

**WELCOME** to the latest "bumper" issue of the newsletter which reflects the increased amount of activity as EuroGentest moves to the end of its second year. I was particularly pleased with the success of the first open accreditation workshop, along with the report on education material, both featured here. Also the project in general continues to gain recognition – for example, we gave a series of presentations in Brisbane at the Human Genetics Conference and were also invited to attend the inaugural meeting of the Human Variome Project which aims to follow on from the Human Genome Project. Next comes our own second annual meeting in Leuven in December where the focus will be on further strengthening our activities.

Jean-Jacques Cassiman

## EUROGENTEST NEWSLETTER 5/2006

# First open accreditation workshops a major success



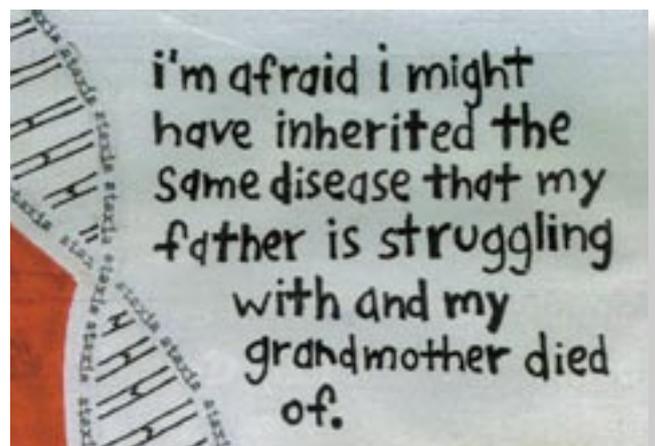
The first open workshop attracted participants from all over Europe.

Practical hands on advice about how to successfully gain and maintain accreditation was the theme of the first workshop open to all genetic testing laboratories held recently in Leuven. Organised by Els Dequeker, Mike Morris and the Unit 1 team, the workshop featured expert-led interactive sessions in small groups. Discussions covered every aspect on quality management and accreditation: ISO and related national standards, document management, non-conformities, auditing, training and IT support. Participants included lab directors, scientists, technicians and quality managers from across Europe. Both organisers and most importantly participants judged the workshop a great success. Here we report two different lab's points of view – the non-accredited with Kadri Raudsepp from Tartu in Estonia and the already accredited with Victoria Aldridge and Anthony Young from London. The next workshop is already planned for 12th-13th April 2007 in Athens. If you are interested register via <http://www.eurogentest.org/unit1/workshops.xhtml>.

### What is your laboratory and what work do you do?

**Victoria & Tony** The Regional Molecular Genetics Laboratory was one of the first such diagnostic laboratories established in the UK (1985). It now has a staff of approximately 26, including state registered clinical scientists, genetic technologists and administrative support staff. The staff works closely with clinical colleagues and other healthcare scientists in the pathology directorate and research staff in the Institute of Child Health. The Molecular Genetics Laboratory along with Clinical Genetics and Cytogenetics, forms a strategic Genetics Unit within Great Ormond Street Hospital and also constitutes the North East Thames Regional Genetics Service that serves a population of approximately 5 million.

The molecular genetics laboratory provides an in-house diagnostic service for a number of single gene disorders including Fragile X syndrome, Cystic fibrosis, Angelman and Prader-Willi syndromes and connexin 26 related deafness. It also provides both a national and international service for craniofacial, metabolic and immune deficiency disorders. In addition the laboratory provides a DNA banking service and can forward samples to other centres for approved requests providing funding is available.



A great deal of work remains to be done on improving public information on genetic diseases as the report on page 4 highlights



► Kadri Tartu University Clinics is a leading center for hospitals in Estonia. Initially all the different hospitals had their own laboratories, which worked without any coordination. Ten years ago all these laboratories were combined and United Laboratories of Tartu University Clinics was formed. There are about 10 departments and many different labs, but they are all working under one management and the same rules. Economically it was a great success, which has enabled us to improve dramatically our technical resources and the quality of our services.

I am responsible for one little lab in the Department of Immunoanalyses. My lab is simply called the PCR lab, since we are dealing with many different analyses: qualitative and quantitative analyses of HIV, hepatitis viruses, CMV, EBV, HLA typing, leukemic chromosomal translocations and some more.

## What is the background to and reason for your seeking accreditation?

V & T The laboratory achieved accreditation with Clinical Pathology Accreditation (UK) Ltd in July 2003 and we are currently working towards accreditation review later next year. Accreditation status has become an important part of any laboratory within the UK, particularly in reference to receiving samples from other centres as part of the UK genetic testing network.

K Well, that's a good question - why accredit at all? Perhaps, to be competitive on the market, but first of all to ensure ourselves that everything is working properly and our results are credible.

Many of our departments are already accredited; in our department some groups of tests have been accredited. My lab started quite recently implementing a quality system. Perhaps next year we are going to apply accreditation from the Estonian Accreditation Board for our laboratory as a whole, but for HLA typing we have to apply accreditation from EFI, because our clinic is collaborating with Nordic Stem Cell Bank and they do not accept our HLA results without EFI accreditation.

## How did you find out about the EuroGentest workshop?

V & T The details regarding the workshop held in Leuven this year had been passed on to us by the director of the laboratory who, in turn, received a direct email from EuroGentest.

K EuroGentest is dealing mainly with genetic disorders, which is not specifically my field. I think my boss received the information from a colleague and she decided that the workshop would be useful for me.

## What was your experience of the workshop?

V & T We found the workshop very enjoyable and worthwhile. Although we had a good idea of the elements of a quality system, the workshop highlighted areas in which we could improve and gave a good overview of all aspects of Quality Management, not just document control. We found the group discussion sessions very worthwhile and it was interesting to hear other peoples views on, amongst other things, laboratory practice and reporting procedures.

K I enjoyed the workshop very much, because I have dealt with quality management for a very short time and on the workshop I received a general overview of it, which I did not have before. When we started our quality system, I (and technicians much more) were quite resistant

against it, because it just seemed to be boring paperwork and we felt that it impedes our everyday work. Nobody gave us the whole picture or explained to us the aim and purpose of the process. In the workshop we also worked through all the stages of implementing QSM and I got a lot of advice and hints. I also got valuable information about software systems for quality management.

Just few days before going to the workshop I told my boss, that I am not able to deal with all the documentation without proper software and also that I am not going to welcome our general quality manager for an internal audit in my lab, unless she presents me with a certificate, that she has planted at least 10 trees. I hate wasting paper. I was even going to design a primitive system on the basis of some microsoft programs to help me in my job. But this would not be a good solution.

## What is the next stage for you?

V & T To finish preparing for our accreditation inspection next year and further developing our document control program (Q-Pulse) to incorporate other aspects of quality management system, i.e. audit and training.

K At the moment we are looking for a software system for quality system management for the whole United Laboratories, to help people in their everyday work and to unify general procedures and documentation.

## Would you recommend the workshop to others and are you planning to become involved with EuroGentest in other ways?

V & T We would definitely recommend the workshop, particularly to laboratories that are yet to start the accreditation process, as a lot of useful and pragmatic information could be gained before undertaking such a process. Additionally, although we have been accredited for a few years ourselves we still gained knowledge and some useful ideas on how we could improve our current system. It would be of interest to see what future activities EuroGentest is planning.

K I will definitely recommend the EuroGentest workshops to others. First I thought that those labs, who are still moving towards accreditation gained more, but later I realized that there is still much to improve and develop for those labs, who have already been accredited for a long time.

I was surprised that so many lab managers seemed to be afraid of computers and new software. Estonians are very keen on computers - most of the public services are available via the internet and we always want the most up-to-date instruments.



► The workshop featured lively practical sessions lead by EuroGentest experts.

# Cytogenetics EQA pilot completed

The first cytogenetics external quality assurance pilot scheme has just been completed by Ros Hastings and her team with intriguing results. As with biochemical and molecular testing sectors, there is a growing awareness of the need for EQA. However the number of laboratories varies widely across Europe, from for example single units in Malta and Luxemburg to around 150 in Italy. Only a couple of national schemes are currently in place. EuroGentest thus has a key aim to facilitate the creation of a pan-European scheme and has just completed a pilot survey. Out of 24 labs invited to participate 15 replied to the web-based questionnaire. "This was very encouraging and shows our project is highly feasible," says Ros. "What was intriguing was the difference in reporting styles. There seem to be differences of opinion over which clinical information in particular should be included – for example the likely phenotype, recurrence risks, offer of parallel diagnosis and the need to refer to a clinical geneticist – as well as the inaccurate use of nomenclature. All of which reinforces the need for harmonization. We are now preparing a report and then intend to run a second pilot in summer next year opened up to 50 laboratories."

## External quality assessment vital for public confidence

A genetic test is an analysis which unlike many medical tests, is usually only carried out once in the life-time of the patient and yet which may have a profound effect on his/her life decisions. Maintaining public confidence in the quality of these tests through external quality of testing assessment schemes is thus seen as essential, particularly by the professionals involved. EuroGentest is involved heavily in all three genetic testing disciplines – biochemical, cytogenetic and, our focus here, molecular, through Rob Elles' group.

In the molecular testing arena, EuroGentest works with the European Molecular Quality Management Network (EMQN) to encourage and help molecular genetic testing laboratories in Europe to participate in External Quality Assessment. At the same time we try to add an additional dimension by encouraging discussion, service improvement and harmonization amongst colleagues in the other various national and international providers of EQA services.

### International dimension needed

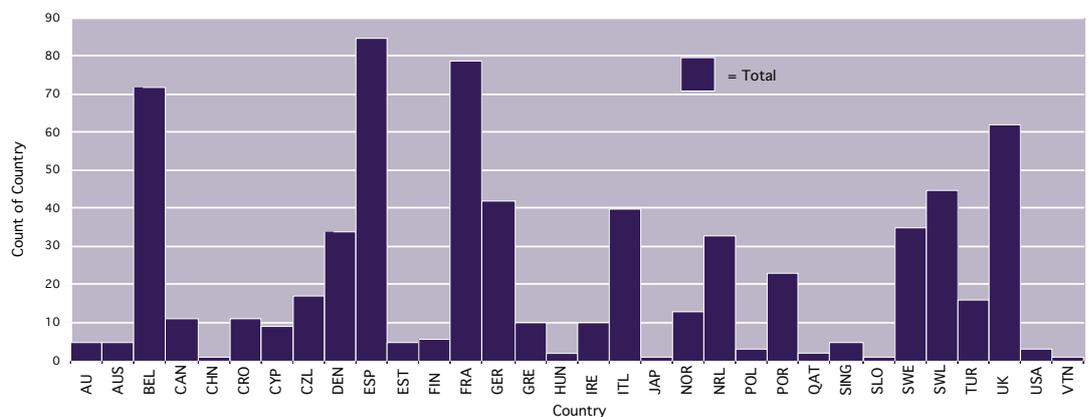
*"An international dimension in EQA is important - especially to set standards for the diagnosis of rare genetic conditions", Rob explains. "There are over 1000 single gene disorders for which a genetic test could be offered. Mostly these are for very rare (orphan) conditions. No country is self sufficient in genetic testing for orphan diseases in the near future with the technologies we use now. So it is not surprising that international surveys show that most genetic testing centres both receive and send referrals across national borders. This cross border flow should be encouraged to contribute to equal access to healthcare. EMQN has argued in evidence to the European Parliament that European collaboration on quality assurance is essential to guarantee acceptable standards for all genetic test services. EuroGentest aims to facilitate such collaboration."*

### European consensus already exists

Over the last 10 years a broad consensus has been reached on the structure of EQA schemes. Most EQA schemes assess two parts of the output from a Molecular Genetic Testing laboratory; firstly the genotype (technical accuracy) and secondly how the lab reports the clinical significance of the result (interpretation). European EQA schemes recognise that there are considerable skills within the laboratory to interpret a test result and that this can both add value to the data for the referring doctor and the patient and be an important factor in safety in helping communicate complex information to the patient.

*"The scope of EQA schemes provided by EMQN has grown over the last 10 years," continues Rob. "Schemes relevant to 15 disease specific services are provided and there are over 400 laboratories mostly in Europe, Asia and Australasia active in the network. However in Europe this represents perhaps only between 30 to 50% of the laboratories active in molecular genetic testing for clinical purposes so we are aware that a great number of laboratories remain outside this type of peer review. EuroGentest is now working to address this situation. Following a successful meeting of stakeholders in Prague earlier this year, we identified that the best way forward was to link EQA and best practice through guideline development. The first of these on the rare neurological disorders Spino Cerebellar Ataxias in discussion with experts is planned for the spring of 2007."*

Table - 2005 participation of genetic testing centres in EMQN External Quality Assessment schemes by country (excluding Cystic Fibrosis).



# Ensuring patients get the right information

One of EuroGentest's key objectives is to promote harmonization of genetic testing patient information across Europe since "It is integral to the delivery of good quality healthcare that patients are provided with information that is accurate, accessible, and well informed." This is especially true in an age when patients are taking greater interest than ever before in managing their health. EuroGentest's unit 6 workshop in Porto has been working to assess whether information currently available to patients and families reflected these criteria. Céline Lewis here describes the results of her research presented recently in a workshop in Porto.

## Material Collection

Unit 6 gathered and assessed written patient information relating to genetic testing, from seven European countries (UK, Netherlands, Germany, Sweden, Belgium, Italy and Poland) that were considered collectively to be representative of the current state of genetic services in Europe. The information collected related to genetic testing for the following five genetic conditions: hereditary breast cancer, Duchenne muscular dystrophy, Tuberous sclerosis, 22q11 deletion, and the Connexin 26 alteration. These conditions were chosen because they cover both the rarer and more common conditions, they cover a broad range of hereditary patterns, and each condition is equally prevalent across the selected states. Written information was either collected directly from genetic clinics in these seven countries, or it was collected from sources that clinicians directed us towards (i.e. patient organisations or other information sources).

## Results

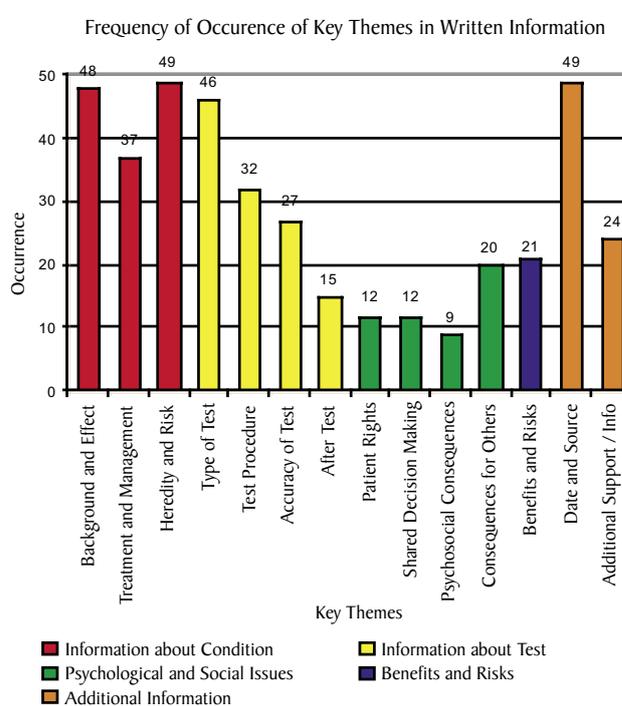
- In total 129 pieces of material, directly related to the five conditions, was gathered. A third of this material had not been produced by the genetic clinic, but was either available from it, or patients could be directed to it.
- Nearly half the material gathered came in the form of a personal letter. Over a third came in the form of a leaflet or booklet, the majority of which had been developed by patient organisations. Only a small number of leaflets and booklets had been produced by a genetic clinic, and the majority of these related to hereditary breast cancer. A small percentage of material came in the form of a standard letter (a template for a personal letter).
- The availability of written patient information varied considerably across Europe, with those countries with better resources and well developed service networks being more active in developing patient information. The majority of material was collected from the UK and the Netherlands. The least was collected from Poland.
- Most of the material gathered related to hereditary breast cancer, the most common of the five conditions. This was then followed by Duchenne muscular dystrophy, Connexin 26 alteration, 22q11 deletion, and lastly Tuberous sclerosis.

## Assessment of Material

Where possible, two pieces of written material for each condition, from each country, were chosen at random, and translated if necessary. This material was then assessed using a number of criteria identified by the recently developed DISCERN Genetics tool (Copyright University of Oxford 2005 [www.discern-genetics.org](http://www.discern-genetics.org)) as well as a few additional criteria identified by other sources. The final tool used identified 14 key issues which were considered as being of key importance when developing or assessing material relating to genetic testing. Each key issue had a number of descriptions alongside it, which provided examples of the way in which the issue might be presented to the reader. Again, many of the descriptions were taken directly from DISCERN Genetics.

Fifty pieces of information were assessed in total. Of these fifty pieces twenty-five were personal letters, twenty-three were pre-written leaflets or booklets, and two were standard letters. Each piece was assessed for the presence or absence of each of the fourteen key issues. A statement fitting any part of the description was counted as a presence of the key issue, and the results were tabulated.

## Results



- Overall leaflets were found to be far more comprehensive than personal letters; they discussed the key issues more frequently than personal letters did.
- The majority of material discussed issues relating to the condition and certain aspects of the test.
- There was very little discussion in the written material concerning the psychological and social aspects of genetic testing.
- Less than a third of the material collected discussed both the potential benefits and harms of genetic testing (considered to be an important aspect in informed decision making). Benefits of genetic testing were more likely to be included (n=40, 80%) than any risks involved (n=23, 46%).
- Less than half the information discussed where to obtain additional information from, and how to contact relevant support services.
- The quality of written patient information varied across conditions. Information on the more prevalent genetic conditions (i.e. hereditary breast cancer) was found to be of a higher quality, and discussed a greater number of key issues, than information on rarer conditions.



## Why were leaflets more comprehensive than personal letters?

- Genetic services are often severely stretched in terms of time and resources.
- Pre-written leaflets can be assessed by patients and professionals during the development stage to ensure they cover key issues.
- Pre-written leaflets are often prepared by patient groups and hence patient driven. They are therefore more likely to tackle the issues important to patients and families.

## Why was there little discussion of the psychological and social aspects of genetic testing?

- Even though there is a body of research relating to the social and psychological effects of genetic testing for the rarer conditions, it appears that much of this research has yet to be translated into practice.
- Practitioners may not believe it to be within their remit to provide information about social and psychological issues. (Nevertheless, this in fact is a required competence of genetic health professionals according to the International Society of Nurses in Genetics (ISONG) and The National Coalition for Health Professional Education in Genetics (NCHPEG)).
- Practitioners might not have access to, or keep up to date with 'non-medical' or social issues relating to genetic testing such as insurance, benefits, specialist education services etc.

## Why was written information more forthcoming in discussing the benefits of genetic testing as opposed to possible risks and limitations?

- The general trend relating to patient information has always been to improve healthcare through early diagnosis and treatment, hence practitioners might be more inclined to present the benefits than the risks.
- There is a desire not to 'worry' patients.
- It may be argued that informed choice is a relatively new phenomenon and therefore written information may not yet routinely reflect this trend.

## Why did less than half the material gathered discuss additional information sources and support services?

- Additional information in the patient's own language may not exist, or the clinician might be unaware of its existence.
- The clinician might feel it is unnecessary to discuss additional information sources or support networks. They might feel they have discussed all the key issues and provided all necessary support.
- The clinician might not know whose role it is to provide the patient and family with additional support.
- There might not be a specific patient support group for the patient and family to contact.

## Why was information concerning hereditary breast cancer more comprehensive than for the other four conditions?

- A number of genetic clinics had developed pre-written leaflets due to the high prevalence rate of the condition. These are therefore more likely to have been assessed for their comprehensiveness.
- A number of high profile charities are key players in developing patient driven information.
- There has been much research done on the information needs of hereditary breast cancer patients.

## Recommendations

The findings from this work suggest that there are gaps across both conditions and countries in the availability of good quality written information. In light of these findings, unit 6 will be working towards a number of deliverables, listed below, over the next three years. A great deal of progress has already been made towards these deliverables during the recent unit 6 workshop in Porto.

1. The development and refinement the key issues that should be discussed within written patient information. This work will be undertaken with the help of patient groups and healthcare professionals from a number of different European states.
2. The development generic information leaflets for patients and families. These will cover key issues related to genetics including: the basic biological function of genes, chromosomes etc; inheritance patterns and risk; information about the various types of genetic tests available and their potential benefits, limitations and risks. This information will be developed with the help of professionals, patients and families.
3. A 'Frequently Asked and Useful Questions' leaflet will be developed to support patients and families that are going to speak to a healthcare professional about genetic testing for the first time.
4. This information will be translated into a number of European languages where we have found there to be significant gaps at present. We are in the process of surveying professionals across 27 member states to find out where these gaps currently exist.
5. This information will then be disseminated, both in print and on-line, through genetic clinics, other relevant hospital departments (e.g. paediatrics, maternity, general practice), government, patient support groups and other appropriate public information sources. The information will also be available on the EuroGentest website ([www.eurogentest.org](http://www.eurogentest.org)).
6. There needs to be a commitment to update and maintain the information developed, otherwise it will soon become outdated. It is essential to secure further investment for this after the current EuroGentest project has been completed.
7. WP 6.1 will work with WP 6.2 to identify the minimum set of skills required by any health professional who provides genetic counselling in the context of genetic testing. The elements of this set of skills will be discussed by both patient groups and professionals.

# Towards tighter definitions

Agreement upon definitions is a key step towards progress in any field, genetic testing being no exception. Against this background, unit 3 organized its second expert meeting in Porto on September 21-22.

The group of experts from various fields of genetics was formed during the first months of the EuroGentest project and held its first meeting in May 2005. After that the group of experts expanded, and at the Porto meeting there were 39 persons from all over Europe as well as from US, Canada, South-Africa, Argentina and Ecuador. Cooperation between different units that share common objectives was hoped for and therefore partners from unit 6 and unit 4 joined the workshop. The aim of the second expert meeting was to discuss the goals and the progress of the two original workpackages of the unit. Further, the two new workpackages presented their agendas. Future steps of the workpackages were discussed, and most importantly, a general discussion on assessing the quality of genetic counselling and the utility and the state of genetic testing took place.

## Genetic testing and clinical utility

On the first meeting day the workpackage 3.4 presented its work on collecting definitions of genetic testing. Finding a consensus definition was discussed and different elements involved in the definition of a gene test were evaluated. It was considered that finding a universal consensus definition would be impossible but that a specific definition should be used every time that genetic testing is talked about. A list of items to be considered for a definition will be set down and further discussed with the experts. The other new workpackage 3.3 also presented networking with the CAPABILITY project that deals with the utility and benefits of genetic testing and the involvement of developing countries.

The second meeting day was divided between the workpackages on genetic counselling and on the clinical validity and utility of genetic testing. In the morning session the topics were discussed together and in the afternoon the experts were divided into two working groups.

Genetic counselling workpackage 3.1 presented the background research, on basis of which a draft of minimal criteria recommendations for counselling in context of genetic testing had been created. The recommendations were discussed and it was thought that clear



"What exactly is a genetic test?" was a lively topic of debate in Porto

definitions of different test types are needed, and that the level of information in each situation should be discussed thoroughly. Assessing the quality of genetic counselling was also discussed, and introducing such a system was considered to benefit everyone from individual patient to the whole service system. The expert group created a list of possible indicators for assessing the quality of counselling.

The workpackage 3.2 on the clinical validity and utility of genetic testing presented the background document on differences in access to testing, uptake of testing and costs in European countries as well as different approaches to assessing clinical utility. It was discussed whether there is a need for recommendations for defining clinical validity and utility of genetic testing. The experts suggested that same test type classifications and definition of genetic testing should be used within the unit. The ideas on possibilities of making use of a decision-making model in context of evaluating the utility of a genetic test were presented.

The work of the unit 3 proceeded significantly with the experts' contribution at the meeting in Porto, as valuable feedback on recommendations and background documents was received. It was regretted that the meeting was a little bit too short so that there was not enough time for in-depth discussions, but it was decided that the expertise of the participants would be utilized better during the following periods between the meetings.

## EuroGentest General Assembly

The second General Assembly will be held again in Leuven from December 11-13 and as well as unit reports will feature a series of presentations from leading experts on genetics related topics.

- Epidemiologic studies: how to draft good surveys/questionnaires  
*Ségolène Aymé - Director Orphanet, France*
- An update on the CETT program to facilitate translation of genetic tests from research to practice, including the biochemical workgroup meeting; the GTQC program for materials; the program to enhance communications between the laboratory and care provider; and the genetic testing oversight issues  
*Joe Boone - Centers for Disease Control and Prevention, USA*
- Diffusion of innovation and genetic testing into the society: a personal view.  
*Hori Tomoshige - Japan Bio-industry Association, Japan*
- Outcomes of a Public Consultation on the OECD Guidelines for Quality Assurance in Molecular Genetic Testing.  
*Elettra Ronchi - OECD, France*
- Genatlas  
*Martine Le Merrer - Genatlas, France*

# EuroGentest acts on reference materials



As genetic testing and related technologies begin to enter the mainstream of clinical practice, the need for appropriate Reference Materials (RMs) becomes increasingly urgent. Accordingly, EuroGentest for the EU and the CDC for the US, brought together an international group of stakeholders to discuss key issues, such as new regulations, current RM availability and prioritising future needs. The meeting was held, appropriately, at the Institute for Reference Materials and Measurements (IRMM) charged with promoting common and reliable European measurement systems in support of EU policies.

## European and International Perspectives on RMs

The EU regulates genetic testing as a medical device, through the in vitro diagnostic (IVD) medical devices Directive (98/79/EC) which covers tests, rather than testing; moreover, its scope is limited to those IVDs having a medical purpose. The Directive deals with all aspects of safety and performance, taking on board the need for common technical specifications such as sensitivity - its main purpose is to introduce harmonized controls on these IVDs throughout the EU. At present, DG Enterprise is looking at the Directive with responses expected from Member States this year – although it is felt it is sufficiently robust not to require major modifications.

According to ISO, which looks at standards at the international level, a standard is a written document with rules and guidelines, covering consolidated technologies and processes. ISO prefers to concentrate upon 'horizontal' standards which cover general aspects and are widely applicable.

ISO TC 212 (whose secretariat is the Clinical Laboratory Standards Institute – CLSI) is focused on lab medicine and IVDs and will develop horizontal standards to apply to all IVDs and globalize regional standards where these have global impact. As an international organisation, ISO is working with countries outside Europe and the Americas - Thailand and China are members of 212 – but it is proving hard to get some developing countries involved. Global harmonisation is important though, to avoid the emergence of a 'two tier' world as far as genetic testing is concerned.

## What is a Reference Material anyway?

At the meeting Philippe Corbisier began with a review of what we actually mean by the term 'reference material'. In the ISO Guide 35, RMs are defined as materials sufficiently homogeneous and stable with respect to one or more specific properties. If they have no further characteristics they are known as Quality Control Materials (or, variously, as lab reference materials, lab controls, materials for EQAs, in-house materials).

In addition, Certified Reference Materials (CRMs) carry a certificate which provides certified property values, with uncertainties, and stated metrological traceability (ISO Guide 35).

The uses of RMs include:

- Method development and validation; estimating the uncertainty of measurement
- Calibration
- Proof of a method's performance
- Proficiency testing



## Needs of Stakeholders for Reference Materials for Genetic Testing

Contributors from both sides of the Atlantic shared observations on what people want when it comes to RMs. Christine Brady reported on three recent surveys on users' needs, revealing a wide range of current practices and perceived need across Europe. Prioritising which RMs need to be developed will not be easy!

- The NGRL survey of opinion on RMs in 111 UK genetic testing labs found that RMs are most wanted for tests for clotting disorders, cancer and core monogenetic diseases. See [www.ngrl.org.uk/Manchester/pages](http://www.ngrl.org.uk/Manchester/pages).
- The ongoing CRMGEN survey of demand for CRMs found a need for RMs for muscular dystrophy, FragileX (FraX) and Huntington's disease (HD) testing. Download the survey from [www.crmgen.org](http://www.crmgen.org).
- The EuroGentest survey on positive controls among assessors of EQA schemes run by the European Molecular Genetics Quality Network found that most respondents were using in-house RMs. They wanted as many RMs as possible, especially for rare diseases.

Meanwhile, in the US, the Coriell Cell Repository has been distributing cell lines and QCMs for many years. Jeanne Beck discussed a survey of their DNA shipments between 2002 and 2005 which shows that 20 per cent, of a total of 80,000, are for positive controls, mostly for Cystic fibrosis (CF) or FraX. In fact, 38 per cent of these positive controls shipped outside the US are for genetic disease. Other findings included:

- More than 550 DNA samples shipped outside the US (20 per cent of the total shipped as positive controls) have been for CF, FraX, Factor V Leiden/MRHFR, HFE and HD.
- 33 per cent of DNA samples purchased by non-US researchers as positive controls were for CF, 11.5 per cent for FraX, one per cent HD, 8.5 per cent for diseases in the Ashkenazi Jewish panel.

## Companies using/needing RMs

Delegates from a number of companies shared their experience of RMs

- Innogenetics wants RMs for its CF and HLA (transplantation) diagnostic tests and is setting up a databank with accessible and well-characterised samples.
- Roche uses its own RMs for its Factor V Leiden and Factor II (prothrombin) diagnostic tests and wants material that can detect polymorphisms which are not currently represented in control materials.
- Applera/Celera Diagnostics is developing test reagents, and would like to have RMs available for Fragile X and expanded CF mutations.
- Qiagen has been working with whole genome amplification (REPLI-g) for very small samples and genome-wide studies and is offering collaboration opportunities.





■ Affymetrix wants to develop RMs for its own and other platforms as it moves from research to products. The company has been active in the International Meeting on Clinical and Laboratory Genomic Standards ([www.imclgs.org](http://www.imclgs.org)) which is working to accelerate the establishment of clinical and laboratory standard controls and global harmonization in this area.

## Current availability & development of control materials for genetic testing

David Gancberg listed the current barriers to the supply of RMs, which are:

- Lack of QA
- Lack of certified RMs
- Need for normative and regulatory framework application
- Need for networking
- Impact of patents

However, progress is definitely being made. David Barton gave a summary of CRMGEN, a four year EU-funded feasibility study on developing RMs which he co-ordinated. CRMGEN made and sent out RMs in four forms: (PCR products, cell lines, genomic DNA, synthetic DNA) for the following diseases:

- CF
- FraX
- Thalassaemia
- HNPCC
- Haemochromatosis
- Sickle cell anemia
- Factor V Leiden
- DMD

with the result that four FraX and six HNPCC RMs have now been generated in all formats.

Meanwhile, EuroGentest continues to work on identification of present and future needs for RMs, setting priorities, implementation of traceability and building up a network. The National Institute for Biological Standards and Controls (NIBSC) is involved in the World Health Organisation (WHO) Biological Standardization Program and is one of the two (soon to be the only one) labs which holds and distributes these international standards.

The first WHO genetic testing RM was for FV Leiden from a well characterised patient. NIBSC also distributes a prothrombin standard and is working on RMs for FraX, Haemophilia A, hereditary haemochromatosis, HLA and in future hopes to work on a reference material for BCR/ABL detection. (See [www.nibsc.ac.uk](http://www.nibsc.ac.uk))

Joe Boone spoke about the international Genetic Testing Quality Control Material Program, which started by looking at pressing QC material needs for DNA-based genetic tests and has been coordinating the collection and verification of cell lines with the mutations needed. The Program welcomes input – needs, ideas, material donation, verification and support. Co-ordinator Lisa Kalman added that the GTQC is developing QC materials for HD testing (through allele sizing), Ashkenazi Jewish panels (nine disorders), FraX and CF. Next steps include

- Completion of current verification projects
- Developing improved information resources
- Identifying new targets for QC material development
- Exploring human subjects and regulatory issues
- Co-ordination with Europe (see [www.phppo.cdc.gov/dls/genetics/qcmaterials](http://www.phppo.cdc.gov/dls/genetics/qcmaterials))

From the UK, Helen White of the Wessex NGRL reported on their development of plasmid-based controls for HNPCC gene anomalies and breast cancer. Plasmid DNA is diluted in TE 0.1x at 104 cp/μL in a background of 50 μg/ml tRNA This is based on blood from eight consenting 'normals'. They have positive controls for all mutations and have done field trials on these.

The lab has also constructed 52 plasmids for BRCA1, BRCA2, MLH1 and MLH2 to be tested after sub-cloning in pUC18 (originally the sequences were all cloned in pCR2.1). Meanwhile, LGC, the UK's National Measurement Institute has a number of programs in genetic testing, including one on microarray performance indicators.

For more information, go to [www.mfbprog.org.uk](http://www.mfbprog.org.uk)

## The EU Experience

David Barton listed the following issues which need to be considered when prioritizing which RMs to develop.

- The number of potential users of a RM
- Geographical distribution of testing
- Current availability of a RM
- National and international guidelines
- The nature of the mutation
- Range of assays used
- Feedback from EQA/PT schemes
- Availability of source materials for RM (e.g., patient consent)
- IP issues – such as the cost of licensing, legal assessment, potential of these to block RM development



## Looking to the future

The EU and the US want to work together on the RM issue, although so far there are no formal collaborations. Ensuring work is not duplicated is important – in so far as the respective regulatory systems will allow (but it is not clear whether EC marked materials would be acceptable as controls in the US, or if validated Coriell material is allowed as controls in Europe). Maybe a joint EU/US 'think tank' is now needed.

EuroGentest also needs an advisory working group on Reference Materials and is to carry out some discrete recruitment. Helen Parkes of LGC invited nominations of some of the many RMs mentioned at the meeting to JCTLM (Joint Committee on Traceability of Laboratory Materials [www.cstl.nist.gov/jctlm.htm](http://www.cstl.nist.gov/jctlm.htm)), a non-governmental organization on which several of the current delegates serve. See also [www.bipm.org/en/committees/jc/jctlm/](http://www.bipm.org/en/committees/jc/jctlm/) and [www.ifcc.org](http://www.ifcc.org).

## Future Plans

The current meeting was part of the CDC series (no 4) and EuroGentest (first). A CDC meeting will be held alongside the Association for Molecular Pathology meeting in Orlando, Florida in November 2006. The AMP meeting itself will feature a special session on Reference Materials. Ireland will host the next EuroGentest meeting, on 15-16 May 2007 in Dublin.

# Letter from America

Genetic testing is obviously a global issue and EuroGentest as you will have read in other articles, has strong collaborative links around the world. One of these is the US Centers for Disease Control and Prevention (CDC). Here Dr Lisa Kalman, reports on their Genetic Testing Quality Control Materials Program (GTQC) for developing Reference Materials which complements and will help EuroGentest's own efforts.

The completion of the human genome sequence and subsequent genomic research has led to an amazing increase in the number of laboratory tests for genetic diseases. Although the volume of genetic testing in the United States (U.S.) has been rising steadily over the last 10 years, there are almost no verified quality control (QC) materials available. These materials are urgently needed by the genetic testing community to improve the measurement, detection and diagnosis of a variety of genetic disorders.

To address the lack of available genomic QC materials, the Centers for Disease Control and Prevention (CDC), in partnership with the genetics community, established a new program- the Genetic Testing Quality Control Materials Program (GTQC). The GTQC coordinates a self-sustaining community process to improve the availability of appropriate materials with confirmed mutations for quality control, PT, test development, and research. In addition, the GTQC facilitates and coordinates information exchange between users and providers of QC materials, and coordinates efforts for contribution, development, verification and distribution of QC materials for genetic testing.

The GTQC Program is coordinated by the CDC, but all of the actual work, including decisions about QC material priorities, mutation confirmation schemes, specimen collection, material development and mutation confirmation, occurs through voluntary collaborations with laboratories in the genetics community.

The GTQC develops QC materials from anonymous residual patient blood specimens or established cell lines with known genetic mutations. Blood samples or cell lines are submitted to the National Institute of General Medical Sciences (NIGMS) Human Genetic Cell Repository at the Coriell Cell Repositories (Camden, NJ), which performs the necessary transformation/immortalizations, cell culture and DNA preparations. Subsequently, DNA samples are sent to multiple volunteer testing laboratories, which characterize the materials using a variety of analytical techniques to confirm the presence of the mutation of interest.

## Huntington disease

The GTQC program has recently developed genomic DNA QC materials for Huntington disease (HD) genetic testing. QC material needs for HD genetic testing were identified through numerous discussions with clinical laboratories and other experts. Fourteen HD cell lines were selected from the NIGMS Human Genetic Cell Repository at Coriell. These cell lines contained a large range of allele sizes and combinations, including normal alleles, alleles near important diagnostic cutoffs, homozygous alleles, two alleles with similar but not identical CAG repeat sizes, and alleles with large CAG repeat sizes. Aliquots of DNA from each cell line were sent to 10 volunteer clinical genetic laboratories for CAG allele measurement using laboratory-developed PCR-based HD assays. The CAG repeat size of each sample was also determined by DNA sequence analysis. We found no significant differences in the

analytic values obtained using different HD assays or methodologies among the 10 laboratories. There was also very good agreement between the CAG repeat sizes obtained by the laboratories and the DNA sequence analysis. The data from this study can be viewed on the GTQC website and the materials are publicly available from Coriell's NIGMS Human Genetic Cell Repository.

## Ashkenazi Jewish Panel

The GTQC has also developed 27 genomic DNA QC materials for disorders on the Ashkenazi Jewish (AJ) Panel. The QC material needs for AJ genetic testing were defined by consultation with clinical laboratory directors, analysis of current test panels and assessment of available QC materials. Cell lines were selected from Coriell's NIGMS Repository that represented many of the commonly tested alleles for Tay-Sachs disease, Canavan disease, familial dysautonomia, mucopolysaccharidosis IV, Niemann-Pick disease type A, Fanconi anemia type C, Bloom syndrome, Gaucher disease, and glycogen storage disease type Ia. DNA was prepared from each cell line and aliquots were sent to each of 6 volunteer clinical laboratories for testing. The laboratories tested the 27 samples for 32 different disease alleles using a variety of laboratory-developed PCR-based assays. Four of the 6 laboratories incorporated a commercially available test reagent into their assay (Tag-It, Tm Bioscience). Twenty-one different alleles were identified in the samples. All laboratories were able to detect the presence of every allele included in their test panel, and there were no discrepant results. The data from this study can be viewed on the GTQC website and the materials are publicly available from Coriell's NIGMS Repository.

## Fragile X

The GTQC, together with 9 volunteer clinical laboratories and other representatives from academic and commercial clinical genetic testing laboratories, Coriell and the National Institute of Standards and Technology are currently confirming the CGG repeat length of Fragile X alleles in 21 Coriell cell lines. These materials will be available from Coriell in the next few months.

## Pharmacogenetic loci

The GTQC has collected information on pharmacogenetic (CYP2D6, CYP2C9, CYP2C19, VKORC1 and UGT1A1) genotypes of a large number of publicly available cell lines and genomic DNA materials from clinical laboratories and academic researchers, and has compiled the information into easy-to-use tables on the GTQC website. The tables indicate the genotype of each material, the method(s) used to determine the genotype, and the public source of the material.

## Future QC material development projects

We are planning to confirm the genotype of a number of genomic DNA samples in the coming months. The genes/disorders include: Cystic fibrosis, MTHFR, Alpha-1 antitrypsin deficiency, Medium chain acyl-coenzyme A dehydrogenase deficiency, Galactosemia, Maple syrup urine disease, Multiple endocrine neoplasia Type 2, BRCA1/2, Gaucher disease, and Congenital adrenal hyperplasia.

Information about currently available materials (as well as other QC info) can be found on the GTQC Program website: [www.phppo.cdc.gov/dls/genetics/qcmaterials/default.aspx](http://www.phppo.cdc.gov/dls/genetics/qcmaterials/default.aspx)

# DISEASE FOCUS NO 3

## MPS

### Still difficult to diagnose early, but growing reasons for hope

Mucopolysaccharide - or MPS - diseases are rare inherited disorders which cause a variety of developmental problems, often resulting in serious mental and growth problems in childhood. Mucopolysaccharides are long chains of sugar molecules used in the building of connective tissues in the body. There is a continuous process in the body of replacing used materials and breaking them down for disposal. Patients with MPS disorders are missing enzymes which break down the mucopolysaccharides. These remain trapped in the cells of the body, causing progressive damage. Babies may show signs of the disease but as more and more cells become damaged, symptoms start to appear. The good news is that enzyme replacement therapies have been and are being developed for a number of these diseases by companies such as Genzyme, Shire and Biomarin.

The diseases are referred to as MPS I - VII or more commonly by the name of the doctor who first described the condition. These include:

#### MPS I - Hurler, Scheie and Hurler/Scheie syndromes are forms of Mucopolysaccharidosis Type I.

Hurler takes its name from Gertrud Hurler, the doctor who described a boy and girl with the condition in 1919. Children most severely affected are said to have Hurler disease. An ophthalmologist, Dr Scheie wrote about some of his patients who were less severely affected. Scheie patients have normal or near-normal intelligence and live into adult life. Patients who do not seem to fit clearly in either the severe or milder form of the disease are said to have Hurler Scheie disease. Symptoms can include skeletal and facial deformities, skin and cardiac changes, clouding of the cornea, and mental deficiency.

Children with MPS I are missing an enzyme called alpha - L - iduronidase which is essential in cutting up the mucopolysaccharides dermatan and heparan sulphate.

#### MPS II - Hunter syndrome affects one in 150,000 live births in the UK.

Hunter is very varied in its effects. Children with MPS II are missing an enzyme called iduronate sulphate sulphatase which is essential in cutting up the mucopolysaccharides called dermatan and heparan sulphate. A treatment for Hunter as recently been developed. The new drug, Elaprase, developed by Shire Pharmaceuticals, has been approved in the US and is expected to be licensed in Europe by the end of the year.

Given by infusion, it improves breathing and movement. Parents of some Hunter children say it has transformed them.

Hunter has a different form of inheritance from all the other MPS diseases as it is 'sex linked' like haemophilia. Girls may be carriers of the disease but, except in very rare cases, only boys will be sufferers. The few girls who have been found to have the disease have an associated chromosomal abnormality.

MPS III - Sanfilippo syndrome to date four different enzyme deficiencies have been found to cause Sanfilippo disease and so the condition is described as type A,B,C or D. Type A is the most common form found in most populations.

MPS IIIA is missing the enzyme heparan N sulphatase

MPS IIIB is missing alpha-N-acetylglucosaminidase

MPS IIIC is missing acetyl-CoA: alpha-glucosaminide acetyltransferase

MPS IIID is missing N-acetylglucosamine-6-sulphatase

There are no significant clinical differences between the different subtypes of MPS III, although there have been some very mild cases of the B form where the sufferers have remained relatively unaffected into adult life. The latest understanding is that some people seem to produce some enzyme activity which helps to slow down the progression of the disease while those with more severe symptoms appear to have no enzyme activity at all.

MPS IV - Morquio disease shares several symptoms in common with other mucopolysaccharide storage diseases such as short stature, coarse facial features, and skeletal and joint abnormalities. Like Sanfilippo syndrome, onset of symptoms is delayed until after the first year, and life expectancy may exceed 20 years. Unlike Sanfilippo the mental development is often normal. Morquio disease varies widely in its severity; even children from the same family may be affected differently. Some complications arise early in childhood, while others arise much later or may never occur.

Children with Morquio disease are missing an enzyme which is essential in cutting up the mucopolysaccharide called keratan sulphate. The incompletely broken down mucopolysaccharides cannot be used in the proper development of bones and cartilage and remain stored in cells in the body causing progressive damage.

The usual form of Morquio disease is known as MPS IVA to distinguish it from the much rarer B form which is caused by the lack of a different enzyme. Sufferers from the B form have similar problems, but tend to be less severely affected.

MPS VI - Maroteaux Lamy disease causes mild to severe changes in muscle, bone, skin, and other tissues, particularly the heart. Diagnosis is by examining leukocytes and cultured skin fibroblasts, or 24-hour urine collection to search for high levels of dermatan sulfate. Due to heart damage, death usually occurs before age 40. Children with Maroteaux-Lamy disease are missing an enzyme which is essential in cutting up the mucopolysaccharide called dermatan sulphate. Over a ten-year period 5 babies with Maroteaux-Lamy disease were born in Britain. A particularly severe form of the disease has been reported among Australian aborigines. It also occurs in Siamese cats.



In January 2006, BioMarin Pharmaceutical Inc's Naglazyme enzyme replacement therapy treatment was granted marketing approval by the European Union. The drug is administered by weekly infusions. Since then product nine patients are benefiting from treatment.

Sly (MPS VII) Sly disease is characterized by short stature, coarsening of the facial features, clouding of the cornea, striking enlargement of the liver and spleen, skeletal abnormalities, and intellectual deterioration resulting in moderately severe mental retardation.

Sly syndrome is due to deficiency of the enzyme beta-glucuronidase which causes the damaging accumulation of mucopolysaccharides in the central nervous system and other tissues. There are several forms of Sly syndrome, including a much milder form compatible with normal intelligence. All forms of Sly syndrome are inherited in an autosomal recessive manner.

MPS VII was the first autosomal (non-sex chromosome) mucopolysaccharide disease for which chromosomal assignment was achieved. Several laboratories confirmed assignment of beta-glucuronidase to chromosome.

## Similar but not the same

There are other 'storage diseases' and the following conditions are similar to Mucopolysaccharide Diseases:

- MLI Neuramidase Deficiency
- MLII I-Cell Disease
- MLIII Pseudo Hurler Polydystrophy
- MLIV
- Fucosidosis
- Mannosidosis
- Sialic Acid Storage Disease
- Multiple Sulphatase Deficiency
- Aspartylglycosaminuria
- Winchester Syndrome
- Fabry Disease

## What are mucopolysaccharides?

Basically, long molecular chains of sugar. They are used by the body in the building of connective tissues. The word 'mucopolysaccharide' can be broken down as follows:

'muco' refers to the thick jelly-like consistency of the molecules

'poly' means many

'saccharide' is a general term for a sugar molecule

# Exploring the ethics of biobanks

GeneBanC is an independent project recently approved by the E.C. But given the topic and relevance for genetics, the duration and the integration with our research group (Herman Nys and Kris Dierickx are 2 of the seven partners in the new project) it will be developed in close connection with the activities of EuroGentest and unit 4 in particular. A website will soon be released ([www.genebanc.eu](http://www.genebanc.eu)) with reference to EuroGentest.

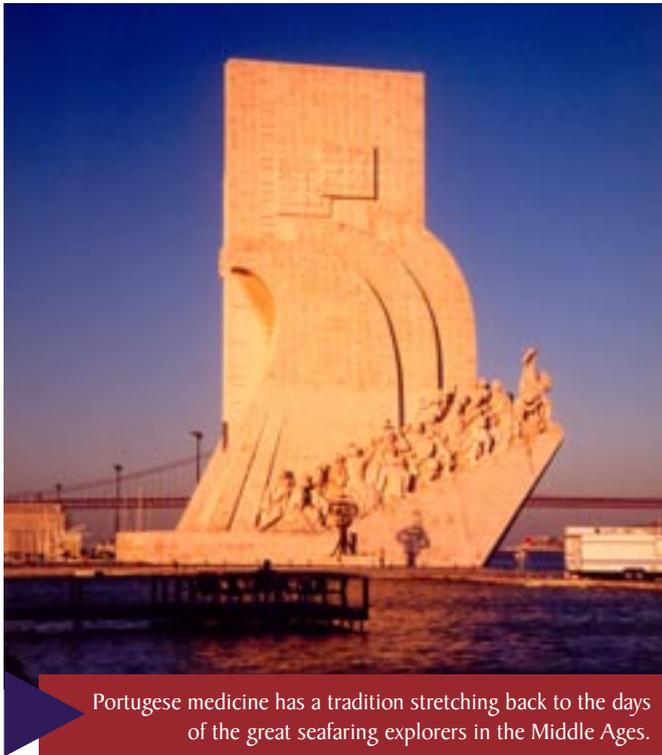
The last few years have witnessed an important expansion of collection and processing of human biological samples and of the related information data. Biobanks are huge repositories of human biological specimens and have a strategic importance for genetic research, clinical care and future treatments. The GeneBanC research project aims to investigate the ethical, legal and social issues of three types of biobanks: classical banking, population banking and forensic DNA databases. There are four key objectives:

- 1) To study the issue of privacy and confidentiality. There are reasons to believe that an unquestioned transfer of the traditional concept of confidentiality to the three types of biobanking described may be problematic, and that the concept needs to be re-analysed in these new contexts.
- 2) To investigate the existing regulatory framework of biobanks across the EU and to focus on the collection and analysis of legislation and regulation regarding the establishment, management and functioning of classical, population and forensic biobanks. The analysis of existing legislation will also provide some suggestions for "best rules".
- 3) To investigate the ethical and policy issues related to forensic databases. In a post 9/11 era forensic genetic databases (i.e. crime, terrorism) generate many questions that have had no attention until now on a European level.
- 4) To investigate governance aspects of biobanks. The objective is to study the social, ethical, scientific-technological, and political-regulatory embedding of biobanks, to help the understanding of the ethical, socio-economic, scientific-technological and political implications of biobank development on the local and the national level, and in the transnational field and thereby to contribute to a better understanding of biobank governance.

The results obtained within the different objectives described above will be of great use for the development of policy-oriented recommendations concerning the organisation and management of small scale biobanks, population databanks and forensic DNA databases. Also, Kris and Herman's group aim to make proposals in order to attain where appropriate a harmonized regulatory framework across the European Union.

## COUNTRY SPOTLIGHT

# Portugal



Portuguese medicine has a tradition stretching back to the days of the great seafaring explorers in the Middle Ages.

Portugal is an enthusiastic supporter of EuroGentest, witness the whole series of workshops hosted there recently and so after the Czech Republic, Netherlands and Poland is the subject of our country focus. Most of the genetic testing in Portugal is done within the national health service, but the number of private labs is increasing, as is their share of the whole testing market. Furthermore, very recently, and through the administrative intervention of the Council of Ministers and Ministry of Health, one of the two national reference centres described in the main story, IGM has been integrated into the other - INSA. It is still uncertain what this measure will bring, though it might mean an immediate downgrading for Clinical/Medical Genetics in this country, and the submission of medical to laboratory genetics.

There are two major national reference institutions for genetic testing: the Medical Genetics Institute (IGM), based in Porto, with molecular genetics, cytogenetics, and biochemical genetics labs, and which is also the base for the national program of newborn screening; and the Instituto Nacional de Saúde, (INSA) in Lisbon, which is a public health institute, and includes a Human Genetics Centre. Together, these two institutions are meant to be responsible for the majority of the molecular genetic testing performed in the country (see below). In addition, still within the national health system, there are regional cytogenetic labs: in the northeast, at the Hospital de Vila Real; in the centre, at the Univ. Hospital in Coimbra, and, in the south, at three hospitals in Lisbon (Hosp. St<sup>a</sup> Maria, Hosp. D. Estefânia and Hosp. Egas Moniz – although the latter has just been discontinued). A few

private labs (2 in Porto and 2 in Lisbon) offer both cytogenetics (with a significant share of testing – almost 50% of all karyotypes) and some molecular testing. A few university-based labs and research institutes also offer some molecular testing, particularly for rare diseases.

The institutions of the national health service (IGM and the hospital labs mentioned above) are funded by the Ministry of Health, which covers buildings, maintenance, staff, equipment and, partly, consumables. In addition, they are reimbursed on a test performed basis, according to a price list approved and reviewed every few years. Testing performed at the private and university labs is reimbursed to them, also on a test performed basis, either according to the same price list or to separate protocol (for tests outside that list). In any case, the patients are responsible only, at the most, for a small nominal fee, provided they have a request form from a hospital (which will reimburse the labs) or a primary care physician (regional health administrations will make the reimbursement). With such a system, family doctors and hospital specialists thus act as gate-keepers, providing access of patients to genetic testing and enabling the labs to be reimbursed (in the case of presymptomatic, susceptibility and carrier testing, only a medical geneticist should make that request).

## Data collection difficult

A national referring network in medical genetics (Rede de Referência Hospitalar de Genética Médica) was recently planned within the national health service; however, it only covers for genetic services and consultations, not the labs. Nevertheless, in the publication that established that network, the working-group of experts estimated that, in 2001, 24,980 cytogenetic tests had been performed (11,959 of which were prenatal tests, 7,199 for lymphocyte karyotyping, and 1,815 FISH analyses); no definite conclusion was achieved on the number of molecular genetic testing, as there was a multitude of small labs involved and conflicting information from different sources. However, in a pilot survey for the OECD, 12 Portuguese labs reported 12,726 molecular tests in 2001 (but ranging 13-3,483 tests per lab) – apart from the private labs that did not respond, and an unknown number of small university and research labs, testing mostly for rare diseases, this could be expected to represent a large majority of the tests then being performed.

In the last official table, published in 2003, for the national health service labs, the prices of disease testing varied from 41,10€ (e.g., haemoglobinopathies) and 1.256,80€ (e.g., index case for dystrophinopathies). In addition to the disease, and locus or loci tested, and the methods used, the practiced prices vary substantially according to the context (i.e., diagnostic versus prenatal testing, or index case versus relatives in families where mutation is known). The price of reagents and other consumables is considerably higher than in other larger countries, one of the reasons why some of the prices are also higher.

## Regulatory framework still lacking

One of the main issues in Portugal is that there is no regulation as yet for new genetic tests (gene dossiers), nor is there yet a national commission for human genetics that might regulate them. Otherwise the recent law 12/2005 (26 January) governing personal genetic information, regulates the use, storage, property and circulation of genetic information and of biological samples, both for testing and research purposes.. Employers cannot ask for or use any kind of genetic information, even with the workers' consent, except for their health protection (in case of hazardous environments), and only if done in the context of genetic counselling and if their employment is not put at risk; the exception could be made in case of serious risk to public security or public health, in which case genetic testing should be conducted by an independent entity. No genetic testing or any kind

of genetic information can be requested in case of adoption, both to the adoptees or the prospective parents. In the case of minors, genetic testing should be done only in their benefit, after written consent from their parents or legal tutors, but also procuring the minors consent. According to this recent law, the government must now also regulate the offer of genetic testing, in order to avoid its direct marketing to the public or by public or private laboratories, and outside of the context of genetic counselling. Licensing by the government of public and private labs, as well as measures of quality assurance, determining their certification and accreditation, should also now be regulated.

## Corino Andrade (1906–2005): a clinical geneticist before his time

Corino Andrade who died last year was a neurologist and is best known for his description, in 1952, of a familial form of amyloidosis (I), which is still the most cited among all scientific papers from a Portuguese author. This became known as familial amyloidotic polyneuropathy, type I or Portuguese (FAP-I), or Andrade's disease though he himself later proposed the name hereditary amyloid neuropathy.

Curiously enough, this entity (the other FAP), which in many ways could have become a perfect model for the study of late-onset dominant disorders, before Huntington disease did, is still insufficiently known to the clinical genetics community. FAP-I was one of the first late-onset dominant disorders to have a biochemical marker prealbumin or transthyretin (TTR) and a presymptomatic test, after the causal mutation (TTR V30M) was found, in 1984. This clearly happened too soon, i.e., at a time when predictive and psychosocial genetics were in their infancy. Dr Andrade saw his first patient with this new disease in 1939, a woman from a fishing village (Povo do Varzim) near Porto, then followed by several others. He studied the disease in the community, noted its familial occurrence, performed careful pathological studies (first autopsy in 1942), and published his landmark paper in 1952 (i.e. after 12 years of clinical observations and careful studies, something unthinkable today, to establish its etiology and prove it as a new clinical entity). This peculiar form of peripheral neuropathy, with its unusual syringomyelia-like dissociation of pain and temperature sensation, was affirmed by the exclusion, among other, of leprosy (he found several patients in leper colonies) and the discovery of widespread amyloid deposits. Far from being a Portuguese rarity, FAP-ATTR V30M later proved to be throughout the world (with

its other larger foci in Japan, Sweden, and Majorca). Dr Andrade also contributed significantly to the description of another hereditary disease (Machado-Joseph disease, which became known also as spinocerebellar ataxia type 3, or SCA3), by studying it, in the Azorean islands, with Paula Coutinho, and unifying previous reports (1972–1976) of three separate entities. He founded strong multidisciplinary groups around FAP-I and MJD and inspired several lines of research, most of which are still very active and productive, and now on its third and even fourth generation at different institutions in the country.



Corino Andrade, in 1976, while examining a young boy (the youngest case known to be affected with Machado-Joseph disease in the country) in the island of Flores (Azores) (courtesy of Abel Roldao, ICBAS).

## Spreading the message



EuroGentest had several high level presentations in Brisbane

EuroGentest was in demand at the recent 11th International Congress on Human Genetics in Brisbane, Australia. Mike Morris and Els Dequeker of unit I were responsible for the workshop on quality assurance in molecular genetics. Mike and Els gave a presentation of both on the OECD guidelines for molecular genetics quality assurance and the work of unit I, whilst Jean-Jacques Cassiman also presented EuroGentest at a workshop on genetics and Public health in developing countries.

## Web and Press Corner

The web continues to attract record numbers of visitors with several new sections being added.



JULY 2006

108,181 hits

AUGUST 2006

116,733 hits

SEPTEMBER 2006

143,389 hits

September 2006 - Average hits per day 4,779 with a maximum of 30,818 per day.

In September the new unit 6 course database received 1,272 hits.

On the press front, EuroGentest was profiled in Bioforum magazine, whilst Jean-Jacques Cassiman was interviewed on the project for the influential GenomeWeb news service.

[www.eurogentest.org](http://www.eurogentest.org)

# EUROGENTEST PEOPLE



For the latest in our profiles we turn to unit 2, Information Databases and Cécile Gaudebout who works out of the Orphanet offices in Paris

#### NAME

Gaudebout Cécile

#### NATIONALITY

Française

#### QUALIFICATION

Master degree in Genetics  
Postgraduate degree in Quality Assurance in Cell Therapy and Gene Therapy

#### LANGUAGES

French, English, German

#### FAVOURITE MUSIC

I like almost every kind of music.

#### HOBBIES

Football: I like watching games particularly with our French team. I'm keen on cinema too.

#### LAST BOOKS READ

Ensemble c'est tout, Ana Gavalda

**Q:** Why did you get involved in EuroGentest?

**A:** I learned Genetics at the University in Paris and I was especially interested in implementing Quality Assurance in this field. That's why I was so happy to be recruited for Orphanet by Ségolène Aymé to be part of EuroGentest project.

**Q:** Do you enjoy working in EuroGentest, why?

**A:** Yes, I do! I think that EuroGentest aims are very important and will benefit to everyone from the "Genetics community". Through the EuroGentest project, it is possible to help Healthcare professionals get involved in a Quality process and to adapt Health Policy in response to the rapid development of genetic testing across Europe.

**Q:** What is your role in EuroGentest?

**A:** Scientific collaborator for unit 2

**Q:** Your hopes for the future of the project?

**A:** To extend our Network to non-EU countries which may have the same goals. And then that everyone in Genetics thinks and acts "Quality"!



## The next big thing?



THE HUMAN VARIOME PROJECT

After the Human Genome Project what next?

EuroGentest's coordinator Professor Jean-Jacques Cassiman was among the high level delegates from various organizations related to genetic health and funding agencies who agreed to launch the Human Variome Project at a meeting in Melbourne, Australia June 20-23, 2006.

At the conclusion the Genomic Disorders Research Centre was elected, and specifically, Professor Richard Cotton to lead the project. In simple terms the project aims to collect human gene variation with associated phenotype information and make it available to those who need it. This will involve global collaboration with a number of major interacting projects developed, funded and carried out by working groups. The scale of the project requires considerable coordination and funding which initially is being sought from Australian Governments.

The HVP intends to collect, curate and electronically record DNA variation (alleles) either mutation or polymorphism, in the canonical human genomic nucleotide sequence, with emphasis on disease and other phenotype relationships. This process is feasible because the Human Genome Project has generated a reference nucleotide sequence for the human species, and because there exists a systematic vocabulary for genes, exons, mutations, etc. Locus-specific mutation databases (LSDBs) provide "inch-wide, mile-deep" views, whereas genomic repositories entail complementary "mile-wide, inch-deep" perspectives. LSDB datasets typically concentrate upon variations that have a major or 'causative' direct influence upon one or more disease-related phenotypes. Whole genome variation databases tend to concern neutral variation and variants that only slightly modify or are only indirectly associated with disease. In other cases whole genome databases represent mutations in genes but fail to distinguish disease causing from benign mutations.

According to Professor Cotton: "The Human Variome Project will achieve improved health outcomes by facilitating the unification of human genetic variation and its impact on human health. It will support the use of human variation information in clinical environments across the world by developing the resources required to undertake the following tasks." ([www.humanvariomeproject.org](http://www.humanvariomeproject.org)).

## Latest fellowships

Congratulations to Ioana Ispas and Tamas Athos from Romania, Céline Lewis from the UK, Jana Camajova from the Czech Republic, Judit Balog from Hungary, Ján Mucha from Slovakia and Xavier Landivar from Ecuador who have received fellowships to carry out EuroGentest-related projects this autumn/winter. Fellowships are open to both EuroGentest participants and outsiders.

*“DNA test could replace the “trial and error method of prescribing drugs.”*

## Press Watch

Further confirmation of the rising public profile of genetic testing came last month with the award of the biggest prize in medical science to two scientists who pioneered a genetic technique that promises to revolutionise medicine in the 21st century, according to The Independent of London, on October 3.

This year's Nobel Prize for Medicine has been awarded for the discovery of RNA interference (RNAi) - a naturally occurring process for switching off specific genes. Andrew Z Fire and Craig C Mello, said the article.

Scientists are already using the technique routinely as a highly effective research tool, but the wider interest comes from RNAi's potential medical applications. Specialists believe RNAi could be used to develop radical new treatments for a variety of incurable disorders from Huntington's disease and certain forms of blindness to heart disease, diabetes and cancer, The Independent reported.

The piece quoted Professor Chris Higgins, director of the Medical Research Council's Clinical Sciences Centre in London, who said that the discovery of RNAi has revolutionised the understanding of how genes can be controlled. "Perhaps even more importantly, it provides a simple tool for manipulating gene expression in the laboratory, and with great promise for altering gene expression to treat diseases such as viral infections and cancer," Professor Higgins said.

Drug companies such as GlaxoSmithKline and Pfizer have already taken out licenses on various RNAi techniques in the hope of developing new therapies, the newspaper said, before going on to explain to readers that disease areas which are likely to benefit include:

**Blindness:** Two biotechnology companies, Sirna of Boulder, Colorado, and Acuity, of Philadelphia, are conducting clinical trials involving patients with macular degeneration. RNAi could block the growth of harmful blood vessels in the eye that cause visual impairment.

**Huntington's disease:** RNAi is being considered as a way of turning off the gene that causes Huntington's.

**HIV and Aids:** Scientists hope to disable the Aids virus by silencing one of the genes it needs for replication.

**Heart disease:** If scientists can switch off a gene involved in the build-up of cholesterol in the body they might be able to treat people who are born with very high levels of this damaging fat.

In September, the US publication Drug Week reported that DNA tests are now available to help determine safe drug dosages, explaining that patients using the popular blood thinner Coumadin (also known as Warfarin) will soon notice a new FDA label attached to their prescription. The warning? The patient's genes may dictate the safe dosage level for the drug.

This is important, the piece explains, because Coumadin affects the blood's ability to clot. If the dose is too low, deadly clots may form; too high, a patient may bleed to death.

Historically, physicians have used the "trial and error" method when prescribing Coumadin because it was never known how the patient would process the drug. Would it metabolize quickly, or stay in the bloodstream at dangerous levels? The only way to determine the correct dosage was to subject patients to frequent (often daily) blood tests. Dosage levels



Nutrigenomics could lead to more effective personalised diets to combat diabetes and obesity

were then juggled until the patient's blood reflected "safe levels," which could sometimes take weeks or months to determine - leaving the patient vulnerable to stroke, heart attack, or deadly bleeding. According to research cited by the FDA, warfarin alone is responsible for 15% of severe drug side effects. A new DNA test that determines the proper and safe dosage for Coumadin (within 1.5 mg/day) is now available to the public. The test reveals data from two specific genes that accurately forecast how the patient would respond to Coumadin.

Also in September, The Irish Times reported a debate among scientists at Dublin's Festival of Science about the value of personalised diets based on gene testing. The piece quoted Dr Siân Astley, of the Institute of Food Research, presenting the case for nutrigenomics and personalised nutrition.

"What we eat interacts with our body to affect long-term health. The 'one size fits all approach' [to healthy eating] isn't actually working," Dr Astley said. Personalising the health message would be more effective.

However, the newspaper also quoted leading sceptics Dr Helen Wallace, of GeneWatch UK, and Dr Tim MacMillian, from the Food Ethics Council, who questioned the ethics and efficacy of this approach. Nutrigenomics was "a marketing ploy with little actual health benefit", Dr MacMillian cautioned. Dr Wallace voiced concern about the increase in do-it-yourself genetic testing as seen in the United States and some European countries. She said she was concerned about the limited regulation of gene-testing companies and the lack of evidence that functional foods actually promote health.

In August, The New Zealand Herald reported the results of a study by Otago University which strongly supports the clinical value of pre implantation genetic diagnosis (PGD).

Government funding for genetic testing of human embryos will not bring about the age of the designer baby, reports the newspaper. The piece also reports that the New Zealand Government has budgeted \$500,000 a year to pay for PGD where there is risk of passing on a serious genetic disorder.

### Special thanks to contributors to this issue –

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