Recent Developments in US Patent Law, and Their Impact on Biotechnology, Personalized Medicine and Molecular Diagnostics

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Patent Eligibility Does Not Equal Patentability

- Requirements of patentability
  - Patent eligibility, i.e. patentable subject matter (35 USC 101)
  - Utility (35 USC 101)
  - Novelty (35 USC 102)
  - Nonobviousness (35 USC 103)
  - Enablement (35 USC 112)
  - Written Description (35 USC 112)
  - Definiteness (35 USC 112)

35 U.S.C. 101

- **Inventions Patentable**
  - 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 therefor, **subject to the conditions and requirements of this title**.

35 U.S.C. 101

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Pre-1980: A Relatively Narrow View of Patent Eligibility

- Classes of subject matter viewed as ineligible for patent protection
  - Business methods
  - Computer programs
  - Living organisms?
  - Biotechnology?

1980-2005: An Era of Expanding Patent Eligibility

- Product claims
  - *Diamond v. Chakrabarty* (1980)
  - *J.E.M. Ag Supply Inc. v. Pioneer Hi-Bred* (2005)
  - PTO Guidelines on patentability of animals (1987) and isolated genes (2001)
    - Parke-Davis & Co. v. H.K. Mulford & Co. (1911)

1980-2005: An Era of Expanding Patent Eligibility

- Process claims
  - *Diamond* v. Diehr (1981)
  - *State Street Bank and Trust v. Signature Financial Group* (1998)

Traditional Test for Patent Eligibility

- Product or process
- “made by man”
  - “isolation/purification” of natural substance was generally assumed to be sufficient
- Not a “fundamental principle”
  - Principle of nature
  - Natural phenomenon
  - Abstract idea
  - Mental process

LabCorp v. Metabolite 548 U.S. 124 (2006)

- Claim 13: A method of molecular diagnosis/personalized medicine
- A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
  - assaying a body fluid for an elevated level of total homocysteine; and
  - correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

Supreme Court's Question in *Metabolite v. LabCorp*

- Is the patent invalid because one cannot patent "laws of nature, natural phenomena, and abstract ideas"? *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

US Government's Amicus Position

- [No] one patent a process that comprises every "substantial practical application" of a law of nature, because such a patent "in practical effect would be a patent on the [law of nature] itself."
  - I.e, the test is one of **"preemption"**
- The record is not sufficiently developed to permit comprehensive consideration of the question whether claim 13 satisfies the subject matter requirements of Section 101.
  - For example, what does "assay" mean?

LabCorp v. Metabolite 548 U.S. 124 (2006)

- June 22, 2006
  - Writ of certiorari dismissed as improvidently granted.
  - Dissent by Justice BREYER, with whom Justice STEVENS and Justice SOUTER join.

Breyer's Dissent

- "The justification for the principle does not lie in any claim that 'laws of nature' are obvious, or that their discovery is easy, or that they are not useful. . . . Rather, the reason for the exclusion is that sometimes **too much patent protection** can impede rather than 'promote the Progress of Science and useful Arts,' the constitutional objective of patent and copyright protection"

Breyer's Dissent

- "The problem arises from the fact that patents **do not only encourage research by providing monetary incentives for invention**."
- "Sometimes their presence can **discourage research by impeding the free exchange of information**, for example by forcing researchers to **avoid the use of potentially patented ideas**, by leading them to conduct **costly and time-consuming searches** of existing or pending patents, by requiring **complex licensing arrangements** []."

Breyer's Dissent

- "One way in which patent law seeks to [avoid the dangers of overprotection] is through rules that bring certain types of invention and discovery within the scope of patentability while excluding others."
- **CMH: That is what 102, 103 and 112 are for!**

Breyer's Dissent

- "There can be little doubt that the correlation between homocysteine and vitamin deficiency set forth in claim 13 is a 'natural phenomenon.' . . . At most, respondents have simply described the natural law at issue in the **abstract patent language** of a 'process.' But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge."

Breyer's Dissent

- "One might, of course, reduce the 'process' to a series of steps, *e.g.,* Step 1: **gather data**; Step 2: read a number; Step 3: compare the number with the norm; Step 4: **act accordingly**. But one can reduce *any* process to a series of steps. The question is what those steps **embody**."

Breyer's Dissent

- "[H]ere, aside from the unpatented test, they **embody** only the correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable 'natural phenomenon,' and I can find nothing in claim 13 that adds anything more of significance."

Classen v. Biogen, No. 04-2607 (N.D. Md.)

- Claim 1 of the ‘283 patent :
  - A **method of determining** whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, **which comprises immunizing mammals** in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and **comparing** the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

Classen v. Biogen, No. 04-2607 (N.D. Md.)

- Claim 1 of the ‘739 patent :

A **method of immunizing a mammalian** subject which comprises:

(I) screening a plurality of immunization schedules, by

(a) identifying a first group of mammals and at least a second group of mammals, [and]

(b) comparing the effectiveness of said first and second screened immunization schedules [and]

(II) **immunizing said subject** according to a subject immunization schedule [].

Classen v. Biogen, No. 04-2607 (N.D. Md.)

- August 16, 2006
  - The district court held that the relationship between vaccination schedule and autoimmune disorders is without question a **natural phenomenon**, and that the claims at issue impermissibly **embodied** that natural phenomenon.
  - The court did not address the issue of whether a biological phenomenon that exists only as a result of human intervention (the introduction of vaccine in the human body) is accurately characterized as a natural phenomenon.

Ariad v. Lilly, 529 F.Supp.2d 106 (D. Mass. 2007)

- Claim
  - A method for inhibiting expression, in a eukaryotic cell, of a gene whose transcription is regulated by NF-κB, the method comprising reducing NF-κB activity in the cell such that expression of said gene is inhibited.

Ariad v. Lilly, 529 F.Supp.2d 106 (D.Mass 2007)

- July 6, 2007
  - The district court found the claims patent eligible based on the following findings:
    - The relevant natural phenomenon is the so-called NF-kB “Autoregulatory Loop”
    - The Autoregulatory Loop is “an incomplete model ... subject to a significant amount of ambiguity and inconsistency” and
    - “Lilly has failed to prove by clear and convincing evidence that the Autoregulatory Loop exists in living cells in a way that is encompassed by Ariad's claims.”

Prometheus v. Mayo, 2008 WL 878910 (S.D. Cal. 2008)

- Claim
  - 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 in said subject having said immune-mediated gastrointestinal disorder
    - wherein the levels 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 levels 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.

Unpatentable Mental Step?

- March 28, 2008
  - "[T]he claims include only two active steps: 'administering' the drug and 'determining' metabolite levels, which are ***merely data-gathering steps***; plus the additional ***mental step*** that the doctor be warned (by the metabolite levels) that an adjustment in dosage may be required. Therefore, the claims recite the correlations themselves."

Unpatentable Natural Phenomena?

- “[T]he inventors of the patents-in-suit did not ‘invent’ the claimed correlation.”
- “Rather, 6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity.”
- “[T]here can be little doubt that the claimed correlations are ‘***natural phenomena***.’”

Persuaded by *LabCorp* Dissent

- The facts of the present case are clearly analogous to those of *LabCorp*
- Although this Court notes that the dissent in *LabCorp* does not have precedential value, the Court finds Justice Breyer's reasoning persuasive

“Wholly Pre-empts”

- The case law is clear, if a claim that recites unpatentable subject mater “***wholly pre-empts***” all practical use of the unpatentable subject matter, the claim is invalid under Section 101

District Court Applies "Wholly pre-empts" Test

- [T]he "administering" and "determining" steps are ***merely necessary data-gathering steps*** for any use of the correlations, and the "warning" step is only a mental step whereby the metabolite levels warn the doctor that an adjustment in dosage may be required.
- Thus, the claims cover the correlations themselves.
- Because the claims cover the correlations themselves, it follows that the claims "wholly pre-empt" the correlations.

District Court Applies "Wholly pre-empts" Test

- Plaintiff outlines six possible uses not foreclosed by the claimed methods: (1) use in research; (2) for diseases other than autoimmune or gastrointestinal diseases; (3) use when results are given in units other than red blood cells; (4) building upon the correlations; (5) publishing articles in scientific journals concerning the correlations; and (6) testing and determining metabolite levels so long as no warning is given.

District Court Applies "Wholly pre-empts" Test

- Despite these supposed alternate uses, the claims "wholly pre-empt" use of the correlation such that the "practical effect is a patent on the [correlation] itself."
- The law does not require that every conceivable use be preempted to invalidate the claim. Rather, it is enough that the unpatentable subject matter recited in the claims has "no substantial practical application" outside the context of the claims.

In re Bilski, 545 F.3d 943 (Fed. Cir. 2008) (en banc) (Bilski I)

- Claim
  - A method for managing the consumption risk costs of a commodity sold by a commodity provider at a fixed price comprising the steps of:
    - (a) initiating a series of transactions between said commodity provider and consumers of said commodity wherein said consumers purchase said commodity at a fixed rate based upon historical averages, said fixed rate corresponding to a risk position of said consumer;
    - (b) identifying market participants for said commodity having a counter-risk position to said consumers; and
    - (c) initiating a series of transactions between said commodity provider and said market participants at a second fixed rate such that said series of market participant transactions balances the risk position of said series of consumer transactions.

The Fundamental Test

- The fundamental test is:
  - whether Applicants' claim recites a ***fundamental principle*** and, if so,
  - whether it would ***pre-empt substantially all uses*** of that fundamental principle

The Fundamental Test

- Unfortunately, this inquiry is hardly straightforward. How does one determine whether a given claim would pre-empt all uses of a fundamental principle?
- The Supreme Court, however, has enunciated a definitive test to determine whether a process claim is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself

The Machine-Transformation Test

- The Supreme Court test addresses what is ***sufficient*** for patentability
  - A claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing
- The Federal Circuit subverts it into a test for what is ***necessary*** for patentability
  - The machine-or-transformation test is a two-branched inquiry; an applicant may show that a process claim satisfies § 101 either by showing that his claim is tied to a particular machine, or by showing that his claim transforms an article

Insignificant Extra-Solution Activity

- The use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility
- The involvement of the machine or transformation in the claimed process must not merely be ***insignificant extra-solution activity***.

What Constitutes an Article?

- The transformation [of an article into a different state or thing] must be central to the purpose of the claimed process.
- [W]hat sorts of things constitute “articles” such that their transformation is sufficient to impart patent-eligibility under § 101[?]
- It is virtually self-evident that a process for a **chemical or physical transformation of *physical objects or substances*** is patent-eligible subject matter.

Data-Gathering Steps

- [A]t least in most cases, ***gathering data would not constitute a transformation of any article***, and adding a data-gathering step to an algorithm is insufficient to convert that algorithm into a patent-eligible process
- A requirement simply that data inputs be gathered-***without specifying how***-is a meaningless limit on a claim to an algorithm because every algorithm inherently requires the gathering of data inputs
- [T]he inherent step of gathering data can also fairly be characterized as insignificant

Questions Raised by *Bilski I*

- What constitutes a transformation?
  - Is therapeutic treatment transformative?
- Under what circumstances can a claim limitation be dismissed as mere “insignificant extra-solution activity”?
  - Many personalized medicine claims will include a data-gathering step

Bilski I Dissents

- Newman - Test excludes from patentability many of today's most important innovations, particularly in the growth industries of the U.S. economy, such as the computer and information service fields
- Mayer - Test easily circumvented by clever drafting of patent claims, will prove exceedingly difficult to apply in practice, and will only lead to further uncertainty regarding the scope of patentable subject matter.

Bilski I Dissents

- Rader
  - Metabolite claim (*Labcorp*) provides an elegant and simple way of testing for a vitamin deficiency
  - Denying patent protection for this sort of innovation will undermine and discourage future research for diagnostic tools
  - The machine-transformation test “inadvertently advises investors that they should divert their unprotectable investments away from discovery of scientific relationships within the body to diagnose breast cancer or Lou Gehrig's disease or Parkinson's or whatever."

Classen v. Biogen, 2008 WL 5273107 (Fed. Cir., unpublished)

- "In light of our decision in In re Bilski, 545 F.3d 943 (Fed. Cir. 2008) (en banc), we affirm the district court's grant of summary judgment that these claims are invalid under 35 U.S.C. § 101. Dr. Classen's claims are neither "tied to a particular machine or apparatus" nor do they 'transform[] a particular article into a different state or thing.' Bilski, 545 F.3d at 954. Therefore we affirm."

Prometheus v. Mayo, 581 F.3d 1336, (Fed. Cir. 2009)

- Claim
  - 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 in said subject having said immune-mediated gastrointestinal disorder
    - wherein the levels 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 levels 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.

Administering step is transformative

- The transformation is of the human body following administration of a drug and the various chemical and physical changes of the drug's metabolites that enable their concentrations to be determined
- The asserted claims are in effect claims to ***methods of treatment, which are always transformative*** when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition.
- The invention's ***purpose*** to treat the human body is ***made clear in the specification and the preambles*** of the asserted claims.

Determining step is transformative

- Determining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation, for those levels cannot be determined by ***mere inspection***.
- Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration.

Determining step is transformative

- [T]his transformation is central to the purpose of the claims, since the determining step is, like the administering step, a significant part of the claimed method of treatment.
- The determining step, by working a chemical and physical transformation on physical substances, likewise sufficiently confines the patent monopoly, as required by [Bilski I].

Mental steps are not patent-eligible

- We agree with the district court that the final "wherein" clauses are ***mental steps and thus not patent-eligible per se***.
- A subsequent mental step does not, by itself, negate the transformative nature of prior steps.
- Thus, when viewed in the proper context, the final step of providing a warning based on the results of the prior steps does not detract from the patentability of Prometheus's claimed methods as a whole.

Product Claims Found Patent Ineligible in *AMP v. PTO*, 702 F.Supp.2d 181 (SDNY)

- US patent number 5,747,282
  - 1. An **isolated DNA coding for a BRCA1 polypeptide**, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
    - Compare with claim found valid and infringed in *Amgen v. Chugai*
  - 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. **[cDNA]**
  - 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

Gene Patents and Biologic Drugs

- *Amgen v. Chugai* (1987)
  - "A purified and **isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin**."

The Court's Rationale for Invalidating Product Claims

- Case law pre-dating *Chakrabarty* and Federal Circuit
- Claimed molecules lack "**markedly different characteristics**" from naturally occurring genetic sequences
  - Nobel Prize for PCR?
- Genetic Exceptionalism: DNA is qualitatively different from other biomolecules capable of conveying information

Why Was Eligibility of Isolated DNA Not Resolved Earlier?

- Biotech litigants have not surprisingly refrained from challenging patent eligibility of gene patents
- Judge Dyk recently took pains to point out that Federal Circuit silence on the issue of patent eligibility does not imply assent. *Intervet v. Merial Ltd.*, (Fed. Cir 2010).

Examples of Invalidated Process Claims

- US patent number 5,710,001
  - 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises gene[sic] **comparing a first sequence** selected form the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

Examples of Invalidated Process Claims

- US patent number 5,753,441
  - 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 wild-type indicates an alteration in the BRCA1 gene in said subject.
- Court applied *In re Bilski* machine-or-transformation test

Court Dicta Contrary to *Prometheus*

- "Even if the challenged method claims were read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than data-gathering steps that are not central to the purpose of the claimed process."
  - This appears contrary to *Prometheus*, which explicitly found analytical processes used to determine drug metabolite levels sufficiently transformative

Importance of Method Claims

- Myriad's Amicus Brief filed in Prometheus
  - "Fundamental composition of matter claims, e.g., isolated nucleic acids and proteins, are unavailable because the Human Genome Project has made the entirety of the genome, along with all of its encoded proteins, prior art. Claims like those at issue in this case, therefore, are virtually all that remains to incentivize the research and development of new personalized medicine products."

Bilski v. Kappos, 130 S.Ct. 3218 (2010) (*Bilski II*)

- The Supreme Court clarified that involvement of machine or transformation is highly relevant, but not exclusive test for patent eligibility
- Returns focus to whether patent "claims" a fundamental principle, such as abstract idea, natural phenomenon or mental process

Bilski v. Kappos, 130 S.Ct. 3218 (2010) (*Bilski II*)

- Only applies to method claims, but these claims will be critical for biopharma, particularly with respect to personalized medicine
- Prometheus and Classen vacated and remanded to Federal Circuit

Critical Issues to Be Addressed Post-Bilski II

- What exactly is a “fundamental principle”?
  - Particularly in the context of personalized medicine, what is a biological “natural phenomenon”?
- What does it mean to impermissibly patent a biological “natural phenomenon”?
- What does it mean to impermissibly patent “mental processes”?

What constitutes claiming a fundamental principle?

- "**Wholly preempts**"
  - *Benson* (1972) suggests this is the test, but *Diehr* (1981) and *Bilski II* arguably refute
  - This was US government position in *LabCorp*
    - [No] one can patent a process that comprises every "substantial practical application" of a law of nature, because such a patent "in practical effect would be a patent on the [law of nature] itself."
  - District court applied "preemption of every substantial practical application" test in *Prometheus*

What constitutes claiming a fundamental principle?

- "**Embodies**"
  - Justice Breyer in *LabCorp*
  - Used by district court in *Classen*
  - Implied in *Bilski II*
    - Finding that dependent claims are patent ineligible implies wholy preemepted is not the test
    - Patent ineligibilty "cannot be circumvented by limiting claim to a particular technological environment or adding insignificant post-solution activity"

What constitutes claiming a fundamental principle?

- Treated as part of the **prior art**
  - *Parker v. Flook* (1978)
  - *In re Comiskey* (prior to revision)

What constitutes claiming a fundamental principle?

- Supreme Court has given lower courts a **wild card** to invalidate unworthy claims

Prometheus v. Mayo, 628 F.3d 1347 (Fed. Cir. 2010)

- On remand, Federal Circuit came to the same conclusion for essentially the same reasons
- "In light of the Supreme Court's decision in *Bilski*, patent eligibility in this case turns on whether Prometheus's asserted claims are drawn to a **natural phenomenon**, the patenting of which would **entirely preempt** its use as in *Benson* or *Flook*, or whether the claims are drawn only to a **particular application** of that phenomenon as in *Diehr*. We conclude they are drawn to the latter."

Prometheus v. Mayo (Fed. Cir. 2010)

- "[A]s applied to the present claims, the 'useful and important clue, an investigative tool,' [i.e., the machine-or-transformation test] leads to a clear and compelling conclusion, viz., that the present claims pass muster under § 101. They do not encompass laws of nature or preempt natural correlations.

Prometheus v. Mayo (Fed. Cir. 2010)

- "Prometheus's asserted method claims recite a patent-eligible application of **naturally occurring correlations** [?] and thus do not wholly preempt all uses of the recited correlations."
- "As discussed below, the claims recite **specific treatment steps**, not just the correlations themselves."
- And the steps involve a particular application of the natural correlations: the **treatment of a specific disease** by **administering specific drugs** and **measuring specific metabolites**.
- As such, [] the claims do not preempt all uses of the natural correlations; they utilize them in a **series of specific steps**

Prometheus v. Mayo (Fed. Cir. 2010)

- "While it is true that the administering and determining steps gather useful data, it is also clear that the presence of those two steps in the claimed processes is not "merely" for the purpose of gathering data.
- "Instead, the administering and determining steps are **part of a treatment protocol**, and they are transformative.
- "The administering step provides thiopurine drugs for the purpose of treating disease, and the determining step measures the drugs' metabolite levels for the purpose of assessing the drugs' dosage during the course of treatment."

In re Grams (Fed. Cir. 1989)

- A method of diagnosing an abnormal condition in an individual, the individual being characterized by a plurality of correlated parameters of a set of such parameters that is representative of the individual's condition, the parameters comprising data resulting from a plurality of clinical laboratory tests which measure the levels of chemical and biological constituents of the individual [sic] and each parameter having a reference range of values, *the method comprising*
  - [a] **performing said plurality of clinical laboratory tests on the individual to measure the values of the set of parameters**;
  - [b] producing [a first representative quantity];
  - [c] comparing the first quantity to a first predetermined value[];
  - [d] [successively testing a plurality of different combinations]; and
  - [e] identifying as a result of said testing a complementary subset of parameters corresponding to a combination of constituents responsible for the abnormal condition [].

In re Grams (Fed. Cir. 1989)

- "[The] mere recital of an algorithm does not automatically render a claim nonstatutory [], but the inclusion of a mathematical algorithm in a claim can render it nonstatutory if the claim **in essence covers only the algorithm**."
- "In all instances, this critical question must be answered: '**What did applicants invent?'"**
  - "Semantogenic considerations preclude a determination based solely on words appearing in the claims. In the final analysis under § 101, the claimed invention, as a whole, must be evaluated for what it is."

In re Grams (Fed. Cir. 1989)

- "Though that analysis can be difficult, it is facilitated somewhat if, as here, **the only physical step involves merely gathering data for the algorithm**."
- "Whether section 101 precludes patentability in every case where the physical step of obtaining data for the algorithm is the only other significant element in mathematical algorithm-containing claims is a question we need not answer. **Analysis in that area depends on the claims as a whole and the circumstances of each case**."

In re Grams (Fed. Cir. 1989)

- "The sole physical process step in Grams' claim 1 is step [a], i.e., performing clinical tests on individuals to obtain data. **The specification does not bulge with disclosure on those tests**.
- "To the contrary, it **focuses on the algorithm itself**, although it briefly refers to, without describing, the clinical tests that provide data."

Prometheus v. Mayo (Fed. Cir. 2010)

- The Grams process was unpatentable because "it was merely an algorithm combined with a data-gathering step," i.e., performing a clinical test.
- The claims did not require the performing of clinical tests on individuals that were transformative—and thus rendering the entire process patentable subject matter—because **the tests were just to "obtain data."**
- The patent and thus the court focused only on the algorithm rather than the clinical tests purported to be covered by the claims.

Prometheus v. Mayo (Fed. Cir. 2010)

- Here, unlike the clinical test recited in *Grams*, the administering and determining steps in Prometheus's claimed methods are not "merely" data-gathering steps or "insignificant extra-solution activity"; **they are part of treatment regimes for various diseases** using thiopurine drugs.
- As a result, the administering and determining steps are not insignificant extra-solution activity, and the claims are therefore not drawn merely to correlations between metabolite levels and toxicity or efficacy.

AMP v. PTO, 653 F.3d 1329 (Fed. Cir. 2011) – U.S. Amicus Brief

- The government attempted to draw a line between patent ineligible genomic DNA that has been merely "excised" from the chromosome and "engineered" cDNA
- There is real concern amongst influential people that gene patents will block personal whole genome sequencing
  - NIH Director Francis Collins fears $1000 genome will require $100,000 licensing fee

AMP v. PTO (Fed. Cir. 2011) - Isolated DNA Molecules

- Judge Lourie based his determination that isolated DNA molecules are patent eligible on his understanding that isolation of DNA from the chromosome involves the breaking of covalent bonds, and hence a **structural change of the DNA molecule**
- Rejected the Attorney General's analogy to a "magic microscope"

AMP v. PTO (Fed. Cir. 2011) - Isolated DNA Molecules

- Judge Lourie suggested that mere "purification" of a biomolecule might be insufficient for patent eligibility
  - This would conflict with long-standing understanding that purification is sufficient
  - Numerous patents to purified biomolecules have been issued and enforced
- Judge Moore stressed importance of investment-backed expectations

AMP v. PTO (Fed. Cir. 2011) – Process Claims

- Decision hinged on interpretation of the word "sequence" as used in the claims.
  - Myriad argued that "sequence" refers to DNA molecule
  - But the court adopted ACLU's definition, i.e., "sequence" refers to information
  - Applying *Prometheus*, the court found that a claim covering the mere comparison of sequence information lacks requisite machine or transformation
    - Under Myriad's interpretation, would claim have been found patent eligible?

Classen v. Biogen, 659 F.3d 1057 (Fed. Cir. 2011) – Patent Ineligible Process Claims

- Claim 1 of the ‘283 patent :
  - A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, **which comprises immunizing mammals** in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

Classen v. Biogen – Patent Eligible Process Claims

- Claim 1 of the ‘739 patent :

A **method of immunizing a mammalian** subject which comprises:

(I) screening a plurality of immunization schedules, by

(a) identifying a first group of mammals and at least a second group of mammals, [and]

(b) comparing the effectiveness of said first and second screened immunization schedules [and]

(II) **immunizing said subject** according to a subject immunization schedule [].

Mayo v. Prometheus, Decided by Supreme Court March 20, 2012

- Unanimous decision authored by Justice Breyer
- Reversed Federal Circuit, held all of Prometheus' claims patent ineligible

A Broad Interpretation of “Natural Phenomenon”

- “While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes.”

A Strict View of What Constitutes an "Application" of a Natural Phenomenon

- The "administering" step:
  - "simply refers to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs. That audience is a **pre-existing audience**; doctors used thiopurine drugs to treat patients suffering from autoimmune disorders long before anyone asserted these claims. In any event, the "prohibition against patenting abstract ideas '**cannot be circumvented by attempting to limit the use of the formula to a particular technological environment**.' [cite to Bilski]."

A Strict View of What Constitutes an "Application" of a Natural Phenomenon

- The "determining" step:
  - "tells doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field. Purely "conventional or obvious" "[pre]-solution activity" is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law. *Flook*, 437 U. S., at 590; see also *Bilski*, 561 U. S., at ___ (slip op., at 14)"

A Strict View of What Constitutes an "Application" of a Natural Phenomenon

- The claimed methods as whole:
  - "inform a relevant audience about certain laws of nature; 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. [The] steps are **not sufficient to transform unpatentable natural correlations into patentable applications** of those regularities."

Court Explains Different Outcome in *Diamond v. Diehr*

- "[*Diehr*] nowhere suggested that . . . the combination of those steps, were in context obvious, already in use, or purely conventional. And so the patentees did not seek to pre-empt the use of [the] equation, but sought only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process."

Court Explains Different Outcome in *Diamond v. Diehr*

- "These other steps apparently added to the formula something that in terms of patent law's objectives had significance—they transformed the process into an inventive application of the formula."

Court Uses Patent Eligibility to Address Obviousness

- "[Supreme Court precedent insists] that a process that focuses upon the use of a natural law alsocontain other elements or a combination of elements, sometimes referred to as an "inventive concept," sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself. *Flook*, *supra*, at 594;"

Court Uses Patent Eligibility to Address Obviousness

- "Purely "conventional or obvious" "[pre]-solution activity" is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law. *Flook*, 437 U. S., at 590; see also *Bilski*, 561 U. S., at ___ (slip op., at 14)"

Court Uses Patent Eligibility to Address Claim Scope

- "[Supreme Court precedent warns] us against upholding patents that claim processes that too broadly preempt the use of a natural law. Morse, supra, at 112– 120; Benson, supra, at 71–72."
- "[U]pholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries."

Latest Development

- On March 26 the Supreme Court granted certiorari in Association for *Molecular Pathology v. Myriad Genetics*, and sent the case back to the Federal Circuit to reconsider in light of *Mayo v. Prometheus*.

Personalized Medicine and Diagnostics

- No clear demarcation between personalized medicine and diagnostics
  - Genentech patents claim methods of detecting over-expression of HER2 gene
  - Metabolite patent claims method of detecting vitamin B deficiency
  - Myriad patents claim methods of detecting BRCA mutations
- Can patent eligibility doctrine distinguish between diagnostic patents and personalized medicine?

Divided Infringement Claims

- Recent decisions demonstrate challenges in enforcing method claims wherein the method steps are not all performed by the same entity
  - Muniauction v. Thompson, 532 F.3d 1318 (Fed. Cir. 2008)

Divided Infringement Claims

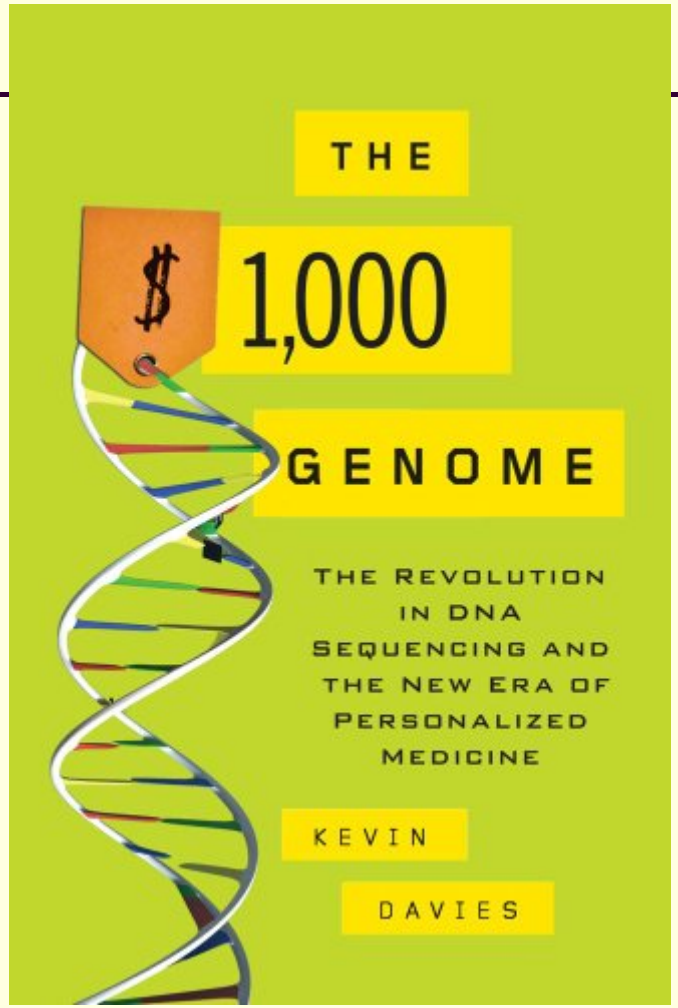
- Could result in Catch-22 for personalized medicine inventors
  - Inclusion of treatment step, or data acquisition step, could result in divided infringement
  - Omission of such steps could render claim patent ineligible for preempting a natural phenomenon
  - But see, *Eli Lilly and Co. v. Actavis Elizabeth LLC,* 676 F.Supp.2d 352 (D.N.J. 2009)("The actions of the doctors and patients will be treated together, and will be considered a directly infringing act.") (reversed-in-part on other grounds).

Do we want personalized medicine to be patentable?

- Drug companies might prefer freedom to operate
  - Extract value from sale of drug
- Patent on diagnostic component might play important role in extracting value from personalized medicine invention, particularly if drug is off patent
  - FDA might require generic drug to include diagnostic testing on label, resulting in induced infringement

Is patent eligibility the appropriate policy lever?

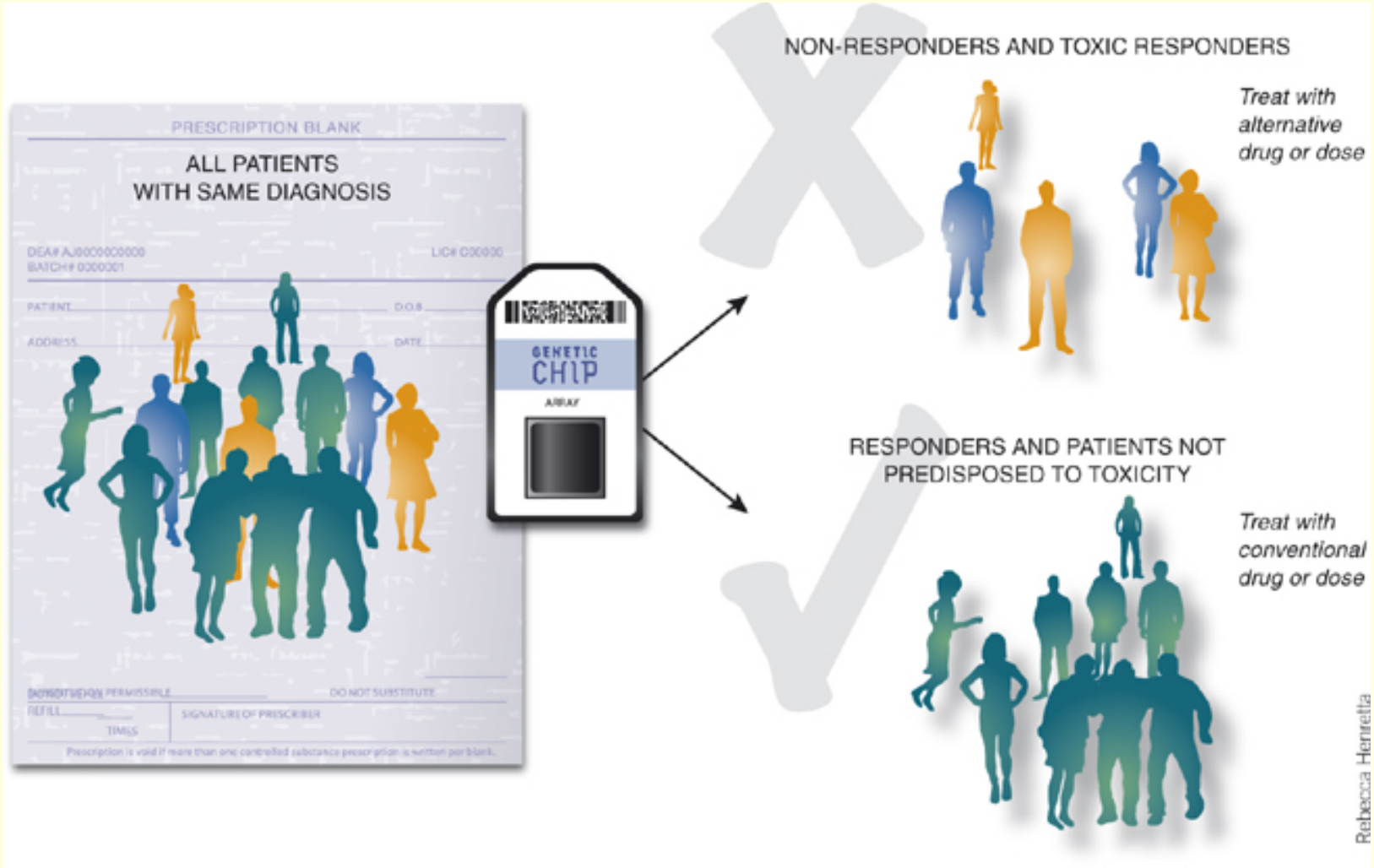
- Concerns that have been expressed implicate Sections 103 and 112
- Exemption from infringement liability for doctors, patients and researchers could defuse much of the concerns
- Ariad NF-kB claims
  - Amgen defeated using claim construction
  - Eli Lilly defeated using written description
- After arising technology could confer patent eligibility


THE
$1,000
GENOME
THE REVOLUTION IN DNA SEQUENCING AND THE NEW ERA OF PERSONALIZED MEDICINE
KEVIN
DAVIES

The $1000 Genome

- *Academia's $1,000 Genome*, Nature Biotechnology (November 2011)
  - “In August, the National Human Genome Research Institute (NHGRI) awarded $14 million in grants to support technologies that will enable rapid sequencing of a human genome for $1,000 or less by 2012.”

The Promise of Personalized Medicine



But what about all the gene patents?

- Conventional wisdom
  - 20% of human genes are “patented”
  - Sequencing genome will require licensing thousands of human gene patents
  - $1000 genome with “$100,000 licensing burden”
- See, for example,
  - Sam Kean, *The Human Genome (Patent) Project*, 331 Science 530 (2011)

AMP v. PTO ("Myriad") (Fed. Cir. 2011)

- Patent eligibility of DNA product claims upheld
- Some method of genetic diagnosis claims ruled patent ineligible
- Judge Lourie's opinion for majority explicitly assumes that 20% of human genes are patented

Judge Lourie in Myriad

- “[It] is estimated that the PTO has issued 2,645 patents claiming “isolated DNA” over the past twenty-nine years, and that by 2005, had granted 40,000 DNA-related patents covering, in non-native form, twenty percent of the genes in the human genome.”

Judge Moore in Myriad

- “[T]here are now thousands of patents with claims to isolated DNA.”

AMP v. PTO ("Myriad") (Fed. Cir. 2011)

- Judge Bryson's strong dissent based largely on his perception that gene patents will impede whole genome sequencing and multiplex testing
- U.S. Government amicus brief driven in large part by same concern

Judge Bryson dissenting-in-part

- “[I]n order to sequence an entire genome, a firm would have to license thousands of [gene] patents from many different licensors.”
- “[Gene patents] present a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing.”

AMP v. PTO ("Myriad") (Fed. Cir. 2011)

- During oral arguments, the attorneys disagreed as to whether the patents at issue in the case would be infringed by whole genome sequencing
- Neither side was able to provide any convincing rationale in support of their conclusory positions
  - No human gene patent has ever been found to be infringed by DNA sequencing (or genetic diagnostics for that matter)

America Invents Act Reflects Concern Over Gene Patents

- Section 27 of the AIA charges the Director of the USPTO with delivering to Congress a study and recommendations no later than nine months after the enactment of the Act (i.e., by June 15, 2012) regarding independent second opinion genetic diagnostic testing where patents and exclusive licenses exist that cover primary genetic diagnostic tests.

Conventional wisdom: 20% of human genome is “patented”

- “Urban legend” routinely treated as fact
  - Example: Sam Kean, *The Human Genome (Patent) Project*, 331 Science 530 (2011)
- When citation is provided, typically it is to a secondary source
  - Example: *Myriad* decision cites to a law review article, which cites to NAS report, . . .

Conventional wisdom: 20% of human genome is “patented”

- Ultimately, it all comes back to a single “Policy Perspective” article
  - Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 Science 239 (2005).
- This appears to be only reported empirical attempt to identify all gene patents
  - DNA Patent Database does not identify “gene” patents

The Jensen and Murray article

- Main text of the article:
  - “20% of human genes are ***explicitly claimed*** as US IP”
- Supporting online material:
  - 20% of known human gene sequences (or the corresponding protein sequence) are “***explicitly mentioned***” in US patent claim
  - Patent data set was not provided

My study

- Jensen and Murray graciously provided me with the full data set of 4270 patents identified in their study as “gene patents”
- I analyzed the claims from a random sample consisting of 533 patents
  - Evenly spaced over the temporal range of 1993 to 2005
  - Caveat: sparse guidance from case law in interpreting claim scope

I identified three categories of patent

- Category I
  - 139 of the patents do not include a single claim that could be infringed by ***any form*** of genetic testing
- Category II
  - 366 of the patents include a product claim covering a DNA molecule
- Category III
  - 48 of the patents include a method claim potentially infringed by some form of genetic testing (***not necessarily DNA sequencing***)

Category I (139 patents)

- Most should not be considered gene patents at all
  - Many only include protein claims
  - Others are directed towards subject matter such as gene fusions, vaccines, specific methods of using or analyzing DNA unrelated to genetic analysis
- All of these patents contribute to the myth that 20% of human genes are patented

Example

- US Patent number 5,843,888
  - Claim 1. A ***non-naturally occurring mutant human hemoglobin*** wherein the valine residue at position 96 of the alpha chain (SEQ ID NO: 1) is replaced by a tryptophan residue.

Category II (369 patents)

- Most are limited to “isolated” DNA
  - Some recite “purified” or “isolated and purified”
  - A few have no limitation to explicitly exclude naturally occurring DNA
  - Many are limited to recombinant DNA, gene therapy vectors, antisense molecules, etc.

Does DNA sequencing necessarily entail “isolation”?

Is claimed DNA “isolated” during DNA sequencing?

No US case law directly on point, but a European court recently held that “the average person skilled in the art would understand the term isolated DNA as DNA that has been retrieved from the cell of an organism for further treatment.”

- *Monsanto Technology LLC v. Cefetra BV*, Court of Justice of the European Union, Case C-428/08

“The stronger a patent claim is, the weaker it is” – G.S. Rich

- Some assume that “isolated” covers any form of DNA removed from its native environment, but if that is the case these claims to isolated DNA would appear vulnerable to invalidation by a large body of prior art

Full length gene claims unlikely to be infringed

- A majority of the product claims analyzed are directed to full-length cDNA molecules, full-length gene sequences, or large fragments thereof
  - But in conventional gene and genome sequencing, only relatively small fragments are analyzed
- See also W. Nicholson Price II, *Unblocked Future: Why Gene Patents Won't Impede Whole-Genome Sequencing and Personalized Medicine*

Attorney General Apparently Agrees with This Assessment

- During arguments before the Federal Circuit in *AMP v. PTO* an attorney representing the U.S. government stated that the "vast majority" of the claims to isolated DNA that have been issued by the PTO are to "cDNA, recombinant DNA, process claims and the like," and hence would not cover genomic DNA (nor, by implication, genome sequencing).

Gene fragment claims unlikely to be valid

- Claims directed to relatively small fragments (which are relatively uncommon) might plausibly be infringed by genome sequencing, but a recent article points out substantial prior art issues
  - Thomas B. Kepler, Colin Crossman and Robert Cook-Deegan, *Metastasizing patent claims on BRCA1*, Genomics (2010).

Recent Developments in Inherent Anticipation

- *In re Crish* (2005)
  - Prior art disclosing a DNA molecule in inherently anticipates a claim reciting the molecule, even if the prior art does not disclose the sequence of the DNA molecule, and even if that DNA sequence was unknown in the prior art
- See also *Schering Corporation v. Geneva Pharmaceuticals* (2003) and *SmithKline Beecham v. Apotex* (2005).

A Wealth of Prior Art Disclosing "Isolated" DNA Molecules

- Southern Blotting (1975)
- Genomic DNA Libraries (Maniatis, 1978)
- Sequence of Human Genome Published in 2001 (draft) and 2003 (complete)

A non-representative example of a DNA product claim

- U.S. Patent Number 6,500,938
  - Claim 1: A combination comprising a plurality of polynucleotide probes, wherein said plurality of probes are ***SEQ ID NOs:1-1490***.

A more typical example

- U.S. Patent No. 6,436,667
  - 1. An isolated polynucleotide, or complement thereof, comprising a polynucleotide sequence that is at least 95% identical to a polynucleotides sequence of ***nucleotides 1-1101*** of SEQ ID NO:1, wherein said isolated polynucleotide ***encodes a polypeptide which promotes development of pancreatic beta cells***.

Category III (47 patents)

- While these 47 patents would cover some forms of genetic testing, most would probably not be infringed by DNA sequencing

Example of Category III claim that would not cover sequencing

- 1. A method of detecting aberrant or abnormal expression [], comprising:
  - a) contacting a sample [];
  - b) detecting expression []; and
  - c) ***comparing the expression of the nucleic acid molecule*** in the sample that hybridizes to the hybridization probe with a standard [].

Category III (47 patents)

- 13 claims purport to broadly cover detection of a particular genetic variation
  - These 13 patents would probably only be infringed by one who ***physically determines the sequence of the DNA molecule, and also analyzes resulting sequence data*** for the presence of the claimed genetic variation
    - Divided infringement

Example

- U.S. Patent No. 6,458,541
  - 1. A method for predicting the likelihood that an individual will be diagnosed with a bipolar disorder, comprising the steps of:
    - a) ***obtaining a DNA sample*** from an individual to be assessed; and
    - b) ***determining the nucleotide present at the nucleotide position*** corresponding to position 404 of SEQ ID NO: 2, ***wherein the presence*** of an "A" (adenine) at position 404 ***indicates*** that the individual has a lower likelihood of being diagnosed with a bipolar disorder than an individual having a "G" (guanine) at that position.

6,432,644: The only example of a truly broad method claim

- A method for diagnosing the presence of a polymorphism in human KCNE1 (the coding region of which is bases 193-579 of SEQ ID NO:3) which causes long QT syndrome wherein said method is performed by means which identify the presence of said polymorphism, wherein said polymorphism is one which results in the presence of a KCNE1 polypeptide of SEQ ID NO:4 with an altered amino acid, said altered amino acid being selected from the group consisting of: a) a Leu at residue 74.

The Incyte patents

- Only 37 of the 398 Incyte patents identified in the study are still in force
  - The others have all expired for failure to pay maintenance fees
- These patents, like many patents in the study, were drafted primarily to cover use of genes (cDNA) for recombinant protein production, or (in some cases) analysis of RNA expression, not DNA sequencing

Typical Incyte Patent: 6,168,920

- 1. An ***isolated and purified polynucleotide*** encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:1. **[i.e., a full length cDNA molecule]**

- 2. An isolated and purified polynucleotide having a sequence which is fully complementary to the polynucleotide of claim 1.

  3. An isolated and purified polynucleotide comprising the polynucleotide sequence of SEQ ID NO:3.

  4. An isolated and purified polynucleotide having a sequence which is fully complementary to the polynucleotide of claim 3.

Typical Incyte Patent: 6,168,920

- 5. An ***expression vector*** comprising the polynucleotide of claim 1.

  6. A ***host cell*** comprising the expression vector of claim 5.

  7. ***A method for producing a polypeptide***, the method comprising the steps of:

  a) culturing the host cell of claim 6 under conditions suitable for the expression of the polypeptide; and

  b) recovering the polypeptide from the host cell culture.

Typical Incyte Patent: 6,168,920

- 8. A method for detecting a polynucleotide, the method comprising the steps of:

  (a) hybridizing the polynucleotide of claim 2 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and

  (b) ***detecting the hybridization complex***, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.

  9. The method of claim 8 further comprising amplifying the polynucleotide prior to hybridization.

Huys, I. et al., *Legal uncertainty in the area of genetic diagnostic testing*, Nature Biotechnology 27:903-909 (2009)

- This article reports, for example, that US patent number 5,693,473 (BRCA, University of Utah) includes “gene” (i.e., “polynucleotide sequence”) and “oligo” (i.e., “primers or probes”) claims that are ***“almost impossible to circumvent”***

US patent number 5,693,473 “gene” claims

- 1. An ***isolated*** DNA comprising an ***altered BRCA1 DNA*** having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO:1.
  - “BRCA1 DNA” is not defined

US patent number 5,693,473 “gene” claims

- 2. An isolated DNA comprising an altered BRCA1 DNA having one of the alterations set forth in Tables 12A or 14 with the provision that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO:1.
- 3. An isolated DNA comprising an altered BRCA1 DNA having one of the alterations set forth in Tables 18 or 19.

US patent number 5,693,473 “oligo” claims

- 4. A nucleic acid ***probe*** specifically hybridizable to a human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables, 12A, 14, 18 or 19.
  - “The probes will include an isolated polynucleotide attached to a label or reporter molecule”

US patent number 5,693,473 “oligo” claims

- 5. A nucleic acid probe specifically hybridizable to human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables 12A or 14 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO:1.
- 6. A nucleic acid probe specifically hybridizable to human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables 18 or 19.

Huys, I. et al., *Legal uncertainty in the area of genetic diagnostic testing*, Nature Biotechnology 27:903-909 (2009)

- "The claims at hand were interpreted in the light of the patent specification, the drawings and the other claims and were ***compared to the best practices guidelines (when available) for the testing of susceptibility to these genetic diseases in Europe and the United States***, to assess the essentiality (i.e., the neccessity of having access to the technology) of the specific patent claims for carrying out a genetic diagnostic test using those guidelines."

Huys, I. et al., *Legal uncertainty in the area of genetic diagnostic testing*, Nature Biotechnology 27:903-909 (2009)

- "By applying this methodology, three impact levels were distinguished, and a color was attributed to indicate whether the ***currently practiced genetic diagnostic tests*** are covered to a minor degree (green), partly (orange) or completely (red) by the claims (Fig. 1). . . . . 'Red claims' are almost impossible to circumvent and are therefore also called 'blocking claims'."

Huys, I. et al., *Legal uncertainty in the area of genetic diagnostic testing*, Nature Biotechnology 27:903-909 (2009)

- 'Green claims' can easily be circumvented by ***using a different genetic diagnostic testing technique***. 'Orange claims' can be circumvented but this requires a ***substantial investment of money and time, as well as a large amount of inventiveness***. 'Red claims' are ***almost impossible to circumvent and are therefore also called 'blocking claims'***.

US Patent Number 6,984,487 – Difficult to circumvent gene claim

- 1. A ***purified*** DNA molecule, comprising a cystic fibrosis transmembrane conductance regulator (CFTR) DNA sequence selected from the group consisting of: (a) a DNA sequence encoding a normal CFTR protein having the amino acid sequence depicted in FIG. 1; (b) ***a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence depicted in FIG. 1***; and (c) a DNA sequence complementary to the DNA sequence of (a) or (b), ***wherein said DNA sequence*** of (a), (b) or (c), when present as part of a coding sequence of a normal CFTR gene, ***is expressed in human epithelial cells as a normal CFTR protein which is not characterized as having cystic fibrosis associated activity.***

US Patent Number 6,984,487 – Almost impossible to circumvent oligo claim

- 5. ***A detectably labeled normal CFTR probe***, comprising a purified DNA or RNA nucleotide sequence, said DNA or RNA nucleotide sequence having at least 16 contiguous nucleotides being the same as, or complementary to, a DNA sequence according to claim 1, wherein, in said RNA nucleotide sequence, each thymidylate in said DNA nucleotide sequence is replaced with a uridine, and wherein said probe is detectably labeled and distinguishes a normal CFTR gene from a mutant CFTR gene.

US Patent Number 6,984,487 – Almost impossible to circumvent method claim

- 12. A method for screening a subject to determine if said subject is a CF carrier or a CF patient, comprising: (a) ***providing a biological sample*** of said subject to be screened; and (b) ***assaying the biological sample for the presence of the CFTR DNA sequence of claim 1***, or a mutant CFTR DNA sequence of claim 7, wherein said assay is a DNA screening assay which detects normal or the .DELTA.F508 mutant CFTR DNA sequences by at least one assay method selected from the group consisting of probe hybridization, ***direct DNA sequencing***, restriction enzyme analysis, electrophoretic mobility, RNase protection, chemical cleavage and ligase-mediated detection.

Unblocked Future: Why Gene Patents Won't Hinder Whole Genome Sequencing and Personalized Medicine (WN Price II)

- Some good points are raised, but . . .
  - The article incorrectly states that my Science article classified "gene ***patents*** into four categories," when in fact I classified gene patent ***litigations*** into four categories
  - The article oversimplifies the nature of gene product claims by assuming claims are directed to either full-length coding sequences ***or*** very short fragments

Price's Example of "Biotechnological Gene Patent"

- 4,703,008
  - 1. A purified and isolated DNA sequence encoding erythropoietin, said DNA sequence selected from the group consisting of:

    (a) the DNA sequences set out in FIGS. 5 and 6 or their complementary strands; and

    (b) DNA sequences which hybridize under stringent conditions to the DNA sequences defined in (a).

    2. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.

Price's Example of "Diagnostic Gene Patent"

- 5,747,282
  - 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

It's Not as Simple as "Full Length or Fragment"

- 5,817,784
  - 2. An isolated nucleic acid molecule of SEQ ID NO:1, or a ***biologically active fragment*** thereof.
- 5,883,241
  - 1. Isolated human DNA comprising the nucleotide sequence of SEQ I.D. No: 1 herein and ***fragments thereof, wherein the protein encoded retains metalloproteinase activity***.

It's Not as Simple as "Full Length or Fragment"

- 6,858,714
  - 1. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
  - . . .
  - c) a fragment of a polypeptide having the amino acid sequence of SEQ 1) NO:1, said **fragment having cyclic nucleotide phosphodiesterase activity**, and d) an **immunogenic fragment of a polypeptide of at least 5 amino acids** of the amino acid sequence of SEQ ID NO:1, said immunogenic fragment is used to make an antibody which specifically binds to an isolated polypeptide selected from the group consisting of a), b) and c).

The name of the game is the claim

- *Science* recently reported that a lawyer for a company developing multiplex genetic diagnostic tests initially feared that his company would need to spend $35 million in legal fees investigating whether their technology would infringe gene patents, but that later after he had "fully analyzed the patents on a handful of genes that [his company] might use, he was encouraged, finding plenty of room to operate."

“But can you guarantee a gene patent won’t be asserted?”

- No, but . . .
  - Remedies?
    - Would injunction be appropriate post-*eBay*?
    - “Lost profits” for NPE?
    - Reasonable royalty on contribution of single gene (or base) in WGS?

What if gene patents do create a problem?

- Congress could enact a statutory exemption
- NIH could “authorize and consent”
- Trend toward decoupling DNA sequencing from genetic analysis
  - Actual sequencing might very well move overseas
  - But anecdotally, those developing whole genome sequencing do not view gene patents as an issue

So what about a gene patent pool?

- Could incentivize maintenance and enforcement of gene patents that would not otherwise be problematic
- Gene patents are fundamentally different than patents on technology like DVD or sewing machine

What would be the harm in invalidating gene patents?

- Thousands of gene patents have issued over the last 30 years
- Patents have played an important role in incentivizing investment in biotechnology
- Disruption of investment backed expectations
- Problem is largely hypothetical, and largely based on enforcement activities

What can history teach us?

- Medical procedure patents?
  - 35 USC 287(c)
- Gene patents and DNA hybridization arrays (i.e., gene chips)?
  - A gene patent has never been asserted in connection with DNA hybridization arrays

Looking forward

- Category II (DNA product) claims are probably not much of a concern
  - Myriad has acknowledged this point in filings to the courts

Looking forward

- The real policy concern should be Category III (method of diagnosis) claims
  - It makes little sense to focus specifically on genetic diagnosis , i.e., ***genetic exceptionalism***
  - The real question might be whether there will be sufficient patent protection to adequately incentivize innovation in diagnostics and personalized medicine
    - These inventors face a patent eligibility-divided infringement squeeze

Looking Forward

- PTO should play more active role in promoting notice function of patents
  - Avoid genetic exceptionalism
- Some statutory exemptions from liability might be in order
  - Focus on classes of infringing activity, rather than classes of patents