GENE-BASED BIOTECHNOLOGICAL INVENTIONS AND PATENTS: EVOLVING NEW PARADIGMS

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Abstract

As the TRIPS Agreement stipulates, patents are to be 'available for any inventions, whether products or processes, in all fields of technology' and this aspect of neutrality applies for biotechnological products and processes including that of gene-based inventions. However, especially in international practice, there are observed deviances – the Amercian and European positions are illustrative in this context. This paper analyses the Myriad dictum in the USA and the aftermath of the same reflected through subsequent case laws such as the Ariosa Diagnostics, Inc. v. Sequenom, Inc., Ameritox, Ltd. v. Millennium Health, LLC and others. Further, the European stance evidenced through the relevant Directives as well as case laws and interpretations of the European Patent Office and the courts is scrutinized so as to bring out a contemporarily relevant international landscape on such gene-based inventions. The TRIPs exemption on medical and diagnostic methods of treatment also pose a challenge- as procedures, reagents, even artificial DNA that are categorizable as such products or processes and those that exclude essential processes within the human body, may overcome this exemption. However, across the globe, uniformity in patent standards of gene-based inventions is not apparent. This paper primarily focuses on the recent developments in the patent eligibility standards of gene-based inventions and attempts to draw out inferences from the same.

Keywords: Biotechnological Inventions, Gene-Based Inventions, Biotechnological Patents, TRIPS.

1. Introduction

The 2020 Nobel Prize for Chemistry was awarded to two scientists - Jennifer A. Doudna and Emmanuelle Charpentier – for ground-breaking work in genetics, to be

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precise "for the development of a method for genome editing.[1]" The CRISPR-Cas9 gene editing technology that is now brought to the forefront of widespread media and public attention is one example of the cutting-edge revolutions going on quietly and not-so-quietly in genetic and biotechnological labs and institutions all over the world. While promising cures and potential viable therapies for hitherto untreatable health conditions and diseases, these developments present numerous contentious choices to regulators globally. Alongside overwhelmingly difficult questions on morality, safety, quality, certainty, and viability of these, intellectual property issues gain prominence. This century has witnessed changing equilibrium of patent systems in response to patenting in controversial categories such as DNA patents. Computer related inventions as well as Artificial Intelligence- biotechnological and medical inventions occupy a significant portion of these discourses, as these involve questions of laws, particularly the patentability establishment. Generally, across the world most of such subjects are excluded including products of nature, mental processes, method patents and abstract ideas. The section 3 of the Patent Act 1970 in India entails what are not inventions and most of such subjects covered under it.

2. The Special Case of Biotechnological Inventions

Although intellectual property rights had primarily emerged as a branch of law that protects industrial property and copyright, it has attained great significance in the post-WTO world as a maker and breaker of international agreements. In particular, the matter of patent term and grounds for grant and rejection has played a role in defining and changing international relations in many instances. Simultaneous to the rising importance of patent laws and its ubiquitous presence, technological developments have shaped patent jurisprudence across the world to the extent that parity rather than disparity in patent norms seems to be desirable. As the TRIPS Agreement stipulates, patents are to be 'available for any inventions, whether products or processes, in all fields of technology[2]', thus underlining the importance of uniformity in global patent standards, mainly keeping in mind the obligatory conditions of non-discrimination and national treatment standards. Even so, we find that the exceptions enumerated in the TRIPS

[1] Declaration of Nobel Prize in Chemistry, 2020, *available at*: https://www.nobelprize.org/prizes/chemistry/2020/summary (last visited on December 18, 2022).

[2] The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), *available at:* https://www.wto.org/english/docs_e/legal_e/27-trips.pdf (last visited on December 20, 2022).

Agreement has enabled varied and wide-ranging responses by national systems in response to patent applications covering novel technologies and new inventions based on biomedical technologies.

The ever-burgeoning frontiers of biotechnological and biomedical innovations have expanded patent jurisprudence as perhaps no other sector. The case of biotechnological and medical inventions is peculiar, on the one hand, due to the conversion of bodily entities as well as hitherto uncommodifiable natural elements to property due to the very nature of patent laws; on the other, inventions, such as gene editing as well as possibilities of genomic and other interventions have effectively blurred the lines between natural evolution and human intercession in how we may move forward as a species. The theoretical and practical outcomes of such revolutionary technologies have multi-faceted ramifications, and parameters that are to be considered by regulatory frameworks would definitely have to take into account patent implications of the same as well.

3. The Historical Basis of Biotechnological Patents

As per the universally acknowledged post-TRIPS standards, an invention is considered to be patentable if it satisfies the tests of novelty, non-obviousness, utility as well as disclose optimal enablement[3]. In the parlance of biotechnological inventions, these standards become tricky because the success of these as inventions is predicated on their uses within the living organisms and are defined and fortified by their mimetic ability to replace active living elements within these organisms. An example would be an artificial hormone such as insulin, which though created outside the human body, is successful as a man-made invention because it mimics the naturally occurring hormone. Its success and utility depend on how closely it resembles and replaces the natural hormone within the living organism.

From the patent granted to Louis Pasteur in 1873 for purified yeast,[4] to the latest CRISPR-Cas9 patent dispute, the history of biotechnological patents is rife with

[3] Carrie P. Smith, "Patenting Life: The Potential and the Pitfalls of Using the WTO to Globalize Intellectual Property Rights", 26 *North Carolina Journal of International and Commercial Regulation* 143 (2000); Jidesh Kumar, "Biotechnology Patenting", 9 *Journal of Intellectual Property Rights* 471(2004).

[4] US Patent No. US141072A.

controversies and contradictions. After the famous *Diamond* dictum decreed, "the Congress intended statutory subject matter to 'include anything under the sun that is made by man'"[5], there has been a spate of litigations across the globe that expanded the scope and extent of patentability of biotechnological inventions.

Today, while it has become a crystallized precept that laws of nature, natural phenomena, and abstract ideas are not patentable, its exact contours keep evolving as per the perceived needs of the societies as well as by advancements in technologies that bring new definitions of 'newness' and 'inventiveness'.

To examine patentability standards in this context, *Funk Bros. Seed Co*. v. *Kalo Inoculant Co*.[6] is relevant. The Court held thus about the product patent involving the use of nitrogen-fixing bacteria-based inoculant[7]:-*"The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end*[8]*."*

While the Court in *Funk Bros.* did not examine the process itself, as the patent application only covered compositions claims, it held that the claim is not patent-eligible as a mere 'discovery of some of the handiwork of nature' cannot confer monopoly to the discoverer of such phenomenon, notwithstanding the ingenuity of such discovery. However, the decision, particularly where the Court has stressed that an outcome not producing a new bacteria, nor causes an increase of range of utility or effectiveness[9] cannot be protected as a patent-eligible subject matter is noteworthy. One can conclude

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5 *Diamond* v. *Chakrabarty*, 447 US 303 (1980) at p. 309.

6 *Funk Brothers Seed Co*. v. *Kalo Inoculant Co*., 333 US 127 (US 1948) at p. 134.

7 Claim No. 1 of the issued patent US Patent No. 2200532: An inoculant for leguminous plants comprising - a plurality of selected cultures of different species of bacteria of the genus Rhizobium, one of the said cultures being Rhizobium trifolii alpha, said cultures being substantially free of influence from each other in their ability to fix nitrogen in the defined class of leguminous plant to which they apply specifically.

8 *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 US 127 (US 1948).

9 *Id*. at 131.

that an application of a law of nature may nevertheless be patent-eligible if it is *markedly different* from the former in form and structure and is new and useful.

Diamond v. *Chakrabarty* [10], a game-changer in the true sense of the word, single-handedly tipped the balance in favour of human contributions being incentivized infinitely, even if the invention involves life or its concomitant components, as long as the standards of patentability are competently and sufficiently satisfied. The plaintiff, Ananda Mohan Chakrabarty, a genetic engineer and an employee of General Electric, had developed a bacterium derived from the *Pseudomonas* genus, capable of fractionating crude oil. Such an ability to break down oil was not an attribute possessed by any naturally-occurring bacterium and, therefore, could be used in treating oil spills. Mr. Chakrabarty filed for a patent for the bacterium in the United States over three categories of patent claims:

i. firstly, process claims -the method of producing the relevant bacteria
ii. secondly, claims for an inoculum which consisted of the carrier material and the new bacteria and
iii. third, claims to the bacteria itself.

The patent examiner allowed the first two claims but rejected the third which claimed the bacteria as a patentable invention. His decision rested on two grounds:

i. that microorganisms are 'products of nature', and
ii. that as living things, they are not patentable subject matter.

The Board of Patent Appeals and Interferences concurred with the decision of the Examiner. However, the US Court of Customs and Patent Appeals decided the case in favour of Dr. Chakrabarty, holding that the fact that microorganisms are alive is not of any legal significance for purposes of patent law. The Commissioner of Patents and Trademarks, Mr. Diamond, filed an appeal at the US Supreme Court.

In a 5:4 ruling, the US Supreme Court ruled in favour of Chakrabarty and upheld the patent, holding thus*:"...A live, human-made microorganism is a patentable subject*

[10] *Supra* note 5.

matter under Title 35 USC 101. Respondent's microorganism constitutes manufacture or 'composition of matter' within that statute[11]*.....”*

It was further held that in choosing such liberal terms as 'manufacture' and 'composition of matter', modified by the broad term 'any', the US Congress considered that patent laws should be given wide scope. The Court elucidated that the impugned claim of the respondent was not to a ‘hitherto unknown natural phenomenon, but a product of human ingenuity having a distinctive name, character and use’[12]. A factor that probably influenced the Court in distinguishing between the new bacterium and the naturally existing species may be the addition of the four plasmids by the inventor to create the new bacterium, which was structurally and functionally different from earlier existing species and was equipped to clear up oil spills.

Here, the US Supreme Court held that the new bacteria are not products of nature, having been genetically modified. It clarified that microorganisms being alive is without legal significance for purposes of the patent law. The Court saw the exclusion of living subject matter as extraordinary[13], holding that Congress intended that patent protection be broadly available for ‘anything under the sun that is made by man.’

Further, it was affirmed by the Court that the issues of particular exceptions to the patentability of an invention are to be clearly stipulated either by a legislation enacted by the legislature, or by the executive, when it stated[14]: *"...The fact that genetic technology was unforeseen when Congress enacted S.101 requires the conclusion that microorganisms cannot qualify as patentable subject matter until Congress expressly authorizes such protection. Arguments against patentability based on potential hazards that may be generated by genetic research should be addressed to the Congress and the Executive, not to the Judiciary..."*

This case was succeeded by a multitude of decisions that clarified that life-based subject matter is also patentable, provided they involve a process of manufacture[15].

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11 *Supra* note 5 at 318.
12 *Id*. at 310.
13 Rebecca S Eisenberg, “Biotech Patents: Looking Backward While Moving Forward”, 24 *Nature Biotechnology* 317 - 319 (2006).
14 *Supra* note 5 at 318.
15 *Amgen* v. *Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir.), *Genetics Institute* v. *Amgen*, 502 US 856 (1991); *Novartis/Transgenic Plant* (1999) EPOR 12; *Pioneer Hi-Bred International, Inc.* v. *J.E.M. Ag Supply, Inc*., 200 F.3d 1374 (Fed. Cir. 2000); *J.E.M. Ag Supply, Inc*. v. *Pioneer Hi-Bred*

Following these precedents that upheld the patentability of purified versions of such naturally occurring products as adrenaline and vitamin B_{12}, the USPTO freely allowed patents on purified and isolated DNA sequences and recombinant constructs incorporating such sequences[16].

4. Mayo and Prometheus Herald Change

The flow of this pro-patent approach was interrupted by the momentous and controversial decision of Mayo Collaborative Services v. Prometheus Laboratories, Inc.[17] Herein, the US Supreme Court struck down patent claims for a diagnostic method, ruling that the claims are too closely tied to laws of nature. The claim in question outlined an invention involving a blood test to determine the appropriate dosage of a drug to be used in the treatment of autoimmune diseases[18]. The Court specifically addressed the question of how a claim that includes an element of the law of nature or natural phenomenon is sufficiently distinct from the law of nature itself to entitle grant of patent[19]. It was categorically held that mere re-creation of laws of nature in particular technical *milieus* are not eligible for grant of patent as they do not amount to inventions. The Court further reiterated that essential tools of scientific and technological work could not be granted patents as they would only impede advancements and further research in the specific technological sector[20].

The Court held thus[21]:*"Because the laws of nature recited by Prometheus' patent claims—the relationships between concentrations of certain metabolites in the blood and the likelihood that a thiopurine drug dosage will prove ineffective or cause harm—are not themselves patentable, the claimed processes are not patentable unless they have additional features that provide practical assurance that the processes are genuine*

International, Inc., 53 US 12 (2001); *Harvard College* v. *Commissioner of Patents, Canada*, (2002) SCC 76; *Dimminaco A.G.* v. *Controller of Patents Designs*, IPRL 255(2002); *The Harvard Oncomouse Case* T 315/03 [2006] 1 OJEPO 15, [2005] EPOR 31.

16 *Merck & Co.* v. *Olin Mathiesen Chemical Corp.*, 253 F.2d156 (4th Cir.); *See ibid.*

17 566 US 132 S. Ct. 1289 (March 20, 2012).

18 Prometheus Laboratories, Inc., was the sole and exclusive licensee of the two patents at issue, which concerned usage of thiopurine drugs for treatment of autoimmune diseases. These drugs, on ingestion, are metabolized by the body, thus creating metabolites in the bloodstream. The claims related to adjusting the dosages so that the metabolism, hence the effectiveness, could be predicted with precision- the relationship between metabolites of thiopurine drugs and their therapeutic reactions, both efficacy and side effects, was the crux of the patent claim. *See Id.*

19 *Id* at 8-11.

20 *Ibid.*

21 *Ibid.*

applications of those laws rather than drafting efforts designed to monopolize the correlations. The three additional steps in the claimed processes here are not themselves natural laws, but neither are they sufficient to transform the nature of the claims".

All the claims need to be supported inside the specification by mean of complete working disclosure and particularly the best mode that provide practical assurance that the claims are genuine.

The *Mayo* dictum categorically laid down that for an invention as claimed to be patentable; it must possess additional features that provide a realistic guarantee that the processes/products are genuine applications of those laws of nature on which they are based, rather than efforts to monopolize products and processes which are mere variations of what is freely available in the public domain. Thus the divergent eligibility test was laid down, which would prove instrumental in moulding patent law jurisprudence in USA on matters of laws of nature and patent eligibility. The *sine-qua-non* of transformation indicates significant changes in structural and formal composition as well as in functionality and effectiveness. The significance of this decision lies in its rationale being applied over a vast spectrum of patent eligibility disputes including biotechnology as well as in technological fields, the decision in *Alice Corporation Pty. Ltd. v. CLS Bank International*[22] is a case in point.

In this context, it is to be noted that though natural laws, principles, and formulae that explain them are not patentable, inventions that incorporate these to give far superior results than found in nature can be eligible for a patent[23]. The reason for this distinction is straightforward; no invention is possible in isolation from nature itself. The components and elements of the invention, though derived from nature, if proven to be innovative, can yet be patent-eligible[24].

In *Asscn. for Molecular Pathology* v. *United States*[25] the rule that the mere discovery of a law of nature cannot be patented was explained based on the notion

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[22] *Alice Corporation Pty. Ltd.* v. *CLS Bank International*, 573 US 208(2014).

[23] "All inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." As held in Mayo v. Prometheus Labs., Inc., 132 S. Ct. 1289(2012). See also *Merck & Co*. v. *Olin Mathieson Chem. Corp.*, 253 F.2d 156, 162 (4th Cir. 1958), which held that everything "with which man deals and for which patent protection is granted are products of nature in the sense that nature provides the basic source materials."

[24] See generally *Dickey-john Corp.* v. *Int'l Tapetronics Corp*., 710 F.2d 329, 348 n.9 (7th Cir. 1983).

[25] *Asscn. for Molecular Pathology* v. *USPTO*, 702 F. Supp. 2d 181, (2010).

that while natural phenomena are processes, they are not the category of discovery that the statute was intended to encapsulate and protect. This decision, which culminated in 2013 with a unanimous ruling by the Supreme Court, was in favour of the American Civil Liberties Union with the Association for Molecular Pathology as the lead plaintiff.

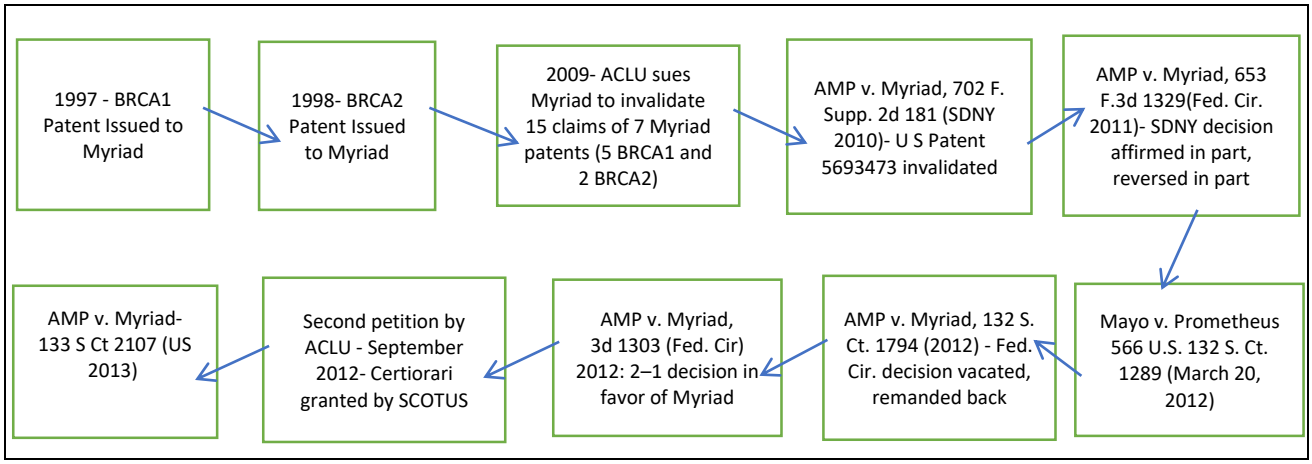

Fig. 1 – **A timeline of the Myriad Genetics Case**

The case relates to two patent claims of Myriad Genetics, Inc., a healthcare and molecular diagnostic company. The isolated human genes: BRCA1 and BRCA2, which, if actively present, increase the chances of breast and ovarian cancer significantly, making it commercially viable for drug testing and diagnostic tests that may help predict the probability of contracting cancer. Myriad charged up to US $3000 per test.

The Court held herein that mere purification or isolation[26] did not transform the DNA, found in nature, into a patentable subject matter. It concluded that the existence of DNA strands in an isolated form did not alter the fundamental quality of the DNA, as it existed in the human body. The patents at issue that encompassed isolated DNA, included sequences found in nature; hence they were not valid as they merely manifest 'a law of nature' and were not considered patentable subject matter under 35 USCS § 101. Mere purification or isolation did not transform the DNA, found in nature, into a patentable subject matter. Similarly, the claimed comparisons of DNA sequences were held to be abstract mental processes, which are also outside the scope of patentability.

[26] "Isolated DNA" was construed to refer to a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, and included both DNA originating from a cell as well as synthesized DNA.

The American District Court clarified its position on extracts or purified forms of substances found in nature in this case in 2010[27]. It held that the extract, isolated DNA in this case, remains the same, no matter its place of origin or extraction process. The Court opined thus: *"A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing itself when obtained cannot be called a new manufacture."*

The Court of Appeals for the Federal Circuit in 2011 reversed the order of the district court in part and held that Myriad's patents on isolated DNA were valid[28] in *Association for Molecular Pathology* v. *US Patent & Trademark Office*[29].

After this ruling, the Association for Molecular Pathology approached the Supreme Court for review of this decision. Through a writ of Certiorari, the Supreme Court in March 2012 vacated the Federal Circuit decision and remanded the case back to the Federal Circuit to reconsider the matter in light of the *Mayo* patent eligibility analysis framework. The Court, however, in a 2:1 ruling, reaffirmed its earlier position.

The second petition for Certiorari by ACLU was granted and in June 2013, in *Association for Molecular Pathology* v. *Myriad Genetics, Inc.*[30], the US Supreme Court decreed *en banc* that while Myriad's claims to isolated, naturally occurring human DNA sequences, *i.e.*, isolated genomic DNA (gDNA), are not patent-eligible, its claims to cDNA are patent-eligible[31]. The Court also stipulated that claims to methods of formulating isolated DNA are eligible to be granted patent[32]

The Court held that isolated DNA may constitute a patentable invention if it satisfies a two-fold test:

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27 *Association for Molecular Pathology v. United States Patent and Trademark Office*, 702 F. Supp. 2d 181 (SD NY. 2010).

28 *Association for Molecular Pathology v. US Patent & Trademark Office* (Molecular Pathology II), 653 F.3d 1329, 1355 (Fed. Cir. 2011).

29 *Ibid*.

30 *Association for Molecular Pathology* v. *Myriad Genetics, Inc.*, 133 S Ct 2107 (US 2013).

31 The Court differentiated between patentability of gDNA and cDNA thus:- "cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. Creation of cDNA sequences from mRNA results in exons-only molecules that are not naturally occurring." *See Supra* note 30.

32 *Ibid*. See *also* Charles R. Macedo and David P. Goldberg, "US Supreme Court addresses patent eligibility of isolated DNA and cDNA in Myriad V", 8(11) *Journal of Intellectual Property Law & Practice* 811-813(2013).

i. the subject matter must have 'markedly different characteristics' from something that exists in nature
ii. the subject matter must have a 'chemical identity distinctive from molecules that exist in nature[33].'

Hence, for extraction or purification to amount to a manufacturing process so as to entitle grant of a patent to it as an invention, investment of treatment, labour, and manipulation is not sufficient. What is required is transformation; a new entity must emerge, which possesses a distinct name, character, or use[34]. Hence, in order to constitute a patentable invention, the claim must prove the existence of something- a product or process markedly different from what occurred previously in nature, both in form and functionality.

In the instant case, the Court found Myriad's isolated DNA molecules, the cDNA or complementary DNA, to be different from native DNA naturally found in the human body as it essentially includes manipulated DNA sequences, which can be considered as human-made,[35] and is not found in nature in such form; therefore is patent-eligible.

Additionally, the claim must be shown to involve an entity that is sufficiently and markedly different from a similar article occurring naturally in the human body. If, for instance, the claim relates to a cardiac valve grown in a petri-dish in laboratory conditions, using stem cell technology, the valve would not have existed in that form but for human effort. The success of the invention lies in it being as closely comparable to the cardiac valve's human counterpart as possible. Here, the scientists must mimic the natural conditions where the tissue grows, providing access to nutrients and a means for waste removal[36]. So, the said tissue, created artificially, must transform itself into a new and hitherto non-existent commercially viable product. If so, such a claim would be patent-eligible.

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33 Here, isolating the DNA required human intervention, cleaving the sugar-phosphate backbone and thereby reducing the number of nucleotides by a factor of about one thousand compared to native DNA. *See ibid.*

34 *Ibid.*

35 The Court found that cleaving native DNA causes the isolated DNA to terminate in a manner not found in the human body. *See ibid.*

36 *See gen.* Oren Ginsberg, "Unwinding the DNA Double-Helix: An Alternate Resolution to the Federal Circuits Decision in Association for Molecular Pathology for Simplifying § 101 Patent Eligibility Determinations", 22 *Fed. Cir. BJ* 563, (2013).

Alternatively, even where a claim for an engineered entity, including a product of nature, does not pass patentability tests, this does not preclude a process claim for such product from patent eligibility. This line of reasoning has been demonstrated by numerous claims that have been granted patents globally.[37] Hence, processes involving such products that satisfy patentability tests are yet eligible to be granted patents.

5. Post-Myriad US Position

It is to be noted that Myriad operated on a business model that leaned heavily on its patent assets. Even though its seven patents were invalidated in 2013, Myriad asserted its remaining gene patents against other players in the field[38]. This matter led to a flurry of litigations, and Myriad sought injunctions against those who used its patents in the gene testing field. Actions were brought by ACLU, AMP, Public Patent Foundation, Breast Cancer Action, AARP, and others at the district court where they filed an amicus brief; this group of medical organizations, health advocacy groups, geneticists, and patients argued against tying up of laws of nature in private monopolies of exclusion and against potentially inhibitive policies that may affect public health interests adversely. Myriad attempted to enforce its patents[39] over PCR primers, which are short RNA sequences that are used in the synthesis of complementary DNA; this being the process by which the gene-based testing is performed. However, the district court ruled against Myriad and declined to grant an injunction as sought[40].

The 2013 Myriad standpoint was reiterated by the Federal Circuit Court in the University of Utah Research Foundation v. Ambry Genetics[41], wherein it stated that *"our*

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37 Human Mesenchymal Stem Cells, US Patent No. 5,486,359 (filed Jan. 23, 1996); Natural Tissue Heart Valve and Stent Prosthesis and Method for Making the Same, US Patent No. 5,861,028 (filed Jan. 19, 1999); Preparing Artificial Organs by Forming Polylayers of Different Cell Populations on a Substrate; US Patent No. 6,428,802 (filed August 6, 2002); Tissue Engineered Female Reproductive Organs, US Patent No. 7,806,937 (filed October 5, 2010); Placental Tissue Compositions, US Patent No. 8,071,135 (filed December 6, 2011); Method of Isolating and Culturing Mesenchymal Stem Cell Derived from Umbilical Cord Blood, US Patent No. 7,704,739 (filed Apr. 27, 2010); Cardiac Muscle Regeneration Using Mesenchymal Stem Cells, US Patent No. 7,892,829 (filed February 22, 2011); Treatment of Stroke Using Placental Stem Cells; US Patent No. 7,976,836 (filed July 12, 2011).

38 Amelia Rinehart, "Myriad Lessons Learned" *Utah Law Faculty Scholarship* 16 (2015).

39 Myriad owns US Patent Nos. 5,753,441 (the '441 patent); 5,747,282 (the '282 patent) and 5,837,492 (the '492 patent), which were outside the scope of the 2013 SCOTUS decision.

40 *In Re BRCA1 and BRCA2-Based Breast Cancer Test Patent Litig*., 3 F. Supp. 3d 1213(D. Utah 2014)

41 *In re BRCA1- & BRCA2- Based Hereditary Cancer Test Patent Litigation*, Nos. 14-1361 (Fed. Cir. December 17, 2014); 774 F.3d 755 (2014). *University of Utah Research Foundation, Trustees of the University of Pennsylvania, HSC Research and Development, Endorecherche and Myriad Genetics, Inc*. v. *Ambry Genetics Corpn.* US District for the District of Utah, Case No. 2:13-cv-00640-RJS (2014).

analysis of the primer claims under § 101 is guided by the Supreme Court's Myriad decision[42]", while examining Claim 16 of the '282 patent[43]. The Court held that *"the primers before us are not distinguishable from the isolated DNA found patent-ineligible in Myriad and are not similar to the cDNA found to be patent-eligible[44]".*

The Court also stated that separation or isolation of DNA strands from its surrounding natural environment could not render the action patentable and reaffirmed the divergent eligibility test endorsed in Myriad[45].

With respect to the methods claim over the comparison of sequences and analysis of the outcome in order to perform the test, the Court applied the Alice dictum[46] on abstract ideas and held that the claims were "*directed to the patent-ineligible abstract idea of comparing BRCA sequences and determining the existence of alterations,"* thus rendering the methods claim as patent-ineligible. Significantly, the Court stated that *"allowing a patent on the comparison step could impede a great swath of research relating to the BRCA genes, and . . . allow these basic building blocks of scientific research to be monopolized."*[47]

This viewpoint is of great relevance in the biotechnological sector, particularly in the diagnostics products and processes, as a monopoly in these areas means that very often, it is impossible to have a practically effective second opinion. This fact defeats the public interest vested in incentivizing biotechnological inventions through rewards as, if the patent holder can effectively neutralize efforts by other entities to compete effectively and offer viable alternatives, then the quid-pro-quo system envisaged by patent law is not met. Such a detrimental effect on patient's interests, which is particularly apparent in the

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42 *Ibid.*

43 Claim 16 of the '282 patent is representative. It is directed to: A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene...

44 It further clarified, "Primers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature."

45 *Ibid.*

46 *Alice Corporation v. CLS Bank International*, 573 US 208(2014).

47 *Supra* note 41.

case of DNA-based cancer diagnostic tests, drives home the negative impacts of the right to subjective enclosure conferred as a corollary of patent rights.

In Ameritox, Ltd. v. Millennium Health, LLC,[48] the district court found a claimed method of measuring metabolite levels in urine samples and comparing them to creatinine levels as patentable. Interestingly, the Court held thus: "if inventors engage in activities that run counter to scientific thought, those activities can hardly be considered conventional under § 101. This latter concept would similarly apply when a patent involves a combination of elements that the scientific community would not have thought to use or implement to deliver a new, improved, and useful result…. When the invention is based on the combination of elements that cuts against the grain of scientific thought, this heightens the novelty of the invention itself.[49]"

Another case that may be discussed here is the Ariosa Diagnostics, Inc. v. Sequenom, Inc.[50] In this case, Sequenom Inc. was the exclusive licensee of US Patent No. 6,258,540, of which three claims were argued as being invalid by Ariosa.[51] The invention in question was a non-invasive prenatal diagnostic test that could detect pre-eclampsia along with other screening, using a simple blood test that effectively could eliminate the need for invasive techniques like amniocentesis. The basis for the invention was the cell-free fetal DNA ('*cffDNA*') discovered in maternal plasma and serum by Dr. Dennis Lo and Dr. James Wainscoat.[52] The significance of the same lies in the fact that the basis of

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48 LLC, 2015 WL 728501(WD Wis. February 19, 2015)., plaintiffs Ameritox, Ltd., and Marshfield Clinic, LLC allege that defendant Millennium Health, LLC infringes two of their patents: US Patents No. 7,585,680, purporting to describe a method for drug screening and compliance protocols for one sample of urine from a patient on a prescribed medication regimen; and US Patents No. 7,785,895, purporting to describe a similar method for one biological sample generally.

49 *Ibid.*

50 788 F.3d 1371 (Fed. Cir. 2015).

51 The three claims were: 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.
A method for detecting a paternally inherited nucleic acid on a maternal blood sample, which method comprises: removing all or substantially all nucleated and anucleated cell populations from the blood sample, amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally [sic] inherited fetal nucleic acid.
A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises obtaining a non-cellular fraction of the blood sample amplifying a paternally inherited nucleic acid from the non-cellular fraction and performing nucleic acid analysis on the amplified nucleic acid to detect a paternally inherited fetal nucleic acid.

52 *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* - 788 F.3d 1371 (Fed. Cir. 2015), *available at*: https://www.lexisnexis.com/community/casebrief/p/casebrief-ariosa-diagnostics-inc-v-sequenom-inc last visited on December 20, 2022).

the test is based on elements of maternal blood samples that were formerly discarded as medical waste. Sequenom marketed the invention as its MateniT21 test.[53]

The patentee in the application for patent did not claim cffDNA at all, but only some specific methods of using cffDNA. The District Court held that the three claims were patent-ineligible and ruled in favour of Ariosa. The basis for the judgment was that "groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry."

The Court further went on to hold that *"appending routine, conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept. Where claims of a method patent are directed to an application that starts and ends with a naturally occurring phenomenon, the patent fails to disclose patent-eligible subject matter if the methods themselves are conventional, routine, and well-understood applications in the art."* A higher threshold is mandatorily to be applied in patentability tests as the courts adhere religiously to the *Myriad* dictum.

A three-judge panel of the Federal Circuit affirmed the district court judgment on appeal.[54] The petition for rehearing *en banc* by Sequenom was denied by the Federal Circuit in December 2015.[55] An attempt by Sequenom to petition for certiorari by the Supreme Court was unsuccessful.[56] This decision is rife with controversy as it was viewed by many jurists as being 'dangerously broad'[57].

Thus, we find that there have been numerous attempts made in the post-*Myriad* biotechnological landscape to clarify the position of such inventions that involve laws of nature or natural phenomenon. The refrain that gets repeated is that the twin tests of patent eligibility that rule the roost presently levels out the playing field; that the building blocks

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53 See generally https://www.ncbi.nlm.nih.gov/gtr/tests/501985/.

54 *Ariosa Diagnostics Inc. v. Sequenom Inc.*, 788 F.3d 1371(Fed. Cir. 2015).

55 *Ariosa Diagnostics Inc. v. Sequenom Inc.*, 809 F.3d 1282 (Fed. Cir. 2015).

56 SCOTUS Order List dtd. 06/27/2016, *available at: https://www.supremecourt.gov/orders/courtorders/062716zor_4fbi.pdf* (last visited on December 21, 2022).

57 Devlin Hartline, "Federal Circuit Should Reconsider Ariosa v. Sequenom: The Panel Decision Threatens Modern Innovation", *IP Watchdog* (August 30, 2015); Patent Publius, "Federal Circuit Threatens Innovation: Dissecting the *Ariosa v. Sequenom* Opinion Center for the Protection of Intellectual Property" *George Mason University Blog* (June 23, 2015).

of human ingenuity remains in the public domain and increases possibilities of improvements and downstream innovations.

Simultaneously, while some opine that the 2013 Myriad decision demolished the stronghold by genetic patent estates, it remains to be seen in practice. The reason being that most gene/DNA-based diagnostic testing kits use synthetic DNA to perform its diagnostic functions; thus, the 2013 dictum that validated complementary DNA being patent-eligible has still left the floor open to possibilities of monopolies as well as prohibitive influence on competition as well as downstream innovation. Thus the saga of 'billion-dollar patent molecules[58]'continue to rule the day.

6. The European Stance on Gene-Based Inventions

As per Article 53(c) of the European Patent Convention (EPC), "patents shall not be granted in respect of … methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body." This reflects the inherent public interest in the patent system that excludes such methods of surgery, treatment as well as diagnostics from patent eligibility in order to enable medical practitioners to be able to cater to the best interests of those in need of medical care and interventions.

In case of diagnostic methods in particular, the nature of test is relevant- products that carry out such tests, *in vitro* diagnostic tests, as well as inventions that do not involve actions and essential steps or processes within the human body and are not mere mental acts are patent eligible in the European jurisdiction.

The Opinion G 1/04 of the Enlarged Board of Appeal is illustrative in this context. The Board, iterates thus regarding diagnostic methods, stating that the invention must outline all steps and phases resulting in the diagnostic outcome[59]:-

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[58] Ker Than, "7 Takeaways from Supreme Court's Gene Patent Decision", National Geographic (June 14, 2013), *available at:* http://news.nationalgeographic.com/news/2013/06/130614-supreme-court-gene-patent-rulinghuman genomescience/?rptregcta=reg_free_np&rptregcampaign=20131016_rw_membership_r1p_us_dr_w#finished (last visited on December 21, 2023).

[59] Opinion G 1/04 of the Enlarged Board of Appeal, EPO, *available at:* https://www.epo.org/law-practice/legal-texts/html/caselaw/2019/e/clr_i_b_4_5.htm. See also Reuben Jacob and Fiona Kellas, IP Considerations for Diagnostic Methods (April 8, 2020), *available at:* https://www.maucherjenkins.com/commentary/diagnostic-methods-patent-europe (last visited on December 21, 2022).

i. the steps relating to the investigation, including collection of relevant data,
ii. analysis of such obtained data and its evaluation with standard values,
iii. resultant findings including significant deviations that may be evident from the appraisal
iv. the potential diagnostic conclusions that may be drawn from such findings and arrival at clinical conclusions that may contribute to formulation of therapeutic or other intervention strategies.

Herein, the distinction between use of such methods for drawing clinical and non-clinical conclusions becomes relevant – in the European context, the former is considered as excluded from the scope of patentability whereas the latter, as a prognostic conclusion that may not contribute to curative output, may still be patent-eligible. The distinction with the American position is also clear from the fact that the BRCA patent survived the opposition and appeal in the EU[60], though its scope was narrowed down[61]. Isolated genes are patentable inventions, as per Rule 29(2) of the Directive 98/44/EC of the European Parliament,[62] so also are elements "isolated from the human body or otherwise produced by means of a technical process'[63]. As per Rule 29(3) of the Directive 98/44/EC[64], the invention must evince industrial applicability, i.e. the gene that has been isolated must be capable of being integrated into a commercializable product or process, which justifies the grant of the patent to it. Thus, presently, the European interpretation and practice relating to inventions involving genes used in diagnosis and other applications seems more permissive when compared to the post-Myriad US position, especially as there are no additional qualifiers prescribed regarding the patent eligibility of such inventions.

60 T80/05, T666/08 and T1213/05 (2008).
61 Huys, I., Van Overwalle, G. & Matthijs, G., "Gene and Genetic Diagnostic Method Patent Claims: A Comparison under Current European and US Patent Law", *European Journal of Human Genetics*19, 1104–1107 (2011).
62 Directive 98/44/EC, European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions, *available at*: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31998L0044:EN:HTML (last visited on December 21, 2022). The case of *Monsanto Technology LLC* v. *Cefetra BV and Others* C-428/08 (2010) illustrates the European position regarding patentability of such genes and sequences.
63 *Ibid*.
64 *Supra* note 62.

7. Conclusion

After the US Supreme Court pronounced the Myriad decision on June 2103, many diagnostic kits based on the underlying technology were brought to the market, at prices as low as 1/3rd the Myriad Bracanalysis kit's original price, which was placed at approximately $3,200. The truth is that the invalidation of Myriad's major claims paved the way for alternatives in the market. At the same time, consumer interests are undoubtedly protected as the matter involved the interests of millions of cancer patients across the world; ultimately, the right to life and health is protected in such a situation.

Another example that co-operation rather than competitiveness may be a better option in the best interests of humanity, particularly in the field of cutting-edge biotechnological inventions, is the CRISPR-Cas9 debate between the UC Berkely and MIT Broad Institutes over the illustrious gene-editing technology. This all-important technology of genome-editing technology based on clustered, regularly interspaced, short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) is now in the news as the reason the Doudna-Charpentier team were awarded the Nobel Prize in 2020. However, the patent battle fought out between the two teams, one led by Jennifer Doudna from the University of California, Berkeley (UC Berkley) and Emmanuelle Charpentier, from the Helmholtz Centre for Infection Research, and the other by Feng Zhang of Massachusetts Institute of Technology (MIT), had the potential of determining the ultimate benefits that may have been reaped by the different uses of this technology[65].

One can safely say that the trend of increasing patent applications in the CRISPR field is only going to be accelerated in coming years[66]; at the same time, that fact that the dispute is still ongoing between UC Berkley and MIT-Broad also brings home that fact that certainty in the field of biotechnological patents is sometimes a very expensive commodity.

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[65] David Fajardo-Ortiz, Stefan Hornbostel, *et al.*, "Funding CRISPR: Understanding the role of government and philanthropic institutions in supporting academic research within the CRISPR innovation system", 3(2) *Quantitative Science Studies* 443-456 (2022).

[66] Heidi Ledford, "Major CRISPR patent decision won't end tangled dispute", *Nature* (2022), *available at*: https://www.nature.com/articles/d41586-022-00629-y (last visited on December 21, 2022); Franc Mali, "Key Socio-Economic and (Bio) Ethical Challenges in the CRISPR-Cas9 Patent Landscape", in Marcello Maresca and Sumit Deswal (eds.) *Genome Editing in Drug Discovery* 315-327 (2022).

On September 2020 is the Patent Trial and Appeal Board (PTAB) ruling that the Zhang team has priority in its patents for CRISPR application in eukaryotic cells while simultaneously giving comparable benefits to the Doudna-Charpentier team on some aspects of the practical technical applications of the CRISPR. Later, in February 2022, the PTAB Interference proceedings, favoured the Broad Institute claims, however, the dispute is ongoing[67]. Of particular significance is the fact that while there is no indication of a truce between the parties, the press release by MIT-Broad states thus: *"The best thing, for the entire field, is for the parties to reach a resolution and for the field to focus on using CRISPR technology to solve today's real-world problems*[68]*."*

This, in a nutshell, sums up the best position going forward in the field of biotechnological patents. Considering the niche that health, particularly public health, maintains in the interrelationship between Patent laws and its exceptions and the importance of having alternatives, especially in the case of evolving revolutionary fields of technologies, such a framework seems most facilitative and conducive.

The constructs of patent law, while should be constant for obvious reasons of reliability and predictability, must also be dynamic enough to encompass and find answers to these burning questions of balancing private and public interests in the increasingly significant domain of gene-based biotechnological patents.

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67 Jacob S. Sherkow, "Immaculate Conception? Priority and Invention in the CRISPR Patent Dispute", *The CRISPR Journal* 174-180 (2022).

68 Jon Cohen, "The latest round in the CRISPR patent battle has an apparent victor, but the fight continues", *Science* (2020), *available at*: https://www.sciencemag.org/news/2020/09/latest-round-crispr-patent-battle-has-apparent-victor-fight-continues (last visited on December 23, 2022).