

DNA patenting: implications for public health research

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Abstract I weigh the arguments for and against the patenting of functional DNA sequences including genes, and find the objections to be compelling. Is an outright ban on DNA patenting the right policy response? Not necessarily. Governments may wish to consider options ranging from patent law reforms to the creation of new rights. There are alternative ways to protect DNA sequences that industry may choose if DNA patenting is restricted or banned. Some of these alternatives may be more harmful than patents. Such unintended consequences of patent bans mean that we should think hard before concluding that prohibition is the only response to legitimate concerns about the appropriateness of patents in the field of human genomics.

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Introduction

Patents are tools for economic advancement that are supposed to contribute to the enrichment of society. Society benefits from the wide availability of new and useful goods, services, and technical information, that derive from inventive activity.

DNA and the economics of patents

Economic activity depends on the production, circulation and further development of such goods, services and information. In pursuit of these aims, inventors protect their inventions through a system of property rights, the patent system. Once patents have been acquired, the owners seek to exploit their inventions in the marketplace. The possibility of commercial benefit encourages innovation and investment, especially in fields that require a lot of research and development, such as biotechnology and pharmaceuticals. Without such a period of legal exclusivity, such high-risk investment, it is argued, would not take place. But after a limited time, these legal rights are extinguished and the unprotected inventions are freely available for others to use and improve upon.

Patents can be exploited in various ways. For example, patents can be sold or licensed even before a product based on the invention has been developed. More advantageously, they can be converted into market monopolies if the corresponding invention results in a

commercial product, that is neither protected by more than one patent, nor in competition with substitute products on the market.

The second benefit is that information about the invention as revealed in the patent and by the invention itself is diffused throughout the economy. In this context, it is helpful to conceive of a patent as a contract between the holder and the government on behalf of the citizenry. The holder receives an exclusive time-limited right over the invention in exchange for the payment of fees and, more importantly, for disclosing the invention for others to study. Without a patent, the inventor would have no incentive to disclose the invention. This would be a loss for society if such lack of protection left the inventor with no alternative but to maintain maximum secrecy.

One reason that patents are so controversial is that the intellectual property incentive, as far as it actually works, functions by restricting use by others of the protected invention for a certain period. Yet follow-on innovation by others is more likely to happen if use is not restricted. Thus a balance between private control over the use of technical information and its diffusion needs to be struck. In genetics, it is often argued that the patenting of deoxyribonucleic acid (DNA) on the basis of the disclosure of the sequence and of one discovered function or use is overprotective, thereby hindering follow-on innovation.

The view of most businesses and patent practitioners is that DNA is a chemical, no more or less. As such, it should be possible to claim a disclosed DNA sequence in the same way as a newly characterized chemical can be claimed for all known and yet-to-be-discovered uses. For 100 years, isolated and purified chemicals “manufactured” in living things including humans have been patented in Europe and North America. For example, adrenaline was first patented in 1903, and insulin in 1923. Shortly after the Second World War, Merck was granted patents on two products extracted from a microorganism, the antibiotic streptomycin and vitamin B₁₂.

Legal and scientific objections to the patenting of DNA

At first glance, this DNA-as-a-chemical position is persuasive. Nonetheless, DNA is undeniably a product of nature. Neither describing its composition and naming a function, nor editing the non-protein-coding nucleotides and cloning it, can turn the discovery of a piece of nature into a human invention.

Furthermore, the state of the art in molecular biology is rapidly changing. If the recent past is even a modest guide to the near future, much of what we assume to be true today will seem pathetically misguided in a few years. And yet the patent rules and examiner guidelines are based on today's knowledge. Scientists now believe, for example, that as much as

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98.5% of human DNA is non-protein-encoding even though much of it is still transcribed into ribonucleic acid (RNA) for reasons that we do not fully understand. Until recently, this 98.5% was dismissed as junk DNA.

Each gene contains within its DNA the instructions for the synthesis of one or more proteins. Just as proteins consist of chains of amino acids, genes may be sub-divided into units called codons that comprise three nucleotide base pairs and code for, by way of a closely related chemical — the aforementioned RNA — the preparation of a particular amino acid. These amino acids are then combined in a specified way to form the required protein, that is, the one “expressed” by the gene. However, RNA appears to perform many functions unrelated to protein manufacture. The conundrum is that “either the human genome ... is replete with useless transcription, or these non-protein-coding RNAs fulfil some unexpected function”.¹ Apparently, “these RNAs may be transmitting a level of information that is crucial, particularly to development, and that plays a pivotal role in evolution”.¹

Moreover, the widespread assumption — one evidently shared by patent applicants, attorneys and examiners — that genes operate independently and perform single functions is now demonstrably false. Indeed, the “gene” itself is beginning to look like a rather shaky concept. According to one scientist, “we tend not to talk about ‘genes’ anymore; we just refer to any segment that is transcribed to RNA as a ‘transcriptional unit’”.² It has been known for some time that a gene can produce more than one protein, for example, by means of a process called alternative splicing, in which coding sections of the gene are selectively deleted. But it is now more apparent that genomes consist largely of multiple intersecting “mini-ecosystems” forming a larger one — the genome itself. Genomes are not single collections of separately functioning Lego bricks that can be combined and recombined precisely, predictably, and with no possibility of unintended consequences.^{3,4}

Consequently, one can argue on sound legal and scientific grounds that treating genes as patentable inventions on the basis of a single disclosed function or discovery — such as coding for a particular protein, or association with a

disease — is a rather generous interpretation of the inventor’s work. However, such discoveries are not necessarily easy or inexpensive to make, or undeserving of any reward. The point is that more facts of scientific and commercial interest may remain to be discovered about the gene in question.

Patenting single genes may also hinder innovation. Broad patent protection can stifle innovation in new industries, especially those operating in fields like molecular biology where the learning curve is particularly steep. Broad protection potentially limits opportunities for researchers to carry out further investigations on patented genes, to find out how they interact with other parts of the genome and any relationship they may have to particular diseases.

A disproportionately large quantity of patents is being granted compared to the number of commercial products based upon them. This is because of the enormous quantity of patents on genes and gene fragments that are basically research tools. Companies file such patents because they are allowed to do so, but their patenting decisions are dictated also by competition in the field, and by small companies’ need for finance. New biotech firms thus provide genetic information by selling patented products of their research to be used as tools for further research by their customers — drug development corporations. In order to protect these “products” and to secure funding to produce further ones, the biotech firms have a strong incentive to privatize their information through patents. But since the development of future commercial products such as therapeutic proteins or genetic diagnostic tests often requires the use of multiple research tools, many of which are patented, companies and public sector researchers intending to develop such products will need to acquire licences from other patent holders. In doing so, they will incur large, and possibly prohibitive, transaction costs. Heller & Eisenberg warned of an emerging intellectual property problem in the USA in the field of biomedical research which they called the “tragedy of the anticommons”.⁵ What they were referring to is a situation in which the increased patenting of pre-market, or “upstream” research “may be stifling life-saving innovations further downstream in the course of research and product development”.

As for patent office rules and examination practices, the US patent system tends to be relatively permissive in terms of applying the non-obviousness criterion with the result that inventions patented in the US may be too obvious to be patentable in Europe. Admittedly, there has been some tightening of the rules. In 2001, the US Patent and Trademark Office announced that henceforward patent applications disclosing DNA sequences must provide convincing evidence that their utility is “specific, substantial, and credible”.⁶ This is worth bearing in mind when patent filing or granting statistics are used to measure levels of innovation. Indeed, a study found that of 74 US human gene patents examined by researchers, 73% of them contained one or more claims considered to be “problematic”.⁷ Such permissiveness hardly seems the right way to encourage genuine inventiveness.

Is DNA patenting a bad thing?

It is difficult to prove that extending the coverage of the patent system to DNA sequences will guarantee more investment in public health research and development. However, proving the opposite is just as difficult.⁸ The well-publicized patenting by Myriad Genetics of two genes (BRCA1 and BRCA2) linked to a certain proportion of breast cancer cases and the aggressive assertion of these patents by the company lends plausibility to the view that DNA patenting is bad for public health research.^{9–14} Human Genome Sciences’ patenting of the CCR5 receptor gene that was subsequently discovered by other scientists to have a link to HIV infection raises serious doubts about the wisdom of allowing genes to be patented when very little is known about them.¹⁵ Nonetheless, such use of a limited number of examples cannot prove that DNA patenting is necessarily a bad thing. While empirical studies have found little evidence to support the view that there would be more and better public health-oriented research without DNA patenting,^{16,17} one should not rely too much on such findings. It is very difficult to estimate the size of the “chilling effect” of patents on such research, which anecdotal evidence suggests may be substantial. Furthermore, reliable empirical evidence exists to support the claim that the aggressive assertion of DNA patent rights is unduly restricting the availability of diagnostic tests for patients.¹⁸ This is

sometimes the case even when testing does not require access to information disclosed in a patent.^{4,14}

So far the debate concerning DNA sequence patenting has been mostly confined to the developed world. In developing countries the patenting of drugs rather than of genes has understandably been more controversial. Nonetheless, developing countries are largely importers, rather than producers or manipulators, of genetic information. The few exceptions are China, which played a substantial role in the public Human Genome Project, Brazil and India. Companies could be in an even stronger position in developing countries to use their patent rights to charge extortionate prices for diagnostic tests.

Concerns about DNA patenting are not confined to their effects on research. For one thing, many people consider it immoral for anybody to claim property rights over the genetic heritage of humankind or of products and processes derived from it.¹⁹ Such a conviction is particularly understandable given that the public Human Genome Project made its data immediately and freely available to researchers. And yet, certain companies took advantage of this generosity to access and use the data and then filed patents or asserted copyright protection over related and derived information.

To the extent that patents are legal monopolies that can in some cases, create market monopolies, they are bound to affect the prices of health products protected by patents. The relationship between DNA patents and the prices of drugs, vaccines, diagnostic kits and other health products is complex. Yet patents restrict competition, therefore they will effect prices, in at least some cases.

If not patents ...

Given the rather powerful legal, scientific and social welfare arguments against patent protection of DNA, it might be worthwhile to consider reforms and alternatives. One interesting reform has been put into effect by France and Germany. The two countries have opted, in the case of human sequences, for so-called “purpose-bound protection”. Accordingly, DNA patents can be claimed but only in respect of a specified use. Let us suppose there is a gene that codes for proteins A, B and C. The company that finds the gene discovers only that it codes for A and patents it on that basis.

In the United Kingdom and the United States, that company can control use of the gene for any application or function subsequently discovered while the patent remains in force. But in Germany and France, another company that discovers the gene’s role in producing proteins B and C can independently patent the gene in relation to those functions, but only those functions.²⁰

So what is the appropriate position to adopt: full product protection, purpose-bound protection, or no patent protection at all? I believe that if we are going to allow gene patents at all, the purpose-bound approach makes much sense. It appears to reward discovery without restricting further research. Certainly, supporters of the French and German positions could deploy some persuasive scientific and economic arguments for wider use of this approach.

Diverging radically from patents, discoverer’s rights have been suggested. These would operate as a liability regime. What is the difference between property and liability regimes? A property regime vests exclusive rights in owners, of which the right to refuse, authorize and determine conditions for access are the most fundamental. A liability regime is a “use now pay later” system according to which use is allowed without the authorization of the right holders. There is no right to exclude, but it is not free access. Ex-post compensation is still required. Thus, scientists or their employers who discover a new gene would not be able to own it. However, in exchange for disclosing its sequence to a chosen public database, they would be entitled to a fee from users.

Palombi has proposed a Genetic Sequence Right (GSR), which “would be granted to the first person to file and disclose a genetic sequence defining genetic material of any origin and explaining its function and utility”. The GSR would be filed with a patent office and placed on a freely accessible international electronic database. User fees would be charged varying according to the nature of the use, and an international body would be responsible for collecting and distributing fees. Some uses, such as in teaching and basic non-commercial use could be zero-rated. All users, though, would be required legally to register their use on the database.²¹

GSRs and liability regimes more generally appear to solve the problems with patents. However, it remains to be

seen whether the opportunity to receive such rights is sufficiently attractive to those who would invest and engage in commercial molecular biology research.

Undeniably, businesses innovating in the field of molecular biology are extremely dependent on intellectual property protection since they must invest large sums of money in very risky research. So how might they respond to a ban on DNA patenting? It is possible that investors will shift their attention to other areas of science and technology. But we can also expect businesses facing the restriction or banning of DNA patenting to seek alternative means to protect their investments in molecular biology as they would do in other fields of science and technology. For opponents of DNA patenting, including those concerned about effects on public health, these alternatives may not be preferable. Possible alternatives to patents include copyright and trade secrecy. The problem is that unlike patents, which require the owner to disclose the invention for the 20 year monopoly, these alternative approaches are easier to acquire and offer longer monopoly protection. Copyright, which was originally devised to protect literary and artistic works, lasts for the life of the author and seventy years thereafter. Copyright also protects owners from the deployment of devices to circumvent their technological protection measures for controlling access, use and reproduction of protected works. Trade secrecy offers perpetual protection without public disclosure.

Industry is already exploring such non-patent options. For example, the company Celera, which had been in a race with the International Human Genome Sequencing Consortium to finish sequencing the human genome to be first to complete the task, reported on its achievement in an article in *Science*.²² The article embedded the following notice on data availability in the final endnote:

“The genome sequence and additional supporting information are available to academic scientists at the Web site (www.celera.com). Instructions for obtaining a DVD of the genome sequence can be obtained through the Web site. For commercial scientists wishing to verify the results presented here, the genome data are available upon signing a Material Transfer Agreement, which can also be found on the Website.”²²

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Academic scientists expecting unconditional access to Celera's human genome sequence data would have been disappointed. They were required to sign and submit a document known as the "Celera Free Public Access Click-On Agreement", which provided a royalty-free, non-exclusive and non-transferable licence to access the genomic data for non-commercial research use. Such licences were only granted to an "Academic User" i.e. an employee, student or scientist legitimately affiliated with an academic, non-profit or government institution and who uses the information for such interests and not on behalf of a commercial entity. Distribution to other academic scientists was forbidden. The Agreement, which applied to the company's human and fruit fly genome sequence databases, stated that "the Celera Data, both the primary sequence assembly and the representation thereof, is a copyrighted work of PE Corporation (NY)."

What is interesting is their [Celera's] use of contract to assert their position in the marketplace and to control the publication and usage of their information. Celera is not the only firm to indulge in this practice — US firms such as Human Genome Sciences (HGS) and Incyte are also resorting to subscription agreements and the like to restrict access and use of

the contents of their databases of genetic information.⁴

We cannot be certain that business will embrace these non-patent forms of intellectual property more fully if DNA sequence patents are banned or restricted. Besides, Celera's original business model based on the sale of genetic information failed. Nonetheless, it is a plausible response. In fact, a company called Maxygen is reportedly encoding DNA sequences as music and using copyright and trade secrecy rather than patents.²³ This is even more reason for policy-makers to consider alternatives to all of these types of intellectual property protection.

Conclusions

Patent regulation provides numerous examples of how policy decisions have consequences that run counter to what was intended by the makers or supporters of those decisions. One reason stems from the fact that when powerful and organized business interests consider that a new reform, or the blockage of one they desire, inhibits their economic appropriation opportunities and they are unable to influence policy-makers, they seek to make the perceived inadequacies of the law less harmful to their interests. They may achieve this through

alternative legal means or by the adoption of new technologies. As for DNA patenting, industry and policy-makers alike must contend with uncertainty about the science, uncertainty about the effects of patent protection in this field, a rapidly advancing knowledge frontier, and highly polarized views in society on whether DNA patenting should be allowed at all.

For the reasons given earlier, one may accept the view that patents are inappropriate for DNA sequences, and yet question the desirability of an outright ban. A ban could have the effect of encouraging companies to appropriate their discoveries in a less publicly accountable manner. Copyright may be among the most deleterious possibilities.

As long as DNA is patentable subject matter, I would urge policy-makers to opt for purpose-bound protection, consider non-intellectual property forms of legal protection, and be very sensitive to the rapidly advancing knowledge frontier. Patent granting offices need to improve examination standards or maintain high standards where they exist; that way, it is likely that far fewer DNA sequence patents would be granted and their scope would be much narrower than has become the norm in some countries. ■

Competing interests: none declared.

Résumé

Brevetage de l'ADN : conséquences pour la recherche en santé publique

Si l'on pèse les arguments favorables et opposés au brevetage des séquences d'ADN fonctionnelles, y compris les gènes, les objections à l'interdiction semblent convaincantes. Une interdiction pure et simple du brevetage de l'ADN est-elle une réponse adaptée sur le plan politique ? Pas nécessairement. Les gouvernements peuvent souhaiter envisager des options allant d'une réforme de la législation sur les brevets à la création de nouveaux droits. En cas d'interdiction ou de limitation du brevetage de l'ADN, les industriels

trouveront d'autres façons de protéger des séquences génomiques. Certaines de ces solutions de remplacement pourraient avoir des effets encore plus préjudiciables que les brevets. Ces conséquences involontaires des interdictions de breveter doivent inciter à une réflexion de fond avant de conclure que l'interdiction est la seule réponse aux préoccupations légitimes à propos de l'opportunité du dépôt de brevets concernant le génome humain.

Resumen

Patentes sobre ADN: implicaciones para las investigaciones en salud pública

Tras valorar aquí los argumentos a favor y en contra de la concesión de patentes para secuencias funcionales de ADN que incluyen genes, considero en conclusión que las objeciones planteadas son convincentes. ¿Constituye la prohibición absoluta de las patentes sobre fragmentos de ADN la respuesta de política correcta? No necesariamente. Los gobiernos podrían plantearse otras opciones que comprenden desde la reforma de la legislación sobre patentes a la creación de nuevos derechos. Hay otras alternativas al alcance

de la industria para proteger las secuencias de ADN en caso de restricción o prohibición de las patentes sobre ADN, y algunas de tales opciones pueden ser más perjudiciales que estas últimas. Debido a esas consecuencias no deseadas de las prohibiciones, es preciso estudiar cuidadosamente el tema antes de extraer la conclusión de que la prohibición es la única respuesta a las legítimas inquietudes acerca de la idoneidad de las patentes en el campo de la genómica humana.

ملخص

تسجيل حقوق الملكية للدنا: تأثيراته على البحوث في الصحة العمومية

الشركات الصناعية طرقاً أخرى إذا ما فُرض الحظر على تسجيل حقوق الملكية. وهناك طرق بديلة لحماية متواليات الدنا، ومن هذه الطرق البديلة ما هو أشد ضرراً من تسجيل حقوق الملكية نفسه، ومن هنا فإن العواقب غير المقصودة لحظر تسجيل حقوق الملكية تستدعي منا التفكير العميق قبل أن نجد في الحظر الوسيلة الوحيدة للتصدي لمشاعر القلق المشروعة حول ملاءمة تسجيل حقوق الملكية في ميدان الجينوميات البشرية.

وزنّت الحجج التي توافقت على تسجيل حقوق الملكية للمتواليات الوظيفية للدنا وتلك التي تعارضه، وتشمل المتواليات الجينات، مع اكتشاف أوجه الاعتراضات التي ينبغي إثارتها. وأثرت التساؤل فيما سيكون الحظر التام على تسجيل حقوق الملكية للدنا هو الاستجابة الصحيحة للسياسات؟ ولعل الجواب أنه ذلك ليس صحيحاً بالضرورة، فقد ترغب بعض الحكومات بالنظر في اختيارات متعددة تتراوح بين إصلاح قوانين تسجيل حقوق الملكية وبين إنشاء حقوق جديدة. وهناك طرق بديلة لحماية متواليات الدنا، فقد تختار

References

1. Mattick JS. The hidden genetic program of complex organisms. *Scientific American* 2004;291:30-7.
2. Quoted in Gibbs WW. The unseen genome: gems among the junk. *Scientific American* 2003;289:26-33.
3. Krinsky S. Risk assessment and regulation of bioengineered food products. *Int J Biotechnol* 2000;2:231-8.
4. Dufield G, Suthersanen U. DNA music: intellectual property and the law of unintended consequences. *Sci Stud* 2005;18:5-29.
5. Heller MA, Eisenberg RS. Can patents deter innovation? the anticommens in biomedical research. *Science* 1998;280:698-701.
6. United States Patent and Trademark Office. Utility examination guidelines. *Federal Register* 2001;66:1092-99. Also available from: <http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf>
7. Paradise J, Andrews L, Holbrook T. Patents on human genes: an analysis of scope and claims *Science* 2005;307:156-67.
8. World Health Organization. *Genomics and world health. Report of the Advisory Committee on Health Research*. Geneva: WHO; 2002. p. 135-40.
9. Aldhous P. Patent battle could hold up tests for cancer gene. *New Scientist* 1996;149:8.
10. Brown P, Kleiner K. Patent row splits breast cancer researchers. *New Scientist* 1994;143:4.
11. Ernhof K. Who really owns your genes? *Christian Science Monitor* 27 Feb, 2003.
12. Henley J. Cancer unit fights US gene patent. *The Guardian* 8 Sept 2001.
13. Krinsky S. *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* Lanham: Rowman & Littlefield; 2003. p. 67-8.
14. Meek J. US firm may double cost of UK cancer checks. *The Guardian* 17 Jan 2000.
15. Nuffield Council on Bioethics. *The Ethics of Patenting DNA: A Discussion Paper*. London: Nuffield Council on Bioethics. 2002: 39-42.
16. National Academies of Science, Board on Science, Technology, and Economic Policy (STEP), and Committee on Science, Technology, and Law (STL). (2005) *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*. Washington DC: NAS; 2005.
17. Howlett MJ, Christie AF. *An analysis of the approach of the European, Japanese and United States patent offices to patenting partial DNA sequences (ESTs)*. University of Melbourne Faculty of Law Legal Studies Research Paper 2004;82.
18. Merz JF, Kriss AG, Leonard DG, Cho MK. Diagnostic testing fails the test. *Nature* 2002;415:577-9.
19. Shorett P, Krinsky S, editors. *Rights and Liberties in the Biotech Age: Why we need a Genetic Bill of Rights*. Lanham: Rowman & Littlefield; 2005.
20. Dufield G. Biotechnology and IPRs in Europe. In Jensen A, Pugatch M, editors. *Intellectual Property Frontiers: Expanding the Borders of Discussion*. London: Stockholm Network; 2005. p. 49-50.
21. Palombi L. *The genetic sequence right: a sui generis alternative to the patenting of biological materials*. Paper presented at the Queen Mary University of London Patenting Lives Conference, December 2005.
22. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. *Science* 2001;291:1304-51.
23. Shachtman N. A good sequence, easy to dance to. *Wired News*, May 21, 2002.