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European Journal of Cancer 41 (2005) 2033–2037

European Journal of Cancer

www.ejconline.com

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Jewish women 'singled out' in BRCA2 patent

Jewish women in Europe may face genetic discrimination in access to breast cancer diagnosis following a decision by the European Patent Office (EPO) on June 29th, 2005, to maintain an amended patent on the *BRCA2* gene.

The patent relates to the use of a particular nucleic acid carrying a mutation of the *BRCA2* gene, which is associated with a 65–70% chance of developing breast cancer. One in 100 Ashkenazi-Jewish women carry the mutation, and it is used for diagnosing the predisposition to breast cancer in this population. The patent claim is believed to be the first time that an ethnic group has been specifically singled out as a diagnostic target.

The claim was strongly opposed by the European Society for Human Genetics (ESHG). Professor Andres Metspalu (University of Tartu, Estonia), President of ESHG, said, ''This is genetic discrimination, as the consequence of this practice would be that some individuals and patients could find themselves legally denied clinical diagnostic services, based on their belonging to a specific genetic heritage. While this particular mutation in the *BRCA2* gene is frequent in the Ashkenazi population, we are equally opposed to similar claims on mutations in this and other genes that may be prevalent in other populations or specific to individual families.''

The US-based Myriad Genetics was an original patent-holder for *BRCA2* but the patent has now been transferred to co-owners, University of Utah. Professor Gert Matthijs (Catholic University of Leuven, Belgium), Chair of the ESHG Patenting and Licensing Committee, said that the original patents granted on both *BRCA1* and *BRCA2* were broad, but that subsequent oppositions have slimmed down the patents to a level which does not generally interfere in daily diagnostic work, except for Ashkenazi-Jewish women. The remaining claim on the specific 6974delT mutation on *BRCA2* was all that was left of the patent on that gene.

Professor Matthijs had mixed feelings about the EPO's decision. ''If we look back to the situation 2 years ago, the original *BRCA2* patent covered all possible uses of the whole gene. The patent as it stands now covers a single mutation. We have done a good job but it is still disappointing that we were not able to convince the EPO that the identification of a specific mutation that happens to be frequent in one population is not innovative.''

The EPO has to work within the constraints of patent law, and could therefore not exclude this patent on ethical grounds. Professor Matthijs said the opponents will consider whether to appeal, but it looks like a more general political initiative will be required to change the situation.

The full reasons for the EPO's decision will be made available on www.epoline.org.

Working Time Directive: 'putting lives at risk'

The European Working Time Directive (WTD) may put doctors' and patients' lives at risk, according to a UK group including Dame Carol Black, president of the Royal College of Physicians (RCP). ''The current NHS shift system could threaten doctors' and, moreover, patients' safety,'' they write (*BMJ* 2005, **330,** 1404).

The WTD stipulates that junior doctors' working hours are limited to a shift of no more than 13 hours followed by a break of at least 11 hours. As a result, their normal work patterns have changed from providing on-call cover to working shifts. A RCP survey in December 2004 found that more than 75% of medical senior house officers and nearly 50% specialist registrars in NHS trusts were working 7 consecutive night shifts.

''These doctors are exhausted,'' the *BMJ* paper states. ''A long stretch of night shifts results in an accumulation of daily sleep deficits and does not encourage adjustment of circadian rhythms.'' It suggests that most doctors should be rostered for single nights with 1 or 2 night shifts over a weekend. There should be a maximum of 3 consecutive nights, with a scheduled 2-hour rest period during the night.

Mr. Simon Eccles, Chair of the British Medical Association's Junior Doctors' Committee said, ''The problem is not necessarily the WTD itself, but the way hospitals have responded… In trusts where work is organised more efficiently – for example by cutting junior doctors' administrative workload and introducing a more team-based approach – patient safety has improved.''

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.07.003

Efficiency, quality and bureaucracy: not always in the same bag!!

The unique role of academic research – and the potential damage inflicted by recent legislation – was amply demonstrated by a recent study using the oral alkylating agent, temozolomide. The study has been credited with creating a new beginning for chemotherapy in brain tumours.

However, without the involvement of academics, it would never have happened. Arguably – despite this study showing that good academic trials produce data robust enough for the purposes of drug registration – it may not have happened today in the legislation-heavy world in which academics have to operate.

To go back: temozolomide was initially developed by Cancer Research Campaign (now CancerResearch UK) and sold at an early stage to the pharmaceutical company, Schering-Plough. The company tested the drug for the treatment of melanoma, and of brain tumours, but results were unexceptional and interest waned.

''ONSITE MONITORING WOULD HAVE COST € 2.5 MILLION''

A joint EORTC-National Cancer Institute of Canada (NCIC) group, led by Dr. Roger Stupp (Universitaire Vaudois, Lausanne, Switzerland) refused to let the matter drop. Many drugs had been tried in the treatment of glioblastoma, but none had improved survival significantly. Dr. Stupp's group wanted to look at the effect of combining temozolomide with radiotherapy.

No pharmaceutical company would be keen to invest the money necessary to test a disappointing drug on a rare tumour. But the EORTC-NCIC group – with no financial interest in the success or otherwise of a trial – went ahead and ultimately, was proved correct.

Patients with newly diagnosed glioblastoma were randomly assigned to receive radiotherapy alone; or radiotherapy plus concomitant and adjuvant temozolomide. The study included 537 patients, recruited from 85 centres between 2000 and 2002. It was an academic trial and there was no on-site monitoring.

The results were more than encouraging: the 2 year survival rate was 10.4% in the radiotherapy group and 26.5% in the combined treatment group (*N Eng J Med* 2005, **352**, 987–996). Hence the editorial ''Chemotherapy for Brain Tumors – A New Beginning'' (*N Eng J Med* 2005, **352**, 1036–1038).

Schering-Plough renewed its interest in the drug and is now testing it in different settings and trying to understand which subgroups of patients may benefit particularly. But an immediate concern was to register the drug for a new indication.

The potential hurdle was the lack of on-site monitoring: standard procedure in studies aiming for registration, but not in academic trials. Each site is visited every 2–3 weeks and the data in patient files checked.

The company employed an independent contract research organisation (CRO) to look at the quality of the data retrospectively. The centres which contributed most patients were visited and individual patient data checked against that provided by EORTC-NCIC. The CRO was satisfied that the data was as robust as if on-site monitoring had been carried out. It recommended that the database could be used as the basis for submission. The US' Food and Drug Administration (FDA) and the European Medicine Evaluation Agency (EMEA) accepted it and temozolomide was approved in March and April 2005, respectively.

On-site monitoring would have added around Euro 2.5 million to the costs of the trial – quite beyond the means of academic groups. Yet this study suggests that it may not be necessary, and should not be mandatory in all situations. Well-established academic networks can conduct important studies, produce good quality data, and attend to patient safety. Basic good clinical practice (GCP) principles are sufficient for this.

''BASIC GCP PRINCIPLES ARE SUFFICIENT TO PROTECT PATIENTS' SAFETY''

The tragedy is that many important studies – like this one – are unlikely to take place in today's climate. It is not impossible, but the barriers are higher than ever. The European Clinical Trials Directive would have increased the costs 3–4 times compared to 1999, when this study was initiated. It would take at least 2 years longer to complete – recruitment alone could take 2 years longer because activation of trials is now so difficult. Any changes that have to be made during a trial could easily add a further 2 years as researchers have to re-negotiate with each regulatory authority.

Future patients are the losers in this situation. We have demonstrated that basic GCP principles protect patients' safety and their interests. Further bureaucracy will serve no useful purpose and may mean that potential improvements and new treatments for many conditions go undiscovered, or untested.

Patrick Therasse
EORTC

Childhood survivors and late effects

Children's quality of life is being jeopardised by ''unnecessary levels of treatment'' for cancer (Editorial. *Lancet Oncol* 2004, **5,** 641). Those with Hodgkin's disease do not always need adjuvant radiotherapy; postoperative chemotherapy for some with Wilms' tumour could be shortened to a quarter with the same event-free survival.

But Dr. Jon Pritchard (Royal Hospital for Sick Children, Edinburgh, UK) said that, since the late 1970s, the objective of those treating children with cancer has been ''cure at least cost''. Since then, for example, the aim of treatment for both Wilms' tumour and Hodgkin's disease has been to reduce the intensity and duration of treatment schedules.

Drugs need to be tested in the paediatric setting, and the editorial noted the Pediatric Research Equity Act (December 2003, USA), which states that all licensing applications of new drugs in the USA must contain information about the drug's effect on children (or include a waiver request if the drug is not likely to be used in a substantial number of children). The European Commission adopted a similar proposal on September 29, 2004. These measures, coupled with financial incentives, mean that investment in paediatric and adolescent research is likely to increase.

However, even now, children with cancer have an overall 70–80% chance of cure. ''Let us be fair to treatment teams,'' said Dr. Pritchard. ''They certainly have the quality of life of the survivors close to their hearts.''

EUROFILE

'Inappropriate' Regulation proposed for Tissue Engineering

Tissue engineering, currently outside the EU legislative framework, is to be regulated under a draft Commission proposal published in late May, 2005. Tissue engineering is an emerging field which promises extraordinary advances in medical technology. It is concerned with the design, specification and fabrication of cells, biomaterials or biomolecules to restore or modify the biological functions of tissues. An example is new cells grown from stem cells.

Human tissue engineering differs from standard therapies in that the engineered products grow with the patient and become part of their body. Products already on the market include engineered skin, cartilage and bone, but it is the prospect of human organs produced entirely in vitro that has prompted the Commission to take action.

No clear boundaries exist so far between tissue engineering and certain other allied areas, which will result in inevitable overlaps with other forms of treatment. A definition, therefore, was essential to provide a sound basis for demarcation between tissue engineered products (or 'advanced therapy medicinal products', as they, together with gene and cell therapy, are called in the consultation paper), on the one hand, and medical devices, pharmaceutical products and cell therapy on the other, says the Commission.

''SOME REQUIREMENTS ARE ABSOLUTELY NOT APPROPRIATE''

A directive establishing the quality and safety standards for handling human tissues and cells was adopted by the Council on 2, March 2004. In May 2005, the Commission launched a public consultation on the regulation of advanced tissue engineering technologies. Under the Commission proposals, tissue engineered products would fall under the same regulations as pharmaceutical products. Eucomed, the trade association for medical device manufacturers, is disappointed that the Commission has abandoned an early idea for independent legislation for such products. According to their scientific director, Richard Moore, they feel that the new proposal may increase the regulatory burden on manufacturers. ''Our view is that some of the requirements [for the pharmaceutical industry] are absolutely not appropriate for human tissue engineering'', he said.

There are many differences between pharmaceuticals and tissue engineered products, he continued. Pharmaceuticals are produced in large quantities and undergo huge clinical trials to establish their safety. ''But some tissue engineered products are made for a single individual. You can't go through an approval process for each use of them, you can really only approve the concept'', he said.

''ONCOLOGISTS HAVE BEEN SLOW TO TAKE A VIEW''

The Commission suggests that a new Committee for Advanced Therapies (CAT), which would include representatives from each of the 25 member states plus about 6 other members, should be set up in the European Medicines Agency (EMEA). The Committee would report to the EMEA's Committee for Medicinal Products for Human Use, with the CHMP able to overrule the CAT in certain circumstances. There has been criticism, however, both of the composition and the powers of the CAT. Some feel that not all member states are likely to have experts in this kind of new technology area, and there is a general feeling that the CHMP should not be able to overrule the CAT. ''We would rather see the nomination of appropriate experts no matter which country they come from,'' says Moore.

The consultation is asking for comments on the following areas: centralised marketing authorisation procedure; expert committee for advanced therapies to be set up within the European Medicines Agency; guidance on good manufacturing practice; requirements for risk management and post-authorisation traceability; financial and administrative incentives for small/medium enterprises (SMEs) to develop new therapies; principles on human rights and respect for dignity of the individual.

In one of the first responses, the Standing Committee for European Doctors (CPME) warned of the importance of strict regulation of the conditions under which tissue samples are taken. In the EU, original samples can only come from donations, which can either be taken from cadavers or from a living person, with the information and consent of the person or their legal successor. The conditions in which the samples are stored after distribution and sale to laboratories or enterprises that process these samples must be specified. Strict measures must be taken to avoid the risk of transmitting undesirable biological agents. To ensure that products, which are the outcome of these industrial procedures, are made accessible to all European citizens, distribution inside as well as outside the EU must be regulated.

Perhaps believing that this is more a matter for industry, oncologists have been slow to take a view on this issue. At the time of writing, no responses to the consultation had been received from the cancer community. But there are a number of issues here which should be of interest. For a start, the new proposals will almost certainly mean that there will have to be yet another revision of the clinical trials directive, so disliked by the oncology community, or at the very least, new guidelines. The re-opening of the whole area of tissue samples and consent, as mentioned by the CPME, is another.

''Ethical decisions on the use of human cells will remain within member state competence but the EU level measures will be designed to respect fundamental human rights and the dignity of individuals'', said a Commission spokesman. The Commission's response to the consultation is expected within the next 6 months.

Mary Rice
Brussels

NCI to restructure clinical trials network

The US' National Cancer Institute (NCI) is to revamp its Clinical Trials System in order to enhance the use of trial data and improve communication among clinicians, according to its Clinical Trials Working Group (CTWG).

The restructuring was initiated by Dr. Andrew von Eschenbach, NCI Director, who established the CTWG in order to advise on whether and in what ways the NCI clinical trials enterprise ''should be restructured to realise the promise of molecular medicine for advancing oncologic clinical practice in the 21st century.''

The CTWG included experts from academia, community oncology practices, the pharmaceutical and biotechnology industries, cancer patient advocacy groups, NCI, the Food and Drug Administration (FDA) and the US' Centers for Medicare and Medicaid Services (CMS).

The goals of the restructure were:

- to improve co-ordination and co-operation among the various components of the current system;
- to improve prioritisation and scientific quality via an open and transparent process for the design of science-driven clinical trials;
- to improve the standardisation of tools and procedures for trial design, data capture, data sharing, and administrative functions to minimise duplication of effort and to facilitate development of a shared infrastructure to support an integrated national cancer clinical trials network;
- to improve operational efficiency by increasing the rate of patient accrual and reducing operational barriers so that trials can be initiated and executed in a timely, cost-effective manner.

The CTWG defined 22 specific initiatives based on these goals, and they have been accepted by the US' National Cancer Advisory Board. A formal system will be developed to evaluate the success of the restructuring, and it is envisaged that it will take 4–5 years to implement all of the initiatives. The process is expected to cost US $113 million over 5 years.

Dr. Howard Fine (Neuro-Oncology Branch, Center for Cancer Research, USA) co-chaired the CTWG, and said, ''This enormous potential for more specific cancer treatment coupled with the complexity of evaluating new, highly specific agents, requires robust clinical trial designs. Development of such trials will necessitate comprehensive information sharing and close collaboration among clinical researchers and basic and translational scientists as well as scientists developing modern molecular diagnostic and imaging techniques.''

Dr. von Eschenbach said the recommendations will lead to the creation of ''a clinical research infrastructure that will unravel the molecular mysteries of human cancer and rapidly implement interventions that will pre-empt the cancer process.''

The full report, called ''Restructuring the National Cancer Clinical Trials Enterprise'' is available at http://integrated-trials. nci.nih.gov/ict/CTWG_report_June 2005.pdf.

The US Supreme Court rules against medicinal marijuana

On June 6, 2005, the US Supreme Court ruled that medicinal use of marijuana is illegal under federal law, despite the fact that ten states have previously passed legislation allowing the use of medicinal marijuana in certain diseases. Some patients with cancer use the drug to improve appetite, reduce nausea and vomiting, and alleviate moderate neuropathic pain.

The case was brought by two seriously ill Californian women, one of whom had several diseases including a brain tumour. After a raid of one of the women's crop of six marijuana plants, both women sued the then US Attorney General John Ashcroft. They asked for a permanent injuncton allowing them to possess, obtain, or manufacture marijuana for personal medical use without fear of arrest or home raids. The Supreme Court's ruling could damage other state's efforts to pass laws allowing the use of medical marijuana.

''From the perspective of cancer patients who may use marijuana, it adds the threat of personal prosecution to the existing obstacles to medical marijuana use in the USA, namely inability to secure a legal supply of the drug and reluctance of many doctors to prescribe it'', says Wayne Hall (Office of Public Policy and Ethics, University of Queensland, Australia). However, Hall also comments that as an antinausea agent marijuana has probably been ''superseded by more effective antiemitic drugs'' and ''the analgesic effects are modest compared to opioids''.

Manuel Guzman (Complutense University, Madrid, Spain) agrees that there are ''more efficient medicines than marijuana for the treatment of every isolated cancer-related problem for which the drug is used''. Yet he adds: ''with marijuana it is possible to treat certain patients who do not respond to conventional antiemetics, painkillers, or appetite stimulants. Ideally, combined treatments should be pursued. Who decides for the patients, the doctors or politicians?''

Laura Barton

This story originally appeared in Lancet Oncol 2005, **6,** 448.

Low dose radiation 'increases cancer risk'

Nuclear workers who receive low doses and dose-rates of radiation have a small increase in cancer risk, according to a study conducted by International Agency for Research on Cancer (IARC).

A retrospective study included more than 400,000 nuclear industry workers in 15 countries. It used individual real-time measurements of external radiation dose and found that 1–2% of deaths from cancer (including leukaemia) may have been caused by radiation exposure. The risk estimates statistically similar to those of the atomic bomb survivor data.

Dr. Peter Boyle, IARC Director said the results ''support current evidence on the carcinogenic potential of ionising radiation yet provide reassurance concerning the likely impact of ionising radiation on the global cancer burden.''

PODIUM

The evolution of EMEA

Professor Michel Marty is Head of Therapeutic Innovations at St. Louis Hospital, Paris. His research interests include the molecular biology of leukaemias and breast cancers, intensive chemotherapy with stem cell support and early clinical trials. Since 2004, he has chaired the Oncology Scientific Advisory Group of the European Medicines Agency (EMEA)'s Commission for Medicinal Products for Human Use (CHMP).

Professor Michel Marty

What does EMEA do?

The primary aim is to determine whether new drugs are efficacious and safe. But EMEA also maintains a database of ongoing trials (EudraCT), where all clinical trials initiated in the European Union must be registered. Another area – which is not yet up and running – is in pharmacovigilance. Suspected serious unexpected adverse reactions (SUSARS) which appear during clinical trials have to be reported to the local network, EudraVigilance; this is being extended to include problems which arise post-authorisation. In terms of ensuring the safety of patients entered into clinical trials, EMEA is the best agency in the world.

Why was EudraCT set up?

In France at least, the clinical trials database shows that almost 70% of academic-sponsored trials are never completed and reported. In terms of ethics, and acquiring knowledge, this is poor. A trial dealing with a toxic therapy might expose patients to severe risks, but have even greater benefits. The benefits will not be discovered if the trial is not completed.

Higher hurdles for setting up a trial may decrease the number of trials, but could increase the likelihood of those that are started, being completed.

Why aren't studies completed?

Some did not interest enough patients or researchers and failed to enter sufficient patients. Others did not take into account competing trials, or did not have the resources to cover their costs. It's a problem for academic research: to get a grant, researchers have to set up the trial; but if they don't get adequate funding, it won't run to the end.

How will EudraCT help?

In colorectal cancer, for example, it might be reasonable for 5 competing trials to ask the same question. But for some rarer tumours, a national trial will never be able to answer the question posed. If a trial in France is the same as one in Sweden, this will be apparent on EudraCT and it might be best to merge the trials to reach an optimal size.

How does the EMEA compare with the US' Food and Drug Administration (FDA)?

EMEA's weakness is that it is less of an integrated body for drug assessment. EMEA has to rely on national agencies in 25 member states to provide expertise – and it comes from different cultures and philosophies. The FDA has 8000 staff, all of whom have received similar training within a similar culture. It's much more straightforward.

This is not entirely a weakness, though. In a number of cancers, different approaches in different European countries have led to a more innovative approach. People at the FDA have been working in the same way for years and are unlikely to change their way of thinking. EMEA is evolving faster and is in advance of the FDA in areas such as AIDS and some innovative areas of cancer.

What innovation is taking place within cancer?

The specificities of anticancer agents have lead to the constitution of a Scientific Advisory Group in Oncology. We are aware of possible discrepancies across Europe and unequal access to innovative therapies in cancer. Thus anti-cancer agents in Europe now have to go through the central procedure for approval. This is intended for all therapeutic areas, but cancer has gone first. In other areas, it is still possible to go through the mutual recognition process.

What impact has this had?

We don't know yet. The mutual recognition process should work, but pharmaceutical companies may only be interested in the 8 major markets in Europe, so that elsewhere, patients may not have access to the new drugs. The mandatory central procedure should eliminate this situation.

The UK has NICE to decide whether approved drugs will become available. What happens elsewhere?

France and Germany have similar systems but it is up to each country to decide whether it has the resources to fund a particular drug. And it may depend on the epidemiology: if cervical cancer is much rarer in the Nordic countries than in the Mediterranean, those countries may be less inclined to fund second or third line treatment.

How do you see the interaction between EMEA and industry?

It is not too bad, but the European pharmaceutical industry thinks in global terms and would prefer a single authority to grant whole-world approvals for drugs. There are differences in requirements in Europe, Japan and the States.

What would you like to see changed about EMEA?

I would like it to be staffed – at least partially – with its own full-time personnel. There is a shortage of clinical pharmacologists and it would make sense for EMEA to employ some directly. But who would pay for that?

EMEA was set up as part of the Enterprise Directive, but, despite that, the interaction between EMEA and European start-ups is minimal or non-existent – which is not the case in the States. These businesses get some help if they're researching drugs for orphan diseases, but we should be doing more to get them off the ground. Also – representation of patients at European level is supposed to be improving, but I haven't seen much evidence of that.