event of poor performance help is offered and suggestions for improvement are made. Persistent poor performance has not been observed to date.

## ÖQUASTA (Austrian Society of Quality Assurance and Standardisation of medical-diagnostic tests)



**Co-ordinator:** Prof. Dr. Christine Mannhalter

**Executive Administrator:** Prof. Dr. Matthias M. Müller

**Host Institution:**

Österreichische Gesellschaft für Qualitätssicherung und Standardisierung  
medizinisch-diagnostischer Untersuchungen (ÖQUASTA)

Hörgasse 18

A-1090 Vienna

Austria

**Web address:** <http://62.99.208.26/oequasta/default.htm>

### Structure of organisation

ÖQUASTA is a registered society accessible to societies and companies.

### EQA schemes offered in 2005 through ÖQUASTA

In cooperation with DGKL, Germany	
Factor V	Set A
Factor II (Prothrombin 20210)	
MTHFR	
Factor XIII	
Glycoprotein II b III a	
HFE	Set B
Apo E	
Apo B 100	
$\alpha$ -1-Proteinase Inhibitor	
ACE I/D	
UGT-1 A	Set C
TPMT (Thiopurin-S-Methyltransferase)	
CYP 2D6 (Cytochrom p450 2D6)	
In cooperation with ECAT, The Netherlands	
Antithrombin (activity and antigen)	Thrombophilia Module
Protein C (activity and Antigen)	
Protein S activity	
Protein S Antigen (whole and free)	
APC-Resistance	
Protein C Pathway Test	
Lupus Anticoagulants	
D-Dimer	
Factor VIII	Clotting – Factors module I
Factor IX	
Factor XI	
Factor XII	
Factor II	Clotting – Factors module II
Factor V	
Factor VII	
Factor X	
Antigen	Von Willebrand Factor module
RiCoF	
Collagen Binding	
Multimers	
Homocysteine	

### Cost of participation

Participation in EQA schemes costs between 16 €/survey and 60 € /set of 5-7 diseases.

## **EQA scheme structure**

### **Material**

DNA (in solution). No clinical information is provided with the samples.

### **Distribution**

Distribution of one to four schemes per year.

### **Reporting and Interpretation of results**

Only the genotyping result is requested. Reports are submitted electronically via the ÖQUASTA website. There are no marks/points awarded to evaluate the participants' performance.

### **Outcomes of poor performance**

Poor performance is communicated to the participant, who does not receive a certificate from ÖQUASTA. There are no regulations defining the consequences of poor performance.

## Discussion

The main topics discussed during the meeting included: the structure of different EQA schemes, in particular the type of material distributed; the format of participants' reports and procedures and consequences for laboratories that perform poorly in EQA schemes.

### Structure of EQA schemes

There was a surprising degree of similarity in scheme structure. The majority of schemes distribute genomic DNA samples and request the determination of a specific sequence variant (genotype). Results are returned to the scheme organiser, who performs a horizontal comparison, which is communicated to the participants. A small number of schemes ask additional theoretical questions.

However, schemes differ in their requests for written reports and interpretation of results. As a general trend, schemes for highly penetrant monogenic disorders ask participants to include a written clinical genetic interpretation with the genotype results, whereas, schemes for genetic variants of lower predictive value tend to ask for the genotype alone. The frequency of distributions of each EQA scheme varies from one to four distributions per year as specified in the individual scheme summaries above.

### EQA materials

Most of the EQA scheme providers represented distribute DNA samples from patients or cell lines. There was limited experience with the shipping of blood samples with the exception of the UKNEQAS Thrombophilia genetics scheme. This is due to the administration required to address the biosafety issues associated with unprocessed biological samples. However, due to recurrent problems laboratories experience with the purity and quantity of DNA samples one scheme provider decided to distribute additional blood samples.

The participants agreed on the fact that the origin of the DNA (blood, plasmids, cells, amplified genomic DNA) and the method of DNA extraction have a significant impact on all further steps of the analysis. It was recognised that there is currently no reference method for DNA extraction/purification. A high demand for standardisation of DNA preparation was expressed, although this was considered to be a rather difficult task because of the many different techniques and commercial kits in use. Especially in the case of commercial kits the quality of the DNA is usually not assessed. Furthermore, it was estimated that only 10-20% of the participant laboratories measure the quantity of the DNA and this was generally associated with certain techniques, such as Southern blotting.

There was general agreement that significant attention should be given to the purification and validation of DNA samples for EQA purposes. The question of better defining the quality of the DNA that is sent out in EQA schemes was discussed. One new approach to address these problems could be the use of synthetic blood (Maine Molecular Quality Controls Inc, Scarborough, Maine, USA), which is being evaluated by the CF-Network. The ÖQUASTA scheme also has experience of distributing paraffin embedded samples.

### Minimum requirements for reporting

The format of the reports returned to the scheme providers differs greatly. In some schemes, only the analytical performance (the genotype) is checked, while other schemes request a written report that is evaluated against several criteria. The general content of the report has been adopted from guidelines that specify the requirements for a medical report (e.g. ISO 15189). In addition, some items specific to genetics are requested, e.g. place of birth, ethnic origin, reason for testing, list of mutations tested, method, mutation detection rate, advice on genetic counselling and/or prenatal testing. It was agreed that written reports should in all cases reflect the consequences for the patient and if relevant the need for further tests should be commented upon.

The EQA scheme organisers represented agreed that existing guidelines regarding the content and format of reports should be disseminated more widely amongst service laboratories. In some countries it is a legal requirement that reports should only be sent to the referring physician and not to the patient. (However, this is legally correct and widespread practice in other countries). This is in contrast to some reporting guidelines which are based on an assumption that reports should be written such that the core message could be understood by the non expert.

### **Poor performance**

It was shared experience that every type of error can occur in every step of the whole analytical process. Although, in some schemes, poor performance was mostly observed in the pre- and post-analytical phases. Furthermore, it was noted that poor performance depends on the quality of the EQA sample and is independent of the analytical methods used. When analysing historical data no scheme provider could identify a tendency for mistakes always to be made by the same laboratories. The majority of mistakes in the reports are clerical errors, for example, incorrect patient name, sample number or other incorrect spelling. It was evident, however, that laboratories had learnt from previous EQA exercises and changed the structure of their reports or added essential items to it.

Scoring systems and the marking criteria differ between schemes because they are mostly decided upon internally by the scheme providers. Guidelines that are used as a basis for scoring of reports were from the UK Clinical Molecular Genetics Society (CMGS), the Clinical Laboratory Standards Institute and the Swiss Society of Molecular Genetics.

### **Reactions to poor performance and consequences for the laboratories**

The scheme organiser's responses to laboratories that perform poorly include: Comments in evaluation; Offering training courses; or in the case of UKNEQAS reporting to a regulatory body. Not surprisingly, the consequences for the laboratories are different according to whether participation in EQA is compulsory in that country or not. In some countries there are no consequences for poor performance in EQA, in others no certificate is issued by the scheme provider. Ultimately the accreditation status of a laboratory may be affected as EQA performance is assessed as part of accreditation.

### **Disease specific vs. technical EQA schemes**

With the steadily growing number of medically relevant genes and mutations, the number of disease/gene-specific EQA schemes cannot be increased ad infinitum. At least two EQA providers have realised the necessity to complement disease specific EQA schemes with schemes addressing widely used analytical techniques. EQUAL and EMQN both have run pilot schemes for DNA sequencing. In both schemes, participants have to produce a sequence from a template using primers provided by the scheme organiser. Sequence results were compared using semi-automated methods. The quality of sequencing (as defined by base calling and read length) was generally very high, but a significant number of labs produced sequences of insufficient quality.

EQUAL also carried out a trial for DNA extraction and PCR amplification. Participants were provided with blood samples, DNA samples and primers and asked to perform a specific PCR amplification. Extracted DNA and PCR products had to be returned to the scheme organiser and were horizontally compared in the organiser's laboratory. Again, quality of the DNA prepared and specificity of the PCR products were generally high with a significant number of exceptions.

The issue was raised that technical EQA for rare diseases rather than disease-specific EQA can mean that labs can be technically sound but not so proficient diagnostically. However, EQA can never be provided for all diseases. EMQN concentrates on providing a service for predominantly single gene disorders, where the patient is at significant risk of disease, these therefore tend to be more common diseases.

## Conclusions

This first meeting of its kind was successful in bringing together EQA scheme organisers. There was a productive sharing of information and discussion, participants expressed their willingness to continue these discussions at future meetings.

Opportunities for collaboration were explored, in particular discussions were initiated between EMQN (Drs R. Elles and S. Patton) and EQUAL (Dr M. Neumaier) to explore merger of their sequencing schemes, in order to reach a larger number of participants and avoid competition. The details of this future collaboration are in the process of being finalised.

There was a general agreement that the practicability of technical EQA schemes should be explored more systematically and extended to other relevant methods (e.g. commutability of genomic DNA preparations). This is a topic that work package 1.3 of EuroGentest plan to explore in the future.

In addition EuroGentest work package 1.3 (EQA for Molecular Genetic Testing) aims to produce a template document setting out key recommendations for Molecular Genetic EQA schemes in Spring 2006. This template document will be opened to discussion and will cover aspects of EQA schemes, including: documentation, sample collection and validation, formulation of EQA questions, marking of EQA schemes, selection of assessors/scheme organisers, organisation of assessment meetings, documentation of assessments and scheme reports.

## Glossary of terms

BVDH	Berufsverband Deutscher Humangenetiker (Professional Association of German Human Geneticists)
CEN	European Committee for Standardisation
CF-Network	Cystic Fibrosis Network
CMGS	UK Clinical Molecular Genetics Society
CSCQ	Swiss Centre for Quality Control
CSLI	Clinical and Laboratory Standards Institute
DGKL	German Society for Clinical Chemistry and Laboratory Medicine
DIN	German Institute for standardisation
EAA	European Academy of Andrology
ECAT	European Concerted Action on Thrombosis
EMQN	European Molecular Genetics Quality Network
EQUAL	Multi-National External Quality Assay (EQA) Programmes in Clinical Molecular Diagnostics
EQAP	External Quality Assessment Programme
EUROGENTEST	European Union Network of Excellence key words: genetic testing, quality, harmonisation.
External Quality Assessment (EQA)	Determination of laboratory testing performance by means of inter-laboratory comparisons.
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IEQA	Italian External Quality Assessment in Molecular Genetics
ILAC	International Laboratory Accreditation Cooperation
INSTAND	Institute for Standardization and Documentation in the Medical Laboratory
ISO	International Organisation for Standardisation
ISO 15189	Standard relating to the particular requirements for quality and competence in medical laboratories
ISO 9000	Standard relating to the provision of goods and services.
ISS	Instituto Superiore di sanità
ÖQUASTA	Austrian association for Quality Assurance and Standardization of medical-diagnostic tests
QM	Quality Management
QUALAB	Swiss Commission for Quality Control in the Medical Laboratory

## References

Ibarreta, D. Bock, A-K., Klein, C., Rodriguez-Cerezo E. (2003) Towards quality assurance and harmonisation of genetic testing services in the EU. European Commission Joint Research Centre (DG JRC) Report EUR 20977 EN. [www.jrc.es](http://www.jrc.es).

## Molecular Genetic Testing - External Quality Assessment Scheme provision (2005)

### I) Constitutional mutations

Disorder	Organisation	Contact Point
1. ACE (Angiotensin I Converting Enzyme)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
2. alpha-1-Antitrypsin (PiM, PiS, PiZ); (RV Nr.743)	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf
3. alpha-1-Proteinase-Inhibitor (M/S/Z)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
4. Apolipoprotein B100 (ApoB100)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
5. Apolipoprotein E (ApoE): E2/E3/E4	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
6. Apolipoprotein E (E2, E3, E4); (RV Nr.744)	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf
7. Azoospermia (AZF/DAZ)	EAA <sup>9</sup> /EMQN <sup>10</sup>	M. Simoni, Münster
8. Breast/ovarian cancer familial (BRCA1, BRCA2)	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	C.R. Müller-Reible, Würzburg
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
9. CETP (Cholesterylester transport protein)	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
10. Cyp2D6 (Cytochrom p450 2D6 Enzyme)	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
11. Charcot-Marie-Tooth Disease (CMT)	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	B. Rautenstrauß, Erlangen
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	ETNCF <sup>9</sup> /EMQN <sup>10</sup>	E. Dequeker, Leuven
12. Cystic Fibrosis (CF)	BVDH <sup>1</sup>	M. Stuhmann-Spangenberg, Hannover
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	IEQA-ISS <sup>19</sup>	D. Taruscio, Rome
	EMQN <sup>10</sup>	S. Patton, Manchester
13. Duchenne Muscular Dystrophy <sup>14</sup> (DMD/BMD)	BVDH <sup>1</sup>	C.R. Müller-Reible, G. Meng, Würzburg
	EMQN <sup>10</sup>	S. Patton, Manchester

14. Factor V Leiden	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	RCPA QAP Pty Ltd. <sup>8</sup>	M. Hertzberg, D. McDonald, Australia
	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf
	UKNEQAS <sup>17</sup>	F. Preston, Sheffield
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
15. Factor XIII	QualiCont Kht. <sup>20</sup>	L. Dux, Szeged
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
16. Familial Adenomatous polyposis colon cancer (APC)	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	IEQA-ISS <sup>19</sup>	D. Taruscio, Rome
17. Fragile-X-Syndrome (FRAX)	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	P. Steinbach, Ulm
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
18. Friedreich Ataxia <sup>14</sup> (FRDA)	IEQA-ISS <sup>19</sup>	D. Taruscio, Rome
	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	Ch. Zühlke, Lübeck
19. GP IIIa (Glycoprotein IIIa)	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
20. Hereditary Haemochromatosis (HFE)	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	H. Gabriel, Osnabrück
	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
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	INSTAND <sup>11</sup>	J. Bertrams, Essen
	RCPA QAP Pty Ltd. <sup>8</sup>	M. Hertzberg, D. McDonald, Australia
	UKNEQAS <sup>18</sup>	C. Darke, Pontyclun
	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
	QualiCont Kht. <sup>20</sup>	L. Dux, Szeged
	21. Hereditary non-polyposis coli (HNPCC)	EMQN <sup>10</sup>
BVDH <sup>1</sup>		W. Friedl, Bonn
UKNEQAS <sup>13, 14</sup>		S. Ramsden, Manchester
22. Huntington Disease (HD)	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	F. A. Laccone, Göttingen
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
23. Mitochondrial disorders	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
24. Methylenetetrahydrofolate Reductase (MTHFR)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
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	QualiCont Kht. <sup>20</sup>	L. Dux, Szeged
25. Morbus Wilson: Cu-Transporter-Protein ATP7B (H1069Q); (RV Nr.745)	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf
26. Myotonic Dystrophy (DM)	BVDH <sup>1</sup>	M.C. Koch, Marburg

We would like to acknowledge the Austrian Government <http://www.gentechnik.gv.at/> which originally published the base list in 2002. This list has now been substantially updated for 2005 and is presented in this document.

	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
27. Phenylketonuria (PKU)	EMQN <sup>10</sup>	S. Patton, Manchester
28. PAI-1 (Plasminogen activator inhibitor)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
29. Prader-Willi/Angelman syndromes (PWAS)	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	B. Horsthemke, Essen
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
30. Prothrombin 20210	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
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	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf
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	LABQUALITY <sup>16</sup>	M. Keinanen, Helsinki
	QualiCont Kht. <sup>20</sup>	L. Dux, Szeged
	UKNEQAS <sup>17</sup>	F. Preston, Sheffield
31. Retinoblastoma (RB)	EMQN <sup>10</sup>	S. Patton, Manchester
32. Spinal Muscular Atrophy (SMA)	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
33. Spinocerebellar Ataxia (SCA's)	EMQN <sup>10</sup>	S. Patton, Manchester
	BVDH <sup>1</sup>	J.T. Epplen, M. Gencik, Bochum
	UKNEQAS <sup>13, 14</sup>	S. Ramsden, Manchester
34. $\delta$ / $\beta$ -Thalassaemia	BVDH <sup>1</sup>	B. Dworniczak, Münster
	RCPA QAP Pty Ltd. <sup>8</sup>	M. Hertzberg, D. McDonald, Australia
	IEQA-ISS <sup>19</sup>	D. Taruscio, Rome
35. PPMT (Thiopurin S-Methyltransferase)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
36. UDP-Glucuronosyltransferase 1 (UGT-1A)	DGKL <sup>2</sup> (RfB) <sup>12</sup>	M. Neumaier, Mannheim
	ÖQUASTA <sup>4</sup> (in collaboration with DGKL)	W.-M. Halbmayer, Ch. Mannhalter, Wien
	ECAT Fdn. <sup>7</sup> (in collaboration with DGKL)	P. Meijer, Leiden
37. UDP-Glucuronosyltransferase 1 (TATA-Box); (RV Nr.742)	INSTAND <sup>11</sup>	R.-R. Flörke, Düsseldorf

## II. Methodological EQA

Method	Organisation	Contact point
1. DNA sequencing	EMQN <sup>10</sup>	S. Patton, Manchester
	EQUAL <sup>15</sup>	M. Neumaier, Mannheim, M. Pazzagli, Florence
2. Quantitative PCR	EQUAL <sup>15</sup>	S. Ramsden, Manchester, M. Pazzagli, Florence
3. Qualitative PCR	EQUAL <sup>15</sup>	M. Pazzagli, Florence
	QualiCont Kht. <sup>20</sup>	L. Dux, Szeged

<sup>1</sup> Berufsverband Deutscher Humangenetiker e.V. (BVDH), Deutschland

<sup>2</sup> The German Society for Clinical Chemistry and Laboratory Medicine (DGKL) is the controlling body of the Reference Institute for Bioanalytics (RfB)

<sup>3</sup> Arbeitsgruppe für Qualitätssicherung in der Molekularpathologie der Österreichischen Gesellschaft für Pathologie

<sup>4</sup> Österreichische Gesellschaft für Qualitätssicherung und Standardisierung medizinisch-diagnostischer Untersuchungen

<sup>5</sup> European Academy of Andrology

<sup>7</sup> European concerted Action on Thrombosis (=ECAT) Foundation: International Thrombophilia External Quality Assessment Scheme

<sup>8</sup> Royal College of Pathologists of Australasia (=RCPA) Quality Assurance Programs Pty. Limited, Australia: RCPA Haematology QAP Molecular Diagnostics

<sup>9</sup> European Thematic Network for Cystic Fibrosis der EC i. R. d. 5.Rahmenprogrammes (CF European Network)= European Community Concerted Action for Cystic Fibrosis (ECCACF)

<sup>10</sup> European Molecular Genetics Quality Network

<sup>11</sup> Institut für Standardisierung und Dokumentation im medizinischen Laboratorium e.V.

<sup>12</sup> Reference Institute for Bioanalytics (RfB) of the DGKL

<sup>13</sup> United Kingdom National External Quality Assessment Scheme for Molecular Genetics

<sup>14</sup> Participation restricted to laboratories from The United Kingdom, Ireland and The Netherlands

<sup>15</sup> Multi-National External Quality Assay (EQA) Programmes in Clinical Molecular Diagnostics

<sup>16</sup> Labquality Inc.

<sup>17</sup> United Kingdom National External Quality Assessment Scheme for Haematology

<sup>18</sup> United Kingdom National External Quality Assessment Scheme for Immunology

<sup>19</sup> Italian External Quality Assurance - Istituto Superiore di Sanità

<sup>20</sup> Hungarian External Quality Assessment organisers (QualiCont Kht.)

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## Appendix 2

### A repository and database of EQA materials

Dr Simon Patton (EMQN, Manchester, UK)

A database of EQA materials has been set up by EMQN and UKNEQAS. The database currently comprises 168 Cell lines from 17 diseases. Information including DNA preparation (Year, scheme etc.) and validation data is recorded. The materials have been submitted either directly or from cell line repositories (Corriell, ECACC). Materials submitted directly to EMQN have informed consent information with them. Information on consent for all other materials is held by the cell repositories from which they have been purchased.

#### Availability of materials

Materials in the form of DNA are provided to EMQN and UKNEQAS schemes at cost. For all other schemes, DNA will be provided at cost only from cell lines established in Manchester. For all other cell lines, we will provide information on the cell line including data on validation and a reference to the cell line in the relevant repository. However, the requester will have to purchase the cell line directly from the relevant repository.

Table showing number of cell lines for each disease.

Angelman syndrome	12	Breast cancer (BRCA1)	15
Breast cancer (BRCA1)	10	Charcot-Marie Tooth	5
Costello syndrome	1	Cystic Fibrosis	2
DRPLA	1	Duchenne Muscular Dystrophy	14
Fragile-X syndrome	14	Friedreich ataxia	8
Haemochromatosis	7	HNPCC	9
Huntington disease	16	Myotonic dystrophy	6
Prader-willi syndrome	10	Retinoblastoma	14
Y-chromosome microdeletions	24		

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