Special issue

A New Era for Biotech Patents? Empirical and Theoretical Considerations on the current Patent Dilemma

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ABSTRACT: During the last two decades, the genomics revolution has contributed enormously to the development of novel research approaches in the field of biological sciences. We have seen the development of new biotechnological tools capable of modifying organisms in order to perform specific tasks designing and assembling novel biological components. All these scientific and biotechnological innovations present also a substantial challenge for the law and especially for intellectual property rights. In particular – as a consequence of relevant patent case law in the United States and Europe affecting precision medicine – the debate on the possible future of biotech patents gained increasing momentum. Considering this multifaceted scenario, the purpose of this article is to analyse the impact of various judicial decisions with respect to patents subject-matter eligibility and the prosecution of biotech-related patent applications.

KEYWORDS: Gene patents; genetic engineering; biotechnology; patents; CoViD-19

SUMMARY: 1. Introduction – 2. The old era of Biotech Patents – 3. A paradigm shift on future biotech patents? – 4. The problem of Intellectual Assets in the Life Sciences Industry – 5. The impact of court decisions for the Life Sciences Industry: Myriad and Mayo – 6. The impact of court decisions for the Life Sciences Industry: Brüstle – 7. Conclusion.

1. Introduction

Legal questions concerning the interpretation and application of patent laws to the scientific area have started to be challenged more frequently also in courts in different countries. In particular, the effects and consequences of these controversial judgments have been intensively discussed both in academia and policy circles. Courts and scholars have reopened and rekindled the debate over the benefits and risks associated with patent protection to diagnostic methods and other scientific research techniques. For the most part, these discussions are focused on patent applications with the aim to determine the patentability of a particular invention related to human DNA sequences or stem cells developed in vitro and used for scientific research.

In recent years – especially in the United States – there have been a series of highly controversial court decisions involving subject-matter eligibility for patents in genes.[1] At the same time in Europe,

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the patentability of inventions relating to human embryonic stem cells has raised morality-related issues culminated in a series of decisions of the Court of Justice of the European Union in an attempt to define uses of human embryos for industrial and commercial purposes.

In particular, these decisions have triggered a series of questions about the future of patentability in the field of innovative diagnostic methods, biomarker and personalized medicine "with potentially profound implications for the biotech industry".[2] The question here is whether there is empirical evidence that these judgments actually had a negative impact in the field of precision medicine and in DNA-based diagnostics depriving certainty in patent law. This is a topic on which – as far as I know – very few empirical studies have been conducted to date and it is thus a particularly interesting field of investigation.[3] This debate has found its way into various scholarly works, without finding yet a pertinent solution for the questions raised.[4]

In the following pages, we will try to clarify the possible and actual negative effects arising from these disputes by reviewing some recent studies that have empirically evaluated how these cases actually affect the future of biotech patents, including patent filing and prosecution.[5]

2. The old era of Biotech Patents

The exceptionally rapid technological progress in the field of biotechnology has resulted in more appropriate legislative and judicial responses to the evolving regulatory regime especially with regard

[1] See *Mayo Collaborative Servs. v. Prometheus Labs*., Inc., 132 S. Ct. 1289 2012; *Association for Molecular Pathology v. Myriad Genetics*, Inc., 133 S. Ct. 2107 2013.

[2] M. ABOY et al., *Mayo's impact on patent applications related to biotechnology, diagnostics and personalized medicine*, in *Nature Biotechnology,* 37, 2019, 513, 513.

[3] E.J. HAANES, J.M. CANAVES, *Stealing Fire: A Retrospective Survey of Biotech Patent Claims in the Wake of Mayo v. Prometheus*, in *Nature Biotechnology*, 30, 2012, 758.

[4] See e.g. J. LIDDICOAT et al., *The Effects of Myriad and Mayo on Molecular-Test Development in the United States and Europe: Interviews from the Frontline*, in *Vanderbilt Journal of Entertainment and Technology Law,* 22, 2020, 785; M. ABOY et al., *One year after Vanda, are diagnostics patents transforming into methods of treatment to overcome Mayo-based rejections?*, in *Nature Biotechnology,* 38, 2020, 279; J. PILA, *Adapting the ordre public and morality exclusion of European patent law to accommodate emerging technologies*, in *Nature Biotechnology,* 38, 2020, 555; M. ABOY et al., *Was the Myriad Decision a 'Surgical Strike' on Isolated DNA Patents, or Does it Have Wider Impacts?,* in *Nature Biotechnology*, 36, 2018, 1146; M. ABOY et al., *How does emerging patent case law in the US and Europe affect precision medicine?*, in *Nature Biotechnology,* 37, 2019, 1118; M. ABOY et al., *After Myriad, what makes a gene patent claim 'markedly different' from nature?*, in *Nature Biotechnology,* 35, 2017, 820; M. ABOY et al*., Myriad's impact on gene patents*, in *Nature Biotechnology,* 34, 2016, 1119; A. MAHALATCHIMY et al., *The impact of European embryonic stem cell patent decisions on research strategies*, in *Nature Biotechnology,* 33, 2015, 41.

[5] In particular, M. ABOY et al., *After Myriad , What Makes a Gene Patent Claim Markedly Different' from Nature?,* in *Nature Biotechnology,* 35, 2017, 820; M. ABOY et al., *Mayo's Impact on Patent Applications Related to Biotechnology, Diagnostics and Personalized Medicine*, in *Nature Biotechnology,* 37, 2019, 513; M. ABOY et al., *Myriad's Impact on Gene Patents*, in *Nature Biotechnology*, 34, 2016, 1119; M. ABOY et al., *Was the Myriad Decision a "Surgical Strike" on Isolated DNA Patents, or Does It Have Wider Impacts?*, in *Nature Biotechnology*, 36, 2018, 1146; G.D. GRAFF et al., *Not Quite a Myriad of Gene Patents*, in *Nature Biotechnology,* 31, 404, 2013; E.J. HAANES, J.M. CANAVES, *Stealing Fire: A Retrospective Survey of Biotech Patent Claims in the Wake of Mayo v. Prometheus,* in *Nature Biotechnology,* 30, 2012, 758.

to intellectual property rights, trying to balance the interests of both rights-holders and individuals.6 The key to the success of the biotechnology industry was – *in fact* – the result of numerous supporting and "favourable government policies toward the sector in combination with a liberalized regime for the governance of biomedical research".[7] Debates and "concerns about the need to regulate the disruptive potential of biological manipulation were apparent almost from the moment when genetic engineering became feasible in the 1970s".[8] The emergence of all these issues and concerns set the basis for a new discussion on how to regulate the use, access, distribution, and appropriation of essential public knowledge assets in the life sciences.

We are presently living within one of the clearest proofs of the failure of this model: the current COVID-19 pandemic is showing us all the contradictions of the current patent system. If democratic States may legitimately interfere with certain fundamental rights through limitations or derogations in order to contain the COVID-19 pandemic, it is certainly incomprehensible how – also in respect of a proper balance of rights – it is not equally reasonable to temporarily derogate from patent protection in order to guarantee safe and equitable access to life-saving drugs and vaccines.9 Today, interests antagonistic to the right to health, freedom of movements, freedom of enterprise and access to scientific knowledge are emerging distinctly, requiring a careful balance between public and private interests. A significant proportion of DNA-related patents are owned by companies with a direct interest in commercialising genetic diagnostics. These patents often claim whole genes, gene fragments, cDNA, mutations, nucleic acids and DNA sequences "which hybridise under stringent conditions to the primary DNA sequences just to stop competitors taking advantage of redundancies in genetic code".[10]

Considering this scenario, the purpose of this investigation is to briefly outline the past and take a closer look at the future of biotech patents. In particular, the reason behind this analysis is to assess if – as a result of some court rulings – there are actual data for believing that the number of gene patents is declining and will continue to decline as well as whether it is a good or bad thing.[11] It was more than a decade ago when some US Supreme Court decisions (hereinafter *Mayo*[12], *Myriad*[13] and *Alice*[14]) have – in fact – completely changed US patent eligibility criteria for biotechnology reversing more than 30 years of case law questioning the enforceability and validity of patents on naturally occurring genetic material (even if isolated). Specifically, in *Myriad*, the Supreme Court held that

[6] See N. LUCCHI, *The Impact of Science and Technology on the Rights of the Individual*, 2016, 67.

[7] See S. VALLAS, D.L. KLEINMAN, D. BISCOTTI, *Political Structures and the Making of U.S. Biotechnology, in State of Innovation: The U.S. Government's Role in Technology Development*, in F. BLOCK, M. KELLER (eds.), *State of Innovation. The U.S. Government's Role in Technology Development,* 2011, 57.

[8] See S. JASANOFF, *Rewriting Life, Reframing Rights*, in ID. (ed.), *Reframing Rights: Bioconstitutionalism in the Genetic Age,* 2011, 1, 9.

[9] See E. BONADIO, A. BALDINI, *COVID-19, Patents and the Never-Ending Tension between Proprietary Rights and the Protection of Public Health*, in *European Journal of Risk Regulation,* 11, 2020, 390 (illustrating the patent race in the context of the Covid-19 pandemic).

[10] See K. LIDDELL et al., *Patents as incentives for translational and evaluative research: the case of genetic tests and their improved clinical performance*, in *Intellectual Property Quarterly,* 3, 2008, 286, 296.

[11] See e.g. M.M. HOPKINS et al., *DNA Patenting: The End of an Era?,* in *Nature Biotechnology,* 25, 2007, 185.

[12] *Mayo Collaborative Servs. v. Prometheus Labs*., Inc., 132 S. Ct. 1289, 2012.

[13] *Association for Molecular Pathology v. Myriad Genetics*, Inc., 133 S. Ct. 2107, 2013.

[14] *Alice Corporation v. CLS Bank International*, 132 S. Ct. 2347, 2014.

naturally-occurring DNA is not eligible for patenting just because it has been isolated from its natural state. Naturally occurring DNA remains a "product of nature" even after isolation and, therefore, falls under the "laws of nature" exception to patent eligibility. In other words, isolation of naturally-occurring DNA is not enough for the naturally-occurring DNA to be considered man-made. At the same time in *Mayo*, the US Supreme Court held that certain diagnostic methods are not patentable because they involved standard conventional steps. In particular, the Court found that the procedure by which a drug is chemically converted in the body to a metabolite must be considered as a natural process, and so the relationship between the quantities of metabolites and the efficacy of drug dose is a law of nature. In other words, simply observing such a naturally-occurring relationship – without adding anything else – cannot be considered enough to transform the concept of the claims into a patentable invention. Finally, in *Alice*, the US Supreme Court entirely reaffirmed the Mayo framework applying it to claims directed to computer-implemented process, computer system, and computer readable medium for mitigating settlement risk. In particular, the court determined that the method claims, which merely required generic computer implementation, are not sufficient to transform the abstract idea into a patent-eligible invention.[15]

In Europe, biotech patent disputes were raised by the landmark case of *Brüstle vs Greenpeace*, where the Court of Justice of the European Union was confronted with moral and legal dimensions of embryonic stem cells research. In this decision, the CJEU held that processes that require the use of stem cells gathered from a human embryo involving the destruction of that embryo cannot be subject to a patent. In particular, the Court recognized that "any human ovum after fertilization, any non-fertilized human ovum into which the cell nucleus from a mature human cell has been transplanted, any non-fertilized human ovum whose division and further development have been stimulated by parthenogenesis constitute a 'human embryo'"[16] thus constituting an unpatentable subject matter within the meaning of Article 6(2)(c) of the Biotech Directive.[17] Just two years later – surprisingly enough – the CJEU then allowed the patenting of human stem cells derived from unfertilized ova.[18] And finally, in 2005 the CJEU upheld the interpretation established in the *Brüstle* case that the concept of the human embryo within the context of the biotech directive must be understood in a broad sense.[19]

All these cases illustrate the difficulties of courts in reviewing scientific and technological issues as well as their huge power in creating a significant overlay of doctrine that may change completely the meaning or the interpretation of statute law. In particular, the role of the judiciary seems to have become decisive in "patent law assessment of legal subject matters".[20] In addition, these cases show how the granting of patents in the biotech sector may imply – at least in Europe – heterogeneous

[15] *Alice Corporation v. CLS Bank International*, 132 S. Ct. 2347, 2014.

[16] See *Oliver Brüstle v Greenpeace* eV (C-34/10), 2012. 1 C.M.L.R. 41, at § 38.

[17] Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, OJ EC L 213, 30 July 1998, 13-21.

[18] Case C-364/13, *Int'l Stem Cell Corp. v. Comptroller Gen. of Patens, Designs and Trade Marks*, ECLI:EU:C:2014:2451

[19] Case C- 456/ 03, *Commission v. Italy*, 2005 E.C.R. I-5355, recital 24.

[20] See F. MOLNÁR-GÁBOR, *Science, ethics, and patents. Ethically-motivated barriers for the patenting of the results of human embryonic stem cell research*, in C. HAUSKELLER et al. (eds), *The Matrix of Stem Cell Research: an Approach of Rethinking Science in Society*, 2019, 50.

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and controversial ethical or moral elements that are difficult to harmonize at both national and European level. In contrast with the European Patent Convention and the EU Biotech directive, the United States patent system does not explicitly outline what categories of inventions or discoveries are placed outside the umbrella of patentability.[21] It is thus left to the Courts to define – time by time – where the boundary of patentability lies, and they are bound only by the provisions of the legislation. At the same time, the "public morality argument" as well as the phenomenon of the "ethicalization of law" are not particularly evident within American patent law.[22]

The comprehensive new approach resulting from these different decisions narrowed "de facto" patent-eligible protection over living organisms and created significant ambiguity among both patent applicants and patent examiners. In order to mitigate this confusion, the United States Patent and Trademark Office (USPTO) arranged a series of guidance on subject matter eligibility. These new challenges faced by biotechnology innovators have possibly fuelled the debate over new effective instruments for supporting innovations in the biotech sector: this discussion – which also came to reconsider the idea of using alternative form of intellectual property in order to protect engineered nucleic acid sequences[23] – is probably demonstrating the need to draw a completely new set of principles for biotech patents.

3 A paradigm shift on future biotech patents?

The standard approach of the Trilateral Patent Offices [i.e. the United States Patent and Trademark Office (USPTO), the Japan Patent Office (JPO) and the European Patent Office (EPO)] with respect to

[21] See T. Minssen, D. Nilson, *Standing on shaky ground: US patent-eligibility of isolated DNA and genetic diagnostics after AMP v USPTO* – Part I, in *Queen Mary Journal of Intellectual Property*, 1, 2011, 223 - 224.

[22] See R. A. Spinello, *A Defense of Intellectual Property Rights*, in *Elgar*, 2009, 68 (noting that that the public morality aspect is feeble in American patent law).

[23] See D.L. Burk, *DNA Copyright in the Administrative State*, in *UC Davis Law Review*, 51, 2018, 1297; N. Lucchi, *Genetic Copyright: An Alternative Method for Protecting and Using Essential Public Knowledge Assets?,* in European intellectual property review, 40, 2018, 766; R. Neethu*, Rekindling the debate on genetic copyright in Europe in the era of biobanks and synthetic biology*, in European intellectual property review, 40, 2018 172; C.M. Holman, *Charting the Contours of a Copyright Regime Optimized for Engineered Genetic Code*, in *Oklahoma Law Review,* 69, 2017, 399; C.M. Holman, *Copyright for Engineered DNA: An Idea Whose Time Has Come*, in *West Virginia Law Review,* 113, 2011, 699; C.M. Holman, *Developments in synthetic biology are altering the IP imperatives of biotechnology*, in *Vanderbilt Journal of Entertainment and Technology Law,* 17, 2015, 385; C.M. Holman, *Copyright for Engineered DNA*, in *GQ Life Sciences*, available at https://bit.ly/3dJnRBe, (last visited 27/04/2021); A. W. Torrance, *Synthesizing Law for Synthetic Biology*, in *Minnesota Journal of Law, Science & Technology,* 11, 2010, 629; M.D. Murray, *Post-Myriad Genetics Copyright of Synthetic Biology and Living Media*, in *Oklahoma Law Review,* 10, 2014, 71; D. Walker, *Patent Protection or Copyright for Nucleic Acid Sequences?*, in *Licensing Journal*, 36, 2016, 1; J. Roig, *Can DNA Be Speech?*, in *Cardozo Law's Arts & Entertainment Law Journal,* 34, 2016, 163; J.J. Zhuang, *Copyright: Better Fitting Genes*, in *Journal of the Patent and Trademark Office Society,* 97, 2015, 442; J.N. Michelotti, *Genes as Intellectual Property*, in *Michigan State University Journal of Medicine and Law*, 11, 2007, 71; T. Chen, *Can a Biological Sequence Be Copyrighted*, in *Intellectual Property and Technology Law Journal,* 19, 2007, 1.

patents on biological subject matter is to grant ownership rights only for isolated and purified gene sequences with a demonstrated specific utility.[24]

A clear dividing line between patentable subject matter and non-patentable products of nature was established for the first time by the United States Supreme Court in Diamond v. Chakrabarty.[25] This historical court decision – in combination with the judgement in Moore v. Regent of University of California[26] – not only significantly impacted the U.S. patent system, but provided a new lens to look at how genetic resources can be used and privatized. A few years later, the USPTO, EPO, and JPO released a joint policy statement claiming that "purified natural products are not regarded as products of nature or discoveries because they do not, in fact, exist in nature in an isolated form. Rather, they are regarded for patent purposes as biologically active substances or chemical compounds and eligible for patenting on the same basis as other chemical compounds".[27]

The aim of this statement was to identify the relevant global planning policy regarding patentability of genetic material: in particular, it was specified that a purified natural substance was to be considered patentable if the "purification" results in a compound with such distinct characteristics that it becomes a new product commercially or therapeutically valuable. In the process of isolation and purification of genetic materials, it is – in fact – possible to obtain the partition of different compounds from a biological cell. However, it should also be pointed out that various criticisms have been made related to the above interpretation. In particular, it has been stressed that even if genetic materials are purified and isolated, the core elements of such substances – which are the "useful" and exploitable information – "are naturally occurring, not created by the person who isolates and purifies the material".[28] In addition, purified and isolated genetic sequences are "structurally similar or identical to the form that exists in nature".[29]The main point of this interpretation is that patents for biotech innovations are simply based and limited only on the ability of the individuals drafting the claim.[30]

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[24] See M.J. HOWLETT, A.F. CHRISTIE, *An Analysis of the Approach of the European, Japanese and United States Patent Offices to Patenting Partial DNA Sequences* (ESTs), in *Int'l Rev. Indus. Prop. & Copyright L.,* 34, 2003, 581; L.G. RESTAINO et al., *Patenting DNA-Related Inventions in the European Union, United States and Japan: A Trilateral Approach or a Study in Contrast?*, in *UCLA Journal of Law and Technology*, 2003, 2. See also A. REESE, B. OPESKIN, *Current Issues in Gene Patenting*, in I. FRECKELTON, K. PETERSEN (eds.), *Disputes and Dilemmas in Health Law*, 2006, 277, 280; N. LUCCHI, *Understanding genetic information as a commons: from bioprospecting to personalized medicine*, in *International Journal of the Commons*, 7, 2013, 313.

[25] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). In this landmark decision, the United States Supreme Court held that a live and human-engineered microorganism can be considered a patentable subject matter under Section 1010 of the *United States Patent Act*. According to the rule of this decision, patents can be issued on "anything under the sun that is made by man".

[26] *Moore v. Regents of the University of California*, 793 P.2d 479 (Cal. S. Ct) (1990).

[27] See 1988 Joint Statement of USPTO, EPO and JPO; *Comparative Study of Patent Practices in the Field of Biotechnology Related Mainly to Microbiological Inventions*, in *Biotechnology L. Rep*, 7, 1998, 159, 163; Nuffield Council of Bioethics Discussion Paper, *The Ethics of Patenting DNA*, 2002, 26, 3.14.

[28] See Australian Law Reform Commission, Genes and Ingenuity: Gene Patenting and Human Health, Report 99. Sydney: Australian Commonwealth, 2004, at 126. Available at: https://bit.ly/3dTzghW (last visited 27/04/2021).

[29] *Ibidem*

[30] See D. ROBINSON, N. MEDLOCK, *Diamond v. Chakrabarty: A Retrospective on 25 Years of Biotech Patents*, in *Intellectual Property and Technology Law Journal,* 17, 2005, 12, 14.

In more recent years, the patenting of genes and gene fragments has put under debate one of the fundamental principles of the patent law: the requirement of novelty.[31] Consequently, the debate on the status as patentable subject matter has suddenly become topical again. Indeed, many questions surround this issue: "as DNA has existed well before the gene discoverer arrived, how can these molecules be novel?"[32].The answer, as it has been suggested, "is that the actual molecule produced and claimed by the gene discoverer is new in a strict sense of the word".[33] More specifically, "gene sequences exist naturally as part of a much bigger molecule" and "there is no doubt that this much bigger molecule would be unpatentable".[34] But, on the other hand, the gene discoverer's thesis is that "purified and isolated gene sequences are distinct from the overall DNA molecule".[35] This is also the thesis formulated by one of the first U.S. patent infringement litigations involving a gene patent. In Amgen, Inc. v. Chugai Pharm. Co. Ltd., the district court ruled that the patent in suit was to be regarded as valid because the invention "is not as plaintiff argues the DNA sequence encoding human erythropoietin since that is a non-patentable natural phenomenon "free to all men and reserved exclusively to none". Rather, the invention as claimed in claim two of the patent is the "purified and isolated" DNA sequence encoding erythropoietin."[36]

In order to be patentable under the United States and European law, an invention must meet three basic requirements:[37] (i) novelty; (ii) inventive step (non-obviousness in the US); and (iii) industrial application (utility in the US). These statutory limits provide the basic and general requirements that must be satisfied in order to obtain a patent. However, patents on DNA and human genes raise the question of where to draw the line between patentable and non-patentable inventions. In fact, the patenting of genes and gene fragments appears to challenge the novelty requirement. At the same time, there is a growing sensitivity to ethics in patent law.[38] This sensitivity is even more evident in the biotech sector where the structure of the patent system seems to require a more careful assessment of all the possible conflicting rights.

The patent dilemma in the biotech sector is also challenged by a regulatory framework built for a more conventional setting. For example, there are increasing policy and academic discussions about the ethical and social issues raised by owning, managing and using essential public knowledge assets

[31] See e.g. J.J. DOLL, *The Patenting of DNA*, in *Science,* 280, 1998, 689; D.J. KEVLES, A. BERKOWITZ, *The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics*, in *Brooklyn Law Review,* 67, 2001, 233. For a recent overview of the gene patenting controversies, see also L. LARRIMORE OUELLETTE, Access to Bio-Knowledge: *From Gene Patents to Biomedical Materials*, in *Stanford Technology Law Review,* 2010, available at https://stanford.io/2PrVWwl (last visited 27/04/2021).

[32] See O. LIIVAK, *Maintaining Competition in Copying: Narrowing the Scope of Gene Patents*, in *UC Davis Law Review*, 41, 2007, 177, fn 53.

[33] *Ibidem*.

[34] *Ibidem*.

[35] *Ibidem*.

[36] See *Amgen, Inc. v. Chugai Pharm. Co.,* 13 U.S.P.Q.2d (BNA) 1737, 1759 (D. Mass. 1989).

[37] See O. MILLS, *Biotechnological Inventions. Moral Restraints and Patent Law*, 2010, 2nd ed., 4; L. BENTLY, B. SHERMAN, *Intellectual Property Law*, 2018, 5th ed., 551.

[38] See e.g. judgment of the Court of Justice of the European Union in *Oliver Brüstle v Greenpeace* eV (C-34/10) [2012] 1 C.M.L.R. 41.

in the life sciences.[39] From the mere legal perspective, article 27 of TRIPs defines patentable subject matter expressly stating that patents must "be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application" (the so called "Non-Discrimination Principle").[40] It means that genes, gene fragments and cell lines modified or altered by human effort can be patented if the inventor meets the general requirements of a patent.[41] Formally, States may refuse to recognize patents on their territory, but − up to now − very few countries have used this option. At the same time, the European Directive on the Legal Protection of Biotechnological Inventions stipulates that "elements isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene" may represent a patentable invention.[42] In particular, the Directive specifies that "biological material which is isolated from its natural environment or produced by means of a technical process is considered to be an invention even if this material previously occurred in nature".[43] In addition, the European Patent Convention (EPC) excludes the possibility to grant patents for "methods of treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human body".[44] On this basis, the European Patent Office determined that "all methods practiced on the human or animal body which relate to the diagnosis or which are of value for the purposes of diagnosis" are precluded from being patented.[45] Nevertheless, biotech and life science-related inventions are in principle considered patentable under both the EPC and the Biotechnology Directive.[46] Specifically, the European Patent Convention unequivocally recognizes the patentability of biotech inventions in Rule 26(1) EPC.[47] In addition, Rule 27(a) EPC offers complementary details about the "patentable subject-matter" for life sciences inventions, specifying that "biotechnological inventions shall also be patentable if they concern biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature".[48] As a consequence – unlike in the Unites States where, after Myriad, isolated DNA sequences are no more eligible – biological material,

[39] D.M. GITTER, *International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, in *New York University Law Review*, 76, 2001, 1623, 1624.

[40] See Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, art. 27, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, 33 I.L.M. 1125, 1994, [hereinafter TRIPS].

[41] L.B. ANDREWS, J. PARADISE, Essay, *Gene Patents: The Need for Bioethics Scrutiny and Legal Change*, in *Yale Journal of Health Policy, Law, and Ethics,* 5, 2005, 403, 404.

[42] Council Directive 98/44/EC, art. 5(2), 1998 O.J. (L 213) 13 (EC).

[43] *Id*., at art. 3(2).

[44] Convention on the Grant of European Patents, art. 53(c), Oct. 5, 1973, 13 I.L.M. 270 [hereinafter EPC].

[45] See decision T 964/99 (OJ EPO 2002, 4), starting from the interpretation set out in decision T 385/86 and decision T 964/99.

[46] See R.A. SPINELLO, M. BOTTIS, *A Defense of Intellectual Property Rights*, in *Elgar*, 2009, 64.

[47] Rule 26(1) of 5 October 1973 as adopted by decision of the Administrative Council of the European Patent Organisation of December 7, 2006 and as last amended by decision of the Administrative Council of the European Patent Organisation of October 26, 2010 [hereinafter Implementing Regulations]. The Rules cited are to the earlier version. On this, see G. MACCHIA, *Patentability Requirements of Biotech Inventions at the European Patent Office: Ethical Issues*, in *Biotech Innovations & Fundamental Rights*, R. BIN et al, eds, in *Springer*, 2011, 37.

[48] See Implementing Regulations, Rule 27(a).

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including DNA sequences, which is isolated from its natural environment or produced with a technical process, is eligible for patent protection.[49]

4 The problem of Intellectual Assets in the Life Sciences Industry

Biotechnology and pharmaceutical corporations normally follow a conventional business model that is focused on a "closed innovation" scheme supporting a system that is completely enclosed by intellectual property rights. All ideas are internally generated and stay inside until the new product or innovation arrives on the market. In this context, it is relevant to consider how patent rights affect the process of "cumulative innovation".[50] Normally all inventions are based on previous knowledge and inventions: this means that innovation is cumulative because new innovations are grounded on previous innovations. The term "cumulative innovation" is commonly employed to describe a condition in which a second inventor uses previous knowledge protected by a granted patent in order to create a new innovation.[51] In other words, the second innovation would not be achievable without the contribution of the previous scientific knowledge. As a consequence, the second innovator is necessitated to obtain a license from the first innovator in order to use and exploit the new invention. The cumulative effect of innovation necessarily prompts serious concerns regarding the significance of dissemination of and access to scientific information.[52] Privately funded research in the life sciences is normally profit-oriented and patents are the primary strategy that firms use to protect their new ideas. In such specific circumstances, concerns arise because of the nature and extent of protection granted to patent holders. Patents – in fact – may play various roles in the knowledge-based economy. Under the current regulatory framework, patent holders have broad freedom in the exercise of their exclusive prerogatives.[53] Consequently, they are free to negotiate and set royalties, to accept, deny or unreasonably limit licensing requests, or again they may select specific licensees imposing licensing terms freely, as long as the terms and agreements do not override relevant regulations, such as competition or antitrust law.[54] Unfortunately, this scheme – even though designed to support private research – could also bring undesirable results. When patents are licensed too restrictively or when patents are used excessively to protect information "this could hamper research and development, clinical access, and availability of high-quality tests

[49] In accordance with these rules, the EPO considered that isolated DNA claims in Myriad's European BRCA patents were eligible. See The *University of Utah Research Foundation v. Institut Curie* (Mutation), 2008, T 0666/05 (EPO Board of Appeal).

[50] See C. LONG, *Patents and Cumulative Innovation*, in *Washington University Journal of Law and Policy,* 2, 2000, 229, 230-31.

[51] See also D.L. BURK, M.A. LEMLEY, *The Patent Crisis and How the Courts Can Solve It,* in *University of Chicago Press*, 2009, 73-75 (discussing cumulative innovation in patent law).

[52] See L. LESSIG, *The Architecture of Access to Scientific Knowledge, Lecture at Cern*, Geneve, Switzerland, 18 April 2001, available at http://www.youtube.com/watch?v=2me7hptVGzI (last visited 27/04/2021).

53See, e.g. *Bement v. Nat'l Harrow Co.*, 186 U.S. 70, 90-92 , 1902, ("The general rule is absolute freedom in the use or sale of rights under the patent laws of the United States").

[54] See L. BENTLY, B.SHERMAN, *Intellectual Property Law*, cit., 570. In the U.S., an intellectual property rights holder has no obligation to either use or license its property rights. On the point, see H. HOVENKAMP, M.D. JANIS, M.A. LEMELY, *Unilateral Refusals to License in the US*, in *Journal of Competition Law & Economics,* 2, 2006, 1, 13.

for patients".[55] The current Covid-19 global pandemic and lack of vaccine doses, is a clear example of the many challenges associated with exclusive rights, information sharing, affordability of medical treatment, and access to biotech innovations. This provide another piece of empirical evidence for the proposition that patents are not always an efficient means of protecting medical treatments having also a chilling effect on research and innovation imposing substantial barriers on other researchers' ability to undertake further investigation.[56] However, it is also true that in the absence of some form of protection or in the absence of other forms of flexibility, the only alternative would be to maintain secrecy with even more evident problems in this very restrictive scheme.[57]

5. The impact of court decisions for the Life Sciences Industry: Myriad and Mayo

As mentioned before, there are very few empirical studies on the real negative effects on gene-related patents resulting as a consequence of subject matter eligibility disputes.

Did Myriad really result in a reduction of gene-related patents in general (i.e. beyond isolated gene patents)? At first sight, the answer to this question seems to be negative. In particular, according to a study which has been published in 2016 on Nature Biotechnology, gene-related patents increased in number during the three-year period following the Myriad ruling.[58] In order to evaluate the impact and effect of the US supreme court decision, this study used an automated search algorithm intended to explore Myriad's impact by considering the record of granted gene-related patents using relevant key search terms before and after the decision. In addition, another study observed how over the 50% of gene-related patents granted in 2005 are already in the public domain demonstrating how patent protection may not be so important for development of genetic test.[59] This figure depicts that gene-related patent holders "often do not pay maintenance fees, meaning that their rights lapse and become part of the public domain before the full twenty years of patent life is realized".[60]

Another important aspect concerns the potential negative aspects deriving from the Myriad ruling on gene-related patents. In particular, it is interesting to analyse the trends in isolated gene patent activity (granted patents with gene-related claims) in the last 20 years in order to compare it with the trend after the decision. According to the data used by this study, from 2005 to 2016 the trend was

[55] See G. VAN OVERWALLE, *Turning Patent Swords into Shares*, in *Science,* 330, 2010, 1630.

[56] See D.B. RESNIK, *Owning the Genome: A Moral Analysis of DNA Patenting*, 2004, 141.

[57] See D.S. LEVINE, *Trade secrets and the battle against Covid*, in *Journal of Intellectual Property Law & Practice,* 15, 2020, 849 (proposing the creation of voluntary trade secret information sharing and/or compulsory trade secret licensing in order to face the unprecedented public health crisis due to Covid-19 pandemic).

[58] See M. ABOY et al., *Myriad's impact on gene patents*, in *Nature Biotechnology*, 34, 2016, 1119, 1120 (noting that the effects of the ruling on the biotech industry "have been less profound than some practitioners, scholars and patent holders anticipated"). An extended version of the study has been recently released, see J. LIDDICOAT et al., *The Effects of Myriad and Mayo on Molecular-Test Development in the United States and Europe: Interviews from the Frontline*, in *Vanderbilt Journal of Entertainment and Technology Law,* 22, 2020, 785 (analyzing how these court rulings affect business decisions surrounding the development of diagnostic tests).

[59] See J. LIDDICOAT et al., *The Effects of Myriad and Mayo on Molecular-Test Development in the United States and Europe: Interviews from the Frontline*, cit., 800.

[60] *Ibidem.*

down,[61] it means that the situation was not better before the Myriad ruling. Another question answered by this empirical study is whether Myriad negatively affected biotech patents activity such as diagnostic and biomarker patents. Also in this case, it seems that the ruling has not negatively affected the sector: in particular, data demonstrates that general biomarker patents continue to be issued in increasing number.[62]

Essentially these patent data are also useful to understand if – in case of a completely different decision of the Supreme Court – we could have observed also a different trend. In particular, the data on patent filling and granted dates versus priority dates seems to indicate that even if Myriad had reached the opposite decision, the patent activity directed to isolated gene patents would be very similar.[63]

The empirical analysis also considered additional variables such as the claim level analysis:[64] in particular, the analysis addressed the variability of patent claims after Myriad considering also the question if it is easy to draft around Myriad. In general, the results of the study show that in the years since Myriad "there has been much less amending activity than some commentators expected".[65] In over 79.2% of the patents containing isolated DNA claims were abandoned or all the isolated DNA claims were cancelled.[66] At the same time, only 18.6% of patents containing isolated DNA claims were successfully amended.[67] Finally, the investigation claimed that only 21 instances of successful amendments were found after receiving an explicit Myriad-based rejection and "none of these retained the scope (breadth) of the original applications".[68]

Another recent empirical investigation considered the impact of the Mayo ruling on patent prosecution with a particular attention to the future of patentability of diagnostic methods and personalized medicine treatments.[69] Although most legal scholars have described this decision as the tombstone for precision medicine,[70] there is little empirical evidence on these negative claims. The decision in Mayo has in fact opened many practical questions related to the future of biotech patents leaving patent applicants unsure of how to obtain and protect their intellectual property rights. According to the results of one of the few and structured empirical investigations based on a combination of keyword-based and semantic search, since July 2014 US patent examiner cited Mayo

[61] See M. ABOY et al., *Myriad's impact on gene patents*, cit., 1121.
[62] Ibidem.
[63] See M. ABOY et al., *Myriad's impact on gene patents*, cit., 1122.
[64] M. ABOY et al., *After Myriad, What Makes a Gene Patent Claim 'markedly different' from Nature,* cit., 822
[65] See for all, M. M. HOPKINS, et al., *DNA patenting: the end of an era?,* in *Nature Biotechnology*, 25, 2007, 185.
[66] See M. ABOY et al., *After Myriad, What Makes a Gene Patent Claim 'markedly different' from Nature*, cit., 822
[67] *Ibidem*.
[68] *Ibidem*.
[69] See MATEO ABOY et al., *Mayo's Impact on Patent Applications Related to Biotechnology, Diagnostics and Personalized Medicine*, in *Nature Biotechnology*, 37, 2019, 513.
[70] See e.g. E.J. HAANES, J.M. CANAVES, *Stealing Fire: A Retrospective Survey of Biotech Patent Claims in the Wake of Mayo v. Prometheus*, in *Nature Biotechnology*, 30, 2012, 758; J. L. FOX, *Industry Reels as Prometheus Falls and Myriad Faces Further Reviews*, in *Nature Biotechnology*, 30, 2012, 373; R.S. EISENBERG, *Diagnostics Need Not Apply*, in *Boston University Journal of Science & Technology Law*, 21, 2015, 256; C.M. HOLMAN, *The Mayo Framework Is Bad for Your Health*, in *George Mason Law Review*, 23, 2016, 901.

more than 33.000 times to justify rejection under 35 USC §101.[71] In addition, more than 38.000 patents document cited Mayo.[72]

Also in the case of the Mayo ruling – in order to evaluate the implications on the patent-eligibility matters – it was relevant to assess the real impact before and after the decision. According to the empirical results of this study, it seems there is an increase (from 10.5% to 55.5%) in the prevalence of 35 USC §101 rejections in key art units.[73] In addition, the analysis of patented, abandoned and pending patents (post-Mayo) reveals that 49.3% of the patent applications were rejected or abandoned; 27.6% were granted after a successful appeal to the examiner's Mayo-based rejection and 23.1% are still in active examination or prosecution.[74] These data seem to demonstrate that the Mayo decision has had a more significant impact than Myriad on patent prosecution in the life science sector. However, a substantial number of patent applications have been able to overcome objections raised by the Patent Office Examiners through amendments. This demonstrate that "it is possible to draft claim language that satisfies the post-Mayo 35 USC §101 threshold for life science inventions".[75]

Essentially, both these studies prove that – even if there are still many unresolved legal questions which contribute to maintaining high levels of uncertainty – the effects of the Myriad and Mayo decisions on gene patenting have been less extreme (at least at the macro-level) than many of the initial predictions.[76] Certainly, further empirical evidence is needed to fully explore the challenges posed by these decisions and possibly consider the necessity of a law reform. We can, however, say that these data also provide sufficiently convincing evidence to suggest that – at least in the case of genomic sequences – patents are not necessarily needed to foster the process of discovery of genomic elements. At the same time, it can be assumed that there is adequate space for patent protection of medical innovations without claiming genomic sequences.

6. The impact of court decisions for the Life Sciences Industry: Brüstle

Contrary to the cases decided by the US Supreme Court, the European controversies regarding the barriers to the patenting of stem cell research, seem to belong to the so-called phenomenon of the ethicalization of law. In fact, here it could be argued that the CJEU wanted to discourage medical research which requires the destruction of human embryos on the grounds that it is ethically unacceptable. The court basically held that any human embryonic stem cells invention which is not

[71] See M. ABOY et al., *Mayo's Impact on Patent Applications Related to Biotechnology, Diagnostics and Personalized Medicine*, in *Nature Biotechnology*, 37, 2019, 513, 514.
[72] *Ibidem*.
[73] *Ibidem*, 515.
[74] *Ibidem*.
[75] *Ibidem,* 516.
[76] Among the various voices suggesting a very negative impact, see e.g. M.M. HOPKINS et al., *DNA Patenting: The End of an Era?*, in *Nature Biotechnology*, 25, 2007, 185; I. HUYS et al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, in *Nature Biotechnology*, 27, 2009, 903; J.L FOX, *Industry reels as Prometheus falls and Myriad faces further reviews*, in *Nature Biotechnology*, 30, 2012, 373; R.S. EISENBERG, *Diagnostics Need Not Apply*, in *Journal of Science and Technology,* 21, 2015, 256.

based on non-destructive techniques is not patentable,[77] so the ban on the patenting aims at pushing pharmaceutical research towards more (morally) acceptable practices.[78]

On the other hand, however, the stem cell biotech sector and other parts of the ecosystem responded negatively to the decision in *Brüstle* claiming that it would be able to jeopardise, and thus harm, research and development in a medical field which is considered fundamental and promising for the advancement of bio-medical knowledge.[79] The thing that everybody was worried about immediately after the ruling was a sort of brain drain from the EU towards more science and business friendly countries such as US, where there are no statutory limits on patent eligibility of human embryonic stem cells on moral or ordre public grounds.

Another criticism of *Brüstle* is based on an apparent conflict of fundamental rights. Human dignity is not the only fundamental right at stake here. Patents and in general intellectual property rights are also protected as fundamental rights, as confirmed by Article 17(2) of the EU Charter as well as Article 1 Protocol 1 of the European Convention of Human Rights (ECHR).[80] It has been argued that *Brüstle* has strongly limited the fundamental right to patents in the human embryonic stem cells field, and that a similar limitation should have been subject to a proportionality test similar to the one required by the EU Charter and the European Convention on Human Rights.[81] This test requires that any limitations of the fundamental right to properties (including patents) must not have a disproportionate impact on the owner in relation to the target sought. Yet, the CJEU in *Brüstle* made no reference to any proportionality test nor to any balancing exercise between the two rights in question.[82]

At present, it remains also uncertain whether concerns regarding commodification and dignity can be limited to stem cells or can be used in other cases including commercial uses of other human tissue products. Furthermore, the concept of human dignity reveals itself as equally complicated and multifaceted in particular when applied to the field of bioethics and human genetics.[83]

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[77] See S.H.E. HARMON et al., *Dignity, plurality and patentability: the unfinished story of Brüstle v Greenpeace*, in *European Law Review*, 38, 2013, 92, 99.

[78] See also A. PLOMER, *The European Union's IP Policy and Funding of Stem Cell Research*, in D. MATTHEWS, H. ZECH (eds.), *Research Handbook on Intellectual Property and the Life Sciences*, 2017, 230.

[79] See e.g. S. PARKER, P. ENGLAND, *Reaction to the Brüstle decision*, in *Pharmaceutical Patent Analyst,* 1, 2012, 233; T. FALTUS, *No patent-no therapy: a matter of moral and legal consistency within the European Union regarding the use of human embryonic stem cells*, in *Stem Cells and Development*, 23, 2014, 56.

[80] See Article 1 of the European Convention for the Protection of Human Rights and Fundamental Freedoms, as amended by Protocol 1, Sept. 3, 1953, E.T.S. 155 (EC). See also the case *Anheuser Bush v. Portugal* (2007), 45 E.H.R.R. 830, at para. 72 (E.C.H.R.) where the ECtHR held that "Article 1 of protocol No. 1 is applicable to intellectual property as such".

[81] See A. PLOMER, *After Brustle: EU Accession to the ECHR and the future of European patent law*, in *Queen Mary Journal of Intellectual Property*, 2, 2012, 110, 134.

[82] *Idem*. See also E. BONADIO, *Biotech Patents and Morality after Brüstle*, in *European Intellectual Property Review*, 34, 2012, 433.

[83] See J. MALPAS, N. LICKISS, *Introduction to a Conversation, in Perspectives on Human Dignity: A Conversation* 1 (J. MALPAS, N. LICKISS eds., 2007). For more on this topic, see e.g. C. FOSTER, *Human Dignity in Bioethics and Law*, Hart, 2011; M. NOGUEIRA DE BRITO, *Human Reproduction and Human Dignity as a Constitutional Concept,* in M.V. DE AZEVEDO CUNHA et. al. (eds.), *New Technologies and Human Rights*, 2013, 169.

Finally – although European patent law is relatively uniform – some aspects of patent eligibility of human embryonic stem cells seems to remain still inconsistent.[84] In particular – as has been observed by other scholars[85] – a closer look reveals that national divergences still prevail in the interpretation of the most recent case law on stem cells. As a result, new issues need to be solved at the various layers especially in relation to the institutional changes created by the unitary patent package – including the future role of the unified patent court in safeguarding coherence in the European patent system.[86]

It seems clear that the implementation of the moral exclusions will be somewhat problematic from a harmonization point of view, as the morality provisions will be applied by different decision-making bodies (Court of Justice of the European Union, Unified Patent Court, National courts) according different standards with possible conflicting interpretations.

7. Conclusion

Biotech patents raised, and still raise, delicate issues which have been analysed and commented by lawyers as well as legal and medical scholars. Such issues have been debated during patent procedures and disputes in Europe and US. Focuses and approaches in these countries have however been different and centered on distinct legal questions.

Intellectual property rights play an enormous role in the creation of diagnostics and treatments as well as in vaccine development. International organizations, member states and institutions must recognize that now is the time for a broader discussion on how to guarantee that sufficient quantities of these health products are produced, that they are affordable, and that they are equitably distributed globally.

It is probably time of framing this debate in a completely different manner. We are in fact dealing with a more prominent issue dealing on whether genes occupy a more central legal position. A need for a change of paradigm is also clearly necessary because precision medicine is changing the current model of drug development that is essentially based on a small number of very successful drugs that can be sold to millions of patients. As a consequence, lawmakers must realize that it is time to design a new and more efficient legal scheme able to effectively support the developing of these precision treatments.

As a matter of fact, the decisions of the US Supreme Court on biotech patents resulted in an overall lack of harmonization between Europe and the United States creating an asymmetry of subject-matter-eligibility regarding isolated gene patents. Under the new constitutional interpretation of the US isolated gene patents are no longer allowed whereas in European countries – according to the EU

[84] See U. STORZ, T. FALTUS, *Patent eligibility of stem cells in Europe: where do we stand after 8 years of case law?,* in *Regenerative Medicine*, 12, 2017, 37.

[85] See e.g. A. MCMAHON*, An institutional examination of the implications of the unitary patent package for the morality provisions: a fragmented future too far?*, in *International Review of Intellectual Property and Competition Law*, 48, 2017, 42.

[86] *Ibidem*.

Biotech Directive and the European Patent Convention – it is still substantially possible.[87] As noted by other authors, the issues raised in the US cases Myriad and Mayo could also be the occasion for "relight the fire surrounding the Biotech Directive".[88] In particular, as the COVID-19 pandemic is unfortunately showing us, the "product of nature" exclusion under patent law – which prevents the patenting of genomic sequence data – should be preserved and strengthened and possibly extended to other jurisdictions.[89]

At the same time, the US law has no equivalent ordre public or morality statutory provision capable of creating scientific or ethical roadblocks to human embryonic stem cell.[90] It means that U.S. does not currently have a formal ban on the use of germline editing techniques on human tissue while the European Biotechnology Directive deems technologies that require the destruction of a human embryo unpatentable. From this point of view, it is definitely strange that the country which at present has greatest doubts about biotech patent is also the one which does not take into account any ethical or deontological factors related to human embryonic stem cell patenting.

[87] Case T 1213/05, *Univ. of Utah Research Found. v. Sozialdemokratische Partei der Schweiz,* (EPO Boards of Appeal, 2007); Case T 0666/05, *The University of Utah Research Foundation v. Institut Curie* (Mutation) (EPO Board of Appeal 2008).

[88] See e.g. J.C. LAI, *Myriad Genetics and the BRCA Patents in Europe: The Implications of the U.S. Supreme Court Decision*, in *UC Irvine Law Review,* 5, 2015, 1041.

[89] See J. CONTRERAS, *COVID-19 as an Example of Why Genomic Sequence Data Should Remain Patent Ineligible*, in S. BURRIS et. al (eds.), *COVID-19 Policy Playbook: Legal Recommendations for a Safer, More Equitable Future, Public Health Law Watch*., 2020, 137.

[90] See Sherley & Deisher v. Sebelius, 644 F.3d. 388, 388-90 (D.C. Cir. 2011); Sherley & Deisher v. Sebelius, 689 F.3d. 776 (D.C. Cir 2012).