NEWSLETTER 4/2006

The Netherlands looks to continue progress through EuroGentest

With Amsterdam hosting the EuroGentest meeting this year, it seemed a good opportunity to take a look at the current state of genetic testing in a country renowned for its progressive attitudes and modern health service. We find a network of genetic centres in place - Leiden is shown opposite - that is widely admired, leading research, strong and influential patient groups and most surprising in these days of healthcare rationing, annual budgeting negotiations. However, there are also growing concerns over the future and hopes that EuroGentest can help to solve some of the challenges Dutch geneticists share with their European counterparts.

Mendel rediscovered. Waardenburg discovered

As with the Czech Republic profiled in the last issue, there is another strong historical link with Mendel. After his work was published in 1865, it took 25 years before it was "rediscovered" in 1930 independently by three scientists: de Vries, Correns and von Tschermak. The Dutchman Hugo de Vries (1848-1935) was a botanist who started his studies in 1869 at the University of Leiden. Later in 1875 he was appointed professor in Amsterdam and while continuing his plant studies became famous for his mutation theory (1902) and introducing terms such as gene and mutation. Another major contribution to genetics was made in the 1950s by Dutch ophthalmologist Dr. Petrus van Waardenburg in Arnhem when he first described Waardenburg syndrome - a group of hereditary conditions characterized by deafness and partial albinism (pale skin, hair, and eye colour). This is estimated to affect around 1 in 10,000 children and be around 90% hereditary.
Foundations in the 80s

Returning to the present day, and as mentioned previously the Dutch network of genetics centres is widely admired. Bert Bakker, Professor of Human and Clinical Genetics at Leiden University Medical Center and head of EuroGentest Unit 5, explains that this stems from a far sighted cooperative initiative: "Under the guidance of Professor Hans Jalland, 7 ‘Clinical Genetics Centers’ were founded in 1980. Each comprising counselling/clinical cytogenetics, clinical metabolic and prenatal diagnosis/choirs/ultrasound departments. In 1981 when the first DNA tests became available, Dutch researchers were quick to see their potential in molecular genetic testing and prenatal diagnosis. Various university groups sprang up to take the opportunity to start clinical molecular genetic testing combined with counselling right from the outset. In 1986, a survey was undertaken and funded from health insurance agencies was requested for those who were interested and capable of setting up a diagnostic laboratory for specific genetic disorders. This led to a lump sum financing for four clinical genetic centres offering DNA diagnostics – Groningen, Leiden, Nijmegen and Rotterdam - initially for four years. The trial was a success. By 1996, 7 centres were funded.”

Pioneering research
DNA testing had become part of the regular healthcare system and grew at a phenomenal rate, particularly in the closing years of the century. For example, in 1995, a total of 1600 tests were performed for 25 conditions. By 2001 this had risen to 4,000 for 25 conditions. Currently some 32,000 tests are performed. There are now specifically Dutch genetic diseases, although there seem to be specific founder mutations in conditions such as breast cancer and colorectal cancer. Epidemiological research is ongoing into this area, along with population studies into multifactorial diseases taken advantage of the fact that despite their reputation as a screening exploring nation, many Dutch tend to stay put in their local area. Other pioneering work is being done in explaining the need for neonatal screening for specific disorders in immigrant groups.

Strong public and government support
“One of the strengths of the system that has allowed us to grow and wider our services whilst maintaining quality is that there has been a common agreement on both the tests being offered and that for most disorders only one or two laboratories should offer a specific test. In this way we build up real centres of excellence. A few years ago most of the Clinical Genetic Centres moved back into the university medical centres lightening the link between research and practice. Another major bonus is the attitude of government. As with GIG in the UK, the Dutch Genetic Alliance, has been instrumental in creating political understanding and goodwill. We have an annual budget negotiation that gives us much needed flexibility to respond to new needs. However this is balanced by the fact that up to now there is no a single tariff for a clinical molecular test per person per gene (20-25€) which is paid once by the health insurance companies. This includes sequencing of a whole gene even if there >400 exons! Everything is included in this price, staff, space, training of staff, Q-management, equipment etc. So in other countries we have funding challenges," continues Bakker.

Common needs addressed
Turning to EuroGentest, Bakker sees the project as helping address common needs: “Since 1998 our lab in Leiden has compiled to a quality standard (ISO17025), which was needed to fulfill our diagnostic tests at the highest level. The effort to maintain such an accreditation is huge especially in the first few years. Also the strict validation and implementation rules seem to hamper the sale implementation of novel technologies. For the latter we need to collaborate with labs in a similar situation, more resources and forging links with industry. Molecular genetic labs have many good clinical, as well as molecular characterised patient samples which can assist in the development and validation of new technologies. Furthermore, genetics has incredible potential - as we begin to understand the complex gene-environment interactions we can look at improved testing for a whole range of diseases such as cardiovascular, cancer, hypertension, arthritis, migraine, epilepsy, Parkinson’s and Alzheimer’s. Even further down the line, we could control areas such as infectious diseases and wound healing. Through pooling efforts in EuroGentest, we can create a platform for this progress.”

New website look
The EuroGentest website continues to attract record numbers of visitors. The traffic for April and May 2006 was a total of 97,471 with a daily average of 3,249 and a maximum daily number of 6,467. In view of this popularity and the fact that the site has grown significantly and at a very fast pace over the past years the web team decided it was time for a redesign. The new design went live for ESIG and according to Olivia Willock, project manager: “The aim of the new site is to provide an easy to use and more user friendly but novel site. However, we have now shifted the emphasis from the project as a whole to the specific activities of their individual units - the home page has direct links to the sites from the homes - there were sleepy like the periodic table to get a clean and scientific look. The new site has been designed in conjunction with Waypoint’s design partner Carl Jones Designs.”

Quality Assurance database of European genetic laboratories
A public database including reliable information concerning quality assurance in genetic testing is important for consumers, to facilitate informed choice of laboratory partners for performing genetic tests, for genetic services, to allow the selection of partners for referral of tests which cannot be performed locally, and for the laboratories themselves, to valorize their efforts and investment in quality assurance.
EuroGentest WP1.2 is bringing many initiatives together to provide a public database of QAs information in genetics services. As a first step, we surveyed the current status of accreditation, certification and participation in EQA in European laboratories. The survey was distributed to more than 2000 laboratories in 35 countries. To ensure the reliability of the data, the collected information will be validated prior to dissemination to laboratories and consumers via a European QAs database, through www.eurogentest.org and www.epha.org.

To date, over 100 laboratories have replied and the data are currently being validated and analysed. Laboratories who wish to participate are invited to contact gauge@eurogentest.org.

Press Watch
Over 1000 stories in the world’s press over the last couple of months. Here we take just a small selection to show the different ways in which genetic testing is described, not always positively and the kind opinions the public are forming.

Who’s the daddy? Or Mummy for that matter are issues concerning an increasing number of people according to a spate of recent press stories. Figures for the number of men unceremoniously raping a child who is later found to be their own has increased by 40% in the last 25 years. In Australia, such is the level of concern that men’s groups are now calling for DNA testing of children to be made mandatory at the time of birth. The frightening news is that this is not so. While DNA tests aren’t so smart, however saying they are the world’s worst at successfully predicting that a disputed child was actually theirs. In a more amusing tale, the Mail on Sunday reported on ‘The mother with three children who don’t share her DNA’ Lydia Fitchfield, 26, had two children naturally and was expecting a third when the entire family was DNA-tested by benefits agency officials. Although the tests showed her partner Jamie Townsend was the father, a shocked Lydia was told: ‘There’s a problem. ’ No, there’s no you are your mother.’ With just weeks to go before she was due to give birth, the young American was astonished at using someone else’s children to commit benefit fraud. A court agreed that she was not their mother and prosecutors called for them to be taken into care. Faced with the loss of her son Jamie, four, and daughter Jamieelyse, three, and a possible jail sentence for fraud, Lydia agreed to a DNA test on her third child, 3t, within minutes of him being born in the presence of official witnesses. The same was done for her second child. The DNA tests showed the mother was the one who had just delivered her. The court was forced to admit that the ‘reliable’ DNA evidence was wrong and that all three children were 100% Lydia’s. She could have major implications for the use of DNA evidence in courts worldwide. Lydia and her legal team established that she carried two separate sets of DNA the dominant one that showed she was the DNA tested, and a second set that appeared only in the internal organs but was the one she passed on to her children. The incidence of such cases known as ‘chromas’ could be as high as one in seven of the UK population. Scientific also believes that chromas has become common with the increasing use of fertility treatments such as IVF which makes them more likely to occur.

On the scientific front, several papers reported the Nature Genetics paper on Parkinson’s disease being triggered by damage to the DNA of neurons in the substantia nigra area of brain.

Diagnostic tests came under scrutiny, particularly in an article in the New York Times which promised a resolution in the costs. In an article in 2004 the article cautioned that clinical utility must be established and expressed quality assurance concerns over companies manufacturing and performing tests in their own laboratories. A scandal that touched our colleagues in SAFE also broke over the Baby Gender Mentor kit marketed to predict gender. About 4,000 women in the US and UK bought the kit and began making plans for the new arrival but then several weeks later, about 100 discovered that the tests had got it wrong. So in a class action lawsuit filed in the US district court in Boston on behalf of 16 women the maker of the Baby Gender Mentor was accused of breaking their promise. The suit seeks to bar Ana-Gen Biobab from falsely marketing its test and to compel the firm to honour its money-back guarantee. Talking about recently, the recent batch of false tests launched in the new year was matched by news of a gene test to help prevent the chance of early menopause developed by the Medical University of Vienna.

www.eurogentest.org
One of the most common genetic defects, Cystic Fibrosis (CF) affects one in 20 people in northern Europe and one in 40 in the southern part of the Continent. Most of those affected display no symptoms but are carriers of the disease.

Carriers do not pass on the condition to their children unless their partner is also a carrier. If both parents are carriers, there is a one in four chance that each pregnancy will result in a child with CF. Symptoms are extremely serious and life threatening. Most sufferers are diagnosed with the condition in early childhood, but a minority only develop symptoms in their teens.

Sadly, the average age of death of a CF sufferer is around 30-years-old. CF affects vital organs in the body: the lungs and digestive system, particularly the pancreas, are often clogged with sticky mucus which makes it difficult to breathe and digest food.

The gene to identify CF was discovered in 1989 - since then, research has increasingly focused on how to correct the basic genetic defect. The gene is called the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). There are approximately 800 possible mutations of CFTR that can cause CF.

Professor Jean-Jacques Cassiman, who is the co-ordinator of EuroGentest, says: ‘Our efforts are focusing on the harmonization of standards of testing and counselling for the parents of children and young adults with suspected CF. In some hospitals, testing is only offered for one mutation on the CFTR gene. This is not acceptable. All EU hospitals should be offering tests for at least 25-30 mutations, which covers 95% of cases. The information that is given to families is also crucial. Parents need to clearly understand the risk for any other children in the family, existing brothers and sisters as well as future ones.’

Professor Cassiman added: ‘The CFTR gene is an extremely interesting one. It can regulate proteins which cause other conditions. And we have yet to fully understand all the variations, particularly the milder ones.’

What it’s like to live with Cystic Fibrosis

Ulfrik Pypoes, 29 (30 in June) a trainee lawyer from Leuven, Belgium, has moderate CF. Here she explains how the disease affects her every day life and future plans.

I have mixed feelings about my 30th birthday. While I am dealing being in my 30s - like most people of 29 - having CF means that it’s really nice to reach this age.

I have 75% normal lung function, which is very good for a CF sufferer of my age. It means that I can do fitness classes three times a week for an hour and a half.

When people meet me they do not know there is anything wrong with me. I don’t look or sound any different to anyone else - some CF sufferers cough a lot and are underweight. I am a normal weight - 57kg at 1.68m - though I have to eat more than most people - 3.000kcal a day - to maintain my weight.

The only thing that’s different about me when you meet me is that I always refuse to shake hands and kiss unless I am certain that the other person hasn’t got a cold or chest infection. The reason is that CF sufferers are more prone to colds and coughs than other people. I get about four or five every winter and it takes me longer than most people to get over them. We’re talking about a week in bed to recover. Sometimes I do not feel like explaining why I am not shaking hands and it can be awkward - I think sometimes people think I am a bit strange: but it’s such an effort telling people why you are doing it when you are meeting them for the first time! I try not to spend much time with my friends’ children because kids often have colds, which saddens me.

I do a lot of work for a charity in Belgium called the CF Association. There’s a risk of cross infection from other CF sufferers so I don’t meet other sufferers in person. I have webmail instead. It’s important for me to keep in touch with other sufferers because I like to know what it is like to lose a lot of your lung function. CF is a regressive disease which means that eventually, slowly but surely, I will lose small percentage points from my lung function as I get older.

For this reason, I have decided for the moment that I do not want to have children. It’s very sad for me to think I may not be around for my parents as they get old and need my help and I think I would feel worse about my CF if I had children. Being a parent is a lifetime commitment and I am not sure how long I will be around. The other reason is that I take 90-minutes twice a day to do breathing exercises and use a nebuliser to control my CF. The nebuliser makes the mucus less sticky and the exercises help me move the mucus around in my lungs to redistribute it away from my throat, so I don’t think I would have time to look after a baby as well CF can affect your fertility but I have no idea if it has affected mine.

I am realistic about the chances of finding a cure for CF - I don’t think it will be in my lifetime although of course I do hope that this will happen.”

Unqualified welcome to EuroGentest quality initiatives

The desire to harmonize the quality of laboratory genetic testing and genetic counselling for both professional and public confidence reasons was one of the key reasons for starting the EuroGentest Network. Moreover the initiative largely stemmed from professionals in the field who were finding themselves in a sense ‘victims of their own successes’ Els Dequeker and Ros Hastings, co-leaders of EuroGentest’s Unit 1 quality initiatives, explain: “The rapid advances in research and technology in the last 20 years have given us the opportunity to offer both individual testing and screening on a far wider basis than ever before. However, such laboratory tests cannot be implemented without proper evaluation of the new technologies and the availability of reference materials. In addition, the monitoring of laboratory performance through external quality assessment (EQAs) schemes and assurance of the quality management system is essential. Otherwise, there would be no way of gaining and maintaining the publics’ confidence in the service being provided. The increasing workloads, expanding repertoire of tests and growing relative importance of genetic laboratories within healthcare systems also raise the question of the need for a further “layer” of assurance through laboratories seeking and gaining accreditation from internationally recognized accreditation bodies. Since genetics is a fairly close-knit community, we knew colleagues across Europe who were thinking along the same lines and saw the opportunity for a European Network such as EuroGentest to deal with these issues.”

Scale of project greater than expected

As with the other EuroGentest units, the first year’s activities were taken up by evaluating the scale of the challenge. Matters were complicated by the fact that genetic testing is done across three disciplines: cytogenetics, biochemistry and molecular genetics. These laboratories may be part of one institute, but more often than not they are separate sites. Furthermore, private laboratories continue to spring up all over the EU. After extensive research across the member states, it turns out that there are a far larger number of laboratories involved in genetic testing than previously thought - 700 in cytogenetics alone rather than the expected 300.

4 key areas identified that need addressing

In January this year, 2,500 individuals within the EU genetics community were contacted to complete a survey of genetic laboratories on-line. “This unique database of laboratories will enable us to survey labs from all 3 disciplines. We were delighted at the initial positive response,” continue Els and Ros. “Preliminary data replies received to date from 300 laboratories show that 47% are not accredited, although 68% performed EQA. Data from cytogenetics suggests this may not be true representation of EQA uptake when all labs have responded, as a survey of EQA providers suggests that uptake of EQA is in the order of 80% for cytogenetics labs.” Aimed with this confirmation of the need to spread the quality message, Unit 1 is now focused on addressing four key areas - helping laboratories prepare for accreditation, promoting uptake of EQA schemes, facilitating the production of reference materials and accelerating the validation of new diagnostic tests and methods.

First accreditation audits by end of the year

Gaining accreditation is a huge task for any kind of laboratory, even more so for genetic testing laboratories where a large number of tests are developed in-house. Despite advances in automation, work remains highly labour intensive at all stages – from sample reception and preparation to result interpretation and reporting. “Right from the beginning it was decided that one of the key roles for EuroGentest should be to help laboratories prepare for accreditation. Knowing where to start might be a more accurate description, since the situation is very confusing even for the experts. We have, therefore, collated all of the existing requirements and accreditation bodies across Europe. A network of accredited and non-accredited EuroGentest laboratories has been established to give advice and mentor those considering applying for accreditation. As a further encouragement, we have had funding to hold workshops which concentrated on passing on first-hand experience of what is actually involved in gaining accreditation. These workshops were very well received and seem to have had the required effect. We are delighted that the first EuroGentest "mentored" labs are due to be audited in the coming year.”
European EQA scheme to be initiated

A similar situation existed with external quality assessment schemes. Again the first task was to create a directory of available schemes for all three genetic disciplines. Efforts are now being concentrated on bringing together the various bodies running the schemes to encourage harmonization. One key issue, for example, is to establish a consensus on what constitutes “Good and Poor” performance across the three disciplines. This has already been discussed at EuroGenet test meetings in Basel, Prague and London, where it was also recommended that a two-track approach to promoting EQA should be adopted. In the larger member states, where national schemes already exist, these schemes should be continued and membership enlarged. For the smaller member states, where there is an established European scheme, these schemes will also expand their membership and where no European Scheme exists, one will be created. The first steps towards this will be taken during meetings later this year.

First reference materials commissioned

Without reference materials, it is extremely difficult to validate the results of diagnostic tests. However, given the relatively small numbers of tests for some disorders performed in various countries, the production of them on a national basis is both impractical and uneconomical. EuroGenet has therefore taken the initiative in persuading potential suppliers of the viability of producing for a European market. Already NIBSc has been subcontracted to produce PVS/AS materials. The next priorities are now being investigated. Another area where EuroGenet has taken a lead is to see whether the European IVD directive, which requires all routine medical in vitro diagnostic tests to be CE marked before they can be used routinely, applies to the in-house designed assays common in genetics.

Generic SOPs on the way

Finally, along with Unit 5, we are looking at how to validate the increasing number of new diagnostic tests and technologies being offered to genetic laboratories. We find ourselves in a Catch 22 situation – individual labs are being asked to trial new products, but are usually so busy they do not have enough time to properly evaluate technologies that could ease their workload. By pooling the resources of EuroGenet members, we plan to provide a service where genetic SOPs can be produced. We are starting by looking at three key new test/methods in particular – MLPA, CTR screening and DNA extraction. The aim is to have the first SOPs by the end of the year,” report EIs and Ros.

Massive effort bringing rewards

“Another overriding principle is for our work to be as transparent as possible. Through the EuroGenet website for example, the public will be able to check which labs are accredited and the quality schemes they follow. In this way we hope to maintain the public confidence. In general we believe we are making major progress. In particular we have been heartened by the enthusiasm of participants. There are 24 individuals and 2 SMEs in Unit 1 and they, along with the personnel in our laboratories, have all made major contributions, often working in their free time. The few sceptics have been won over and the Network of Excellence is proving the ideal vehicle for our aims, being flexible and practical,” conclude EIs and Ros.

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Workshop on genetic testing in minors

Predictive or carrier genetic testing in minors is a controversial issue. When a genetic disorder is diagnosed in a family, an immediate question usually asked is whether other family members are at risk. When the relatives in question are adults, they can decide for themselves whether or not to undergo a genetic test. Children at risk, however, are dependent on others, usually the parents, for decisions about their health. At the end of last year, Unit 4 (Hetman Nys, Kris Dierickx, Louise Stultens, Pascal Boroy) of the EuroGenetest-project (Ethical and legal issues) organized a workshop on the ethical aspects of genetic testing in minors in Leuven. Open to invitees only, the meeting was attended by representatives from EuroGenet (Unit 3, 4 and 6), the Professional and Public Policy Committee of the European Society of Human Genetics, the European Genetic Alliances’ Network and other leading experts.

Difficult questions

Various difficult questions have to be considered when dealing with this topic. Firstly, who can decide about performing a genetic test in children and adolescents (also in cases where there are no compelling medical reasons to perform a test)? Genetic testing of children different from any other kind of medical procedure that is being done in children and adolescents? Do parents have rights on the genetic information of their children? Or is performing a test at a young age an abrogation of the child’s future capacity to make his own informed, autonomous decision as an adult? Does testing children breach the confidentiality and privacy of genetic information?

Secondly, which decision is serving “the best interests of the child” best? If the test gives a clear result and leads to medical benefit including preventive measures and therapies, a genetic test will mostly be considered as justified. If the medical benefits are uncertain or will be deferred to a later time, this justification will be considered less compelling. In addition, it is an open question if substantial psychological benefits may also be a justification to genetic testing. The benefits and harms of many genetic tests are often considered more psychological rather than physical. Relevant issues include anxiety, self-image, uncertainty, and the impact on decisions relating to reproduction, education, career, insurance and lifestyle. Are these justified reasons to perform a test? And finally, what is the best age to perform a genetic test? In childhood, in adolescence or in adulthood?

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Appeal for further work

Since the introduction of genetic tests, several guidelines have been elaborated on the issue. The latest European professional guidelines, however, on the issue is from 1995 from the German Society of Human Genetics. The only patient perspective on the issue is the statement from the Genetic Interest Group that is issued in the same year as a reaction on the report of the Clinical Genetics Society. Therefore the group that participated in the workshop recommended that further steps should be elaborated in this ethical discussion. The group appealed to organize more activities (conferences, workshops) in this field and to work, together with main stakeholders in the field of genetics, towards concrete results (educational materials, case discussions, recommendations or guidelines) for clinical geneticists and other health care professionals. In Unit 4 of EuroGenet the issue of genetic testing in minors remains a priority.

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EUROGENTEST PEOPLE

EuroGenet has attracted many of the leading names in genetics in Europe. Equally exciting though are the number of enthusiastic young scientists – from recent graduates to PhDs - who have joined reflecting the growing popularity of genetics as a discipline.

Bárbara Rocha Guimarães

Portuguese

Degree in Social Communication.

Post-Graduate Degree in Public Health

English, French

I like almost every kind of music. One number that reminds me of some very nice days is "Disappointed in The Sun".

TORRES

I really enjoy photography and I also like biking, but sometimes I am a bit lazy.

Les Rivières Poupres, Jean Christophe Grangé: Porto de Abrigo, Jorge de Sousa Braga

Science journalist at Abel Salazar Institute for the Biomedical Sciences, University of Porto

Q: When did you become interested in science?

A: Since I can remember my life had everything to do with Science. Daughter and grand-daughter of physicians, I was always very interested in the mysteries of life. I even started a Veterinary Medicine Degree, but soon realised that my ideal occupation would be communicating Science’s advances.

Q: Why did you join EuroGenet?

A: EuroGenet was a fantastic opportunity for me to pursue my objective of communicating Science! I’ve just started and I am loving every second!

Q: What is your role in EuroGenet?

A: Researcher, Unit 3 (WP3)

Q: Do you think EuroGenet will make a difference in Portugal?

A: Genetics opens new fields in medicine; it’s almost an unimaginable universe! EuroGenet is a project that is presenting Genetics and its practical and philosophical aspects to Portuguese people. Portugal must realise that lots of Portuguese scientists are involved in fantastic projects such as EuroGenet that will improve our quality of life.