Personalized Medicine and Companion Diagnostics

Joan Ellis, Ph.D.
Dickinson Wright PLLC
jellis@dickinsonwright.com
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September 2015

Sarah Roques
sroques@jakemp.com
www.jakemp.com
Introduction

• Focus on the recent US decisions concerning patent eligibility
• Consider how the EPO deals with the same/similar claims
Patentable Subject Matter

35 U.S.C. § 101

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.
Patentable Subject Matter

Judicial exceptions mandated by the Supreme Court:

– Laws of nature
– Natural phenomena
– Abstract ideas
Patentable Subject Matter at the EPO

• **Article 52(1) EPC**
  “European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve and inventive step and are susceptible of industrial application.”

• **Article 52(2) EPC**
  “The following in particular shall not be regarded as inventions within the meaning of paragraph 1:
  • discoveries, scientific theories and mathematical methods;
  • aesthetic creations;
  • schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers;
  • presentations of information.”

• **Article 52(3) EPC** .... “only to the extent to which a European patent application relates to such subject-matter or activities as such.”

• The patent claimed methods of optimizing the dosage levels of thiopurine drugs used to treat autoimmune diseases by measuring the levels of the drugs’ breakdown products in a patient’s blood stream

• Prior to the invention
  – Autoimmune diseases were treated with thiopurine drugs such as 6-mercaptopurine (6-MP) and azathiopurine (AZA)
  – It was known that 6-MP and AZA were prodrugs that were broken down into specific metabolites by the body.
  – It was known that levels of 6-TG and 6-MMP in blood correlated with drug harm or efficacy
Claim 1:
A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine said subject having said immune-mediated gastrointestinal disorder,

- Wherein the level of 6-thioguanine less than about 230 pmol per 8x10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

- Wherein the level of 6-thioguanine greater than about 400 pmol per 8x10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.
The district court found that the claimed correlation between thiopurine levels and toxicity was a natural phenomenon and not patent eligible.

The Federal Circuit applied the “machine or transformation test” and concluded that the claims satisfied § 101. According to the court, the administration of the drug transformed the body and determining metabolite levels involved a transformation or manipulation by a machine.
Mayo Collaborative Services v. Prometheus Laboratories

• Supreme Court found that the claims had 3 steps:
  – Administering
    • Instructions to doctors to give drugs to a patient
  – Determining
    • Tells the doctors to perform routine processes to measure metabolite levels
  – Wherein
    • Describes a law of nature; i.e., the relationship between the concentration of drugs in the blood and the likelihood the drug will be beneficial or harmful
Mayo Collaborative Services v. Prometheus Laboratories

The court rejected the application of the machine or transformation test stating that it does trump not the “law of nature” exclusion. Instead, the court performed a two-step analysis.

1. The Court first found that the correlation between metabolite levels in the blood and drug efficacy is a consequence of the way 6-TG is metabolized in the body. It was due to a natural process. Therefore, the claims described a natural law.

2. The question then became whether the other steps in the claim added significantly more to the law of nature.
Mayo Collaborative Services v. Prometheus Laboratories

The Court found that scientists routinely measured metabolite levels and concluded that performing conventional steps did not transform a law of nature into a patent-eligible invention.

“... the claims inform a relevant audience about certain laws of nature; and any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. For these reasons we believe that the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities [emphasis added].

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... the three steps as an ordered combination adds nothing to the laws of nature that is not already present when the steps are considered separately. See Diehr [450 U.S. 175 (1981)].”
The EPO and Methods of Diagnosis

• Article 53 EPC

• European patents shall not be granted in respect of

• “(c) methods of treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.”

• Claims in the form “product X for use in a method of diagnosing Y” are allowable when the diagnosis is practised in vivo

• Claims directed to “in vitro” diagnostic methods are also allowable
“Prometheus” Claims in Europe
- EP 1115403

• The European equivalent of the US patent considered in *Mayo Collaborative Services v. Prometheus Laboratories*

• Measuring 6-thioguanine in a sample from a patient

• Using the measurement to determine the efficacy of treatment of an immune-mediated gastrointestinal disorder or a non-IBD autoimmune disease in the patient using 6-mercaptopurine

• No opposition was filed
An in vitro method for determining efficacy of treatment of a subject having an immune-mediated gastrointestinal disorder or a non-inflammatory bowel disease (non-IBD) autoimmune disease by administration of a 6-mercaptopurine drug, comprising

determining in vitro a level of 6-thioguanine in a sample from said subject having said immune-mediated gastrointestinal disorder or said non-inflammatory bowel disease (non-IBD) autoimmune disease,

wherein said treatment is considered efficient if the level of 6-thioguanine is in the range of about 230 pmol per 8x10^8 red blood cells to about 400 pmol per 8x10^8 red blood cells.
The subject-matter of claims 8-14 appears to be novel and inventive, since methods for determining the efficacy and of toxicity of 6- methyl-mercaptopurine drug treatment was not known or suggested before.

(Examination Report of 28 June 2004)
Three types of claims before the Federal Circuit

• Composition
  – “Isolated” DNA encoding BRCA1

• Method of “analyzing and comparing”
  – Method for detecting a germline alteration
  – Method for screening a tumor sample

• Method of screening for potential cancer therapeutics
Association for Molecular Pathology v. Myriad Genetics, Inc.

Claim 1

An isolated DNA coding for a BRCA 1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
Association for Molecular Pathology v. Myriad Genetics, Inc.

- The Supreme Court held that a naturally-occurring DNA is a product of nature and, therefore, not patent eligible
  - Discovery of the location and nucleotide sequence of a gene does not create or alter genetic information
  - cDNA is not naturally-occurring and may be patent eligible
- The Court specifically noted it was not rendering a decision on
  - method claims
  - claims directed to DNA wherein the naturally-occurring nucleotide sequence was altered
*In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation,* 774 F.3d 755 (Fed. Cir. 2014)

*Myriad* eventually returned to the United States District Court for the District of Utah to consider the remaining claims.

The district court held that four composition of matter claims directed to primers and two method claims were not patent eligible. 35 U.S.C. § 101

The cDNA claims were patent eligible

*Myriad* appeals
Claim 16. A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA2 gene

Myriad argued that primers

1. Are single-stranded and not found in nature; and
2. Have a significantly different function

The Federal Circuit: primers are identical to the naturally-occurring gene sequences and not patent eligible
**BRAC1- and BRAC2-Based Hereditary Cancer Test Method Claims**

In the original 2012 decision, Federal Circuit held that the method of screening for BRCA1 alteration was an abstract idea.

**Claim 1**

A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from the wild-type indicates an alteration in the BRCA1 gene in said subject.
Dependent Claim 7 [claim 1]

. . . wherein a germline nucleic acid is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

Dependent Claim 8 [claim 1]

. . . wherein a germline nucleic acid sequence is compared by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.
BRAC1- and BRAC2-Based Hereditary Cancer Test Patent Litigation

2-step analysis (“Mayo test”)

1. Claim 1 is directed to mental steps of comparing and analyzing two genes sequences
   • Comparison of patient’s gene with the wild-type gene and identification of a difference is an abstract mental process
   • Indeterminate number of comparisons encompassed by the claims, not limited to specific alterations or detection of breast or ovarian cancer risk

2. The “wherein” clauses in claims 7 and 8 describe routine and conventional activity and do not “add” enough to make the claims patent eligible
Patentability of Naturally Occurring Products at the EPO

• Rule 29(2) EPC

• “An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.”

• G-II-3.1 of the EPO’s Guidelines for Examination

• “… A gene which is discovered to exist in nature may be patentable if a technical effect is revealed…”

• A new gene sequence is patentable BUT it must be novel and involve an inventive step
Claims 1, 2 and 7 of the Main Request

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is germline alteration 185delAG -> ter39 in the BRCA1 gene in a tissue sample of said subject, said alteration indicating a predisposition to said cancer.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is mutation 185delAG -> ter39 in the BRCA1 gene in a sample from said lesion.

7. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG -> ter39.
• The key issue was an inventive step!

• “In view of the above considerations, the subject-matter of claim 1 is considered to involve an inventive step. Since claim 2 also requires the determination of the mutation 185delAG -> ter39 in the claimed method, the reasons given above as to why the subject-matter of claim 1 involves an inventive step apply analogously also for the subject-matter of claim 2. Claims 3 to 5 are dependent on claims 1 and 2 and their subject matter thus likewise involves an inventive step. The nucleic acid probe of claim 7 is considered to involve an inventive step because it must contain the mutation 185delAG -> ter39. The same applies to the replicative cloning vector of claim 8 comprising an isolated nucleic acid according to claim 7, and to the host cells of claim 9 which are in vitro transformed with a vector of claim 8.” [Reasons for the Decision 70]
Opponent 6 argued that the sequences of the probes according to claim 7 occur in nature and are therefore a discovery rather than an invention.

This argument was not further pursued by any of the Opponents.

Reasons for the Decision 76

“Claim 7 relates to a nucleic acid probe comprising partial DNA sequences of the human BRCA1 gene, which is described in the patent in suit as having been obtained by technical processes. This probe is thus an isolated element of the human body as defined in Rule 29(2) EPC and thus patentable subject-matter. Accordingly, the subject-matter of claim 7 does not fall within the category of inventions which may not be patentable as being discoveries (Article 52(2)(a) EPC).”
Opponent 4 argued that **method for diagnosing** a predisposition for breast and ovarian cancer or for diagnosing a breast or ovarian lesion for neoplasia in/of a human subject should **not be regarded as a patentable invention**

This argument was not further pursued by any of the Opponents.

Reasons for the Decision 79

“According to present claims 1 to 6, all method steps of technical nature are performed on a tissue sample of a human subject. The Opponents' argument must therefore **fail**. The claims do not refer to subject-matter not patentable according to Article 53 (c) EPC (Article 52(4) EPC 1973).”
The inventors discovered that cell-free fetal DNA (cffDNA) circulates in the serum and plasma of pregnant woman. Previously this material was discarded as waste.

The invention was a new method of prenatal diagnosis that involved detecting paternally-inherited cffDNA in maternal plasma or serum

- Used to determine fetal characteristics
- Avoided risks involved when taking samples from fetus or placenta
Ariosa Diagnostics, Inc. v. Sequenom, Inc.

Claim 1

A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises

- amplifying a paternally inherited nucleic acid from the serum or plasma sample and
- detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample
Mayo 2-step analysis

1. Are the claims directed to a patent ineligible concept?
2. If so, are there additional elements that “transform the nature of the claim” into a patent eligible invention?
Federal Circuit application of the *Mayo* test

2-Step Analysis

1. The method begins with cffDNA in maternal blood which is a natural phenomenon. The method ends with the detection of paternally-inherited cffDNA which is also a natural phenomenon. Therefore, the claims are directed to a natural phenomenon.

2. The methods for preparing and detecting said cffDNA employ routine convention techniques such as serum isolation, the polymerase chain reaction, nucleotide sequencing, etc. and are not sufficient to make the invention patent eligible.
The court acknowledged that the inventors’ “discovery regarding cffDNA may have been a significant contribution to the medical field” and that the maternal plasma was previously discarded as waste, but even “valuable contributions can fall short of statutory patentable subject matter.”

Concurrence: “I join the court’s opinion invalidating the claims of the [] patent only because I am bound by the sweeping language of the test set out in Mayo . . . This case represents the consequence-perhaps unintended-of that broad language in excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain.”
The concurrence argues that the problem is the second part of the two-prong *Mayo* test

... While the conclusion might have been warranted in that case, given the fact that the ‘conventional activities’ in *Mayo* were the very steps that doctors were already doing-administering the drug at issue, measuring metabolite levels, and adjusting dosing based on the metabolite levels-the Supreme Court did not limit its ruling to those particular facts and circumstances.

The Supreme Court’s blanket dismissal of conventional post-solution steps leaves no room to distinguish Mayo from this case, even though here *no one* was amplifying and detecting paternally-inherited cffDNA using the plasma or serum of pregnant mothers.

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... But for the sweeping language in the Supreme Court’s Mayo opinion, I see no reason, in policy or statute, why this breakthrough invention should not be deemed patent eligible.
Ariosa Diagnostics, Inc. v. Sequenom, Inc

Problems with the Ariosa decision

– Are the courts and USPTO required to apply the *Mayo* test whenever a claim includes a law of nature, natural phenomenon or abstract idea?
  - The Supreme Court has warned against rigid, bright line tests
  - *Bilski* - the machine or transformation test was useful, but not the sole test
– Detecting and analyzing cffDNA from maternal serum is an application of a natural phenomenon
  - Ignored *Myriad* - new applications of natural phenomenon may be patent eligible
  - Using maternal serum to analyze cffDNA
– Claims must be considered as a whole
  - The invention is combination of all of the elements recited in the claim
  - *Diehr* - “new combination of steps in a process may be patentable.” The new combination of steps in *Ariosa* produces a novel result.
• Claims of Auxiliary Request 1 filed during the Opposition proceedings

• Upheld on appeal

"1. A detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample, wherein said nucleic acid is a paternally inherited sequence which is not possessed by said pregnant female.

14. A method according to claim 12 or 13, for the detection of a maternal or foetal condition in which the level of foetal DNA in the maternal serum or plasma is higher or lower than normal.

15. A method according to claim 14, for the detection of pre-eclampsia.

16. A method according to claim 14, for the detection of a foetal chromosomal aneuploidy.

17. A method according to claim 16, wherein said foetal chromosomal aneuploidy is Down's syndrome."
• Key issues (no discussion of not patentable subject matter!)

• Sufficiency of disclosure/enablement

19. Having considered the arguments and evidence on file, the board concludes that the objection of lack of sufficient disclosure raised by the appellant is not justified.

• Inventive step

32. Under these circumstances, the board judges that it would not have been obvious to a person skilled in the art, having regard to document (14), either alone or in combination with document (15), to try to detect a nucleic acid of foetal origin which is paternally inherited in maternal serum or plasma, as proposed in claim 1.
Patent-Eligibility Post-Mayo and Myriad

• What’s not patent eligible?
  – Genes and the information they encode
    • Naturally-occurring nucleotide sequence and fragments thereof
    • Naturally-occurring proteins and peptides
  – Microorganisms
Patent-Eligibility *Post-Mayo* and *Myriad*

- What may be patent eligible?
  - Altered nucleotide sequences
  - Altered protein and peptide sequences
    - Changes in amino acid sequence or post-translational modifications
  - Transformed microorganisms
  - Diagnostic assays using biomarkers
  - New methods of using “old” drugs or biomarkers
Statute at issue

- 35 USC § 271:
  
  (a) Except as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent therefor, infringes the patent
  
  (b) Whoever actively induces infringement of a patent shall be liable as an infringer
  
- Cannot have induced infringement when no one has directly infringed the patent
Akamai was the exclusive licensee of a patent claiming a “method of delivering electronic data using a ‘content delivery network’ or ‘CDN.’”

Content providers contracted with Akamai to deliver their web sites’ contents to individual internet users. The patent was said to provide “for the designation of certain components of a content provider’s Web site [to] be stored on Akamai’s servers and accessed from those servers by Internet users. The process of designating components to be stored on Akamai’s servers is known as ‘tagging.’”
Limelight operated a CDN and performed several steps in the patent except for tagging components of its customers’ websites that it wanted to store on its servers. Instead, Limelight provided its customers with instructions and technical assistance to do their own tagging.

- Akamai sued for infringement
- *En banc* panel of the Federal Circuit held that Limelight indirectly infringed under § 271(b) because it carried out some of the steps in the patented method and encouraged others to perform the remaining steps - “even though no one would be liable as a direct infringer in such circumstances, because those who performed the remaining steps did not act as agents of, or under the direct control of [Limelight].”
The Supreme Court held that there can be no induced infringement under § 271(b) when no one has directly infringed under § 271(a).

A patent that claims a number of steps cannot be infringed unless all the steps are carried out.
Thank you
Any Questions?
PHARMA LEADERS
IP CONFERENCE 2015
23 September 2015

A day of discussion and debate on intellectual property issues and opportunities in the pharmaceutical sector

JA KEMP