Patents and public health: European opposition to the Myriad breast cancer patent

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Introduction

On 18 May 2004, after a public hearing, the European Patent Office decided to revoke a patent of the US company Myriad Genetics, on a method for genetic diagnosis of breast and ovary cancer. This decision was taken after an opposition procedure initiated three years earlier by three French medical institutions – the Curie Institute, the Gustave Roussy Institute and the Assistance Publique Hôpitaux de Paris – and a European consortium of eleven Societies for Human Genetics. The main grounds on which European geneticians opposed the patent was their refusal of any restriction on their medical practice and any monopoly on genetic testing. Although the granting of patents on genetic sequences and their new medical applications had been justified in Europe by their positive spin-off for patients and public health[1], opposition to patents on breast cancer genes showed that the relationship between patents, innovation and public health was not as straightforward and automatic as it was expected or made out to be. In particular, the granting of broad patents on genes and their applications was likely to result in monopolies that would cause problems in the health field, and consequently hinder the innovation of constantly evolving techniques.

In this article, after presenting the format of patents granted in Europe on breast cancer genes and genetic tests, I consider the justifications of that opposition. I show that they primarily concerned medical practice and public health, rather than opposition to the patentability of life forms and genes as such. I also show that that opposition embodied the clash between two types of health economy: a clinical economy based on the development, production and offer of genetic tests in hospitals, and an industrial economy in which the tests are produced and sold primarily by biotechnology companies that own patents on the genes and thus control the

[1] Cf. European parliamentary debate on the drafting and adoption of the European directive on the legal protection of biotechnical inventions in 1995 and 1998. Cf. Cassier M., « Brevetabilité du vivant et du génome humain », Regards sur l'actualité, La Documentation Française, mai 2003.

market. Note that the main effect of last May's revocation was to maintain the clinical economy of genetic testing for breast cancer. The diagnostic use of gene sequencing is now free, within the limits of the European patent convention, and clinical laboratories can continue to produce their own tests[2] without any risk of prosecution for infringement. The final status of the gene will nevertheless be determined only after the next two public hearings in January 2005. These will more directly concern product patents on the gene, the protein and occasional mutations associated with cancer risks.

Even if this decision had the effect of eliminating the legal monopoly that might have been extended to breast cancer genetic tests, it was not justified by the EPO in terms of regulation of monopolies in the health field, nor of a change of the patentability standard applied to genetic sequences or genetic diagnosis methods in Europe. The revocation of the patent was justified by the insufficient description of the gene sequence, by errors in the initial patent application, and by the absence of novelty of a latter patent application that had been amended but had since fallen into the public domain. Hence, the patent office's decision cannot be seen as a significant change in the norm concerning the patentability of life forms or genetic sequences. Industrial property experts see it rather as a phase in the normalization of these patents which are examined 'in the same way as a piston engine', according to Jacques Warcoin, the representative of the French opponents. In so far as this revocation changes not the patentability norm, that is, the possibility of patenting gene sequences, but the criteria for examining and receiving sequencing patents, it fails to eliminate all risks of a monopoly in the medical genetics field. For instance, how would the granting of patents in Europe on the gene and the deleterious mutations of haemochromatosis affect the hospital laboratories that currently produce those tests? The collective mobilization witnessed during the opposition to the Myriad Genetics patents is nevertheless likely to dissuade monopolistic behaviours in the genetic test field.

The opposition procedure also triggered amendments to the intellectual property laws in France, with the decision to expand the field of compulsory licences to in vitro diagnostic methods, for public health purposes. More broadly, in countries of the North – Europe and Canada –, opposition to Myriad Genetics' patents revived the debate on compulsory licences

[2] Something they had never ceased doing after the patent was granted in January 2001 and their opposition was filed in October of the same year.

in the health domain, in parallel with debate initiated at the turn of the century in the South, on Aids drugs[3].

1- A very broad method patent, completed by product patents on the gene and occasional mutations

The patent that was recently revoked concerned a method for genetic diagnosis of breast and ovary cancer, consisting of: 1) taking a DNA sample from a patient; 2) detecting an alteration in the BRCA1 gene and comparing the patient's gene to a reference gene; and 3) establishing the medical significance of this alteration, in so far as there are alterations unrelated to cancer predisposition. The scope of this patent is potentially very broad: first, because it lays claim to any genetic diagnosis method that uses the BRCA1 gene, without being limited to particular technical processes; second, because it lays claim to the gene sequence as a genetic diagnosis tool (the patented sequence is the standard used to detect mutations in patients' samples). Although it is not a product patent directly on the gene as a substance, the method patent claims the gene sequence as a genetic diagnosis tool. The sequence, its description, its novelty, and the inventive activity that was required to identify it, are at the centre of debate on the acceptability of this patent – far more than are the various test methods listed, with which the scientific and medical community was familiar when the patent application was filed. The French opponents clearly stated in their opposition report: 'In light of the general knowledge of specialists in this field, there is nothing inventive about a diagnostic method in which mutations in the BRCA1 gene are sought by comparing the patient's gene with a reference gene. The only inventive activity of the present invention could therefore relate not to the claimed method, but to the fact that the reference gene was identified'. Hence, the patent issue is about the sequence and not the genetic diagnosis method. The patent was revoked not on the basis of a discussion on the novelty or inventive activity of the test method, but on flaws in the definition and description of the BRCA1 gene sequence.

This method patent is completed by product patents that enjoy even broader protection. The patent on the BRCA1 gene claims the isolated genetic sequence as a 'product', as well as its

[3] M. Cassier, M. Correa, 2003, « Patent, innovation and public health : Brazilian Public Sector Laboratories experience in copying aids drugs », National Agency for AIDS Research, ANRS, Paris.

by-products (the protein coded by the gene and its antagonistic antibodies, the transformed cells and the transgenic animals in which the gene is incorporated) and its various applications (diagnostic, therapeutic, and the cancer drug screening methods that use a BRCA1 protein, a transformed host cell or a transgenic animal)[4]. The structure of this patent complies with the spirit of Article 9 of the European directive on the legal protection of biotechnological inventions that sets the form and scope of such patents: 'The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in article 5(1), in which the product is incorporated and in which the genetic information is contained and performs its function'.[5] The scope of this type of patent is exceptionally broad and grants the owner vast monopoly powers, for several reasons. First, the claimed ownership of genetic information encompasses a cascade of biological products in which it is expressed. Second, these patents, based on the model of product patents applied to traditional chemical components[6], protects any use of the sequence. As industrial property consultant Bruno Phélip put it: 'The sequence effectively constitutes a product in the sense of patent law and has the right to full protection. Thus, a patent that is the first to define a genome sequence and has given at least one example of a use, covers this sequence in itself in a valid way, irrespective of its application'[7]. Third, this monopoly is absolute because it concerns a natural substance and no one can invent a new gene to bypass the patented sequence. Fourth, the power of control of such patents is likely to encompass several biological functions of the gene, even if they are not described in the initial patent owned by the discoverer of the sequence.

A third type of patent completes the protection. It covers particular mutations of the BRCA1 gene associated with cancer predisposition, and to all derived products and applications – diagnostic, therapeutic, scientific – of those mutations. The mutation patent has several advantages. First, it allows the patent owner's monopoly to be extended as new deleterious mutations are discovered, provided they are adequately represented in the population. Second, in case of invalidation of the complete sequence of the gene, it allows certain ownership

[4] European patent 705 902.

[5] Directive 98/44 of the European Parliament and of the Council on the legal protection of biotechnological inventions.

[6] USPTO guidelines on utility requirements january 2001.

[7] Académie des Sciences, « La propriété intellectuelle dans le domaine du vivant », janvier 1995.

positions to be maintained. Third, it is easier to describe well-defined occasional mutations than the sequence of a large gene like BRCA1. These three types of patent claim overlap (diagnostic applications are covered by method patents, product patents on the complete sequence, and patents on specific mutations). Consequently, the European medical institutions that decided to oppose Myriad Genetics' patents were forced to oppose each of the three patents issued by the European Patent Office on the BRCA1 gene.

2- A clash between two economies of health and innovation

The granting of industrial property rights on genes and their medical applications plays a crucial part in the construction of reserved genetic test markets. It can consequently tilt the health economy from a regime of free use of genes to one of exclusive rights. This switch is clearly described by the industrial strategy of a US biotechnology company specialized in medical diagnosis: 'Historically, the diagnostic market has been characterized by weak industrial protection […] The Company believes that the industrialization of diagnostics R&D now being catalysed by genomics will transform the diagnostic industry from its current dependence on non-patented products generated sporadically by academic researchers into a market characterized by a steady flow of novel, proprietary tests protected by strong IP positions, thereby achieving a premium pricing and margins similar to those enjoyed by drugs and vaccines… The Company believes the diagnostics market is poised for a comparable value transition as a result of genomics and patenting' (Diadexus, subsidiary of Incyte and of SmithKline and Beecham, 2000). The legal opposition by European geneticians aims precisely to prevent this switch in the particular field of breast cancer genetics.

The European geneticians' opposition thus stems from the clash between two health economies: one, maintained essentially by biotech firms with patents, aims to create reserved genetic test markets; the other, defended by opponents of the Myriad Genetics patent, is based on free use of the gene and free development of test methods by local laboratories. As soon as the gene was published, and even shortly prior to that, during research to locate it, European geneticians set up an economy of genetic tests without patents. How can the existence of this particular economy be explained? Simply because Myriad Genetics' industrial property rights, that were potentially vast, were not valid during the period between the disclosure of genetic sequences in the patent applications, in 1994 and 1995, and the actual issuing of the patents by the European Patent Office in 2001 and 2002. During this period the knowledge contained

in the patents and gene sequences was in the public domain. Any European genetician could use it freely, with neither authorization nor licence, to develop genetic tests and make them available to patients. European genetic laboratories were thus able rapidly to build up a real genetic test economy located in the labs of public hospitals and not-for-profit clinics. The concept of a real economy refers to the creation of genetic diagnosis laboratories, the adaptation or development of technologies, the training of specialized technicians and researchers, the accumulation of know-how and publications, and the creation of financial circuits – generally public – to finance free access for patients to tests. In 2002 in France, seventeen laboratories produced just over 2,000 genetic tests. In the UK, BRCA tests were produced in some fifteen genetic centres; in Germany in about twelve laboratories; and in Belgium in eight hospital and university laboratories. The revocation of the patent on the breast cancer genetic diagnosis method maintained the existence of this clinical economy – an economy that is, moreover, able to adjust to the patenting of processes on test techniques.

3- 'A European rebellion against the patent on a gene for breast cancer' (Nature, 4 October 2001): reopening of the clash between patent and health

In the article in Nature headed 'Testing time for gene patent as Europe rebels', jurist Rebecca Eisenberg considered the European clinicians' opposition: 'The knee-jerk reaction of the research and medical communities is to say "stop the patents". That's not going to happen, so I'd like to see what their backup position is'. How did the European clinicians and geneticians explain their action? What did they propose, if anything, regarding regulation?

Their strongest argument related to criticism of monopolies in the medical field. European practitioners were above all opposed to any restrictions on medical practice due to patents: 'Myriad wants to enforce a monopoly on the provision of a service. This is an unwarranted and novel restriction on medical practice' (Rob Elles, secretary of the British Society for Human Genetics). Use of these patents by Myriad was almost unanimously rejected. The US company wanted to centralize the production of all genetic tests in its Salt Lake City genetic diagnosis laboratory, which would mean a steep reduction of European labs' activity and their loss of autonomy in test production. The geneticians defended not only the use of tests but also their particular organization in Europe, that is, their inscription in the hospital framework and the close association between medical genetic consultations and test laboratories – a continuity that would be broken if the tests were carried out in an industrial lab, especially if it

were located in the US. By refusing any restriction on medical practice due to the existence of patents, European clinicians revived the longstanding clash between patents and medicine that had existed since the early nineteenth century.

A second justification for the opposition, linked to the first, highlights the impact of a commercial monopoly on the price and accessibility of tests for patients. Clinicians pointed out the increasing cost of tests and the resulting expense for the health system.

The opponents' third argument was centred on the conditions of technical innovation in the genetic test field, and on the most suitable patent format. In so far as it laid claim to all genetic diagnosis methods for breast cancer, irrespective of the technique used, Myriad's patent allowed it to control and thus to exclude any test technique other than its own. But European laboratories had developed their own test techniques since the publication of the gene in 1994, and intended to preserve them – especially since their cost was far lower (three times less) than the patented test method. For instance, the twelve genetic test centres in Germany clearly expressed their wish to maintain their techniques: 'There was a resentment in the group, in all twelve centres. We do not want to support this patent. We need to get our own results based on our own technology'. Geneticians of the Curie Institute, who were highly active in the improvement of test methods, criticized the very broad scope of the patents and suggested reverting to more clearly defined patents on process inventions, that allowed technical improvements without lock-in. 'The monopoly thus clearly becomes an impediment to any diagnostic optimization and to any technological development' (Curie Institute).

Apart from the denunciation of a situation of lock-in caused by the Myriad patent, the opposition was to feed on a challenge to the reliability of Myriad's genetic tests. With their particular test method, developed in collaboration with the Pasteur Institute, the geneticians of the Curie Institute detected a mutation in a US patient that had not been identified by Myriad (published in The Journal of Medical Genetics, June 2001). This consolidated their grounds for opposing the patent's monopoly and continuing with the free development of their own technique. The latter technique had, moreover, been patented by its inventors at the Pasteur Institute, which helped to fuel debate on the format of patents and to justify the application for well-defined process patents, likely to stimulate innovation rather than hinder it. This debate also had a public health dimension in so far as the Curie Institute showed that the type of

mutations not detected by the Myriad Genetics test accounted for between 10 and 20% of mutations in certain groups.

Another cause for European opposition related to the confiscation of new mutations identified by Myriad as soon as it had total control over complete screening of the gene. These were mutations that it could, moreover, patent.

Apart from these reasons, based on the refusal of a monopoly in the health and biomedical research fields, there was another reason for opposition, although not all the opponents defended it equally: the idea of the patentability of genetic sequences and life forms in general. This line of opposition, excluded by the French opponents who feared that their action might be confused with the controversy over the European directive on the legal protection of biotechnological inventions, was present in the opposition reports of the European consortium of the Societies of Human Genetics. The consortium demanded the non-patentability of the sequence and mutations: 'the discovery of a mutation in the genome of a human who exists in nature. This is a discovery and is excluded by Article 52a EPC'. Although the subject of patentability of life forms was mentioned by the opponents, their most advanced arguments related to their refusal of restrictions on medical practice and on biomedical research. The map of opposition clearly illustrates this situation: it was the genetician-doctors of the Curie Institute who had launched the movement. The French opponents were medical institutions. The consortium of European opponents was coordinated by a genetician at the Louvain hospital in Belgium. Opposition to this patent was more a clash between the new extension of industrial property rights on medical genetics and the medical community than a clash over the patentability of life forms. The latter topic was more present in opposition to product patents on genes and mutations (Greenpeace opposed product patents but not patents on diagnostic methods).

4- Justifications for the revocation: inadequate definition and description of the gene sequence

The EPO's revocation of the Myriad breast cancer genetic test patent was justified by an incorrect definition of the sequence claimed by Myriad on September 1994[8], and by a lack of

[8] Ten erroneous amino acids were identified by the opponents, compared to the correct sequence.

priority of the corrected sequence in the patent applications filed by Myriad in March 1995, compared to the correct sequence disclosed, including by Myriad, in the public data bases in autumn 1994 and early 1995.

What conclusions can be drawn on this decision?

First, the decision, that invalidates the EPO's issuing of a patent in January 2001, shows the difficulties involved in examining this type of patent on a sequence: 'Finding such small differences in large genes is close to impossible' (Siobhan Yates, Head of Biotechnology at the EPO, Nature, 27 May 2004). For instance, the reconstruction of the history of the gene sequence patent application in public data bases is a particularly arduous task. Here the opposition represented a second process of examination of the patent, that benefited from a joint effort by scientists and patent engineers for the two and a half years that the procedure lasted.

Second, this decision tends to reinforce the criteria of acceptability of sequence patents and to weaken patents on insufficiently defined sequences. By thus selecting patents more carefully, disputes could be reduced. However, that might imply a more thorough examination by the EPO and more vigilance by the stakeholders (doctors and researchers). Can it be envisaged for the huge flow of patents that exist in the medical genetics field? Even if this decision is seen as a green light for doctors, researchers and medical and scientific institutions to keep a watch on patents applied for and issued in their field of practice and expertise, and even if the revocation can improve the quality of patents applied for, the fact remains that surveillance of the quality of patents cannot claim to be exhaustive.

Third, the revocation of this patent does not in any way modify the norms of patentability of genetic sequences in Europe. Rather, it affects their interpretation and application. Patents similar to that of Myriad could be issued by the EPO if they contained a definition and description of the gene sequence that the Office considered to be more satisfactory. Certain opponents regret that the decision to revoke the patent was taken on the basis of technical criteria only, rather than on ethical principles.

The argument on the legitimacy of the patentability of the mutations discovered and of genetic diagnosis methods was not taken into consideration by the EPO's opposition division. The fact that the revocation of the patent was based on traditional patentability criteria – clarity of the description, sufficiency of the description, novelty – satisfied the EPO specialists and patent engineers who saw this decision as a sort of normalization of patents on

genes. That is why Jacques Warcoin commented that the EPO applied the usual patent rules as if it were a matter of a piston engine.

Ethical issues – patentability of gene sequences as regards Article 53 of the European patent convention, or inventions that run counter to public order and moral standards – were not addressed. Yet the European consortium of Societies for Human Genetics had put forward this cause for opposition on the basis of the personal nature of genetic information: 'This intensely personal information must be kept patent free'.

Fourth, the question of the definition and granting of inventive activity was not either discussed, since the patent was cancelled before it could be addressed. Some members of the Breast Cancer Linkage Consortium would have liked this type of discussion: 'Our concerns are about how the inventive process environed in patent law can be reasonably applied to disease genes' (Mike Stratton, Sanger Institute, co-discoverer of the BRCA2 gene). In fact, discovery of the gene took place mostly in the framework of an international consortium, the Breast Cancer Linkage Consortium. This point was emphasized by all the opponents in written procedures, but the patent was revoked before it could be discussed in the oral procedure. The issue is the following : how to establish inventive step in a collective process of invention ? It is raised whenever the location and identification of genes involve structures of exchange and cooperation between many actors. Although the revocation penalized Myriad's early appropriation strategy and rehabilitated the collective discovery of the gene, it set no indication in this respect.

5- Opposition and changes to intellectual property law in France

Even before the outcome of the opposition to Myriad Genetics' patents was known, the conflict over breast cancer predisposition genes triggered an amendment to French intellectual property law.

As part of the recent amendment to bioethical law, in December 2003, parliament broadened the scope of compulsory licences for public health purposes, to include in vitro diagnostic methods. Until then compulsory licences had concerned drugs only.

It also passed an amendment intended to limit the scope of sequence patents to the application described in the patent. The idea was to ensure that the invention of new applications, dependent on the first patent, was not blocked.

In Canada the Ontario government refused to recognize Myriad Genetics' monopoly and authorized clinical laboratories to continue their tests. A report commissioned by the health ministry on 'Genetics, screening and patenting' (January 2002) proposed a reform to Canadian patent law and particularly the introduction of a period of opposition to a patent, extended protection for health providers against prosecution for infringement, and restrictions on the issuing of very broad-scope patents. In short, even if diagnostic techniques could still be patented, the use of a patented gene for diagnostic purposes should not be a cause for prosecution. The report also recommended the use of compulsory licences in the area of genetic testing.

In the US, congresswoman Lynn Rivers tabled a bill in March 2002, providing for 'exemption of patents for diagnostic uses of genes'. The idea was to protect practitioners who used patented genes from prosecution for infringement.

6- The opposition procedure, infringement and the strengthening of the clinical economy in Europe

The opposition procedure affected more than intellectual property law, it also impacted on the clinical economy of genetic tests in Europe.
First, although the patent issued in January 2001 was immediately applicable to laboratories carrying out tests, the opposition procedure had suspended its implementation. All European laboratories had continued to do BRCA tests in which they applied their own test methods, without applying for patent licences or paying royalties.

Second, the French health ministry set up a specific programme to organize and promote genetic tests for cancer, and laboratories substantially enhanced their testing capacities. The ministry, which supported the French medical institutions' opposition, reinforced the sector of the clinical test economy by encouraging infringement of Myriad's patent rights.

Simultaneously, test laboratories like the Curie Institute continued their work in improving genetic diagnosis techniques, in collaboration with the Pasteur Institute. If the revocation of Myriad's other two patents is confirmed in January, these laboratories and their activity will be stabilized. Whereas, in terms of Myriad Genetics' patent, the test methods developed by European clinicians were dependent on it, the revocation of the said patent reopened possibilities for technical improvement and invention without new generations of inventors being in a position of dependence. Inventors can patent the particular test methods – new technical processes – that they develop.

7- Opposition and enlargement of the circle of actors in the industrial property field

The opposition procedure facilitated the intervention of new actors in the industrial property field (health professionals, scientific societies, researchers and, to a lesser degree, patient organizations). The EPO noted that this patent 'has been the subject of public discussion' (Myriad breast cancer patent revoked after public hearing', EPO, 18 May 2004). It attested to the arrival, in the intellectual property field, of scientific and medical institutions such as the Curie Institute, that were both opponents and patent applicants. The opposition case was put together and monitored by the Curie Institute's technology transfer division. By opposing patents on genetic tests and breast cancer genes, this scientific and medical institution has contributed towards the regulation of intellectual property in the field of health and genetics, with the introduction of compulsory licences for in vitro diagnoses and the strengthening of patentability criteria for genetic sequences in Europe. Its intervention in the intellectual property field is both industrial and civic: it protects and valorizes innovations through patents, and it opposed Myriad's patents to challenge a monopoly in the health sector.