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Redressing the Patent Imbalance in Genetic Testing

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In one of the most highly anticipated decisions emanating from the apex Court in the US in recent times, the US Supreme Court in *Association for Molecular Pathology v Myriad Genetics Inc* was asked to consider, in the main, the patentability of a naturally occurring gene sequence which had been specifically isolated from the human genome. Although the patent was eventually denied, this seminal case will certainly not be the last word on what is clearly a very controversial subject, at least outside of the US.

Introduction

Hollywood actress Angelina Jolie recently made headlines when she disclosed to the world that she had undergone a preventive double mastectomy. The decision was taken after genetic testing by Myriad Genetics Inc ("Myriad") revealed that she had a heightened risk of breast cancer. Ironically, it was Myriad's turn to be in the news shortly after when its patents for the BRCA1 and BRCA2 genes (collectively, the "BRCA genes") were challenged before the apex Court in the US on the basis of patent eligibility. The US Supreme Court handed down a unanimous decision in *Association for Molecular Pathology v Myriad Genetics Inc* (No 12-398) (*"Myriad"*) on June 13, 2013.[1]

Myriad, the respondent, had obtained a number of patents in the US for having discovered the precise location and sequence of two human genes (BRCA1 and BRCA2), mutations of which could substantially increase an individual's risk of developing breast and ovarian cancer. Prior to Myriad's medical breakthrough, scientists were in the dark as to which genes were associated with these cancers. However, knowing the exact location and nucleotide sequence of the BRCA genes allowed Myriad to develop medical tests for detecting mutations in these genes, leading to a better assessment of a patient's risk of contracting cancer.

Interestingly, after its isolation of the BRCA genes, Myriad discovered that it was not the only entity to conduct such tests. For example, the University of Pennsylvania's Genetic Diagnostic Laboratory ("GDL") also provided genetic testing services for women. Apparently, a former researcher at New York University School of Medicine, Dr Harry Ostrer, would routinely send his patients' deoxyribonucleic acid ("DNA") samples to GDL for testing, and this would necessarily involve the isolation of the BRCA genes. On the basis of its patents, Myriad believed that it had the exclusive right to isolate an individual's BRCA genes as well as to synthetically create complementary DNA ("cDNA").[2] Therefore, it issued letters asserting patent infringement to these parties who, in response, agreed to cease all allegedly infringing activities. Myriad had also sued other third parties who performed BRCA testing but these lawsuits were all subsequently settled.

Some years later, the validity of Myriad's patents was challenged in Court by the Association for Molecular Pathology (the lead petitioner on behalf of its members who include clinical pathologists and laboratory scientists) pursuant to s 101 of the US Patent Act 1952 (35 USC §101).[3] Insofar as the merits of the case are concerned, the US District Court held – in a summary judgment ruling – that Myriad's patent claims for the BRCA genes as well as cDNA were invalid because they covered "products of nature".[4] On appeal to the US Court of Appeals for the Federal Circuit,[5] Justices Lourie and Moore (Justice Bryson dissenting) decided that isolated DNA constituted patentable subject-matter, although all three Justices were in agreement that cDNA was clearly eligible for patent protection. The dispute eventually reached the US Supreme Court.

The Decision of the US Supreme Court

The principal issue which the US Supreme Court (the "Court") had to consider was whether a naturally occurring segment of DNA – such as the BRCA genes in the present suit which Myriad had specifically isolated from the rest of the human genome – was patent eligible under s 101 of the US Patent Act 1952. Additionally, the Court also examined the patent eligibility of synthetically created exons-only strands of DNA nucleotides, known as cDNA.

In delivering the unanimous judgment of the Court, Justice Thomas – in a sort of prelude – forayed into the sophisticated field of molecular biology (upon which Justice Scalia expressed no opinion) as well as the fascinating study of genetics. In particular, it was explained that scientists today can isolate specific segments of DNA (such as a particular gene) by extracting DNA from cells using well known laboratory methods. Processes are also on hand for scientists to create synthetic DNA molecules – or cDNA – in the laboratory. Significantly, the Court noted that "… the study of genetics can lead to valuable medical breakthroughs".

In Part II-A of the judgment, Justice Thomas made two important observations of a policy nature. First, citing the Court's earlier decision in *Mayo Collaborative Services v Prometheus Laboratories Inc*,[6] it was emphasised that s 101 of the US Patent Act 1952 had always been subject to the **implicit** qualification that "laws of nature, natural phenomena and abstract ideas" – being "the basic tools of scientific and technological work" – could never qualify for patent protection. This exception was necessary to ensure that future innovation premised upon such tools would not be inhibited, in keeping with the primary objective of patent law which is to incentivise creation. Second, in addressing the issues raised in the present dispute, the Court perceptively paid deference to the need to keep the infamous intellectual property ("IP") balance in check – ie between creating incentives which lead to further discovery and innovation on the one hand, and hampering the flow of information which might otherwise spur invention on the other.

Returning to the principal issue at hand, the Court placed considerable weight on the fact that in isolating the precise location and genetic sequence of the BRCA genes, Myriad had simply made a pure **discovery** – it had not created nor altered the genetic structure of DNA, or indeed any of the genetic information found encoded in the BRCA genes. As Justice Thomas rightly observed, "[t]he location and order of the nucleotides existed in nature before Myriad found them".

His Honour was also quick to distinguish Myriad's patent claims for the BRCA genes from the claim to a modified bacterium – found to be patentable – in the seminal decision of the US Supreme Court in *Diamond v Chakrabarty* (*"Chakrabarty"*).[7] Whereas the *Chakrabarty* claim was "not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter" (due to the scientists' addition of four plasmids to a bacterium which could then be used to break down various components of crude oil), Myriad's claims were not patent eligible because, by merely isolating the BRCA genes from the rest of the human genome, it had not created anything new or different from that found in nature. The Court reiterated that groundbreaking, innovative or even brilliant "discovery" – even if it entails extensive research effort – does not, *ipso facto*, amount to an act of "invention". As such, Myriad's **discovery** of the BRCA genes – which was somewhat reinforced by the language used in its patent drafting – fell squarely within the "laws of nature" exception, notwithstanding that Myriad had reached a significant milestone in the history of bioscience.

Justice Thomas also gave no weight to the fact that Myriad's isolation of the BRCA genes had the effect of severing the chemical bonds which bind DNA molecules together, thereby creating new, non-naturally occurring molecules with unique chemical compositions (evidence which Justice Lourie – but not Justice

Bryson – in the Court below had found to be dispositive). The apex Court noted that Myriad's patent claims were not expressed in terms of chemical composition (or molecular structure), nor did they rely on the chemical changes resulting from the isolation of a particular segment of DNA. Instead, the claims focused on the genetic information encoded in the BRCA genes (ie the information contained in the genetic sequence) and were not at all concerned with the specific chemical composition of a particular DNA molecule.[8]

In a last-ditch attempt, Myriad tried to persuade the Court to pay heed to the US Patent and Trademark Office's ("PTO") long-standing practice of granting gene patents. Justice Thomas, however, refused to do so, on the basis that Congress had not hitherto enacted legislation to specifically endorse the views of the PTO insofar as gene patents were concerned. This appears to echo the views of Justice Bryson in the Court below (but *contra* Justice Moore's position to the contrary), who, in disregarding the PTO's practice, opined that "the PTO lack[ed] substantive rulemaking authority as to issues such as patentability".

Turning to the second issue concerning the patentability of cDNA, the Court had no problem in coming to the conclusion that cDNA was clearly patent eligible under s101 of the US Patent Act 1952 because the exons-only cDNA molecule was a non-naturally occurring, synthetic creation by man. In other words, even though the nucleotide sequence of cDNA may have been dictated by nature (insofar as its order of the exons is concerned), the lab technician nevertheless would have created a new product when cDNA was made because of the deliberate removal of introns from the DNA sequence. Unlike the naturally occurring, isolated BRCA genes, cDNA was, therefore, not a "product of nature".

Before concluding the Court's judgment, Justice Thomas made the following important observations as to the reach and impact of the *Myriad* decision: (i) that the case was not concerned with method claims; (ii) that the case did not involve patents concerning new applications of knowledge about the BRCA genes; and (iii) that the case was not concerned with the patentability of DNA in which the order of the naturally occurring nucleotides had been altered.

Analysis

In deciding that a naturally occurring DNA segment – notwithstanding that it had been isolated from the surrounding genetic material – was a product of nature and not patent eligible, the US Supreme Court had categorically reaffirmed the important distinction in patent law between genuine inventions (which are patentable) and mere discoveries (which are not). Myriad's isolation of naturally occurring BRCA genes, without more, was viewed simply as an act of **discovery** – devoid of any "human ingenuity" and inventive attribute, even though the process may have involved "extensive research efforts" and may be hailed as a valuable "medical breakthrough".

The invention-discovery distinction (or, in the words of the Court, the "laws of nature, natural phenomena and abstract ideas" exception) is an important one. In some jurisdictions, this distinction is expressly codified in patent legislation. For example, s 1(2) of the UK Patents Act 1977 states, *inter alia*, that a discovery, scientific theory and mathematical method (as such) are not considered "inventions".[9] However, for jurisdictions which do not have a similar statutory prohibition (such as the US and Singapore), this exclusionary rule is likely to be maintained and enforced, albeit judicially and on an implicit basis.

Ultimately, whether the subject-matter of a patent constitutes an invention or is held to be a mere discovery of a naturally occurring element depends very much on which side of the "delicate" IP balance a Court leans. In *Myriad*, public policy considerations and consumer interests (particularly those which

relate to healthcare) had clearly trumped the economic interests of the patent owner. Supporters of Myriad (and similar companies in the bioscience industry) would argue that upholding the validity of such patents was necessary in order to encourage and sustain investment in biotechnology as well as promote innovation in genetic research and diagnostic testing, so that new – and especially life-saving – gene-based medicines and diagnostic tests can be introduced in the market for the public's benefit.

On the other hand, that the decision was largely dictated by considerations of policy and that the sympathies of all nine Justices of the Court lay with the consumer came through most clearly from Justice Thomas' judgment. It is well known that costs in the healthcare industry, as with almost everything else, have escalated significantly over the years. If its patents had not been invalidated in the US, Myriad would have had the legal right to stop all third parties from isolating BRCA genes and hence from conducting genetic testing (for breast and ovarian cancer) altogether. As such, in Justice Thomas' words, Myriad would have "solidified its position as the only entity providing BRCA testing", with the probable consequence of charging healthcare consumers monopolistic prices. Furthermore, second opinions of BRCA testing – eg to verify the accuracy of Myriad's test results – are now also possible. This decision can, therefore, be regarded as a major victory for the woman in the street and for proponents of free market competition in the healthcare, diagnostic testing industry.

Whilst the *Myriad* decision will likely be welcomed and celebrated in many quarters, there now appears to be a sharp divide – as regards the patentability of isolated genes and their nucleotide sequences – between American jurisprudence on the one hand and that of Europe/UK on the other. Take, for instance, the fairly recent decision of the UK Supreme Court in *Human Genome Sciences Inc v Eli Lilly & Co* (*"HGS"*),[10] which concerned the validity of an isolated gene sequence patent for a novel human protein (namely, Neutrokine-α).

Although the primary issue before the UK Supreme Court – namely, the extent to which a patent for biological material must disclose and hence satisfy the requirement of industrial applicability in arts 52 and 57 of the European Patent Convention 2000[11] – was not identical to that in the *Myriad* decision, the apex Court in England, after overruling the Court of Appeal which had upheld the trial Judge's decision, nevertheless handed down a unanimous judgment which affirmed the validity of the patent in suit (as did the Technical Board of Appeal in parallel, opposition proceedings brought before the European Patent Office). Interestingly, the highest Courts on both sides of the Atlantic arrived at diametrically opposed conclusions despite the following discernible features: (i) that the respective patent claims in *HGS* and *Myriad* were, *inter alia*, for **naturally occurring** nucleotide sequences of encoding genes; and (ii) the patent specification in *HGS* contained "contentions"/"predictions" (or "wide-ranging and generalised suggestions") as to the biological properties and therapeutic activities of Neutrokine-α,[12] whereas the patent descriptions in *Myriad* disclosed the location and nucleotide sequence of the BRCA genes which then enabled the patentee to develop diagnostic tests for the **specific purpose** of assessing an individual's risk of contracting breast and ovarian cancer.[13] One way of rationalising the *Myriad* decision – in light of *HGS* – is to argue that underlying the US Supreme Court's judgment against patentability were far deeper ethical and policy concerns, particularly in relation to the patenting of genes used in diagnostic testing.

Be that as it may, in preferring not to set too high a standard for industrial applicability in the context of biological patents (which the Court below appeared to have done), Lord Neuberger and Lord Hope (who delivered the main, but separate, judgments in *HGS*) were particularly swayed by a number of factors, including the astronomical costs associated with research and development ("R&D") which bioscience companies must invest in, as well as the fact that funding for such R&D is very much dependent on the patent portfolios of these companies. As Lord Neuberger cautioned, setting the bar for patentability too high "would cause UK bioscience companies great difficulty in attracting investment at an early stage in the research and development process".[14] Or, as Lord Walker put it, a strong policy argument for allowing

the appeal would be "to reduce the risk of a chilling effect on investment in bioscience", although his Lordship did acknowledge that the arguments in this regard "were certainly not all one way".[15]

Indeed, the decision in *HGS* – described by Lord Hope as a "difficult and troublesome case"[16] but a decision that is clearly pro-patentee nonetheless – should not come as a surprise because the spirit of it is actually in keeping with current legislative thinking in Europe/UK. Pertinently, art 5 of the EU Biotechnology Directive (98/44/EC) confirms that a **naturally occurring** gene sequence which has been **isolated** from the human body – and hence, arguably, no longer a mere "discovery" – may constitute a patentable invention, with the qualification that its industrial application must be disclosed in the patent application.[17]

Finally, before concluding, how would our Courts in Singapore respond to similar attacks on patent validity, assuming that the *Myriad* dispute were to be litigated here? In this author's view, this will largely depend on which side of the policy divide our Courts lean. In order for Singapore to maintain its edge as a regional hub for research and development in the life sciences, it is likely that we will arrive at an outcome which is similar to that in Australia (ie pro-patentee).[18] Additionally, our Courts may well adopt the European/UK position (cf. *HGS*), where a naturally occurring gene sequence which has been **isolated** from the rest of the human genome is patentable so long as its **industrial application** has been adequately disclosed in the patent application (which is a non-issue insofar as Myriad's patents are concerned).[19]

On the other hand, despite the repeal of the **as such** proviso (in the guise of the **former** s 13(2) of the Singapore Patents Act 1994) which detailed a list of items which did not count as "inventions", the invention-discovery distinction – our version of the "laws of nature" exception – is still very much alive and well in Singapore's patent law landscape.[20] It may also be possible to raise objections against the patentability of genomic DNA pursuant to (the current) s 13(2) of the Patents Act 1994, which contains the *ordre public*/morality exception.[21]

Be that as it may, and for the reasons given by the US Supreme Court (see above), the patentability of cDNA is likely to pass muster in Singapore. Even as regards the more controversial BRCA genes, the difficulties encountered along the path to patentability are not entirely insurmountable. As the US Supreme Court had already hinted, one possible answer to Myriad's defeat in the US is for the relevant claims in the specification to be drafted with reference to the **chemical composition/structure** of the isolated DNA molecules.

Conclusion

The decision of the US Supreme Court in *Myriad* as well as the earlier decision of the UK Supreme Court in *HGS* clearly demonstrate that we are presently dealing with highly sophisticated and controversial issues of policy in IP law. As Lord Neuberger aptly observed, "[q]uite where the line should be drawn in the light of commercial reality and the public interest can no doubt be a matter of different opinions and debate".[18] Insofar as the jurisprudential divide highlighted above is concerned, whether or not the famous expression "East is East, and West is West, and never the twain shall meet" continues to hold true for the foreseeable future remains to be seen. For now though, both Angelina Jolie and the US Supreme Court must be congratulated for having raised the public's awareness of and accessibility to the testing of BRCA genes, respectively.

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Notes

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

2 cDNA only contains "exons" (nucleotides which contain protein-coding information) and omits portions in the DNA segment that do not code for proteins (known as "introns").

3 Section 101 of the US Patent Act 1952 (35 USC §101) provides that: "Whoever invents or discovers any new and useful … composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

4 *Association for Molecular Pathology v United States Patent and Trademark Office* 702 F Supp 2d 181 (SDNY 2010).

5 *Association for Molecular Pathology v United States Patent and Trademark Office* 689 F 3d 1303 (Fed Cir 2012).

6 132 S Ct 1289 (2012). See also *Bilski v Kappos* 130 S Ct 3218 (2010).

7 447 US 303 (1980).

8 It is arguable whether the US Supreme Court was actually suggesting that Myriad's claims to isolated DNA might have been upheld if they had been expressed in terms of chemical structure, rather than in terms of genetic sequence. If so, this may well pave the way as to how gene patents in the US ought to be drafted in the future.

9 English case law has affirmatively endorsed the invention-discovery dichotomy – see eg *Kirin-Amgen Inc v Hoechst Marion Roussel Ltd* [2005] RPC 9 at [76]; *Genentech Inc's Patent* [1989] RPC 147, pp 204 and 237.

10 *Human Genome Sciences Inc v Eli Lilly & Co* [2012] RPC 6. See also, for further comparison, the decision of the Court of Justice of the European Union ("ECJ") in *Monsanto Technology LLC v Cefetra BV* [2011] FSR 6 (especially at [43]-[46]). In other areas of biomedical research, there have been significant developments concerning the patentability of inventions in the field of human stem cell research, particularly where the research involves the use and destruction of human embryos – see eg the decision of the Enlarged Board of Appeal of the European Patent Office in *Wisconsin Alumni Research Foundation* /Stem cells [2009] EPOR 15 ("WARF"), as well as the decision of the ECJ in *Oliver Brüstle v Greenpeace eV* (C-34/10) [2012] 1 CMLR 41. In this respect, the European position (which generally denies patent protection for inventions that involve human embryonic stem cells in line with art 6(2)(c) of the EU Biotechnology Directive (98/44/EC)) is likely to soon converge with the position in the US, which has generally awarded patents that cover human embryonic stem cells. Indeed, in light of the US Supreme Court's decision in *Myriad*, a US patent on human embryonic stem cells held by the WARF (Patent No 7,029,913) is now being challenged by the Public Patent Foundation (on behalf of Consumer Watchdog, a public advocacy group) before the US Court of Appeals for the Federal Circuit (*Consumer Watchdog v Wisconsin Alumni Research Foundation*, No 13-1377 (Fed Cir 2013)) – on the basis that this patent claims a "product of nature", which, according to *Myriad*, is not patent eligible. The WARF case is, notably, the first test case before a US tribunal to delineate the reach and import of the *Myriad* decision beyond the patentability of gene sequences.

11 Implemented, domestically, in ss 1(1)(c) and 4 of the UK Patents Act 1977.

12 HGS [2012] RPC 6 at [3], [9] and [103].

13 Apparently, "[t]he range of diseases and conditions which Neutrokine-α and antibodies to Neutrokine-α might be used to diagnose and treat were astonishing and there was no data of any kind to support the claims made" (HGS [2012] RPC 6 at [159]).

14 HGS [2012] RPC 6 at [100].

15 HGS [2012] RPC 6 at [171].

16 HGS [2012] RPC 6 at [141].

17 Article 5 of the EU Biotechnology Directive (98/44/EC) provides thus:
"The human body, at the various stages of its formation and development, and the **simple discovery** of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions". [Article 5(1); emphasis added]

"An element **isolated** from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, **even if the structure of that element is identical to that of a natural element**". [Article 5(2); emphasis added]

"The **industrial application** of a sequence or a partial sequence of a gene must be disclosed in the patent application". [Article 5(3); emphasis added]

See also the domestic implementation of these provisions in paras 3(a), 5 and 6 of Schedule A2 of the UK Patents Act 1977, as well as r 29 of the European Patent Convention 2000 (Implementing Regulations).

18 See *Cancer Voices Australia v Myriad Genetics Inc* [2013] FCA 65 (Federal Court of Australia).

19 This approach is arguably in line with the submission that "… the assessment of whether the subject-matter of the patent is or is not an invention is subsumed within the inquiry for novelty, inventive step and industrial application". (see Ng-Loy Wee Loon, *Law of Intellectual Property of Singapore* (Thomson Sweet & Maxwell Asia, Revised Edition, 2009) at [30.1.20])

20 See the Court of Appeal's decision in *Merck & Co Inc v Pharmaforte Singapore Pte Ltd* [2000] 2 SLR(R) 708 at [63]: "In this regard, we must also point out that the fact that a discovery is made **does not mean** there is an invention. **The latter does not necessarily follow from the former**". (emphasis added) And at [65]: "In our opinion, what the appellants have achieved in the alleged patent is a **discovery**. It does **not** amount to an **invention**". (emphasis added)

21 But see *Howard Florey/Relaxin Patent Application* [1995] EPOR 541 and IPOS' "Guide on Patentability Issues arising during Search & Examination" (September 2010) at [6.19]-[6.22].

22 HGS [2012] RPC 6 at [131]. Indeed, the validity of Myriad's patents for the BRCA genes was recently challenged – yet again – in Australia, with an outcome that is antithetical to that reached by the US Supreme Court. See, in this regard, Justice Nicholas' decision in *Cancer Voices Australia v Myriad Genetics Inc* [2013] FCA 65 (Federal Court of Australia), which is now the subject of an appeal.