

Gene Patents and the Myriad Case

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Claim 1 of US 5747282

- An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having an amino acid sequence set forth in SEQ ID NO:2.
- SEQ ID No.2 contains 1863 amino acids. It depicts the amino acid sequence of the BRCA1 gene and hence the DNA definition is of the cDNA corresponding to the gene with introns omitted.

Claims 2 and 5 of US 5747282

- 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
- SEQ ID NO:1 contains 5914 base pairs. It depicts the coding region of the entire BRCA1 DNA coding region and so includes introns. (3 x 1863 [the number of amino acids in SEQ ID NO:2] = 5589)
- 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

Claim 1 of US 5709999

- A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises *analyzing* a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or *analyzing* a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that ...

Claim 20 of US 5747282

- A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

Background

- The discovery underlying the inventions claimed was identification of the genetic basis of BRCA1 and BRCA2-related cancers based on analysis of DNA samples from families with inherited breast and ovarian cancers and correlating the occurrence of cancer with the inheritance of certain marker DNA sequences.
- The location of the BRCA genes was known previously but the patentee was the first to establish their DNA sequence.

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- Women with mutations in BRCA genes have increased risk of breast or ovarian cancer and this fact lead to development of diagnostic tests to indicate the likelihood of whether any particular woman will develop cancer.

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- Myriad obtained patents containing claims including those noted above and established a business of genetic testing to determine those who were predisposed to breast or ovarian cancer.
 - Myriad “discouraged” others from offering such tests.

District Court for the Southern District of New York

- Judge Sweet accepted that Myriad's "discouragement" created a "case or controversy" sufficient to give several plaintiffs standing to bring a declaratory judgment action to challenge the validity of the various claims of the patents, including those noted above.

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- He further held that all of the isolated DNA claims were invalid as not being “markedly different” from the DNA as it existed in the genome because the isolated DNA did not possess a new or distinct quality or property compared to the naturally occurring article. In reaching this conclusion, the judge focused heavily on the “information carrying” role of DNA.

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- Judge Sweet further held that the method claims were invalid as not requiring the use of any particular machine or the transformation of anything into a different state or thing as was at the time the test for patent eligibility of a method claim. (Judge Sweet's decision was before the Supreme Court's decision in *Bilski v Kappos*.)

The Appeal

- Myriad appealed to the Court of Appeals for the Federal Circuit where the appeal was heard by a panel of Judges Lourie, Bryson and Moore.

Propriety of a Declaratory Judgment Action

- Under the U.S. Constitution, matters can only be brought before the federal courts if there is a “case or controversy” between the parties. Whether such a situation exists is decided by looking at the totality of the circumstances.

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- The Supreme Court has made it clear that important factors are 1) whether the party seeking relief from the courts has suffered an actual injury in fact or such injury is imminent; 2) there must be a causal connection between the conduct complained of and that injury; and 3) it must be likely that the injury can be redressed by an action that the court can take.

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- In this case, all judges agreed that in order for a causal connection to exist in cases where a declaratory judgment of patent invalidity was requested, the patent owner had to be shown to have undertaken some affirmative act related to enforcement and the party addressed by that act had to have undertaken some meaningful preparation to carry out a potentially infringing act.

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- The judges all agreed that only one of the plaintiff's met this test. Dr Orstrer was ready to carry out diagnostic tests and had received a demand for royalties from the patent owner. Because he was aware that others were being sued for patent infringement under these patents, he did not carry out the tests. This was found to be a sufficient injury linked to the patent owner's conduct to justify bringing the case before a federal court.

The substantive issues

- The judges were not all agreed on the substantive issues, however.

The claims fell into four groups:

- 1. Isolated DNA that was identical in sequence to genomic DNA;
- 2. Isolated DNA that differed from genomic DNA but coded for the same protein as genomic DNA (such as cDNA);
- 3. Methods in which the only positive step recited was one of “analyzing” or “comparing” DNA; and
- 4. Methods of screening in which the steps of growing cells and comparing growth rates were required.

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- All judges agreed that the second type of isolated DNA claim and the second type of method claim were eligible for patent protection and that the first type of method claim was not eligible for patent protection.
 - Judges Lourie and Moore agreed that the first type of isolated DNA claim was eligible for patent protection but gave different reasons. Judge Bryson did not agree that this type of claim was eligible for patent protection.

Where they Agreed

1) claims to cDNA

- As noted above, the second group of isolated DNA claims relates to complementary or cDNA.
- One of the functions of DNA in a cell is to provide directions to the cell on how to make particular proteins. The cell has mechanisms whereby groups of three nucleotides in the DNA are read as “codons” giving direction to the cell to assemble amino acids in a particular sequence to produce a polypeptide or protein.

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- In the state in which DNA exists in the genome, however, extra nucleotides (“introns”) are present. When making cDNA, these are omitted. cDNA can, however, be inserted into a host cell to produce the same polypeptide or protein as the genomic DNA.
 - On this basis, all of the judges agreed that cDNA was not a natural product which they agreed would not be eligible for patent protection, and so was potential patentable as long as it was new, not obvious and properly described.

Method claims requiring only “analyzing” or “comparing” steps

- Since Judge Sweet gave his decision, the Supreme Court has given its decision in *Bilski v. Kappos* that held that while the “machine or transformation” test used by Judge Sweet was useful in determining whether a method claim was eligible for patent protection, the basic test was whether what was claimed was an abstract idea and the machine or transformation test was only one way of doing this.

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- Based on the Supreme Court's holding in *Bilski v. Kappos*, all three judges in the present case concluded that these method claims recite "nothing more than the abstract mental steps necessary to compare two different nucleotide sequences". Such claims do not apply the abstract idea to any particular process.

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- The claims were therefore different from those in *Prometheus v. Mayo Clinic* (which is currently awaiting action by the Supreme Court) where acts of administering and measurement were at least implicitly present in the claims and the Federal Circuit had held the claims patent-eligible.

The screening claims

- This was not the problem with Claim 20 of US 5747282 which specifically included the step of growing cells and so was not abstract.

Claims to Isolated DNA having the same sequence as Genomic DNA

- All three judges start from a consideration of the Supreme Court's decisions in **Diamond v. Chakrabarty** and **Funk Bros Seed Co. v. Kalo Inoculant Co.**
- In **Chakrabarty**, the Court had found that a bacterium genetically modified to digest oil was patent eligible as “a non-naturally occurring manufacture or composition of matter – a product of human ingenuity having a distinctive name, character and use”.

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- In **Funk**, the Supreme Court held that a mixture of bacteria of different species for inoculating seeds of leguminous plant was not patentable because each species acts in the same way in the mixture as it had always acted and mixing them effected no change from what they did naturally.

Judge Lourie

- Judge Lourie drew the conclusion that the “Supreme Court has drawn a line between compositions that, even if combined or altered in a manner not found in nature, have similar characteristics as in nature, and compositions that human intervention has given ‘markedly different’ or ‘distinctive’ characteristics.
- On this basis the claims were patent eligible as covering “molecules that are markedly different – have a distinctive chemical identity and nature – from molecules that exist in nature.

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- The government had argued against the patent eligibility of such claims saying that if one had a “magic microscope” and looked at a portion of genomic DNA and the isolated equivalent of it they would look the same.
 - Judge Lourie rejected this saying:

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- The government's microscope could focus in on a claimed portion of any complex molecule, rendering that claimed portion patent ineligible, even though that portion never exists as a separate molecule ...anywhere ...in nature, and may have an entirely different utility. That would discourage innovation. One cannot visualize a portion of a complex molecule, including a DNA containing a particular gene, and will it into isolation as a unique entity. Visualization does not cleave and isolate the particular DNA; that is the act of human invention.

Isolation is not the same as Purification

- Another argument used by the plaintiffs was that isolation was tantamount to purification.
- Judge Lourie:
- Isolated DNA is not purified DNA. Purification makes pure what was the same material, but was previously impure. Although isolated DNA must be removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body.

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- In other words, in nature, isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity. In fact, some forms of isolated DNA require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

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- Bryson J questioned the significance of the breaking of a covalent bond as opposed to some other types of separation, Lourie J :
 - “a covalent bond is the defining boundary between one molecule and another.”
 - Thus contrary to the dissent, breaking such a bond is not the same as snapping a leaf from a tree.
 - “Snapping a leaf from a tree is a physical separation, not one creating a new chemical entity”

Judge Moore

- Judge Moore, although reaching the same result as Judge Lourie had somewhat different reasons:
- She first addressed the chemistry in more detail than Judge Lourie, pointing out the nature of the different “end groups” in genomic and isolated DNA.

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- She went on:
 - Although the different chemical structure does suggest that claimed DNA is not a product of nature, I do not think this difference alone necessarily makes isolated DNA so “markedly different,” from chromosomal DNA so as to be per se patentable subject matter.

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- In her view the key was
 - whether these differences impart a new utility which makes the molecules markedly different from nature.
 - In her view they did

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- She commenced with consideration of the 15 nucleotide sequences such as those of claim 5 of US 5747282, noting:
 - For example, these sequences can be used as primers in a diagnostic screening process to detect gene mutations ... Naturally occurring DNA cannot be used to accomplish these same goals. Unlike the isolated DNA, naturally occurring DNA simply does not have the requisite chemical and physical properties needed to perform these functions.

However

- Longer strands of isolated DNA, in particular isolated strands which include most or all of the entire gene, are a much closer case. ... Unlike the shorter strands of isolated DNA, the chemical and structural differences in the isolated gene do not clearly lead to an “enlargement of the range of . . . utility” as compared to nature.
- If she had a blank canvas she might decide that such sequences were not patentable.

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- However the PTO has accepted many such patents and issued guidelines accepting their patentability if their function is also disclosed. She commented:
 - I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved.

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- The settled expectations of the biotechnology industry—not to mention the thousands of issued patents—cannot be taken lightly and deserve deference. This outpouring of scientific creativity, spurred by the patent system, reflects a substantial investment of time and money by the biotechnology industry to obtain property rights related to DNA sequences. The type of fundamental alteration in the scope of patentable subject matter argued in this case “risk[s] destroying the legitimate expectations of inventors in their property.”

Judge Bryson

- Read Chakrabarty and Funk as meaning that only that which had “markedly different characteristics from any found in nature and having the potential for significant utility” was eligible for patent protection.

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- He analogized isolating human genes to extracting a mineral from nature or taking a plant cutting. Although these resulted in physical and chemical changes, they did not produce a patent eligible product. As noted by the Supreme Court in Chakrabarty
 - “A new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter” because they are products of nature.

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- During the transcription phase of protein synthesis, the BRCA genes are separated from chromosomal proteins. The transcription ...proceeds from a starting point called the promoter to a stopping point often called the terminator. The only difference between the naturally occurring BRCA genes during transcription and the claimed isolated DNA is that the claimed genes have been isolated according to nature's predefined boundaries, i.e., at points that preserve the ability of the gene to express the protein for which it is coded.

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- In the case of the BRCA genes, nature has defined the genes as independent entities by virtue of their capacity for protein synthesis and, ultimately, trait inheritance. Biochemists extract the target genes along lines defined by nature so as to preserve the structure and function that the gene possessed in its natural environment. In such a case, the extraction of a product in a manner that retains the character and function of the product as found in nature does not result in the creation of a human invention

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- The purification cases were helpful. They held that only when purification “results in a product with such distinct characteristics that it becomes for every practical purpose a new thing commercially and therapeutically” would the purified product be patent eligible.

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- The Supreme Court in *Chakrabarty* requires us to focus on two things: (1) the similarity in structure between what is claimed and what is found in nature and (2) the similarity in utility between what is claimed and what is found in nature. What is claimed in the BRCA genes is the genetic coding material, and that material is the same, structurally and functionally, in both the native gene and the isolated form of the gene.

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- The structural differences between the claimed “isolated” genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form.
 - Hence claims to isolated BRCA genes should not be patent eligible

As to short DNA sequences

- The claims were so broad that they inevitably covered products of nature.
- Of course, in light of its breadth, claim 5 of the '282 patent is likely to be invalid on other grounds, and thus a ruling as to patent-eligibility with respect to that claim may be superfluous.
- He then went on to discuss the problems that broad DNA patents cause for subsequent research.

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- On Judge Moore's reasonable expectation argument, Judge Bryson's view was that judges should interpret the law as decided by the courts and not give any deference to the PTO since the PTO did not have law-making authority in this area.

Thank you!

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