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CONFERENCE REPORT

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Aspects of Personalised Medicine
for Society
- A Challenge Yet to be Met -

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Personalised medicine: be prepared

Clinical research professionals must prepare society to accept the consequences of personalised medicine. That was the central message from the EFGCP Annual Conference, held in Brussels on 26 and 27 January. Newsletter Editor Peter Wrobel reports on a lively two days' discussion and debate.

Over two days, clinicians and patients joined with industry representatives, ethicists and policymakers to thrash out the issues coming from this emerging field. It is going to be new, more expensive and more difficult to manage, said outgoing Chair Jean-Pierre Tassignon, but it was ever thus.

The very first presentation, by Matthias Schwab from the Dr Margarete Fischer-Bosch Institute for Clinical Pharmacology, Stuttgart, Germany, laid out the main lines of discussion. In an overview of the current status of personalised medicine, he cited tremendous advances in treatment – for example, of chronic myeloid leukaemia – based on genetically targeted therapy.

But Schwab stressed that it's not all about genetics. Many disciplines have to come together, including physiology, the study of diseases, environmental factors and diet. On top of this, ethical, legal and social issues will also determine the impact of genomics on new medicines.

He was followed by Richard Tiner from the Faculty of Pharmaceutical Medicine, UK. Between them, Schwab and Tiner highlighted the core questions that need to be addressed: the importance of biobanks, the need for networks, the role of diagnostics, the training and education of researchers and patients, issues around standards and, last but not least, ethical approval.

Huge potential

The potential benefits are huge: improved healthcare, reduced side effects, more personal involvement by patients, potentially greater value for money for payers, and perhaps greater confidence by regulators in allowing earlier approval of promising new drugs.

But, warned Tiner, personalised medicine is not a quick fix: costs are not going to come down overnight. Indeed, he said, it is quite likely that drug development will become dearer before it becomes cheaper.

That might be seen as a problem, because healthcare is generally becoming more and more expensive. Yet as Tiner pointed out, a key economic issue is poor adherence to medicines and considerable waste. That's where personalised medicine can help save money. Indeed, said Erik Tambuyzer from Genzyme, autopsy studies in New York suggest that 30 per cent of people are being treated for diseases that they don't actually have.

Tambuyzer was comparing the issues around personalised medicine with those around orphan medicines. The two fields are not identical, but they have much in common, and he was keen to call for the experience gained in orphan drug development to be applied by regulators and reimbursement authorities.

For example, the small numbers of patients involved in both fields require the creation of biobanks, centres of excellence and good networks. Clinical trials, he warned, will be difficult to set up and perhaps more costly, and might involve translation, travel and care of the patient's

family. So the trials must be designed to result in what he called “value” outcomes for reimbursement agencies.

If personalised medicine is to flourish, he said, regulatory requirements in different parts of the world will need to be harmonised. With small patient groups it will be too costly to develop different standards for each region. Companies, too, will need to adapt. “There will be more stringent regimes. If companies don’t cope with this the whole field will be stifled,” said Tambuyzer

Diagnostic testing will become crucial. Yet, said Tambuyzer, the reimbursement climate for diagnostic testing “is not as it should be”, with too much attention on activity and not enough on value. “It is very difficult to develop a test and wait for reimbursement if the test is outdated before reimbursement is agreed.”

Tambuyzer called for regulators to take the “long view”. “Personalised medicine is in its infancy,” he said. “All new technologies need time to develop and be adopted.” It took 20 years for monoclonal antibodies to make their way into mainline treatment. “If we are denying treatment today to a patient whose biomarkers may not correlate ideally, we may be on a slippery slope of stopping innovation.”

Societal aspects

As Tambuyzer said, in order for the new system of personalised medicine to work, the general public must be involved. That requires a societal debate and partnership with all stakeholders involved. But what are the ground rules?

Unesco could help here. Henk ten Have from the Paris-based organisation was at the conference to talk about how it tries to find agreement among different governments globally in bioethics – a programme that goes back to 1973.

“Unesco is not a university,” he said. “It is trying to mediate between the expertise that exists in some of

the member states in the European Community, for example, in bioethics and make it available for the majority of our member states that lack the expertise and infrastructure but still have policy decisions to make.” Clinical research is more and more international, and there will be clinical trials in developing countries regardless of whether they have a bioethics infrastructure.

Ten Have pointed to a “growing international consensus” around bioethics. “There might be one too in personalised medicine,” he said, based around the concepts of human dignity and fundamental equality that have been adopted by Unesco over the years.

Whatever we do, we need a global approach, said Vincenzo Costigliola from the Brussels-based European Association of Predictive, Preventive and Personalised Medicine (EMPA) – what he called “an international legislative medicine”.

Costigliola also stressed the need for changes to professional education. “We need to interfere with universities, curricula, with actual educational programmes,” he said. “It’s not simple. It’s not easy. It needs investment.”

He and others created EMPA to raise awareness about personalised medicine and to help to create an effective and multidisciplinary European network. “I am convinced that preventive predictive and especially personalised medicine will be the future, if not for our generation for the next one,” he said.

Can we trust the sequencers?

With genomic information pouring out of sequencers by the minute, does that mean that diagnosis is just a matter of looking at genetic data? Detlef Niese from Novartis, Switzerland, was worried that the public see diagnosis as a black-and-white issue.

"Patients are uncomfortable with probabilities, risks and likelihoods," he said. "Could one of the problems we face in personalised medicine have to do with the fact that the technologies we use do not provide us with facts but with likely correlations?" That requires education, said ten Have.

"We have to separate research, science and practice," said Costigliola. "First we have to inform the patients and clarify the ethical limitations of these tests." The media, too, has a role to play here.

The technologies need further development, said Niese. Sequencers are "more concerned with providing a genome for \$100 than with what it means". Adam Heathfield from Pfizer, UK, offered a test for whether genetic information is useful – whether it gives better information than the family history patients give their doctors: "That's the standard of care."

There are tests that can predict genetic deficiencies in, say, breast cancer, where you can screen a set of specific genes, said Jean-Jacques Cassiman from Leuven, Belgium. But, he added, "There is nothing for common diseases that could be commercialised sensibly."

Some 98 per cent of patients with neuromuscular disorders are diagnosed not through predictive tests but from their symptoms, said Stephanie Weinreich from the Dutch Association for Neuromuscular Diseases.

Patient groups are concentrating on rare diseases for which there are specific tests and for which treatment is beginning rather than on the general tests, said Cees Smit from the European Genetic Alliance Network, the Netherlands.

"There should be some certification of tests and some assurance that patients won't be discriminated against on the basis of nonspecific test results," he said.

But what are the rare diseases? Neuroblastoma, for example, has different incidence in Asia than in Europe, said Georgi Mihaylov from the Bulgarian Medical Association – so it might be worthwhile to develop a predictive test in Asia but not in Europe.

Jan Geissler from the European Cancer Patient Coalition was concerned about the "slippery slope" mentioned by Erik Tambuyzer. "In general what's happening allows more targeted therapy. But what if we have the right technology but make the wrong use of it? There are patients who might benefit but might not have the right genetic profile for an optimal response," he said.

Many tests are implemented without proper evaluation of their clinical utility, said Corianne De Borgie from the Academic Medical Center of the University of Amsterdam. "We have a lot of diffusion of techniques, but many of them are not properly implemented or evaluated in patient care."

In practice, the world of assays and their reimbursement can be less than ideal. David Haerry of the European Aids Treatment Group, Switzerland, gave the example of CCR5 development – a specific drug class approved for the first time two years ago. It was developed with an assay to be used before the drug to detect whether a patient is CCR5-tropic. "But the assay is not that accurate. It can't detect a minority of cases where tropism is less than 10 per cent,"

said Haerry. "Once the drug was approved, it turned out to be relatively safe, to our patients' surprise. But the assay was and still is expensive, and the drug is approved only with that precise assay... which is not that precise!"

Genetic tests: a special case?

Do we need specific provisions for genetic tests that might predict disease, asked Elmar Doppelfeld, and Chair of the Permanent Working Party of the German Ethics Committees? No, was his answer. You wouldn't ask the question in relation to cardiac testing, he said, and his view was supported by others.

Erik Tambuyzer was part of the multi-stakeholder Strata Group of the European Commission that discussed the ethical, legal and social issues of genetic testing in 2004 and 2005 and produced a report for the European Commission. "We stand by the results: we don't need genetic exceptionalism," he said, since privacy should be respected in all diagnostic testing.

Matthias Schwab compared genetic tests with biomarkers: in both cases what matters is their predictive value. Diagnostic testing should only be used, he said, when the predictive value is high.

But Schwab noted a difference between the genetic testing of individuals with established biomarkers and screening for research that might, for example, establish important biomarkers relevant to specific ethnic populations.

Detlef Niese was concerned drawing conclusions from testing when so little is known about many major diseases. "We have no clue what diabetes is. We don't know whether it is a single disease – it's all described by phenotypic factors. Then we draw conclusions about the value of correlation with genetic factors and are surprised that the value is not reliable."

The answer, for Niese and Doppelfeld, is more research. "It's a work in progress," said Doppelfeld. "We need more genetic research and more biobanks."

Insurance

One of the central issues in testing is the link between diagnosis and insurance. That's a comparatively modern problem. Henk ten Have said that health insurance started as a collective enterprise; now it has moved towards profit. "There should be at least a minimum guarantee that you will have certain health benefits regardless of your condition," he said. "No one should be a victim of genetic techniques just because insurance has changed."

Richard Tiner pointed out that before genetic testing for Huntington's disease, insurance companies placed a great deal of weight on family history, so people not at actual risk were discriminated against. "There is a potential that genetic testing may help this situation," he said, though he stressed that it should not be used in all cases. But insurance companies already use such information, for example in life insurance for mortgage cover.

It shouldn't be an issue, said Arvid Helberg, a medical geneticist from the University of Oslo, Norway. He argued that Huntington's disease is so rare that it doesn't really matter to the overall economics of the insurance industry – so companies should not bother with it.

But the question won't go away. "One of the major reasons why people refuse to enter research is because of fears of discrimination," said Michael Bone, a consultant physician from the UK and EFGCP Secretary.

That discrimination remains even though, as Vincenzo Costigliola reminded the conference, "Genetic tests are just a possibility of developing something. Nothing is certain." Petra Knupfer, Managing Director of the Ethics Committee of the Landesärztekammer Baden Württemberg, Germany, compared it with the discrimination against women because they have the potential to give birth to children – even though no one knows whether they will actually have children.

The need for anonymity

It would be nice and simple if data on patients could be guaranteed anonymity, but there are four problems with this. The first, and not so hard to deal with, is that the person concerned should be informed about the consequences of total anonymisation – in other words, that they cannot be identified and contacted if something is found. The second, as Doppelfeld explained, is how to go about giving feedback if someone does not want anonymisation.

The third problem: it is not easy to guarantee anonymity. Matthias Schwab explained this through studies in progress using complete data from NMR scans.

Lastly, total anonymisation can seriously hamper research into rare diseases because, as Erik Tambuyzer said, "with total anonymisation you can't go back to the patient to get more data". "It's a gold standard in terms of data protection and perceived positively by public," said Marianne Maman from Novartis, Switzerland. "But it means you can't go back and link extra information, or do prospective trials, and it restricts use in biobanks."

There was also support for the notion of patients' right to say whether they want information fed back to them – even if, said Michael Bone, that is often in conflict with what a lot of researchers intend to do when they are submitting research proposals. And for Detlef Niese, there have to be ways in which anonymisation can coexist with feeding information back to patients: "We simply haven't thought about it enough."

Will business buy into it?

Unless companies feel there is good business in making personalised medicines, they won't be made. So can they be financially viable? The short answer is yes, said Adam Heathfield from Pfizer, UK. "But it's not always a clear-cut yes."

The background is that success rates in traditional drug development are low, and the picture is not getting better. Personalised medicine is going to be different, and difficult too, in particular because the idea is that by the time a company launches a drug it will have the diagnostic as well as the medicine."

There is another way of looking at, said Heathfield. With diagnostics – and even if you reduce the number of patients – it helps in reimbursement negotiations if you can show targeted efficacy. "Patient selection could increase the 'efficacy signal'. That is important for business. It is efficacy that drives your price." Companies also want to build market share and volume of sales. And Heathfield mused that personalised medicine might lead to smaller and less costly clinical trials, though "we haven't seen that yet".

One crying need is for more biomarkers. Without them, delays build up. Pfizer had no biomarker data available when it started a phase III melanoma trial. Around 10 per cent of patients appeared to respond very well, but the company couldn't work out why. It went back to look at the data, and working with Debiopharm found a way to segment the population. "But we used up two years of our commercial life because we didn't have the biomarker data available. Those are not the kind of business efficiencies you want," he said.

Whatever the medicine, many things have to be functioning well to allow companies to innovate. In personalised medicine, said Heathfield, two things stand out: joint ventures and precompetitive consortia to drive up knowledge; and the need for biomarkers.

Diagnostics are a minefield for pharmaceutical companies. There are lots of positives around them, he said, but problems too. The tests must be “unambiguous, effective and useable by clinicians”. Regulation of diagnostics is “a mess”. And then “people don’t want to pay for them”. Patients need education about another step in the process, but in fact there may be “repeat processes that are invasive and not desirable”.

On top of this, companies are going into development not knowing whether test will be a requirement. And it’s often another part of the business that is outside a drug company’s control: “We don’t control supply and quality of reagents.”

Heathfield called for collaboration under the European Commission’s Innovative Medicines Initiative. “In personalised medicine and elsewhere we need a much deeper knowledge of the targets and mechanisms we’re working on. Companies and academics need to work together,” he said. “There is no value in developing this in-house.”

The fundamental factors for business success remain unchanged, said Heathfield: applying the best science; productivity; innovation; value to patients, clinicians and payers; and competitiveness. “Personalised medicine is clearly a key part of making companies profitable and successful in the future,” he said.

“Would you suggest that there should be a network created to think about areas in the medical device directive on diagnostics?” asked Detlef Niese.

“Yes, I think that would be a great thing to do,” responded Heathfield. “The other perspective that is lacking is the clinicians’. There is no point in developing the perfect diagnostic if for whatever reason it doesn’t fit into the physicians’ paradigm. Otherwise you get great technology on the shelf.”

And will governments pay?

There’s a paradox in the UK, neatly put by David Taylor from the School of Pharmacy, University of London. Per head of the population the country – via the public, industry and government – probably funds more cancer research than the US, but it is a slow adopter of new anticancer drugs.

That paradox is related to NICE, the National Institute for Clinical Excellence, said Taylor. “What is affordable depends on the methodology you use to judge value,” he said, calling on clinicians to engage in the debate about value.

New cancer drugs tend to have higher unit cost and lower volumes than established drugs – but the total cost is “not much different”. Typically, said Taylor, cancer medicines account for 10 to 15 per cent of cancer costs; and cancer accounts for about 7 per cent of health costs – so cancer drugs as a whole cost 0.1 per cent of the OECD nations’ GDP.

In most OECD countries medicine costs are falling as a proportion of health spending, in part because of cheap off-patent medicines such as statins. Most healthcare costs are not pharma-related. “What matters is not the limits on resources but how we value them,” he said.

For Taylor, the fundamental challenge for relatively rich de-industrialising countries is how they earn their living in the future: maintaining a competitive base while labour costs are so high.

"One could argue that we should cut down on innovation and not provide money for the provision of medicines for old age at high cost. I would rather argue that the development of personalised medicine will help us compete," he said.

Against that background, he saw no reason why the developed societies shouldn't develop personalised medicine: "We can afford it within the overall envelope of health spending." Clinicians should try to defend this, Taylor said. "We need consistent funding over the next twenty to thirty years to get to what we desire."

A central issue is the perceived cost of treating cancer early. This has led to court cases in the UK with, for example, one patient winning the right to early treatment with Herceptin. It's the same situation as applied in HIV, said Detlef Niese: "We had a hard time to convince the regulators that it would be valuable to prevent progression rather than treat late-stage disease."

The ethical framework for this needs developing, said Adam Heathfield, in particular as regards the data required by the regulators. It is logical and reasonable to reckon that if something works late stage it will work earlier.

"If I have a cancer that is eating me, how do I get a structure that treats me but is affordable for the community?" he asked. "We haven't really had that debate."

Focus on the patient

Contemporary medicine is there mostly to save lives, restore and improve health, to restore and improve quality of life, to treat and cure as much as possible, said Jozef Glasa from Slovak Medical University, Slovakia. "The public is coming to think we are almost omnipotent...we are almost the opposite sometimes, you might say."

Personalised medicine, he said, is about diagnostics, therapy, prevention, and more and more about prediction. It also raises questions about efficacy, safety, efficiency, and now the sustainability of health systems, pharma industries and research institutes. But is the technology running too fast to keep up with the ethical and social values we seek to sustain?

The solution is to look on patients as partners. "Patients could have a strong influence on the ethical and social implications of personalised medicine," he said. "Each patient is a voter."

The new patients could be more and more co-decision makers in their own health and in health policy, said Glasa. That includes partnership in the design of policy and politics, as well as influencing developments in biomedical sciences and technologies. He called for improvements in the process of informed consent not just on an individual but also on a societal level – including support for a broad and well informed public debate.

But if patients are to be better informed, who will inform them? In the absence through personal circumstances of Alastair Kent from the Genetic Interest Group, UK, Ysbrand Poortman from the World Alliance of Organisations for the Prevention of Genetic and Congenital Treatments, the Netherlands, stood in and picked up that challenge (basing himself on Kent's presentation).

What patients want is transparency and clarity from people who know what they are talking about, said Poortman. The information should come as soon as possible (within the limits of current knowledge), and always be "balanced, honest and clear about implications and time spans – sometimes much more than a couple of years", he said.

A good model for communication was worked out in EuroGentest, the genetic testing network. It started with asking patients and families what information they want – "a difficult question to answer". That information was then discussed with professions, who checked and improved it.

The information went back to patients to be amended for clarity, and was then published and used, with requests for feedback on improvement and updating.

Biobanks have particular education needs. The UK Biobank, for example, does not give personal feedback. "If you participate you should realise what is involved. You don't get a treatment out of it. That means education and information before donation," said Poortman.

There is, though, a complication, highlighted by Frank Wells, the EFGCP's Ethics Officer. Given that the techniques are changing rapidly, how competent are the people to whom one looks for information at communicating it?

Again, the solution may simply be to work more with patients. Celia Brazell from GSK, UK, related how it began using pharmacogenetics routinely in clinical trials with what it thought was a fine consent form. "We were soon corrected." So GSK worked with patient groups, who told the company what they wanted to know about. "We took that to heart, put together a video and a supplementary brochure and got a much more positive response," she said.

But there was a twist to Brazell's tale. "When we actually went to the clinical sites some of them did not want to have the video available." Her conclusion: it's important to connect researchers, patients and ethics committees.

Getting personal: down to definitions

What is personalised medicine? It is a catchy description, but it can be misleading. "I have been around in the industry long enough to know that we are probably centuries away from developing drugs for individual people," said Richard Tiner. So-called personalised medicine is really stratified medicine – groups of people or medicines.

Tiner cited the Dane Jan Trøst Jørgensen, who described personalised medicine in 2008 as the management of group of patients with shared biological characteristics by using molecular diagnostic testing to select the optimal therapy in order to achieve the best possible medicinal outcome for that group. "That's what we're about," said Tiner. "It does not mean the creation of medicines that are unique to a patient."

Erik Tambuyzer from Genzyme picked up on the same theme. "Personalised medicine is not the same as personal treatment," he said. "Of course it is impossible to develop therapies for each patient. That is the role of the physician via dosing."

Away from the present, though, Pfizer's Adam Heathfield was keeping an open mind. "Some areas look almost impossible – such as single-patient therapeutics – but we should keep our eye on that. We can't foretell the future."

The discussion of definitions ran through the whole conference. Perhaps the last word should go to Slovak researcher Jozef Glasa: "Personalised medicine should stay personalised in this respect, that I hope that I will be treated when I am in need by human beings not by nano or other bots."

A different answer: pick up a polypill?

Personalised medicine has its place, said Malcolm Law from Barts and the London School of Medicine, UK (above) – but it's more limited than its fans claim. He took the example of cardiovascular disease to make the case that totally unpersonalised medicine is the way forward.

Law based his argument in part on what he called “perhaps the classiest review of pharmacogenomics”, published by William Evans and Howard McLeod in the *New England Journal of Medicine* in 2003. Look closely at the graphs, he said, and you see that the difference between genotypes is “not all that great” – equivalent to rather less than halving the dose of a drug.

“You might reflect that there are some drugs where it would be very much less effective if you halve the dose, but that's not the case with most antibiotics or lipid-lowering drugs,” said Law: in statins the effect of genetic differences is small – a 21 per cent reduction of effect at most.

Although many researchers are impressed by the principle of tailor-made therapy in heart disease, “no one can find any examples where it might be expected to work in any important way” – and people have been looking for 10 years.

“Sceptics might see pharmaco-genomics as having a more limited place than the enthusiasts might suggest,” said Law. Better, he said, to look at “polypills”, combinations of drugs taken in one pill. They work in lowering blood pressure, and they work in pain relief.

The cardiovascular polypill is based on four principles. First, that heart disease and stroke are “virtually entirely preventable” rather than an inevitable consequence of ageing. Second, that we all have high blood pressure (relative to people in hunter-gatherer societies). Third, that lowering even average blood pressure reduces the risk of cardiovascular disease. Fourth, that blood pressure and cholesterol are poor screening tests to identify people who have heart attacks and strokes.

Law's conclusion: give everyone over a certain age a polypill to lower their blood pressure and serum cholesterol. It would be slightly more effective to measure a person's overall risk and offer treatment to those at higher personal risk – but not that much more. “A very simple one-size-fits-all approach is successful in treating a lot of the approaches we have today,” he said.

From race to genetics

If personalised medicine is potentially game-changing for healthcare, then it is likely to be game-changing for clinical trials as well, said Ron Waife from consultants Waife Associates, US. “For clinical development there is this consequence: Does phenotype-based research lead to gene-ism rather than racism? You can substitute religion, gender, or sexual orientation for race...any or all of these are limiting. Is this only a societal consequence or also a scientific one?” he asked.

Race itself is a problematic term for genetics as it is for many disciplines. We need to get rid of the idea that races are different as races rather than as populations and subpopulations, said Jean-Jacques Cassiman. “If you take the Japanese, the Chinese and the Europeans, you find

as much genetic differences between subpopulations as between climate and language. We should stop using the word race and start talking about populations and subpopulations," he said. "There is not a single drug that will benefit all blacks or all whites or all yellows. Race has a lot of emotional and psychological connotations which stand in the way of good application of our knowledge."

"I couldn't agree with you more," said Richard Hubbard from Pfizer, US. "We should abandon the term race in medical discussion, but it is still relevant in the public health discussion, in relations to outcomes. But personalised medicine is different from public health." Waife also pointed to research that shows that race is a good predictor of health outcomes, not necessarily because of genotype but because of all the "confounding variables".

The Indian-born writer Kenan Malik wrote in The Times of misunderstandings of sickle-cell anaemia. Commonly called a Black disease in the US, it is actually a disease of populations originating from areas with a high incidence of malaria. "So there is an assumption that race is linked to genetics, whereas these are associations not necessarily related to phenotype," said Waife. "Apparently we still have to learn that race is a societal construct not a genetically determined state. Its influence has led to wasted efforts and detriment to public perceptions."

Personalised medicine need not be associated with racism if genetic cause and effect is clear. "But it's not clear," said Waife. "Best-we-can-do, 'loose' associations (like tamoxifen) will lead to misperceptions and missed opportunities. People are still going to be uncertain, and it leads to opportunities for exploitation of people's mistrust of clinical trials."

The general public, he said, is ignorant of science, suspicious on the one hand and unreasonable in its positive expectation of what personalised medicine can bring on the other. The media write as if the field is much more advanced than it is. Online media inflame the situation. "Clinical research professionals must prepare society to be receptive and accepting of the implications of personalised medicine. This dialogue has to continue for many years to come," said Waife.

Moving from ethnic to genetic categories has societal consequences, said David Haerry of the European Aids Treatment Group, based in Switzerland. "As a patient I don't expect a paradigm shift to happen," he said, adding, "Some genetic information is used more and more to complement or refine ethnic information. In HIV we have seen genetic information being used in drug development and post-approval to make drug use a little safer."

Who, though, will lead the move away from race to genes, wondered Ingrid Klingmann from Pharmaplex, Belgium and the EFGCP? "Would scientists then have to be the people to lead the education of the population in this paradigm shift? If not, who? Politicians? Ethicists?"

Cassiman was enthusiastic. Given the enormous interest in the public generally in knowing their origins, he said there is a "fantastic opportunity". "We see with SNPs that no one's DNA is pure, they are all admixtures. No one is of a pure race. Perhaps with that we can convince the public that we should leave this concept of race based on skin colour behind us."

Don't shoot the messenger

The public gets its information about new developments in medicine from a number of sources – not just TV but also the Internet, patient groups and increasingly bloggers. But how much of the information is accurate? As Trish Groves from the British Medical Journal explained, scare

stories can cost lives: "You only need one or two alarming studies for the public to lose confidence." A recent example was the publication of a paper in *The Lancet* in 1998 suggesting a link between the MMR triple vaccine and autism.

At the other end, miracles are promised. And yet it can be very difficult to find much information about the effects and successes of gene therapy, Groves said. That doesn't mean you don't cover it, but it does mean you need to be careful about explaining this branch of science: "Trying to increase patient knowledge about genomics is a risky business."

Take neuroblastoma, for which there are more than 130 different markers – and an average of about one study per marker. "If that's your study, you say, 'We've found it.' But what does it all mean? And that's just one condition."

The *British Medical Journal* has published a lot on personalised medicine, but Groves said, "I think we're on the sceptical end of the spectrum." The journal would love to see it come up with the goods, but is more interested in papers on public health and other topics; the field might get covered in the news section.

Journalists, meanwhile, are interested in stories with big impact and relevance to their readers. "But what they can't do because they lack expertise and especially time is get into the sensitivities of the research," said Groves. "The 'What does it mean' needs to be very short." So journalists rely heavily on journals – which is reasonable, she said.

The risk of hype

Therein lie some of the risks, in particular hype by authors. Groves explained that as a journal editor she often finds that authors write in their papers about the studies they wished they had done rather than what they did. "[The authors] take that out of the discussion, but when they talk to journalists off they go again," she said. "They mean well. But they also need their next grant."

The result: a study in the *Annals of Internal Medicine* of press releases issued by academic medical centres found exaggeration common. Almost all press releases included investigator quotes – of which a quarter overstated their findings.

On top of this, there are problems in conveying risk to people who aren't statisticians. "It's difficult to take on board several risks at once. What's the individual risk?" said Groves. And sometimes it is hard to convey risk when you only have preliminary results, or simply observational evidence where you cannot say that A causes B, only that A is associated with B.

Groves talked about work that has been done on how to display risk. "Researchers have found that people who are not experts find it easier if you cover it from several angles, using words, pictures and numbers," she said.

It helps if you use the same sort of numbers, and give the absolute rather than just the relative risk, she said. "A doubling of a large risk is significant, of a small one not." And give both positives and negatives: a 3 per cent chance of dying is also a 97 per cent chance of being cured.

So don't blame the journalists, she said. They have a tricky job, and they rely on the journals and on scientists to convey information that is accurate and in a form that is easy to understand.

A surreal experience

The social visit on the evening of the first day of the conference provided a welcome break from reality – a private visit to the new Musée Magritte, which had only recently opened to the public. From the top floor down to the ground, the museum presents a chronological and themed trail of René Magritte's works. The visit was made even more enjoyable by the excellent animateurs who accompanied groups of delegates.

In depth: workshop reports

Workshops – three on the first day, and three on the second day – are the heart of the EFGCP conference.

Workshop 1: Informed consent process in clinical trials involving genetic testing. Chair: Gerd Mikus, University Hospital Heidelberg, Germany.

Genetics plays an important part in drug action, though so do many other processes. The workshop (see picture, above) discussed the problems and limitations of genetic testing, including an apparent lack of agreed quality standards, and sometimes the use of incorrect genotypes. And there is still much mistrust about how data protection is handled in genetic studies, including by universities.

The important factors are privacy, further use of samples, and information about the result of testing, said rapporteur David Haerry.

Workshop delegates decided that informed consent for genotyping should be part of the general consent process for the main study if the genotyping is integral to the study – otherwise, the consent should be separate. However, the information for consent to both processes should all be given at the same time.

Biobanking is a problem area. Many countries seem not to have biobank laws in place, and the OECD guidelines, while interesting, are not enforceable.

Delegates felt that patients taking part in a study should be given information on aggregated data. They also noted that Germany's ethics committees require the informed consent form to cover dissemination of results, while in other countries this requirement does not exist. It was agreed that when subjects withdraw from a study, non-anonymised samples should be withdrawn.

There will soon be a legal requirement to post data on clinical trials on the EudraCT database. (The data fields have been set.) However, publication of a study's results in a peer-reviewed journal cannot be guaranteed.

Finally, the workshop considered genetic testing and children, widening the discussion to include vulnerable populations in general. Noting that in some cases the parents would need to be tested as well, delegates felt that genetic testing of children is appropriate only if the results are likely to benefit the child, and only in the context of a clinical diagnosis.

Workshop 2: Informed consent for future research on patient tissues. Chair: Cees Smit, VSOP/EGAN, The Netherlands.

Ethical approval is essential for two reasons, said rapporteur Frank Wells: for the collection of tissue in the first place, including for biobanks; and then once the tissue is in a biobank, for each project using that tissue.

The workshop (see picture, right) looked at four different types of consent, which Wells summed up as:

1. My tissue now belongs to the biobanks and I want to know nothing about how it is used.
2. As above, but with the stipulation that any interesting research that might emerge from my tissue's use should be published.
3. My tissue is now yours, but if you happen to discover something useful to me I want to be told about it. That requires some kind of link or key specifying where research could be of benefit to a donor. "Unusual, but there should be provision for it," said Wells.
4. My tissue to be taken now is for a specific project only.

Finally, workshop delegates queried whether data protection laws are more beneficial to society than an appropriate ethical review process. Can data protection laws actually benefit patients in the context of future research on patient tissues?

That set off a lively discussion, with Trish Groves suggesting a further model: I consent acknowledging the small risk that I may potentially be identifiable in a future publication. People need to know there is a balance of risk and benefit in publication, she said, adding that medical journals used only to be read by medics: "Not so now," she said.

Workshop 3: Getting it right! Advice and remedies in dealing with consent, recruitment and retention in genetic research – recent lessons from Switzerland and the UK. Chair: Hans Kummer, Past President, REC Basel, Switzerland.

Get genetic research wrong, and you can end up with big problems, as rapporteur Michael Bone outlined. The workshop addressed, for example, a current legal case in the US: a tribe of Native Americans in Colorado Gorge have been given leave to pursue a suit against the University of Arizona, where blood samples allegedly taken for diabetes are being used in a study about schizophrenia and migration.

Research ethics committees in the UK are tending to work with a more consistent approach, said Bone. But he bemoaned a frequent lack of clarity in some applications for ethical approval. Information is sometimes contradictory, and fails to give a clear explanation of a study and its implications. He professed himself "often disappointed by the ethical considerations put forward by geneticists".

At the other end of the scale comes the SESAM study in Switzerland, a planned but then abandoned study into the cause of mental disorders. It aimed to start during pregnancy and follow people through for 20 years. Detailed questionnaires were designed by psychologists and sociologists, and the plan was to take a wide range of tissue samples.

After detailed ethical review, leading to several changes in the study design, approval was granted. But almost no one wanted to take part: against a recruitment target of 3,000 in two years, only 17 had been recruited after six months. Why? A reluctance to engage the unborn child (and family members) in a 20-year study affecting personal and sensitive spheres, said Bone. And the demands of the study were "really quite exorbitant".

The study was abandoned, having spent millions of Swiss francs in vain. The story illustrates the point if you don't get it right and are not seen to be protecting the population, the population will take it into their own hands, said Bone. The right way of going about it would have been to start the project – with ethics committee involvement – as a pilot study.

Workshop 4: Criteria to decide on need for and affordability of genetic testing as a basis for treatment. Chair: David Gillen, Pfizer, UK.

The workshop decided to focus on genetic testing (rather than screening) for medicines (rather than for diseases), said rapporteur JanHasker Jonkman, from the University of Groningen, the Netherlands. The main objective here is to reduce adverse drug reactions and their associated costs, and to identify patients who would not respond to a drug.

Tests should be reliable and well validated, widely available – though most felt not over the counter – and not too expensive. The test should be cheap relative to the price of the medicine, and should be provided by an independent body not linked to the company making the medicine.

Who decides whether the test is used? That should be the physician, thought workshop delegates, because the test forms a part of the diagnosis.

Who pays? The patient/health insurer or the drug company? The workshop preferred the insurer, on the grounds that the test should be part of diagnosis and reimbursed if medically indicated. In any case, to avoid a conflict of interest payment should be independent of the drug company.

But reimbursement is often an issue, leading to decisions being made too late – which dilutes the incentive for a diagnostic company to develop a test. An option put forward by the workshop would be to include the cost of the test in price of medicine.

Workshop 5: Tracking and storage of personal data in registries and biobanks – how to handle the conflict between researchers' needs for information and the patients' needs for data protection. Chair: Olga Kubar, Pasteur Institute, Russia.

The workshop looked at three models for genetic databases: opt-in (such as the Czech IZIP), where patients have to consciously decide to have their data incorporated; opt-out (such as Iceland's deCode), where the default is that data will be included; and a third possibility, where a database record is created automatically, but the patient has the right not to share the clinical data in that record – but the data cannot be deleted.

So far, so simple. But in all cases the main problem is when and in what form data donors should give informed consent. Such consent may fall under three broad categories, said rapporteur Arvo Tikk from the University of Tartu, Estonia: consent for explicit uses, broad consent, and blanket consent.

Workshop delegates felt it impractical for biobanks to use explicit consent for each project, and that then broad, open consent is appropriate – though without giving access to the data to courts, police or health insurance. They also thought that biobanks should be governed by domestic law, since it is legally binding in the patient's country.

Clearly, patients' rights, such as the protection of confidentiality, dignity and privacy, are paramount. But we need to have an "appropriate balance" between patients' interests and the public interest – and it is not clear how to do this, especially with registries.

Another issue is access to databases. Access to genetic biobanks is more or less regulated, with anonymisation, REC approval, special acts and other regulations. But most genetic studies are now international, so it is important to have flexible domestic systems for international access to data records. "To get permission from governments takes us in Estonia four months," said Tikk, which is often too late to be useful.

Also noted was the recent rapid development of electronic health record databases. They can also be used for research, but this is a new field, with no regulations, we don't know how to do this. The creation of international and national guidelines could be useful – but who would draw them up?

Jean-Pierre Tassignon raised the issue of negotiating power. Japan, he said, has put together a prospective databank of 300,000 patients. Europe has to establish similar-sized databanks in order to be able to negotiate international access.

Workshop 6: Prenatal screening and the consequences of knowing about potential future diseases. Chair: Joris Vermeesch, University Hospital Leuven, Belgium.

It was a fascinating workshop, said rapporteur Michael Bone, highlighting the experience of workshop chairman Joris Vermeesch from the Centre for Human Genetics at KU Leuven, Belgium, in looking at the new microarray and genome screening techniques. Vermeesch made the point that genetic material is highly changeable and that we are all “mutants”; the difficulty is in knowing the relevance of the mutations to disease.

We are entering a terra incognita, and we need to know how to deal with issues such as unclassified variants, late-onset disorders, and so on. Full genomic screening is coming, not only for the living, and at any age. We have now to consider who will have access to the information, when, and to what extent.

The workshop went on to look at the changing responsibility of the physician, with delegates disagreeing about whether scientists should withhold what they considered to be non-relevant material from physicians.

Certainly, the screening environment is changing rapidly. The new techniques have led to 500 new diagnoses in the past two years, for example. Another point to ponder is the realisation of the huge amount of genetic variation between cells. “Only 1 to 2 per cent of births cause a developmental disorder, but the information seems to be that [cell abnormality] happens much more frequently – but that normal cells develop faster and take over,” said Bone, adding that this will have implications for the future on how we interpret established disease association.

The physician has a relationship with the patient, and knows to some extent what is best for the patient, said Vermeesch, but physicians themselves cannot read the whole genome for all possible diseases. “You come to clinic and the interpretation will be different when you come as a child or later for diabetes. These are different questions that have to be addressed by different physicians,” he said. “The genome has so much information, some of it relevant to the individual, but if a patient just comes in for a headache I am not sure the physician wants to give all that information.” His conclusion: “We need to disconnect the genotype from the physician’s duty to inform patients.

It’s very difficult to keep up with developments when in four or five years you might have a different story to tell the patient, said Ingrid Klingmann. All of this prompted Frank Wells to note that next year’s EFGCP conference is about training. “I feel a session coming on about training on this aspect. A lot will happen in the coming year, it would appear,” he said.

It all comes back to the patients and the public. Hugh Davies from the UK National Research Ethics Service said that processes in clinics must involve patient groups. “We must put the patients at the centre.”

"We have a lot of thinking to do for the future," said Bone, "but we have to engage the public in the process."

The impact of personalised medicine on society

In this edited version of his Joseph Hoet lecture at the EFGCP Annual Conference, Jean-Jacques Cassiman from the Catholic University of Leuven looks at what the new developments mean for patients.

This lecture is not just an honour for me; it is a challenge as well. I'm not an ethicist, I'm a geneticist. But I will try to give a brief overview of what is at present possible, and possible in the near future, and then to look at a few implications of this for the present, near future and far future, and ending with a final comment.

The Human Genome Project required lots of money and tens of laboratories; now it takes around \$60,000 and six weeks to sequence a genome. We have been able to determine that our origins are indeed in Africa – that small groups moved from the continent to Europe and partly to Asia. We're now seeing a third out-of-Africa migration.

These small populations that moved, our ancestors, represent only a part of the original population, which is the basis of the diversity between and within populations. And that diversity is enormous: estimated initially at 0.1 per cent of the genome, it's thought to be 0.8 per cent as new SNPs – where a single nucleotide substitution causes a change in a DNA sequence – are uncovered.

The Human Genome Project is also responsible for some surprising discoveries, including that the 97 per cent of genome that does not code for proteins is responsible for regulating the expression of our genes, and even that genetic defects can be in this "junk DNA".

Variety

More and more gene variations are being uncovered. Copy number variation seems to be important in these variations. That's a completely new insight, though it doesn't mean we now understand the whole genetic basis of disease. We are also learning about the somatic effects: how genetic information is unravelled in the fetus and combines with other influences. We have found up to 40 different somatic variations in one particular type of tumour.

We understand more and more about networks of genes, such as transcription factors, allowing for comparison between species (for example, chimps and humans). We understand better and better how these networks work, and we are moving slowly from an understanding of how DNA works to understanding how cells and organs work, which will open the way to creating artificial organs, eventually.

At the same time, it is clear that DNA can be conditioned by the previous generation. And the period that the embryo and fetus spend in the womb also co-determines one's risk of developing diseases later in life. These environmental factors affect the functioning of DNA – and can also co-affect the ageing process. So it's a bit late for most of us.

Epigenetics – changes in appearance or gene expression over and above the actual DNA sequence – is becoming increasingly important. It is clear now that even identical twins with identical DNA can have different methylation, which governs the expression of DNA.

Even the food environment will affect the expression of our genes. For example, there is a Scandinavian study showing that grandchildren of males who lived in an area with a shortage

of food have a much lower risk of cardiovascular illness than those whose grandfathers lived with plenty of food.

Even with limited knowledge, we see genetic testing offered to confirm the eye or hair colour of babies. Some people cannot wait to make money, but thankfully this is still controversial. Such tests are extremely dangerous because they are not 100 per cent accurate and because they strengthen the feeling that some skin colours are more desirable than others.

In some US states neonatal screening has been extended to more than 50 diseases. This has economic and information consequences. In the prenatal area fetal cells or free DNA can now be used to detect Rhesus incompatibility. It will potentially be possible in future to analyse a whole genome – and then people will be able to choose which babies will be born.

Treatment

Our increasing knowledge is creating new targets for diseases. More and more inherited diseases can be treated with enzyme and hormone replacement. But this is still very expensive, and cost is a challenge now and for the future for more personalised medicine.

Apart from replacement therapies, the past few years have seen a number of breakthroughs in gene therapy in somatic and inherited diseases. In many cases this means treating tissue outside the body and then inserting it back, for example with bone marrow.

Of course gene therapy is helped by our understanding of stem cells. Embryonic, adult and induced pluripotent stem cells can be used to create models for diseases where a protein network that is disturbed by these cells can be analysed. Treatment will become possible. But these are recent developments. The most spectacular is that even brain function is being analysed, albeit in transgenic animals. Our insight into the function of the brain and different brain cells is increasing – which doesn't mean that we can change brain function yet.

Testing

We are seeing the success of lifestyle tests, where people provide their DNA to be tested for a number of variants and they then receive advice on how to behave, such as to take more exercise. There are even websites that claim to match couples on the basis of their DNA: worthless, but based on DNA tests. Maybe this is a way to explain to people what DNA testing can do and in particular what it can't.

Google and in particular Microsoft are looking at holding medical files, so patients can decide how their records are used. If we start discussing personalised medicine in this context, we should distinguish three levels of implementation.

1. Improving the health of individuals by better diagnosis and treatment using validated tests. Everyone will agree with that.
2. Using testing to determine your risk of developing common diseases during later life. This raises a number of questions: Can I use this information? Will I be subjected to compulsory prevention?
3. Using DNA information to determine public health policy in a population. We need to answer the question of the ultimate purpose of this. Do we want a population of healthy people who are never sick and live to 100 years? What kind of society do we want?

There are some dangers and risks of inappropriate implementation of personalised medicine. If we start using genetic diversity we may start discriminating and become socially unjust. If we

don't we might homogenise the population – but we aren't equal at social, genetic and cultural levels.

If the progress of science and increase of population continues, we will have opportunities to do real genetics, to enter the brave new world. But overemphasising the role of genetic factors leads to genetic determinism. And overselling applications leads to a loss of trust in genomics.

Privacy

We should be careful: patient rights are important, but privacy protection is decreasing. It may be a good thing that there are less stringent requirements for consent, because consent restrictions are making it impossible to do research for some serious diseases. We shouldn't have legal documents that are very good for lawyers but not for the medical profession, patients or scientists.

In a recent survey, 92 per cent of people said they wanted their social security number to be protected – but only 28 per cent wanted to protect their family history and 44 per cent genetic test results. So privacy is important, but how important depends on the context.

We have to make sure that in all this quality is there, that the criteria established by, for example, the Centers for Disease Control in Atlanta, Georgia – including the ethical, legal and social implications – are implemented before tests are offered. Many of the tests don't meet these criteria and shouldn't be offered.

We need to look at additional protocol provisions for the European Convention on Human Rights, incorporating individualised supervision, information and genetic counselling and free and informed consent. But we should not overstate the criteria to be met. I'm not convinced that written consent where a patient puts a signature at the end of a whole book is the way forward.

We have to deal with patenting. Yes, we can analyse a whole number of genes, but patents are preventing commercial chip kits from being produced. We should get rid of patenting genes, and patent processes instead.

And we need informative guides, using patients' organisations. But patients' organisations beware! Many of them should realise that it is time to become professional, and that it is very difficult to be a patient requiring treatment and at the same time run an organisation. So we need more people running them and more support for them. And scientists beware! You won't always be able to get what you want by pushing forward a patients' organisation to win it for you.

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