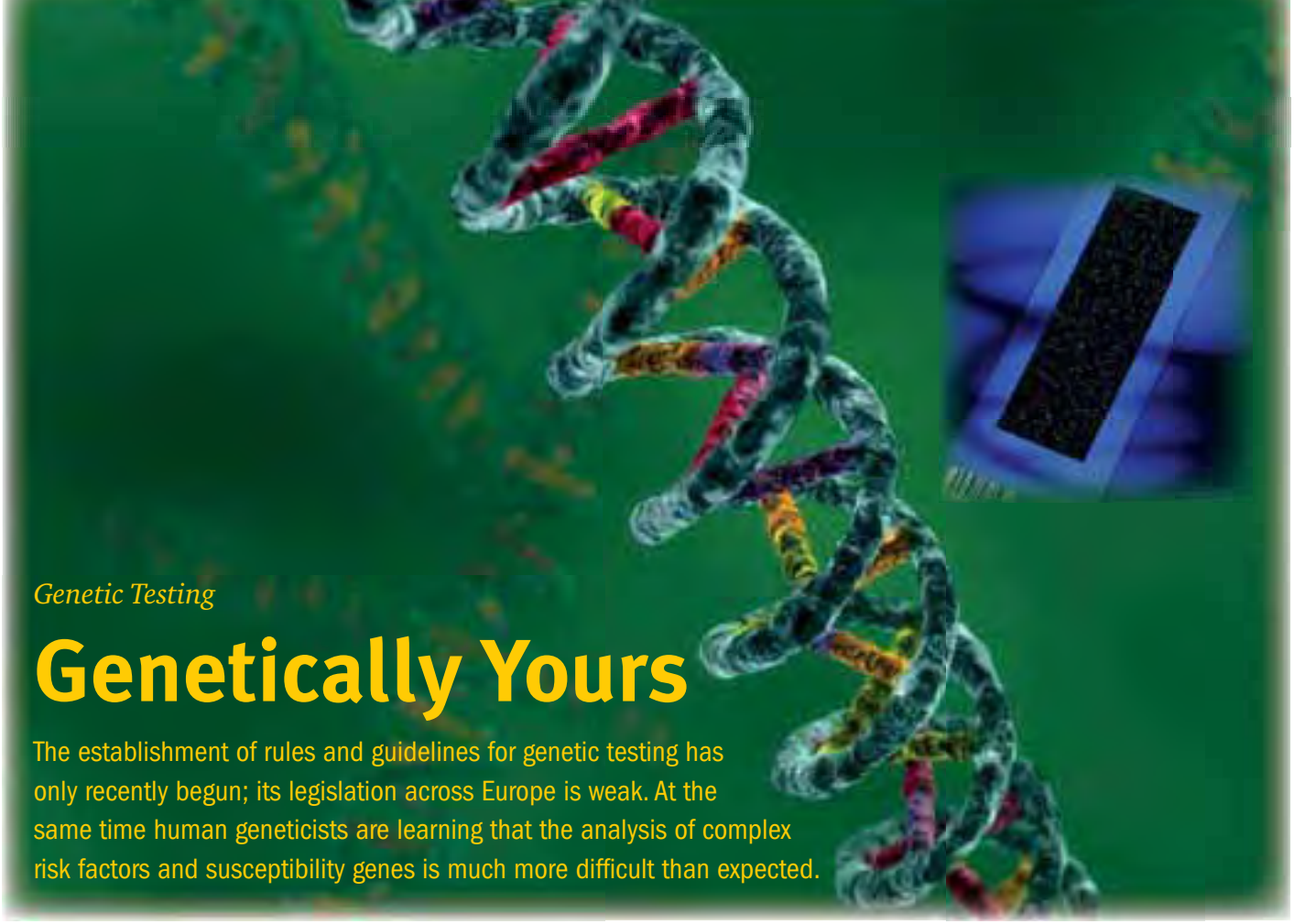


Genetic Testing

Genetically Yours

The establishment of rules and guidelines for genetic testing has only recently begun; its legislation across Europe is weak. At the same time human geneticists are learning that the analysis of complex risk factors and susceptibility genes is much more difficult than expected.

It started more than fifty years ago, in 1956. Using colchicine to arrest cells in metaphases and a hypotonic solution, A. Levan and H. J. Tjio forced human cells to swell in order to get a closer look at their chromosomes and, a logical first step, to count them. As every schoolchild learns today, the total was 46.

This new ability to handle chromosomes not only delivered interesting facts about life but also gave birth to a new field of medicine: cytogenetics, the study of the structure of chromosome material. Abnormalities arising from nondysjunction events moved into the scientific focus and only three years later J. Lejeune discovered that patients suffering from Down's syndrome (Trisomy 21) had an extra copy of chromosome 21. The discovery of the famous Philadelphia translocation, cause of chronic myelogenous leukemia, quickly followed; sex chromosome abnormalities, namely Turner syndrome or Klinefelter's syndrome, were also identified.

Today this list seems endless, as do the genetic tests offered by hospitals and medical institutes. Just take a look at their websites and you will be surprised by how much can go wrong within our genes. Although cytogenetic studies still attract the limelight they have been joined by molecular and biochemical testing. Together, they form what is generally known as genetic testing or the attempt to trace and elucidate human genetic disorders.

700,000 tests per year

According to the website of the EU-funded programme EuroGentest (*http://www.eurogentest.org*), more than 30 million people in the European Union suffer from a genetic disease. Every year around 700,000 tests are performed in approximately 1,500 laboratories and all numbers seem to be on the increase.

Claus Bartram, Director of the Institute for Human Genetics in Heidelberg, Germany and a member of EuroGentest's advisory board, estimates that there are about 4,000 classic genetic diseases, most of which are monogenous, i.e. caused by the alteration of only one gene. Around 1,000 have been elucidated so far. "They actually only affect two to five percent of our patients", explains Bartram. "But as we know today that in almost every disease a genetic disposition is involved, human genetics and genetic testing are entering a new dimension."

As far as techniques are concerned, Ulf Kristoffersson from the Department of Clinical Genetics at the University Hospital Lund, Sweden, is convinced that testing will become increasingly molecular. The clinical geneticist and consultant started work in human genetics almost forty years ago and, besides many other programmes, is involved in EuroGentest as well. In his opinion, in about ten years there will be routine use of microarray testing instead of cytogenetics. "But still we need to know much about normal variation of microarrays", Kristoffersson emphasizes. And, not surprisingly, money will be the determining factor. Microarrays are expensive while cytogenetics need only an incubator, a microscope, nutrients and some tags to stain with.

Parts of a postal system

But let's come back to the present. What does genetic testing look like today? "We are more part of a postal system than testing in our own labs", laughs Kristoffersson. The University Hospital Lund provides nearly any genetic test, a service that is based on collaboration with other labs. "You cannot do all tests yourself. That would not be cost effective".

The University Hospital only carries out basic analyses that need simple, robust techniques and not too much sequencing. "When it comes to sequencing it gets a bit more difficult." Kristoffersson explains the meaning of work sharing: "It is like cooking. It will always take some time until your meat balls taste the same as your mother's." Tools like the European database Orphanet ease the search for laboratories. (*http://www.orpha.net*)

Geneticists in Eastern European countries also use this database. "One very important event for us in 2006 was the joining

of Serbia to the Orphanet", says Dragica Radojkovic, Team Leader at the Institute of Molecular Genetics and Genetic Engineering (IMGGE) in Belgrade, Serbia, and a participant in EuroGentest. In contrast to the system of work sharing in Sweden, a significant problem in Serbia remains fragmentation and lack of centralization. Clinical genetic services are provided by seven regional medical centres that so far have failed to work together in a well-organised way. Radojkovic explains that "the IMGGE itself collaborates intensively with clinical centres, genetic counselling services and hospitals in the whole country, which refer samples to us" in an effort to improve the situation.

One step forwards, two steps back

Differences between Eastern and Western or Northern Europe are also apparent on a technical level. Most of genetic laboratories in Serbia are first and foremost classical cytogenetic facilities. "Doctors are more familiar with cytogenetics than with molecular genetics", Radojkovic says. Nevertheless, recent years have brought some improvement as the introduction of molecular services in prenatal and postnatal testing have had a substantial impact.

In spite of technical and organisational difficulties, the real challenge in the field of genetic testing is the genes themselves. After all, nearly 3,000 of the more 'simple' monogenous diseases are yet to be investigated. And as if this was not enough, the regulation on the post-transcriptional and epigenetic levels makes the work even more tedious. Ulf Kristoffersson: "Genetic modifiers depend on what happened to you in your fetal life or to your mother and father in their fetal life, or even to your grandparents. This leads to YOUR risk of having a disease."

"The market for useless tests is steadily growing and operates according to the mantra: send us some saliva but don't forget the cheque!"

Claus Bartram, Director of the Institute for Human Genetics in Heidelberg, Germany

Furthermore, balancing effects due to counteracting health factors are often overlooked. And what about cases where risk factors are not additive but might even cancel each other out? Kristofferson puts it in a nutshell: "If you only have factor A you may have an increased risk, if you only have factor B it is the same, but if you have A plus B it might be reduced."

According to the geneticist, the analysis of complex risk factor and susceptibility genes on an individual level lies in the very distant future. "I now think we are further from there than I thought

two years ago. Genetic testing will be for rare diseases. I do not think that the challenges for tomorrow are the low penetrant genes."

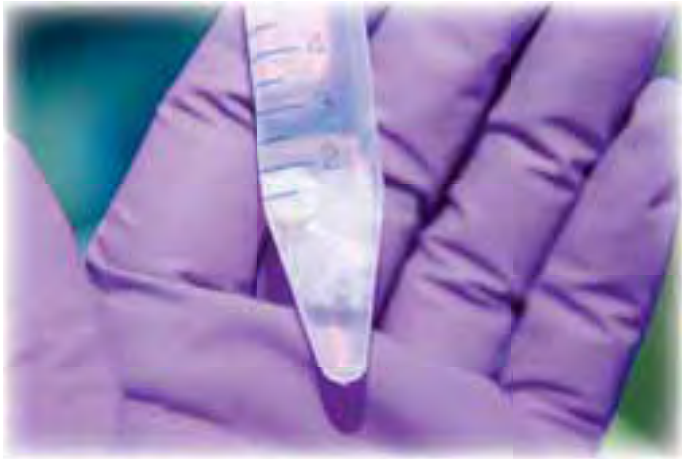
An optimistic outlook

For Claus Bartram, recent developments give more reason for an optimistic outlook. He puts the scientific focus of the years to come on the more complex diseases involving multiple genes as well as environmental factors. "Techniques allowing large-scale analysis will be very useful for this purpose. Gene expression profiling and DNA chips will enable us to analyse subtle defects on all chromosomes at the same time." But the scientist agrees that these techniques need more validation before they can be used for genetic tests targeted at common diseases. "Doing this, we have to be careful not to simply transfer the knowledge of monogenous diseases onto the bulk of common diseases." One of the biggest challenges would be to reduce the accumulating data on individuality to a simpler level.

A low penetrance of a risk factor gene means even more difficulties: if the scientific value of a genetic test is compromised by the complexity of the disease, this affects the risk assessment. Bartram gives an example: "If you have a disposition for Huntington's Chorea, the risk that you will actually get this disease is one hundred percent. The penetrance of the breast cancer genes BRAC 1 and 2 is lower, at eighty percent. These percentages shift downwards until we end up with the common diseases that are based on many different dispositions and environmental factors."

The essential role of proper counselling

For him, counselling is an essential part of genetic testing, especially because of the likelihood that a geneticist will need to explain his results clearly. "This is one of the most prominent difficulties in medicine: to communicate about likelihood in a way patients as well as normal doctors understand", Bartram says. It is necessary to talk not only about relative values but also absolute numbers. If one has, for example, to provide a prenatal diagnosis of risk, one draws upon the age of the woman. If she is around forty, the risk of giving birth to a child suffering from Trisomy 21 is thirty times higher than the risk for a twenty-year-old woman. "This, of course, sounds enormous. But we have to look



at the real risk as well, which for a forty-year old woman lies at one percent" Bartram emphasises. The basic risk of having a child with any genetic disorder is three percent. So this value now goes up to four percent – which does not sound as dramatic as "thirty times higher" at all. Making this plain to patients is the purpose of genetic counselling.

An evaluation of its clinical relevance should accompany each genetic test. How can this be ensured? During his presidentship of the German Human Genetic Society, Bartram strongly pushed for legislation: "We have to prevent the formation of a market of thousands of tests that do not come along with proper interpretation." Although Germany appears to be quite sensitive when it comes to genetic testing, regulation is still absent. According to Bartram, the market for useless tests is steadily growing and operates according to the mantra: "send us some saliva but don't forget the cheque!"

"If you only have factor A you may have an increased risk, if you only have factor B it is the same, but if you have A plus B it might be reduced."

Ulf Kristoffersson, Department of Clinical Genetics at the University Hospital Lund, Sweden

Bartram regrets that "each political party already has a draft. But the political relevance of genetic testing is too small to pass a law". There would be no need to regulate every single test but a broad law to ensure counselling and quality assessment would be indispensable.

"We do not have any statutory regulation of genetic testing" says Dragica Radojkovic. As in Germany, nobody in Serbia is responsible for the evaluation of new tests. New tests are not even added regularly to the register of tests available and laboratory accreditation simply does not exist. To tackle this problem the Serbian Ministry of Health founded the National Committee for Perinatal Medicine. "One role of this committee is to formulate the guidelines for genetic testing in Serbia", Radojkovic explains.

"In Sweden everything is allowed as long as a licensed doctor prescribes it", says Ulf Kristoffersson, describing the situation in the Northern Europe. The doctors are then responsible for the outcome, of course. "It is like prescribing a drug for you. There is no difference."

"Testing is done when there is a reason to do it"

Nevertheless, the rules governing pre-symptomatic testing are a bit more complicated. "Testing is done when there is a reason to do it." Following this guideline, tests for breast cancer are usually recommended from the age of 25 and only when there is a strong suspicion that the patient is a mutation carrier. A further case in point is the availability of therapies. Mutations such as the one in the RET proto-oncogene, a tyrosine receptor on chromosome 10 which causes thyroid cancer in children when they are approximately eight years old, should be traced earlier. Kristoffersson: "If you were a mutation carrier we would remove your thyroid at the age of five. So it depends on when you are expecting to get the disorder and if there is a prevention or therapy."

When it comes to legislation he has to concede that Sweden does not have any specific regulation of genetic testing. Howev-

er, there are at least guidelines covering quality assessment in healthcare provided by the National Board of Health and Welfare. Also, most Swedish laboratories are accredited and soon will even be specifically assessed in clinical genetics.

Addressing another point, Kristoffersson adds: "What I think is very important here is that pedigree data is protected… Sweden is, I think, the only country which has this protection".

But, when it comes to genetic testing, doctors still have a heavy responsibility towards their patients. Are they really prepared for this? "Medical students learn a lot about molecular genetics during their studies. But they are not educated in how to handle a family study" Kristoffersson says. Surveys show that many doctors lack confidence when dealing with genetics. According to Kristoffersson, clinical geneticists should act as teachers to guide and assist their colleagues who handle the patients. "We now have a service in genetic testing for the five to ten percent of the population which, sometime during their life, will experience a genetic disorder. In Europe, less than 1,000 medical doctors specialize in genetics. We have to focus on backstage coaching of our colleagues", he summarises.

First attempts to tackle the European imbalance

It is this coaching which is still missing in Serbia. "Many medical doctors do not even know about emerging new technologies and tests," Dragica Radojkovic says. So some patients have to find their way through the jungle of genetic testing themselves, very often abroad. Radojkovic emphasizes the importance of continuous education and training of medical professionals. This would be the only way of reaching a balance between the level of education and technical advance.

After all, a closer inspection of Europe reveals differences in legislation, education, clinical practice and financing. Radojkovic gives one example: "There are different types of health care systems across Europe. While Finland, Sweden and Great Britain have a national health service, France and Germany are based on social insurance systems."

Furthermore, the number of tests performed is not proportional to the population. While Finland annually carries out more than 4,000 DNA tests per million inhabitants the number of tests in Sweden is about ten times lower. In Serbia the frequency goes down to 75.

In the face of such imbalance a widespread attempt to disentangle the complexities of European genetic testing is taking place. "EuroGentest is at present the broadest programme of its kind I know", says Claus Bartram. Funded by the EU for five years from January 2005 and coordinated by Jean-Jacques Cassiman from the Centre of Human Genetics in Leuven, Belgium, this programme attempts to harmonize genetic testing in Europe. As a Network of Excellence it is not only made up of geneticists and doctors but also integrates ethicists, patient organisations, lawyers and corporate representatives.

"During genetic studies across Europe we gained insight into the differences between countries", Bartram explains. "EuroGentest arose from the wish to analyse deviation and ease collaboration." This is to be done across all areas: six different units deal with quality management, information databases, public health, ethics and legislation, new technologies and education. "That involves dozens of countries and is mainly based on interviewing", Bartram says. For this they focus on several specific topics, for example inherited breast cancer, and systematically get down to detail. "This goes to such lengths that we ask about the primers used."

"We do not have any statutory regulation of genetic testing."

Dragica Radojkovic, Institute of Molecular Genetics and Genetic Engineering (IMGGE) in Belgrade, Serbia

Interviews, meetings, workshops

The hunt for information starts on the web and leads to doctors and professional organisations. "We try to find out who is responsible and gain their opinion. This way we always get feedback on what we are doing," Ulf Kristoffersson explains.

Dragica Radojkovic explains that communication between partners is achieved through regular meetings and workshops. "At the end of each year the EuroGentest General Assembly is held in Leuven, Belgium. There all units submit their yearly report and the plans for the following year are discussed."

Sounds good, but what will happen afterwards? Kristoffersson describes the points to be clarified: "We are now entering the third year. This means that we now have to think about how to keep the sustainability of what we have done. What will we deliver, how should it be delivered and who will be the stakeholder". Because healthcare does not fall under the European Union's remit, sustainability is the most important. "As long as there is nobody to take our results on board, they are only worth the paper they are written on", Kristoffersson says. Legal regulation will, of course, then be carried out in about twenty-five different ways.

But let us just accept this as further proof of the ubiquitous diversity of human beings.

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