Preliminary Literature Review on Patents and Diagnostics

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Part 1 – Analysis

Main Issues of Patents and Diagnostics

Lack of diagnostics in resource-limited settings has been identified as a major obstacle to treating infectious diseases as they are crucial for precisely identifying the presence and cause of disease, defining an appropriate treatment regimen, monitoring the effects of preventive or therapeutic interventions, and determining drug resistance. In fact, a panel of global health experts ranked modified molecular technologies for affordable, simple diagnosis of infectious diseases as the top biotechnology for improving health in the developing world. The causes of the access to diagnostics are manifold and similar to access issues on pharmaceuticals i.e., tests not being designed for low-infrastructure sites, lack of development in general and, our focus, patents and licensing. This literature review gives a

non-exhaustive overview of the literature available exclusively focusing on the issues of patents and diagnostics and certain contextual issues.

The potential issue of patents on access to diagnostics has been on the radar of the Access Campaign for a while, but research and expertise in patents and diagnostics is only just starting up both within MSF and in the access field in general. This literature review aims to lay a groundwork for futher research by looking at the knowledge that is already out there and creating an overview of the main issues regarding patents and diagnostics.

Main issues regarding patents and diagnostics in literature identified are *(i)* the carving out of the diagnostics exception through language of claims and recent case law; *(ii)* the increasing acceptance of patentability of genes overall; *(iii)* because patents are often not enforced yet; .For companion diagnosics the main problem is the incentive that is created to only test for medicines of the party that designs the tests and the possibility of evergreening through patents on the device in companion diagnostics.

Scope and Content

The focus lies on *in vitro* diagnostic (IVD) products as patents on *ex vivo* diagnostics are excluded in most jurisdictions. The diagnostics debate, particularly regarding intellectual property (IP), but also regarding diagnostics more broadly, nowadays takes a overwhelming focus on gene-based molecular diagnostics. Experts note that the debate on whether patent protection on diagnostics in general are more harmful than beneficial 'has been synonymous with the DNA-patenting controversy'. Discussing this memo, one of the main points that was raised is that infectious disease diagnostics and its microbiology based tests, but also immunochemistry, hematology and cytology, and even more general chemistry based tests, are not sufficiently, or not at all, covered, although these tests are of great importance, including to MSF operations. This is true: this reflects how underresearched and fragmented research and literature on patentability and the value or harm of patents on these types of tests is, and improved documentation and analysis is urgently needed.

The Law of Patents and Diagnostics

Most countries have excluded diagnostic methods from the scope of patentable subject matters in their patent systems. Paragraph 3 of Article 27 of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) allows members to exclude diagnostic, therapeutic, and surgical methods for the treatment of humans or animals from the scope of patentable subject matter. While the E.U. does place limits on diagnostic patents, it does not prohibit them outright and has created a test that very much limits the diagnostics exception in patenting. Most jurisdictions have a similar system, but with varying scopes of exception to patentability of diagnostics. The U.S. and some other countries do allow for the patenting of diagnostic methods, but do not allow for that which is found in nature, and take a broader view of this. The most relevant part is the issue of claim drafting language. Research into patents showed that often diagnostic method claims are drafted in such a way as to make them patentable, for instance by focussing on the 'disclosing only a correlation between two things, often the presence of an isoform or mutation and some multigenic disorder or a disorder having a genetic component' or a 'Swiss-type' of claim, practically creating a slightly more narrow method claim.

The Discussion on Gene-Based Molecular Diagnostics

Human gene patents give rise to high level of controversy. Significant public, medical and academic opposition to these patents exists. A certain amount of this opposition stems from principled objections to the patenting of human genetic material. In addition, many are concerned that patents on human genes will have a negative impact on patient access to medical care and diagnostic services. Thousands of patent applications relating to human DNA have been filed in patent offices around the world in the past 15 years (2(E)8). Some relate to the gene sequence as a compound per se, and others claim methods of diagnosis. The legal trend in the E.U. and in the U.S.A. combined with country reports on diagnostics show the controversy, but also the uncertain state of the law in this area.

There is thus significant divergence between the legal and the practical situation depending on the region. Because patents right now are essentially ignored, access is highly dependent on the lack of enforcement of patents by patent holders. It has been said that for instance 'potentially, even one successful case by a patent holder against the NHS, resulting in the NHS licensing and paying royalties to a patent holder, buying in a kit test, or sending samples to a commercial laboratory, could have widespread implications for NHS genetics laboratories.' An interesting quote from an NHS lab worker asked about his concern about gene patents doing his work is: "Well, no, I haven't, and I don't think that's been part of the discussion at all. I mean, the assumption is that the gene sequence is publicly available, that spotting an oligonucleotide on to a chip for a published, publicly available sequence does not infringe anyone's intellectual property. I mean, if that's my ignorance or naivety, but I am not aware that there is an issue" (2(D)8). *Research*

In molecular diagnostics, patent enforcement however is more common in the U.S. than in the E.U., and as we see in this quote many European hospital laboratories have been able to largely ignore IP issues. The general view in literature is that despite the potential for gene patents to have significant negative consequences for genetic testing, in fact, human gene patents have little or no impact yet on practice for those developing genetic tests in the public sector or on access to tests. This is not because patents are not existing or could not potentially affect access; rather, gene patents are essentially ignored because the price of the tests is insignificant compared to the treatment or because of the patented tests are not used. Also, virtually all research is focussed on rich developed countries, making the effects on less developed countries unknown.

There are also very big practical problems with the examination of these patents. Reports on the USPOT indicate that on average a patent examiner spents 18 hours on a patent application. With gene patent applications often involving extensive biological sequence information for each individual claim, it may be that adequate time is not being invested in thoroughly investigating the patentability of the claimed material.

Patent Related to Method of Diagnostics and Licensing

There are two types of barriers in access to gene-based molecular diagnostics: barriers due to test availability and barriers due to test price.

The barrier to access due to test availability refers to the effect that patents and licensing practices have in restricting patient choice of genetic tests in terms of quality and accuracy.

These harms are most clearly seen when an exclusive license is issued by a patent holder resulting in only a single laboratory that can perform a given test. A key example is the Myriad case in which Genae Girard had to make the difficult decision whether or not to undergo a pre-emptive dual mastectomy and hysterectomy. By exercising its patent rights, Myriad eliminated the availability of second opinion BRCA testing. Without broad licensing, the availability of alternative testing techniques, medical second opinions, and testing verification is severely limited.

While price can be prohibitive, it is unclear the extent to which this effect is a result of DNA patents. Studies conducted in the past few years have shown that between 19% and 74% of at-risk individuals who could benefit from *BRCA* testing are not being tested. However, studies comparing the cost of the Myriad BRCA test, of which Myriad is the sole provider, with the costs of Myriad gene tests for the colon cancer genes FAP and HNPCC, in which fields Myriad has four and six competitors respectively, show little monopolistic effect on pricing. respectively, show little monopolistic effect on pricing. MSF focusses on no research has been done, Regarding diseases and tests that MSF focusses on, no research has been done, but, for all diseases, the disconnect between patents and price exists in the sense that downstream costs of a positive test, which can include counselling and possibly surgery, can be far greater than the test itself.

Another example is biotechnology company Chiron, now Novartis, that was the first to clone Hep C in 1987 and used to own more than 100 patents related to the hepatitis C virus and HCV research, and effectively also single-handedly controled U.S. hepatitis C research for nucleic acid-based diagnostics. In that time, researchers have said they'd abandoned plans to enter the HCV field because of Chiron's control of the patents and expensive licence fees. Chiron charged large sums to access its technology; licenses issued by Chiron in 2003 generated $1.8 billion in revenue for the company. Although much of the initial research into the discovery of HCV was conducted by a Centers for Disease Control and Prevention scientist, Chiron paid $1.9 million for exclusive rights to the discovery patent in 1990. There have been case studies of Hep C test prices leaping sixford in 1994, causing the NHS to stop testing. It was only after 2004 that Chiron changed its licensing practices and the current innovation and better availability of Hep C tests came about.

Allen Baum, a patent attorney and a partner with Hutchison and Mason, in Raleigh, N.C., says that there are two schools of thought in terms of how to license a test. “One is that you want to license these diagnostic tools widely and get them into as many hands as possible because you’ll get more extensive use of that particular assay. The other is that you select a single vendor, through which you may get more money initially because you’ve got an exclusive relationship” (1(A)14). Some companies choose the second route, tightly controlling access to their intellectual property. In the United States, where Myriad holds nine patents on the BRCA-1 and BRCA-2 genes, Myriad performs the tests itself (1(A)14).

Patents often ‘Undeserved’ in Gene-Based Molecular Diagnostics

Studies have shown that patents have not lead to tests that were not already available, but that there is a trend in broad patenting combined with exclusive licensing, not allowing for competition. Furthermore the finite number of genes makes it difficult to ‘invent around’ a genetic patent to create an equivalent. Especially upstream patents hinder development

In most analyses by lawyers and policymakers, gene-based molecular diagnostics is directly related to drug research, however identification of disease-linked genes is remarkably cheaper. While the cost of conducting gene wide association studies can still be partially prohibitive for many academic research laboratories, the price is substantially less than that of drug discovery. Once a gene-trait association has been established, genetic tests are said to be more "designed" than "discovered" and are developed through established scientific principles. It is estimated tests that utilize even the more expensive full gene sequencing diagnostic approach (as opposed to the cheaper probe hybridization approach used to detect a single mutation) are on average between $8,000 and $10,000.

Last, but not least, a large portion of the information required for early discovery in gene-based molecular diagnostics is heavily sponsored by government and philanthropic funding, a main example of this would be the Human Genome Project.

Companion Diagnostics

Companion diagnostics themselves show no clear access problems because of patents by themselves. Their relative low cost (compared to drugs) and great cost effectiveness through preventing ineffective use of expensive treatments means that, regardless of patents, even when their costs are often is high, they are low compared to the cure. Rather, they have an incentive problem in development (developed only because the company has a drug to match) and create access problems for medicines they are connected to. (2(C)2)

While pharmaceutical companies are most interested in companion diagnostics that are theranostics and monitoring types of tests, to support the drugs they offer, it is more useful for patients to have diagnostic tests that provide information on multiple potential treatment options in a therapeutic area. Companion diagnostics, in a way, are often thus biased towards one type of treatment, while companion diagnostics with a broader spectrum would be more beneficial to patients. (2(C)3)

The main problem for companion diagnostics is that, unlike for medicines, even the housing or shape of the product, or certain mechanical parts, are patentable. This means that, through minor changes in the machine, together with interweaving of the drug and the machine in the patent claim, the overall patent protection for medicine/device combinations can be extended almost endlessly (2(C)1)

The Danger of Discrimination in Current and Future Gene-Based Molecular Diagnostics

Not directly relevant for this research, but important to note, is the danger of discrimination and biocolonialism that underlies the patentability of genes. Firstly, regarding personalized medicine, in which it was recently shown that there is no clear policy yet, especially in the U.S.A., for patenting of personalized medicines or diagnostics aimed at a specific race. The geneticization of race through the patent process remains a relatively contingent and contested phenomenon, furthering the divide in medical development, but also upholding the non-scientific concept of race.

Secondly, in the search for gene diagnosis where colonial exploitation in the pharmaceutical industry first was done based on traditional medicine, companies have now moved on to exploiting foreign bodies. Isolated communities are more likely to contain the rare "disease

genes" that the pharmaceutical companies seek. Axys, for instance, holds patent rights to the entire genome of Tristan da Cunha's residents and has contracted, with a long list of virtually all major international pharmaceutical companies, to jointly exploit DNA largely from isolated communities that will themselves never have access to, or benefit from, resulting tests.

PART 2 – Literature

PART 2(A) – General Research on or related to Access to Diagnostics

1. Hopkins M, Hogarth S. Biomarker Patents for Diagnostics: Problem or Solution? [Online] Nature Biotechnology, 2012; 30(6). Available on http://www.nature.com/nbt/journal/v30/n6/full/nbt.2257.html

Until recently, the debate has been synonymous with the DNA-patenting controversy, but we argue that the issues raised are of wider relevance as other types of biomarkers become the subject of diagnostic disputes. The recent US Supreme Court case of Mayo Collaborative Services v. Prometheus Laboratories, Inc., which overturned patent claims on thiopurine metabolite measurement (again after a series of prior verdicts), serves to emphasize this point. […] We begin by noting that the context of the debate differs between Europe and the United States. In molecular diagnostics, patent enforcement is more common in the United States than in Europe, and many European hospital laboratories have been able to largely ignore IP issues. Either laboratory directors have not been aware that the biomarkers they test for are patented, or they have willfully infringed patented tests by continuing to offer these services without obtaining the appropriate licenses. Either way, there seems to be little evidence that patenting activity has harmed European healthcare. However, DNA patents are more firmly protected in Europe than in the United States, owing to specific provisions in national laws that ensure the patentability of DNA-based inventions. […] It will probably become increasingly difficult for laboratories to continue to ignore IP, because biomarker patenting is now part of the business strategies of molecular-diagnostics companies and is focused increasingly on applications of greater commercial value than rare-disease genetics, as we discuss below. Already, the pressures have prompted some countries to act: France, Belgium and Switzerland have created provisions for compulsory licensing of diagnostics in patent law. […] After reviewing case studies on the development of ten classes of tests, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) for the US Department of Health and Human Services also concluded that the exclusivity provided by patents or licenses had not been necessary to ensure that tests were developed and made available to patients.

2. European Observatory on Health Systems and Policies. Ensuring Innovation in Diagnostics for Bacterial Infection [Online] Observatory Studies Series, 2016; 4. Available on http://www.euro.who.int/en/publications/abstracts/ensuring-innovation-in-diagnostics-for-bacterial-infection-implications-for-policy-2016

A gene patent holder has absolute power for 20 years from the day the patent is filed to control any use of the respective gene. This means that they have the power to prevent others from developing and marketing cheaper public health genetic testing. With regard to infectious diseases, this could have grave consequences for diagnostic development and drug research surrounding antibiotic-resistant strains. Patentability of the methods to do these analyses adds yet another layer of potential obstacles inhibiting discovery and development of new diagnostics. […] R&D of diagnostics was often hindered by the existence of patents (if and when researchers were aware of these patents). This should cease to be the case for genomic DNA patents. […] It is clear that establishing the negative impact of gene patents is an ongoing and evolving process, and that more data is needed to guide the agencies in charge of regulating patents and patient access to diagnostic tests. Genes straddle the boundaries between patentable and unpatentable substances, and the debate on how to balance business and health care needs must continue. New models will likely be needed.

3. Mitnovetski O, Nicol D. Are Patents for Methods of Medical Treatment Contrary to Ordre Public and Morality or "Generally Inconvenient"? [Online] Journal of Medical Ethics, 2004; 30(5). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1733926/

Another fear of opponents of medical methods patents is the possibility of conflict of interest. This is based on the argument that if physicians have paid licence fees (licensed physicians) to enable them to use a patented method this may affect their discretion when choosing the correct treatment. […] One of the most significant concerns raised by opponents of medical methods patents is the fear of infringement, particularly related to emergency procedures. There are, however, many other restraints on the physician's practice. Insurance, medical malpractice actions, and the issue of obtaining consent of minor or incompetent patients impact significantly on the physician's practice.

4. Simms A. The Case Against Patenting Methods of Medical Treatment. European Intellectual Property Review, 2007; 29(2).

Pharmaceutical drug companies charge as much as the market will bear; it is common for a year's supply of a patented drug to cost tens of thousands of dollars. The pharmaceutical drug companies' loyalties lie with their shareholders, not the public. […] Even if all licence fees were truly nominal, numerous licence fees may be payable per patient. And licence fees are not the only extra expense the public must bear. Litigation will increase with the patentee suing alleged infringers or the patent being challenged, leading to higher insurance premiums for patients and doctors (and the need to further increase licence fees). Patent attorneys will need to be consulted as to whether a certain method can be used. In addition, it will be wise for a doctor, upon developing a new method, to either publish it in a journal or patent it, lest a patentee claims the former doctor has infringed his or her patent.

5. Verkey E. Patenting of Medical Methods – Need of the Hour [Online] Journal of Intellectual Property Law & Practice, 2007; 2(2). Available on https://doi.org/10.1093/jiplp/jpl212

Another fear is that the grant of medical method patents will push up the cost of healthcare through licensing fees that may be imposed by the patent holder. One such instance is where Myriad Genetic Laboraties Inc. blocked access to genetic technologies that diagnosed cancer by asserting patent rights. Many people carry mutations predisposing them to cancer, but early detection can help either to prevent the disease or to treat it effectively. Genetic diagnostic testing is available for detecting the presence of BRCA1 and BRCA2 mutations. Most of the patents for these diagnostic testing methods are held by Myriad Genetics. […] The cumulative effect of the patents granted to Myriad in Europe is that it gives a monopoly on all diagnostic testing for breast and ovarian cancer throughout Europe. The patents cover all methods of diagnosis, specific mutations, and diagnostic kits. Myriad has also patented sequencing work on the BRCA2 gene. The patent protects somatic mutations in the gene associated with breast and other cancers and the use of the mutations for diagnostic purposes, treatment, and pharmaceutical screening.

6. Goldacre B. The Absurdity of Patenting Genes [Online] The Guardian, 3rd of April 2010. Available on https://www.theguardian.com/commentisfree/2010/apr/03/ben-goldacre-gene-patents

[T]hese tests are just the tip of the research iceberg. Almost all basic science research on the BRCA1 breast cancer gene over the past 12 years has infringed Myriad's patent, and although the company has tended not to go after basic science researchers, they have never promised that they won't in the future, so this academic research on a major risk factor for a major killer — the most common cancer in women worldwide — continues only with Myriad's indulgence, making it risky work.

7. Buck N. Greed is Good, for Patients: How the Biotechnology Industry Saves Lives, One Gene Patent at a Time [Online] Northwestern Journal of Technology and Intellectual Property, 2013; 11(2). Available on http://scholarlycommons.law.northwestern.edu/njtip/vol11/iss2/5

Opponents of gene patents argue that the allowance of exclusive rights over upstream research technology will have a deleterious effect on downstream innovation. Researchers termed this theory the “tragedy of the anticommons.” Empirical studies have shown that the “tragedy of the anticommons” does not exist within the realm of biotechnology. Though patents on upstream research tools have increased throughout the years, downstream technology has not been hindered.

8. Kubick M. An Uncertain Future: The Impact of Medical Process and Diagnostic Methods Patents on Healthcare in the United States [Online] Northwestern Journal of Technology and Intellectual Property, 2010; 9(3). Available on http://scholarlycommons.northwestern.edu/njtip/vol9/iss3/8

Due to the potential of creating "class health-care," Europe considers medical treatment methods to be unpatentable: "[T]hese treatments were excluded because it was considered almost "unethical" from the point of view of society, to allow patent protection for this type of inventions … If medical treatment methods were patented, they could become more expensive, which excludes part of the population from enjoying the best treatment method for their medical condition." (In Mayo Clinic Amicus Curae) […] According to Aaron Kesselheim, patent lawyer and clinical fellow at the Harvard School of Public Health, patents can be dangerous to scientific progress "when they are granted in cases where a product is not innovative, [because] they can serve to increase costs and prevent access" to new alternative therapies by blocking competition. […] While patents are crucial in encouraging future medical progress, there must be a cap on both the breadth and length of patent protection in order to protect the free transfer of information of our most basic scientific building blocks. Evidence suggests that longer time periods of patent protection do not necessarily encourage any reciprocal boost in increased medical innovation.

9. Gielen C. Netherlands Royal Academy of Arts and Sciences on Patenting on Human Genes. European Intellectual Property Review, 2004; 26(1).

It underlines that without the possibility of getting patents for human genes it would be extremely difficult to carry out gene therapy clinical trials especially in phases III and IV. In particular the financing of clinical trials in those phases requires commercial enterprises to show that they own a monopoly position on the technology. However, there are negative consequences such as that scientific research into genetic testing may run into obstacles because of the patentability of diagnostic methods used on material outside the body. In order to balance both the interests of the market as well as the interest of augmentation of knowledge in the field of biotechnology via research, a few recommendations are made. […] It is recommended that the government strives for a clearly and unambiguously worded definition of the research exemption that covers every activity intended to enlarge knowledge. The definition as it stands in most national patent laws, namely that patent rights do not extend to acts done for experimental purposes relating to the subject-matter of the patented invention, is too vague. […] in order to avoid going too far with respect to monopolies on diagnostic methods, the government should encourage companies who have obtained patents on DNA diagnostic techniques to grant licences for a reasonable fee and if no such licences are given, to encourage the granting of compulsory licences. […] KNAW sees no reason to treat such DNA sequences differently from other human genes, but encourages a broader application of the research exemption to the use of such tools.

10. Walsh J, Arora A, Cohen W. Effects on Research Tool Patenting and Licensing on Biomedical Innovation in Cohen W, Merill S (eds). Patents in the Knowledge-Based Economy. The National Academic Press, Washington DC; 2003.

The concern with regard to IP access tends to be the greatest when a research tool is rival-in-use and is potentially key to progress in one or more broad therapeutic areas. When a foundational research tool is rival-in-use, the IP holders often either attempt to develop the technology themselves or grant exclusive licenses. As suggested above, exclusive exploitation of a foundational discovery is unlikely to realize the full potential for building on

that discovery because no one firm can even conceive of all the different ways that the discovery might be exploited, let alone actually do so. Geron's exclusive license for human embryonic stem cell technology shows how restrictions on access to an important, broadly useful rival-use technology can potentially retard its development. A more prosaic example is the pricing of licenses for diagnostic tests. Myriad's (and others') licensing practices show that, to the degree that a high price on a diagnostic test puts it out of the reach of clinics and hospitals involved in research that requires the test results, clinical research may be impeded, yielding long-term social costs. The social welfare analysis of this situation is, however, not straightforward Even though knowledge, once developed, can be shared at little additional cost and may be best exploited through broad access, it does not follow that social welfare is maximized by mandating low-cost access if such access dampens the incentive to develop the research tool to begin with. […] [T]he danger remains that progress in a broad research area could be significantly impeded by a patentholder trying to reserve the area exclusively for itself.

11. Love J. Recent Examples of the Use of Compulsory Licenses on Patents. Kei Research Note 2, 2007. Available on http://www.keionline.org/misc-docs/recent_cls_8mar07.pdf

Canada: In a September 2001 Speech on the Myriad Gene Patent, the Ontario Health Minister called for compulsory licensing of patents on genes relevant to tests for breast cancer. In January 2002, the Ontario Advisory Committee on New Predictive Genetic Technologies published "the Ontario Report to Premiers: Genetics, Testing & Gene Patenting: Charting New Territory in Healthcare." This report noted that the Doha Declaration calls upon nations to take measures "to protect public health and, in particular, to promote access to medicines for all," and concluded: In order to prevent the statement from providing a hollow right, the concept of promoting access to medicines for all must include providing access to the diagnostic procedures necessary to determine when and which medicines to provide. The federal government should, therefore, amend the Patent Act to specifically allow thepotential for compulsory licensing of patents relating to the provision of genetic diagnostic and screening tests should this power be necessary. On October 18, 2001, Health Canada overrode the Bayer patents on ciprofloxacin, and authorized generic manufacture for purposes of building a stockpile as protection against an attack of certain strains of anthrax. In announcing the action, Paige Raymond Kovach, a spokeswoman for Health Canada, said: "These are extraordinary and unusual times […] Canadians expect and demand that their government will take all steps necessary to protect their health and safety.''

France: France was among several European countries who were outraged by the high prices of breast cancer diagnostic tests, because of the Myriad gene patents. In 2004, France amended its patent law to allow the broader use of ex officio licenses, and in particular, to authorize the government to issue ex officio licenses to patents on certain dialogistic technologies. The new act provide that: Where the interests of public health demand, and in the absence of a voluntary agreement with the patent holder, the minister responsible for industrial property, may, by order of the minister responsible for public health, request ex officio licenses in accordance with Article L. 613-17 for any patent granted for: a) a medicine, a medical device, a medical device for in vitro diagnosis, a related therapeutic product; b)

processes for obtaining them, [or] for products necessary in obtaining such medicines or for processes for manufacturing such products c) a diagnostic method ex vivo.

12. van Zimmeren E, Verbeure B, Matthijs G., Van Overwalle G. A Clearing House for Diagnostic Testing: the Solution to Ensure Access to and Use of Patented Genetic Inventions? [Online] Bulletin of the World Health Organization, 2006, 84(5). Available on https://www.ncbi.nlm.nih.gov/pubmed/16710543

Currently, two models that may facilitate access to and use of patented genetic inventions are attracting much debate in various national and international fora: patent pools and clearing houses. In this article, we explore the concept of clearing houses. Several types of clearing houses are identified: the information clearing house; the technology exchange clearing house; the open access clearing house; the standardized licences clearing house and the royalty collection clearing house. It remains to be seen whether patent holders with a strong patent portfolio will be convinced by the advantages of the royalty collection clearing house and be willing to participate.

13. Cook-Deegan R, Chandrasekharan S, Angrist M. The Dangers of Diagnostics Monopolies [Online] Nature, 2009, 458(7237). Available on https://www.ncbi.nlm.nih.gov/pubmed/19325608

Most concerns centre on monopoly situations, in which exclusive licensing results in a single dominant provider. But prices of patented and exclusively licensed tests are not dramatically or consistently higher than those of tests without a monopoly — a contrast with the strong price effects of drug patents. For example, unit prices for BRCA testing (for breast cancer susceptibility) — provided solely in the United States by Myriad Genetics in Salt Lake City, Utah — are comparable with similar tests for colon cancer susceptibility available from many labs under nonexclusive licences. We also do not find consistent price effects of patents in other case studies.

14. Terry M. Storming the Molecular Diagnostic IP Fortress [Online] Biotechnology Healthcare, 2006, 3(1). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571035/

At the moment, how genes are patented and how companies exercise those patents by licensing has an important and striking effect on patients' access to medical testing, ethical issues, anticompetitive and monopolistic business practices, laboratory testing quality control, and the future of medical test development. A few laboratories have been driven out of some test markets and laboratory testing prices have been pushed upward.

PART 2(B) – Legal Research on the Patenting of Diagnostic Methods

1. Asif E. Exclusion of Diagnostic, Therapeutic and Surgical methods from Patentability [Online] Journal of Intellectual Property Rights, 2013; 18(3). Available on http://nopr.niscair.res.in/handle/123456789/18370

There should be a detailed research oriented study with regard to the concept of exclusion from patentability of medical, surgical and therapeutic methods. […] The differing approaches of the developed and the developing countries in this regard can be understood and it will help in establishing a uniform and logical system of exclusions in the patent regime of medical, diagnostic and therapeutic methods, and above all the findings of the study will promote the larger idea of social welfare by advancing the concepts of affordability, accessibility and quality in the healthcare sector. At a time when developing countries benefit more from the exclusion clauses rather than the enabling ones, at least in the area of healthcare sector, the area needs expedient attention. […] It is indeed impossible to devise a common exclusion system in the patent regime with regard to the medical, diagnostic and therapeutic methods because of many political, economic and social factors.

2. Minssen T, Schwartz R. Separating Sheep from Goats: a European View on the Patent Eligibility of Biomedical Diagnostic Methods [Online] Journal of Law and the Biosciences, 2016; 3(2). Available on https://academic.oup.com/jlb/article/3/2/365/1751248/Separating-sheep-from-goats-a-European-view-on-the

Significant differences in eligibility standards strain the operation of and cooperation among, the Trilateral Offices (USPTO, EPO, and the Japanese Patent Office, JPO) *inter alia* increasing the cost and complexity of obtaining triadic patent family protection in the life sciences.[47] They raise costs by threatening economies of scale, create uncertainty, and risk fragmenting the global delivery system for innovative medicinal products and diagnostics. They can also disrupt the existing balance among different forms of IP protection sought by technology innovators.

We believe that a more holistic application of the Supreme Court's patent-eligibility rationale would better support investment in biopharmaceutical innovation and the development of innovative treatments and precision medicine towards market approval. Such approach would go a long way towards assuring that differences among the world's patent law systems do not create unnecessary compliance costs ultimately borne by consumers of medical care.

3. Amos B, Miller A. Differing Diagnoses for European and US Patents [Online] Nature Biotechnology, 2017; 35(4). Available on http://www.nature.com/nbt/journal/v35/n4/full/nbt.3839.html?WT.feed_name=subjects_business-and-industry

In contrast to the situation in the United States, the European Patent Office (EPO) has not excluded diagnostic or prognostic methods from patentability. […] To obtain empirical data on this situation, we compared the fate of 31 Patent Cooperation Treaty (PCT) international patent applications published in 2013 that claimed diagnostic or prognostic methods and that entered both the European regional phase and the US national phase. […] As a control, we compared the fate of 20 PCTs published in 2008 that claimed diagnostic or prognostic methods and that entered both the European regional and US national phases and in which prosecution concluded before the 2012 Mayo decision. [..] Of the 20 pre-Mayo applications, eight counterpart applications were abandoned in both Europe and the United States, and

four issued as patents in both jurisdictions. Of ten cases that were abandoned in the US, two had pre-Mayo rejections. Those wishing to protect intellectual property should strongly consider pursuing broad patent coverage in Europe.

4. Basheer S, Purohit S, Reddy P. Patent Exclusions that Promote Public Health Objectives [Online] SCP/15/3 Experts' Study on Exclusions from Patentable Subject Matter and Exception and Limitations to the Rights, 2011; Annex IV. Available on www.wipo.int/meetings/en/doc_detials.jsp?doc_id=154817

This Chapter gives an overview of legislation on exclusions per country including diagnostics.

Amongst the various theories that exist today to explain the purport and rationale of the patent system, the most prevalent is the "incentive" or the "reward" theory. […] More importantly, the issues are technology specific, and evidence that patents may help in an investment heavy industry such as pharmaceuticals may not be readily transposable to industries such as Information Technology and semiconductors. Further, there is also the issue of developing and least developed countries that are net importers of technology. The question is whether patent regimes promote technology transfer to these countries or whether they effectively curb the potential growth that these countries might have experienced, had they had the freedom to imitate and learn; freedoms that many of the developed countries enjoyed in the pre-TRIPS era. For these countries, the potential use of patent eligibility exclusions is far more significant in driving national policy. […] This chapter seeks to evaluate the patent and public health interface from the point of view of ex-ante mechanisms i.e. ways in which countries have sought to limit the grant of patents to certain categories of subject matter in a bid to promote access to public health goods.

5. Thambisetty S. Legal Transplants in Patent Law: Why Utility is the New Industrial Applicability [Online] The Journal of Law, Science, and Technology, 2008; Working Paper No. 6. Available on http://ssrn.com/abstract=1111966

The patent application in Aeomica is remarkable because it lacks 'wet-lab experimentation' and is based on bioinformatics. […] A number of significant strands emerge from the decision of the Hearing Officer. First, the SSCS was clearly applied as a cumulative standard. Given that further experimentation would be required in order to verify the proposed uses of the gene, the disclosed use was not a substantial one. Even if it were accepted that the use of genes as diagnostics, and probes for further research, are common uses of gene sequences and therefore credible from the perspective of a person skilled in the art, the definitive role for such probes and diagnostics is not specific. Therefore, in order to be patentable a substantial, specific and credible use must be disclosed.

6. Wadlow C, Regulatory Data Protection under TRIPS Article 39(3) and Article 10 bis of the Paris Convention: Is there a Doctor in the House? [Online] Intellectual Property Quarterly, 2008. Available on https://works.bepress.com/christopher_wadlow/1/

The proposition that medicine cannot simultaneously be a profession, and an industry, is consistent with the treatment of the patentability of methods of diagnosis, surgery and therapy, which is the one area in which the explicit limitation of the Paris Convention to "industry and commerce" as (implicitly) opposed to the "professions" has historically been important. […] To return to the concept of "industry" in the Paris Convention, it is suggested that for the purposes of the Paris Convention the professional status of the person typically responsible for performing the procedure in question is indeed important. The exercise of one of the historic liberal professions is neither "industry", nor "commerce". That the methods and procedures of its practitioners in their capacity as such are not "industrially applicable" is not a fiction, but a fact, and as such they fall wholly outside the scope of the Paris Convention. It may be acknowledged that the trend of interpretation under the European Patent Convention is against this, but the European Patent Convention is a separate treaty, whose members and organs have no institutional competence, either individually or collectively, to issue binding reinterpretations of the Paris Convention.

7. Bostyn S. No Contact with the Human Body Please! Patentability of Diagnostic Method Inventions after G01/04. European Intellectual Property Review, 2007.

Are "diagnostic methods practised on the human or animal body" within the meaning of Art.52(4) EPC (diagnostic methods) only those methods containing all the procedural steps to be carried out when making a medical diagnosis, i.e. the examination phase involving the collection of relevant data, the comparison of the examination data thus obtained with the standard values, the finding of any significant deviation (a symptom) during that comparison and, finally, the attribution of the deviation to a particular clinical picture (the deductive medical decision phase), or is a claimed method a "diagnostic method" even if it only contains one procedural step that can be used for diagnostic purposes or relates to the diagnosis? […] The EBA itself was not capable of maintaining consistency in the dogmatic framework, when it held that diagnosis *stricto sensu,* as a mental activity, and consequently not technical, is not to be taken into consideration to determine whether all technical steps are performed on the human body. In the decision itself, the EBA suggests that the *stricto sensu* step might be of technical character, if practised by a machine. For patent practitioners drafting patent applications, careful drafting of patent claims will become even more important. The use of the wording "diagnostic method" is to be avoided if the method claimed is not a diagnostic method but relates to intermediate results. Use instead terminology such as "method of imaging", "method for observing", "method for determining", etc. Prior to start drafting claims, identify accurately the invention to be protected, and bring into mind steps I to IV which are typical for diagnostic methods. Also remember that it will not help to leave out an essential step of the invention, with a view to avoid falling within the ambit of Art.52(4) EPC. If the method claimed contains steps I to IV, and thus falls within the ambit of Art.52(4) EPC, clearly identify the technical steps which are performed on the human body. If not all technical steps of the method are performed on the human body, the method remains patentable subject-matter.

8. Nellesen G, Francis T, Flanagan E. Drafting Claims with an Eye Towards Enforcing Patented Methods [Online] Journal of Intellectual Property Law & Practice, 2017; Not yet published. Available on https://doi.org/10.1093/jiplp/jpx056

Method claims with nature-based products are more likely to be patent eligible if they recite 'markedly different' characteristics from products in their natural form. Examiners look for differences such as manipulation with atypical instruments, transformations of form or unconventional steps that add 'significantly more' to a process and distinguish it from routine data gathering. […] The applicant combined the active steps of obtaining, detecting, determining and administering during prosecution to overcome a rejection based on lack of subject matter eligibility. […] Conventional methods, such as physical biopsies and fluoroscopy-based immunoassays, carry little patentable weight when method claims feature laws of nature and/or natural phenomena. Adding practical steps and coupling treatment steps with sampling and diagnosing steps can be effective for overcoming subject matter eligibility rejections, as shown above. These additions, however, can leave patent owners with divided-actor method claims where more than one actor is involved in performing the patented steps. […] To avoid divided-actor method claims, drafters can replace verbs with adjectives to minimize steps. For example, the following claim combines steps under the work of one actor: '*administering* chemotherapeutic X to a patient *determined* to have an allelic polymorphism …'. In contrast, a less preferable construction divides the same concept between two potentially different actors: '*determining* that a patient has an allelic polymorphism … and then *administering* chemotherapeutic X'.

9. Xu R. From Prometheus to Myriad to Classen, What a Messy Subject Matter: A Review on Recent Life Science Method Patent Cases [Online] Northwestern Journal of Technology and Intellectual Property, 2013; 11(2). Available on http://scholarlycommons.law.northwestern.edu/njtip/vol11/iss2/8

These recent decisions suggest that the courts are leaning toward a more liberal interpretation of the "transformative steps" and more lenient view of patent-eligible subject matter. It is still not clear what specific recited steps are the minimum requirements for patent-eligibility. Therefore, patent applicants would be well-advised to expound on all practical applications and physical steps in the method patent application that might be used to explain that the invention is a practical application but not an abstract idea. Below are several practice tips that might better facilitate patent applicants in securing their life science method patents: 1) Transformative Step 2) Machines 3) End Result Step 4) Warning Language 5) Purpose Language 6) Single Infringer 7) Reissue Application

10. Sterckx S, Cockbain J, Pennings G. Patenting Medical Diagnosis Methods in Europe: Stanford University and Time-Lapse Microscopy [Online] Reproductive BioMedicine Online, 2007; 34(2). Available on http://www.rbmojournal.com/article/S1472-6483(16)30607-1/abstract

Since the end of 2005, however, the position of EPO has been that diagnostic methods are patentable if the condition being diagnosed is incurable or is not a 'disease'. This

interpretation of the law came about because questions were referred to the EPO's Enlarged Board of Appeal in proceedings which did not involve a public hearing and in which interested parties could only have a say by filing *amicus curiae* briefs, a procedure that we suspect is unfamiliar to most in the medical profession. In the event, most of the nine *amicus* briefs filed were filed by parties with an interest in the scope of patent-eligibility being as broad as possible and the curability and disease criteria seem to have been adopted with little discussion.

The purpose of Article 53(c) EPC is to allow physicians to carry out their professional duties without having to fear being sued for patent infringement. In opposing the Stanford University patent, and in appealing the Opposition Division decision, ESHRE et al. are seeking to ensure that this Article applies to all forms of medical diagnosis and not just to those concerning a curable disease.

11. PatentWire. In or Out: Method of Treatment [Online] Available on https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2442801

Many a times the construction of claims decides the fate of in and out for patent protection. Claim(s) are thus rightly considered as the heart of a patent. Therefore, every word counts and decides the patentability of disclosed invention. This article gives examples of the so called Swiss clause in which a method claim is linguistically put as a product or as a clause not directed at the body.

PART 2(C) – Research on Companion Diagnostics

1. Beall R, Nickerson J, Kaplan W, Attaran A. Is Patent "Evergreening" Restricting Access to Medicine/Device Combination Products? [Online] PLoS ONE, 2016; 11(2). Available on http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0148939

Unexpired device patents exist for 90 percent of the 49 medicine/device product combinations studied, and were the only sort of unexpired patent for 14 products. Overall, 55 percent of the 235 patents found by our study were device patents. Comparing the last-to-expire device patent to that of the last-to-expire active ingredient patent, the median additional years of patent protection afforded by device patents was 4.7 years (range: 1.3–15.2 years). […] Incremental, patentable innovation in devices to extend the overall patent protection of medicine/device product combinations is very common. Whether this constitutes "evergreening" depends on whether these incremental innovations and the years of extra patent protection they confer are proportionately matched by therapeutic improvements in the standard of care, which is highly debatable.

2. Satanove D. The Challenging Economics of the Companion Diagnostics Industry: a Compelling Case for Invigorated Patent Protection [Online] N.Y.U. Journal of Intellectual Property & Entertainment Law, 2016; 6(1). Available on http://jipel.law.nyu.edu/vol-6-no-1-5-satanove/

Another concern is that greater patent protection in genetics-related research will interfere with research by academics and impede upstream experimental research. Again, this may well be a valid concern for standard genetic research, but in the context of CDx development, it is not. The CDx industry is made up of many private firms because of the substantial costs associated with development and commercialization. Empirical studies have also found that basic researchers follow a practice of ignoring patent infringement, while patent owners ignore enforcement against basic researchers so long as no one is engaged in commercial endeavors associated with the patent. […] Fear that increased patent protection will promote monopoly pricing over CDx tests is another valid concern, especially where payer reimbursement is not increased to match the savings of the CDx, and costs are shifted onto the consumer. Given that the costs of CDx development pale in comparison to therapeutics, however, the concern is arguably less warranted. And while no one wants to have to pay more for diagnostic testing, the CDx tests, as explained in Part I, can save consumers far greater costs in the long-run by preventing them from using up their insurance policies on treatments that prove to be ineffective.

3. Agarwal A, Ressler D, Snyder G. The Current and Future State of Companion Diagnostics [Available] Pharmacogenomics and Personalized Medicine, 2015; 31(8). Available on https://www.ncbi.nlm.nih.gov/pubmed/25897259

Once the decision has been made to move forward with a companion diagnostic, drug developers face the quandary of who should pay to bring the companion diagnostic to market. While almost everyone can agree with the personalized medicine mantra of the right medicine at the right dose to the right patient at the right time, it is in the implementation details where interests start to diverge. While pharmaceutical companies are most interested in companion diagnostics that are theranostics and monitoring types of tests, payers appear to be more interested in [...] diagnostic tests that provide information on multiple potential treatment options in a therapeutic area. […] Given the high costs of many of the drugs with companion diagnostics, which can easily exceed $100,000 per course of therapy, get- ting the optimal drug to a patient is more important than ever. With health care reform on a global basis pushing clinical provider payments based on patient outcomes rather than the number/type of clinical interventions, there is a significant upside to selecting the optimal drug based on diagnostic testing that compares similar therapeutics against one another. This is an area where the interests of payers and drug developers diverge. No drug developer wants a companion diagnostic that could potentially point to the prescription of a competitor's product. Companion diagnostic companies that often seek alliances with drug developers to defray the costs of developing a companion diagnostic will face the unenviable position of being caught in the middle of drug developers and payers. […] One of the key indicators of the future viability of the entire companion diagnostic market is the robustness of the nancing environment for diagnostic and research tools companies.

4. Zhang C, Zhang Y. Maximizing the Commercial Value of Personalized Therapeutics and Companion Diagnostics [Online] Nature Biotechnology, 2013; 31(9). Available on http://www.nature.com/nbt/journal/v31/n9/abs/nbt.2679.html

Accordingly, to protect diagnostic- and treatment-related inventions, it is better to file patent applications styling claims as method-of-treatment claims incorporating the diagnostic procedure into the steps for administering the drugs to the patients. For example, a claim might be drafted as "a method of treating disease X comprising (i) determining that a patient has X profiling (that is, mutation, expression level or other parameters or combinations thereof); and (ii) administering, on the basis of the deter- mination, a therapeutically effective amount of drug Y. […] Ideally, the evidence is based on human clinical studies. As applications for such method patents are typically filed at a later stage of drug-diagnostic co-development than are those for com- pound patents, the method patents typically expire a few years later as well. […]By interweaving the language of the patent claim with that of the drug labeling, the pharmaceutical and diagnostic partners could potentially prevent generic carve-out for a drug launched with companion diag- nostic test(s).

PART 2(D) – Research on Access to Gene-Based Molecular Diagnostics

1. Carbone J, Richard Gold E, Sampat B, Chandrasekharan S, Knowles L, Angrist M, Cook-Deegan R. DNA Patents and Diagnostics: Not a Pretty Picture [Online] Nature Biotechnology, 2010; 28(8). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3026778/

Patent incentives may induce investment in genetic diagnostics, but in none of the case studies did this lead to new availability of a test that was not already available, at least in part. This is in stark contrast with the role of patents in therapeutics and scientific instrument development, where the benefits attributable to private R&D and new products are much clearer. The case studies thus reinforce the wisdom of the nonexclusive norm for licensing genetic diagnostics, unless an unusual situation arises in which exclusivity is needed to get a product to market for the first time. […] Instead of recognizing this reality, some universities continue to seek broad patents regardless of subject matter and then license exclusively, enabling business models that impede competition in genetic testing. While the real risk of being successfully sued for patent infringement in DNA diagnostics may be low, a 2003 survey and recent case studies indicate that laboratory directors change their testing practices and clinicians avoid research areas in reaction to cease and desist letters. […] Changes to remedy problems with the system include the following: (1) a clear definition of research that should be exempt from patent infringement liability, (2) university leadership in promoting the alignment of technology transfer licensing practices with the broader university goal of dissemination coupled with (3) incentives to promote industry compliance and leadership on behalf of AUTM and BIO in recognizing problems and proposing constructive solutions. We also need (4) adequate funding to technology transfer offices to learn about and implement changing practices and (5) greater transparency in reporting patent holdings and licensing agreement terms.

2. Robertson A. The Role of DNA Patents in Genetic Test Innovation and Access [Online] Northwestern Journal of Technology and Intellectual Property, 2011; 9(7). Available on http://scholarlycommons.law.northwestern.edu/njtip/vol9/iss7/2

DNA patents in particular raise several unique issues. DNA has an inherent duality, both as tangible material and intangible information, posing both practical and legal problems for gene patenting and patent enforcement. Further, the finite number of genes within the human genome—approximately 23,000—makes it difficult (if not impossible) to "invent around" a genetic patent in order to create an equivalent, but non- infringing invention. In addition, inventions such as genetic diagnostics could involve multiple patents or licensing agreements, giving rise to concerns of a "patent thicket" or "anti-commons effect," requiring multiple licensing agreements that potentially increase the costs of genetic tests. […] Gene patents directly prevent doctors from testing for various diseases, leaving patients no longer in control of their own bodies. […] Lori Andrews, Professor at Chicago-Kent College of Law, describes this loss of control as if "the first surgeon who took a kidney out of your body then patented the kidney." […] [T]he costs involved in the development of genetic testing, in terms of both R&D and obtaining marketing approval, are much lower than that of drug development. Likewise, the market for genetic tests is growing rapidly, with significant support from the federal government. While downstream patents may help competition in the genetic testing market, upstream patents on DNA sequences can actually hinder innovation and can limit patient access to quality testing due to exclusive licensing practices. These considerations suggest that not only are DNA sequence patents not required for innovation in the development of gene-based molecular diagnostics, but also they actually hinder the advancement and clinical adoption of personalized medicine.

3. Huang K & Murray F. Does Patent Strategy Shape the Long-run Supply of Public Knowledge? Evidence from Human Genetics [Online] Academy of Management Journal, 2009; 52(6). Available on http://amj.aom.org/content/52/6/1193.short

This paper provides the first large-scale systematic evidence of the impact of patenting on the long-run supply of public (published) knowledge in human genetics. Prior researchers who consider these questions typically take a narrow perspective. […] The notion that the negative impact of gene patents is due to patent enforcement is supported by our key result – the impact of patents on long-run public knowledge is increasing in the scope of patents. This evidence shows that it is strong enforcement of broader patents or the probability of strong patent enforcement that drives the dampening effect of patent grant on public knowledge production. […] [W]hile ownership concentration is an important source of competitive advantage for owners of the patent portfolio, fragmentation is more problematic for follow-on contributors to the public knowledge stream presumably because of the complexities and increasing costs of navigating and negotiating with many patent assignees in a fragmented patent thicket. […] [W]e also find that the negative effect of patents on follow-on public knowledge production is greatest for genes closely linked to human disease i.e. that are more immediately useful and with greater commercial potential.

4. Kieran S, Loescher LJ, Lim KH. The Role of Financial Factors in Acceptance of Clinical BRCA Genetic Testing [Online] Genetic Testing, 2007; 11(1). Available on https://www.ncbi.nlm.nih.gov/pubmed/17394399

While price can be prohibitive, it is unclear the extent to which this effect is a result of DNA patents. Studies conducted in the past few years have shown that between 19% and 74% of at-risk individuals who could benefit from *BRCA* testing are not being tested. In these studies, the out-of-pocket costs to individual patients were reduced considerably for those who have health plans. However, of the women who were eligible for testing and whose costs were covered—either through their insurance companies or through programs offered by Myriad—only 70% of them have had the *BRCA* test. If price was the only consideration, presumably a higher percentage of women would have undergone testing. Regardless, price certainly had some effect, because only 22% of out-of-pocket payers chose to get the test performed.

5. Merz JF, Kriss AG, Leonard D, Cho MF. Diagnostic Testing Fails the Test: The Pitfalls of Patents are Illustrated by the Case of Haemochromatosis [Online] Nature, 2008; 415(6872). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2220021/

The hemochromatosis case study can demonstrate how a gene patent, when enforced, can serve to stifle or hinder human genetics research. Despite this example, however, several surveys and case studies indicate that many researchers would pursue the third option—choose to ignore, not inquire, or remain unaware of the intellectual property status of many of the genes being studied. This can be attributed to a number of factors: for example, the decision not to enforce gene patents by patent holders or the assumption that fundamental research is exempt under U.S. patent law. In a 2005 survey of U.S. genetics researchers conducted by the National Academy of Sciences and John Walsh, a large majority of scientists failed to even consider whether the genes they were researching were covered by a patent. Commonly, researchers assumed that any potentially infringing activity in which they were engaged was allowed under the "experimental use exemption," which grants infringers the right to use a patented invention for research and non-commercial purposes.

However, in the landmark case *Madey v. Duke University*, the Federal Circuit made clear that the experimental use exemption was not applicable to certain academic research. The case centered on a former Duke University professor who sued the university for patent infringement when, after he left, it continued to use equipment that he had patented. The lower court held that the university could not be liable for patent infringement, because its uses were "solely for research, academic, or experimental purposes." However, the federal court found that research that is part of the "legitimate business" of the university is not exempt from patent liability "regardless of commercial implications" or lack thereof. In short, any researcher studying a patented gene, whether or not aware that he or she is infringing, is in violation of the patent-holder's rights.

6. Fore Jr J, Wiechers I, Cook-Deegan R. The Effects of Business Practices, Licensing and Intellectual Property and Development and Dissemination of the Polymerase Chain Reaction: Case Study [Online] Journal of Biomedical Discovery and Collaboration, 2006; 1(7). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1523369/

Despite the heavy patent protection and rigid licensing schemes, PCR seems to have disseminated so widely because of the practices of the corporate entities which have controlled these patents, namely through the use of business partnerships and broad corporate licensing, adaptive licensing strategies, and a "rational forbearance" from suing researchers for patent infringement. While far from definitive, our analysis seems to suggest that, at least in the case of PCR, patenting of genomic research tools need not impede their dissemination, if the technology is made available through appropriate business practices.

7. U.S.A. Secretary's Advisory Committee on Genetics, Health, and Society. Gene Patents and Licensing Practices and Their Impact on Patient Access To Genetic Tests, April 2010. Available on https://repository.library.georgetown.edu/bitstream/handle/10822/515456/SACGHS_Final_Gene_Patents_Report_April2010.pdf?sequence=1&isAllowed=y

[T]he prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research. Scientists typically are driven instead by factors such as the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement. Although the prospect of patent protection does not significantly motivate individual scientists to conduct genetics research, this prospect does stimulate some private investment in basic genetic research. Nevertheless, the Federal Government is likely the major funder of basic genetic research. […] Where patents and licensing practices have created a sole provider of a genetic test, patient access to those tests has suffered in a number of ways. First, patients are unable to obtain insurance-covered access to a sole provider's test when the provider does not accept the patient's insurance. The report provides a lot of examples in the U.S.A. […] The most robust method for assuring quality in laboratory testing is through the comparison of results obtained on samples shared between different labs. Moreover, the presence of multiple laboratories offering competing genetic testing for the same condition can also lead to improvements in the overall quality of testing through innovation in developing novel and more thorough techniques of testing. Neither sample sharing nor competition is possible when an exclusive-rights holder prevents others from providing testing. As a result, significant concerns about the quality of a genetic test arise when it is provided by a patent-protected sole provider.

Resting on the underlying assumption that patents on human genes were acceptable, the report recommended that diagnostic (but not therapeutic) genetic tests, be exempted from patent infringement, along with a research use exemption. Exempting diagnostic patents from infringement while still recognizing that diagnostic gene patents could exist was greeted with controversy at the time, especially considering that the case studies that accompanied the report showed mixed evidence of harm to patients as a result of gene patents.

8. Hawkins N. The Impact of Human Gene Patents on Genetic Testing in the UK [Online] Genetic Medicine, 2012, 13(4). Available on https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3319650/

The study found that, despite the potential for gene patents to have significant negative consequences for genetic testing, in fact, human gene patents have little or no impact on practice for those developing genetic tests in the public sector in the UK. This is not because patents are managed optimally; rather, gene patents are essentially ignored. This paper reports the factors that motivate this behavior. At least insofar as there seems to be no apparent problem of lack of patient access, there is no significant public health problem.

PART 2(E) – Legal Research on Patenting Gene-Based Molecular Diagnostics

1. Nicol D. Navigating the Molecular Diagnostic Patent Landscape [Online] Expert Opinion on Therapeutic Patents, 2008; 18(5) Available on http://www.tandfonline.com/doi/abs/10.1517/13543776.18.5.461

[C]urrently it is not the norm for researchers and clinicians operating in the public sector to be exposed to aggressive patent enforcement actions, nor is such a norm likely to emerge in the near future (recognizing that isolated instances of such enforcement actions probably will continue to occur). But a different response might be expected where users are primarily profitdriven. In such circumstances, patent-holders are far less likely to be willing to forego patent licensing revenue. […] It should be recognized that, at the very least, mechanisms need to be put in place to streamline licensing negotiations and agreements for the benefit of patent-holders and users. […] Patent pooling is one strategy that should be considered. […] The use of clearing-house mechanisms should also be explored as a means of reducing the transaction costs in licensing gene and related patents in the molecular diagnostic sector.

2. Huys I, Van Overwalle G, Matthijs G. Gene and Genetic Diagnostic Method Patent Claims: A Comparison under Current European and US Patent Law [Online] European Journal of Human Genetics, 2011; 19(10) Available on https://www.ncbi.nlm.nih.gov/pubmed/21654725

With respect to genes, the ruling in the AMP versus USPTO decision, classifying an 'isolated' gene as a product of nature, clearly differs from the statutory text of the EPC, holding a gene patentable if isolated from its natural environment. With respect to methods, genetic diagnostic method claims did not survive the machine-or-transformation test in AMP versus USPTO and were regarded as laws of nature, hence unpatentable. In Europe, such methods are in principle not excluded from patentability.

Although it is very unlikely that the AMP versus USPTO decision will influence European patent law and practice, it is interesting to look at the possible outcome of the Supreme Court's machine-or- transformation test in Bilski versus Kappos when applied in Europe.

3. Fowler C. Ending Genetic Monopolies: How the TRIPS Agreement's Failure to Exclude Gene Patents Thwarts Innovation and Hurts Consumers Worldwide [Online] American University International Law Review, 2010; 25(5). Available on http://digitalcommons.wcl.american.edu/auilr/vol25/iss5/7/

Myriad's exclusive patent has been troublesome for patients. Women who have had or would like to have Myriad's diagnostic test may face significant roadblocks to their future health. Similarly, women seeking second opinions of Myriad's test results have been unable to obtain them because, until recently, Myriad held exclusive rights to both the genes and the screening tests. […] Independent and follow-on research is negatively affected by genetic patenting. […] Furthermore, researchers have little incentive to conduct important follow-on research or develop more effective and comprehensive diagnostic tests because exclusive patents limit their ability to actually conduct the new tests, let alone market them to turn a profit. […] The Myraiad Genetics example clearly illuminates the problems caused by these inadequacies. It is necessary for the WTO to develop clear and definitive regulations in order to avoid such disparities between Member States. The TRIPS Agreement must be amended to explicitly exclude genes and natural or unmodified genetic sequences as patentable subject matter under Article 27(1). If TRIPS is not amended, the WTO should draft guidelines to encourage the interpretation of the Agreement to exclude gene patents or mandate compulsory licensing of genes.

4. Driehaus J. Patent Landscape in Molecular Diagnostics in Storz U. Intellectual Property Issues. Springer Briefs in Technology Patents, 2012.

This article gives the most comprehensive overview of PCR patents

According to latest figures the molecular diagnostic market in the US alone is worth about $2.9 billion with a predicted annual growth of 15% until 2015 resulting in a volume of $6.2 billion. Specifically, potential is seen in genomic diagnostics due to the now readily available next generation sequencing techniques for sequencing of individual cancer genomes. Thus, this chapter gives an overview of the patent landscape in molecular diagnostics, and discusses issues of patentability with respect to the different technologies and compounds used therein. […] In general, a patent which claims a physical entity per se (e.g., in the chemical field: a compound X), confers absolute protection upon such physical entity; that is, wherever it exists and whatever its context, and therefore for all its uses, whether known or unknown (decision G 2/88, OJ EPO 1990, 93, point five of the reasons). This means that the indication of the use, purpose or function in a product claim is normally not seen as having a limiting effect on the scope of protection.

5. Ku D. The Patentability of the Crispr-Cas9 Genome Editing Tool [Online] Chicago-Kent Journal of Intellectual Property, 2017; 16(2). Available on http://scholarship.kentlaw.iit.edu/ckjip/vol16/iss2/8/

CRISPR patents will most likely be raised under 35 U.S.C. §102 ("§102") for lack of novelty or under 35 U.S.C. §103 ("§103") for obviousness. However, this paper will only evaluate the CRISPR technology under a hypothetical 35 U.S.C. §101 dispute challenging patent- eligible subject matter. […] Although the type II CRISPR system itself is a natural phenomenon, and

the individual components of the claimed CRISPR system can be found in nature, the claimed system as a whole is not naturally found in prokaryotes or eukaryotes. A court that finds the patent claim at issue to not be directed to a patent ineligible judicial exception will stop the eligibility inquiry here, and hold that the claim covering the CRISPR system is patent eligible subject matter under §101. […] future invalidity disputes over genome editing patents will most likely focus on §102 (novelty) and §103 (obviousness) issues rather than §101 issues.

6. Paradise J, Andrews L, Holbbrook T. Patents on Human Genes: An Analysis of Scope and Claims [Online] Science, 2005; 307(5715). Available on http://science.sciencemag.org/content/307/5715

To gain an understanding of whether the claims contained within issued patents covering human genetic material meet the existing statutory requirements under U.S. patent law, we undertook a multiyear project overseen by an advisory board that included two geneticists, two consumer advocates, and the head of an organization that runs a nonprofit tissue bank. […] We used the term "human gene patent" to include not only patents on complete human gene sequences, but patents that cover any human genetic material, such as mutations in a gene, or diagnostic methods that utilize human genetic material that would effectively preclude the use of that material by others. […]We found that 38% of claims were problematic (see table). Some claims had multiple problems, resulting in 677 cumulative problems within the 448 problematic claims. Of the 677 total problems identified, written description and enablement/utility problems were the most frequent. Many patents claimed far more than what the inventor actually discovered. Some applicants took advantage of the redundancy of the genetic code by, for example, claiming the sequence of a protein within a patent and then also asserting rights over all of the DNA sequences that encode for that protein without describing those DNA sequences. […] We also found patent claims that suffered from one or more problems but were saved from being classified as problematic by the drafting language. For example, one claim reads, "(t)he method of claim 1, 2, or 3, wherein the method further comprises amplifying the sequence-altered PAH DNA by use of the polymerase chain reaction (PCR)." Two of the three referenced claims were problematic. Claim 1 had written description, enablement/utility, and novelty/nonobviousness problems and claim 3 had enablement/utility problems. Project personnel concluded that this claim was not problematic, however, because it referenced claim 2, which contained no problems with any of the established categories. This language may create a chilling effect on researchers who want to use methods listed in claims 1 and 3 of the patent, but do not realize that the patent is open to challenge as not validly covering those methods.

7. Jamison M. Patent Harmonization in Biotechnology: Towards International Reconciliation of the Gene Patent Debate [Online] Chicago Journal of International Law, 2015; 15(2) Available on http://chicagounbound.uchicago.edu/cjil/vol15/iss2/9

While substantive harmonization of patent regimes may be difficult and years away, independent licensing agreements offer a realistic possibility for tempering the restrictive practices of patent holders and helping to facilitate greater uniformity in patent regimes. More extensive and coordinated use of voluntary licensing would provide a degree of

certainty for patent holders that their rights would be protected, while also ensuring that patients in both developed and developing nations have access to biotechnology at a lower cost. In most instances, patent holders have the incentive to enter into negotiations to reach voluntary agreements for licensing IP rights. Studies show that patentees are often provided sufficient compensation to recover R&D costs through the royalties received from voluntary licenses."' In comparison to compulsory licensing, independent voluntary licensing allows for terms to be negotiated that were agreed by both parties, rather than having terms imposed through the granting of a compulsory license. […] Due to the reasonable fear of restrictive licensing, the WTO and WIPO have a responsibility to intervene in this effort. By coordinating licensing agreements and monitoring for overly restrictive practices, the fragmented patent regimes may be better used to promote international public health.

8. Huys I, Berthels N, Matthijs G, van Overwalle G, Legal Uncertainty in the Area of Genetic Diagnostic Testing [Online] Nature Biotechnology, 2009, 27. Available on http://www.nature.com/nbt/journal/v27/n10/abs/nbt1009-903.html

At present, a few studies provide empirical information on the granting or litigation of gene patents. Some of these studies primarily analyze anecdotal cases, whereas others examine the impact of gene patents more widely. Some further studies suggest that the patent thicket may emerge more manifestly in the diagnostic sector, resulting in an undersupply of diagnostic testing services or the development of suboptimal diagnostic tools. What has been lacking is a large-scale empirical study that defines the heart of the problem: which types of claims occur in disease-specific patents and to what extent are these claims essential for carrying out genetic diagnostic tests? The present study aims to unravel on a qualitative as well as quantitative basis what is claimed in US and European patents on the inherited diseases most frequently tested for in Europe. This research provides an in-depth analysis of patents, investigating the exact number, status, nature and scope of granted disease-specific patents that are in force. […] In conclusion, the present analysis and accompanying observations do not point to the existence of a wide patent thicket in genetic diagnostic testing. Rather, they highlight a problem of lack of transparency and clarity, leading to legal uncertainty. Neither case law nor patent legislation resolves the legal uncertainty related to patents on genetic inventions.

PART 3 – The Law and Landmark Cases on Patents and Diagnostics

Article 27(3)(a) of TRIPS allows for Member States to exclude 'diagnostic, therapeutic and surgical methods for the treatment of human or animals' from patentability. By virtue of this, almost every member country, except notably the U.S.A., Australia and New Zealand, has excluded the methods for treatment from patentability scope.

PART 3(A) – The E.U.

Statutes For an invention to be excluded by Article 53(c) EPC, it must consist of a method of surgery, therapy, or diagnosis. In order to make this determination, tribunals used to focus on the skill and knowledge needed for a person to use the method in question i.e., the supervision of a doctor.

Diagnostics Methods (G01/04) Case Since the *Diagnostic Methods* case (G01/04 (2006) OJEPO 334 (EBA)) this approach is no longer relevant. The Board categorically held that the question of whether or not an invention falls within the exclusion is not dependent on who carries out the method in question. The the Enlarged Board held that methods of diagnosis typically consist of four subsidiary steps. These are: (*1*) Examination: involving the collection of data (recording the case history); (*2*) Comparison: comparing this data with normal values; (*3*) Identification: identifying any significant deviation from the norm (i.e. symptom); and (*4*) Diagnosis: the 'deductive medical or veterinary decision phase' where the diagnosis for curative purposes is ma de (which represents a purely intellectual or non-technical exercise). The Board took a very narrow interpretation of Article 53(c) and decided that that to fall within the exclusion, all four steps needed to be present in an invention.

The current interpretation of Article 53 EPC means that many diagnostic methods will no longer be caught by the exclusion, despite the express language of the Article and that even common procedure like percussion could be patentable as they as they do not constitute a 'complete' diagnosis. Critics argue that: "As the discussion of European case law demonstrates, the legal definition of diagnostic methods does not reflect the true nature of a medical diagnosis. Modern diagnoses are rarely final and few occur without the aid of data and quantitative results from laboratory testing"

Practice This means that IVD methods carried are now fully patentable in Europe. So are reactants and materials used for implementing diagnostic methods such as probes and primers, labelling or contrast agents, biomarkers, etc. Besides that because of the narrow new view of diagnostics wording of patent claims is more and more used to avoid exclusion.

DNA In the E.U. there is no absolute bar on patenting genes which have been isolated from the human body, even if identical in sequence to natural elements, obtaining patents that claim only isolated gene sequences is not plain sailing. Just like any other invention, gene patents have to satisfy the normal patent requirements of novelty, inventive step and industrial applicability.

PART 3(B) – The U.S.A.

Statutes 35 U.S.C. §101 sets forth what qualifies as patentable subject matter in the U.S.: "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." Federal courts have held that 35 U.S.C. §101 limits patent protection to four categories of subject matter: "a machine, manufacture, composition of matter or a process." A claimed invention may involve a combination of these four categories. USPTO Guidelines state that patent protection is denied for claimed inventions involving "nothing more than an abstract idea, law of nature,

or natural phenomenon." However, a claimed invention is eligible for patent protection if it involves a "practical application of a judicial exception to statutory subject matter." A claimed invention would qualify as such a practical application if it "physically transforms an article or physical object to a different state or thing, or if [it] otherwise produces a useful, concrete, and tangible result." Within the "process" category of patentable subject matter, medical process patents have been particularly controversial. There are three types of process patents typically related to the medical field: (1) medical procedures that do not require the use of any patented medical products, (2) methods for using a patented drug or device, and (3) techniques for isolating chemical compounds or building devices

Re Bilski In *re Bilski* (2008) Federal Circuit clarified the standard for patent-eligible subject matter and applied the restrictive standard for process claims: the machine-or-transformation test. Therefore "mental processes, and abstract intellectual concepts are not patentable, as they are basic tools of scientific and technological work.", which would mean that pharmaceutical and medical diagnostic claims "that merely inform patients of effects of treatments" are not eligible for patent protection, because they are "attempts to claim a monopoly on information." Furthermore, the court held that the particular machine or transformation involved in a process claim must constitute the crux of the claim, not just some "insignificant postsolution activity."

Prometheus In *Prometheus Labs, Inc. v. Mayo Collaborative Services* (2009) reversing direction from its holding in In re Bilski, the court upheld two claims: (1) a method of administering a drug that results in the body's production of potentially-toxic metabolites, and (2) a method of determining the levels of these metabolites in the bloodstream by testing a sample of the patient's blood. According to the court, these claimed methods satisfy the *Bilski* test because they involve "transformative steps utilizing natural processes." According to the court, the transformation at issue "is the result of the physical administration of a drug to a subject to transform—i.e., treat—the subject, which is itself not a natural process."

Practice Recent decisions suggest that the courts are leaning toward a more liberal interpretation of the "transformative steps" and more lenient view of patent-eligible subject matter. It is still not clear what specific recited steps are the minimum requirements for patent-eligibility. Through great focus on the transformative step as an action and 'purpose language' one can influence patentability.

DNA in *Association for Molecular Pathology v. Myriad Genetics* (2013) it was decided that '[a] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring'.

PART 3(C) – Japan

Statutes In Japan, a claim relating to a diagnostic method of human is, in general, not allowed because the claim is regarded as not having industrial applicability. Japan Patent Office (JPO) Examination Guidelines state that as long as the method does not include a step wherein a medical doctor evaluates the conditions or physical conditions of human being,

the method does not correspond to a diagnostic method, which makes certain types of method claims still possible

Practice If a diagnostic method has the technical feature of using a substance for detecting a disease it could be a product-type patent.

DNA The Japanese Patent Office follows an approach similar to that of the EPO, whereby new naturally-occurring gene sequences are patent eligible. However, in order to obtain patent protection in Japan, a gene must be both useful and 'industrially applicable'. The claimed invention must also be novel and involve an 'inventive step'. A newly discovered and isolated gene sequence satisfies these requirements, provided advantageous effects of the claimed invention over prior art DNA sequences can be shown. The act of cutting a length of DNA from a known sequence is seen as a novelty.

PART 3(D) – Korea

Statutes Methods of medical treatment for humans cannot be patented in Korea. Although the Korean Patent Law does not explicitly prohibit patenting medical method claims, the courts are clear that these claims cannot be patented primarily because of the concern about the misuse of privately owned patent rights against public health. Diagnostic method similary claims cannot be patented when they require a human body to carry out the invention.

Practice Claims may be redrafted in the claim format "A method for providing information for diagnosis..." which is then patentable.

DNA Where Korea is very narrow in patenting methods of diagnostics, it is very open to patenting genes. In Korea that genes, cDNAs, vectors and other biological materials isolated from nature are patent eligible regardless of their sources. Human genes are, therefore, patentable. Although it is in a legally separate issue, proving utility of claimed genes is often discussed on the same level with the patent eligibility. To this issue, the Korean court states that specific, substantial and credible utility is required for genes to be patented.

PART 3(E) – China

Statutes In China, according to Article 25.1(3) of the Patent Law, methods for diagnosis or for treatment of diseases can not be granted patent rights. That is, the processes of identifying, determining, or eliminating the cause or focus of diseases which are practiced directly on living human or animal bodies are not patentable in Chinese Practice.

Based on 4.3.1.1 of Chapter 1, Part II of the Guideline for the Examination, where a method involving diagnosis of a disease complies with the following two requirements, it is considered as a diagnostic method and cannot be granted a patent right: (1) it is practiced on a living human or animal body; and (2) its immediate purpose is to obtain the diagnostic result of a disease or health condition. China thus is very restrictive in the patenting of methods.

Practice Also in China it has been observed that during re-examination, many applicants have chosen to amend claims to overcome a rejection for lack of eligibility under Article 25.1(3) deleting claims for diagnostic methods. Though in China often after revision patents fail the substantive novelty and inventiveness assessment.

DNA In China a gene or a DNA fragment per se and the process to obtain it can be patented if the gene or DNA fragment is unknown in the prior art and can be accurately characterised and exploited industrially.

PART 3(F) – India

Statutes India adopted the exemption of Article 27(3) (a) of TRIPS and under section 3(i) of the Patent Act 1970 excluded inventions related to any process for the medicinal, surgical, curative, prophylactic, diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products from patentability.

Under section 3(i) of Indian Patents Act, no plant or animal or part thereof is patentable. As genes and DNA fragments are part of a plant or animal, they are considered non-patentable. However, modified genes or DNA fragments are allowed. The argument generally given in favour of such an approach is that as the genes are modified, they are not present per se in nature, but are the result of human technical intervention. As far as isolated genes or DNA fragments are concerned, section 3(c) provides that discovery of any living thing or non-living substance occurring in nature is not to be considered patentable. As an isolated gene or DNA fragment is considered to be something existing in nature, it is not patentable. This argument is extended to genes snipped from a piece of known DNA.

Practice Also in India there are a variety of linguistic ways to go around the method patent, in practice it is said that the Indian Patent Office is more strict with this than other offices.

DNA While the Patent Act 1970 prohibits naturally occurring substances, patents covering genetic material and nucleotide sequences have been granted. To an extent it seems clear that the mere identification of the location of a human gene, or part of a gene, as it exists in nature is not patentable under Sec. 3 (c). What is vague is whether isolated synthesized cDNA would fall within the scope of the exclusions under Sec. 3 (c). The history of gene patents granted by the Indian Patent Office shows a high level of inconsistency involved in the reasoning for granting various gene patents.

PART 3(G) – Brazil

Statutes In Brazil diagnostic methods, for use on the human or animal body are not considered to be inventions according to Article 10 (VIII) of the Brazilian Industrial Property Law, Law no. 9.279/96. Furthermore, the Brazilian Patent Office Guidelines for the Examination of Biotechnology and Pharmaceutical Patent Applications defines that methods of diagnosis are those that directly conclude about the state of health of a patient as a result of the technique used and, as such, may not be regarded as patentable subject matter in light of the dispositions of the Brazilian Industrial Property Law. Article 18, item III, states that living beings, in whole or in part, are not considered patentable. Article 10, item IX,

states that natural living beings, in whole or in part, and biological material encountered in nature or isolated including the genome or germplasm of any natural living being, are not considered as inventions.

Practice When a method however does not contain the step of 'comparing the results obtained in said tests with normal values, and attributing the deviations from the norm to a particular medical condition – the medical deductive phase' it is not regarded as diagnostic. Through the change of wording certain tests can be patented in which collected data only show an immediate result,

DNA Before 2015 the Brazilian patent law No.9.279 excludes genes from patentability. The law does allow for the patenting of chemical products, provided they fulfil patent criteria: if sequences of DNA are interpreted as chemical products they may be patentable; but if Brazil were to conclude that DNA is not merely a large polymer, it could permit chemical product patents while blocking patents on genes. Since 2015 Guidelines provided that naturally occurring substances that have been modified in any may be patentable. Similarly, the processes of obtaining or modifying natural substances may also be patentable provided they meet the general patentability requirements of novelty, inventive step and industrial applicability. However, for naturally occurring substances the above-mentioned language can also be used for methods of detecting the presence or quantifying a molecule, DNA or antibody.