ABSTRACT IDEA OR TANGIBLE APPLICATION?

ASSN. FOR MOLECULAR PATHOLOGY V. USPTO

AND THE FUTURE OF INTELLECTUAL PROPERTY PROTECTION FOR DIAGNOSTIC METHODS

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I. PERSONALIZED MEDICINE

Traditionally, healthcare practitioners have taken a "one size fits all" approach to pharmaceutical treatment, in which a blockbuster drug is selected for every patient with a given condition based on its past success in treating others. Very often, the drug will be successful at treating the new patient as well. However, this approach fails to take into account any individual differences that may exist among the patients in a population. Due to an individual's genetic makeup, the same drug that worked successfully for so many others may be ineffective in someone lacking a protein necessary to metabolize the drug in their body, for example. In some cases, individual differences in the ability to process a drug result in adverse reactions in a subset of the population that are sufficiently serious to warrant removing the drug from the marketplace all together.

Personalized medicine has been hailed as the next generation approach to medical treatment. The promise of personalized medicine is that it will allow a practitioner to assess an individual's genetic makeup and tailor a treatment strategy specifically for them. The completion of the Human Genome Project in 2001 ushered in a wave of research and discovery in the personalized medicine space by making the entire sequence of the human genome publically available[1] for the first time. See, *e.g.*, David Baltimore, Our Genome Unveiled, 409 Nature 814 (2001). This massive sequencing effort coincided with the development of new research tools that enabled investigators to sequence large amounts of genetic information with ease. These tools made the process of detecting alterations in the sequence or expression level of known genes routine. The information gained by examining the sequence and expression level of particular genes has provided a foundation for the development of new diagnostic and therapeutic tools.

For example, researchers have identified genetic markers that can be used to diagnose and stage cancer. Thus, a mutation in a given gene may be used to determine an individual's predisposition to developing a certain type of cancer. Likewise, particular mutations detected in a cancer sample obtained from a patient can indicate whether or not the cancer is likely to be particularly aggressive. Alternatively, the expression pattern of multiple genes may be used to identify gene expression "signatures" characteristic of

[1] While the sequence of every gene in the human genome became publically available in 2001, many human gene sequences are not 'in the public domain'.

certain types of cancers. For example, the gene expression profile of human hepatocellular carcinoma samples allows scientists to identify the patients at greatest risk for experiencing relapse following treatment. Yujin Hoshida *et al.*, Gene Expression in Fixed Tissues and Outcome in Hepatocellular Carcinoma, 359 N. Engl. J. Med. 1995 (2008). The information gained from gene expression signatures has also been used to design drugs that specifically target pathways that are affected in individuals having particular genetic alterations. Drug manufacturers have used genetic profiling to identify patients who are most likely to benefit from such targeted therapies, and conversely, to identify subsets of patients who are most at risk for adverse events following administration of a given drug.

A 2009 study by PricewaterhouseCoopers estimated the personalized medicine market in the U.S. alone at $232 billion, with projected growth of 11% annually. PricewaterhouseCoopers, The New Science of Personalized Medicine (2009). Personalized medicine thus presents an extraordinary opportunity for the pharmaceutical and biotechnology sector at a time when the blockbuster drug era is coming to a close.

II. INTELLECTUAL PROPERTY PROTECTION FOR PERSONALIZED MEDICINE

As is the case for many nascent technologies, intellectual property protection is critical for encouraging innovation in the field of personalized medicine. Inventors seeking patent protection for genomics-based discoveries have attempted different strategies for claiming inventions relating to biomarkers. A sampling of such claims is presented in Table 1:

Table 1: Representative patent claims drawn to biomarkers.

Claim type	Claim Language	Patent No.	Assignee
Composition of matter	1. An isolated nucleic acid encoding human amyloid precursor protein 770 (APP No) including the nucleotides encoding codon 670 and 671 of human amyloid precursor protein 770, wherein the nucleic acid encodes asparagine at codon 670 and/or leucine at codon 671 or an isolated fragment of said nucleic acid having at least ten nucleotides and encoding at least positions 4 and 5 of SEQ ID NO:1.	US 5,455,169	Alzheimer's Institute of America
Diagnostic method - individual gene (detecting step)	1. A method of diagnosing pancreatic cancer in an individual, the method comprising *detecting a higher level of ASCT2 protein* in a sample from the individual as compared to levels of ASCT2 protein in pancreatic tissues of healthy individuals, wherein the	US 7,473,531	Celera Corporation

	amino acid sequence of the ASCT2 protein comprises SEQ ID NO:56, and *wherein the higher level of ASCT2 protein indicates that said individual has pancreatic cancer*.		
Diagnostic method-gene signature (assaying step)	1. A method of diagnosing pediatric systemic lupus erythematosus in a pediatric individual comprising *assaying a blood sample from the pediatric individual for an increase in the mRNA level* of each of the genes GTPBP2, PCTAIRE2BP, DNAPTP6, GPR84, B4GALT5, FRAT2 and PAFAH1B, *wherein the increase in the mRNA level of each of the genes indicates that the pediatric individual has systemic lupus erythematosus (SLE)* and wherein the mRNA level is increased relative to the mRNA level in a normal control.	US 7,608,395	Baylor Research Institute
Detection method (assaying and correlating steps)	13. 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*.	US 4,940,658	University Patents Inc./Metabolite Laboratories
Treatment method (detecting and administering steps)	1. A method of treating a proliferative disorder in a mammal, comprising: (a) *detecting constitutive ras-MAP signaling* in cells of said proliferative disorder in the presence and absence of serum; and (b) *if constitutive ras-MAP signaling is detected, administering* to the mammal an effective amount of one or more reoviruses under conditions which result in substantial lysis of cells of the proliferative disorder.	US 7,815,914	Oncolytics Biotech Inc.

A typical invention in the field of personalized medicine is based on the discovery of a *relationship* between a particular biological marker (*e.g.*, a mutation in a gene, an elevated level of a protein, etc.) and a given condition (*e.g.*, a subject's disease state or amenability to a particular treatment regimen). In the event that the marker is a previously unknown genetic mutation, the broadest scope of protection may be obtained through claims drawn to isolated nucleic acid and/or polypeptide molecules containing the mutation as compositions of matter (see, *e.g.*, Table 1, US 5,455,169). It is generally necessary to use such compositions in diagnostic assays, either because the molecules must be isolated in some form in order to detect the mutation(s) in question, or because the isolated molecules are used as control reagents. Thus, composition of matter claims effectively prevent the use of a novel biomarker in any type of diagnostic method.

In the event that a biological marker has been previously described, but its relationship with a given condition was unknown, inventors have traditionally been able to obtain patent protection for methods that make use of the newly discovered correlation. Diagnostic method claims typically recite one or more "assaying" or "detecting" steps, in

which a subject of interest is determined either to have or to lack the marker in question. In addition, such claims also may recite a "correlating" or "concluding" step, in which the information gained from the "assaying" step is used to make the inference recited in the preamble (*e.g.*, diagnosing cancer, detecting a vitamin deficiency, etc., see Table 1, US 7,473,531, US 7,608,395, US 4,940,658). Some applicants have included an additional step of "administering" a compound to a subject based on the results of the "assaying" step (see, *e.g.*, Table 1, US 7,815,914).

Notably, applicants have generally avoided narrowing their claims by reciting any particular means to be used for performing the "assaying" or "detecting" steps. As a practical matter, many diverse methods for determining the presence or absence of a biomarker in a sample are used routinely, and new techniques that can be used for making such a determination are being developed all the time. These techniques are not tied to the detection of any given marker, but rather can be easily adapted to detect any marker of interest in a sample. For the performance of diagnostic methods, it generally matters not how a biomarker is detected; the same inference may be drawn regarding the condition of a subject regardless of how the information gained from the "assaying" or "detecting" steps is actually obtained.

The patentability of composition claims drawn to isolated nucleic acid molecules has recently been called into question as a result of a decision by the U.S. District Court for the Southern District of New York in Ass'n for Molecular Pathology (AMP) v. United States Patent and Trademark Office (USPTO), No. 1:09-cv-04515-RWS, 2010 U.S. Dist. LEXIS 35418 (S.D. N.Y. April 2, 2010), which held that claims drawn to isolated DNA molecules encoding BRCA polypeptides are invalid for encompassing non-statutory subject matter under 35 U.S.C. § 101. This case is currently on appeal to the Court of Appeals for the Federal Circuit, with a decision anticipated later this year.

In view of the uncertainty surrounding the patent eligibility of claims drawn to biomarkers as compositions of matter, the value of diagnostic method claims has been heightened. Notwithstanding, the patentability of claims drawn to diagnostic methods has also been called into question in view of the Supreme Court's decision regarding statutory subject matter in In re Bilski, 130 S. Ct. 3218 (2010). Prior to this decision, the court in AMP v. USPTO invalidated a series of method claims based on a correlation

between the presence of mutations in either of two genes designated BRCA1 and BRCA2, and a subject's susceptibility to breast cancer. The Federal Circuit will have the opportunity to decide the manner in which the Court's reasoning in Bilski should be applied to claims drawn to diagnostic methods when it reviews the diagnostic method claims at issue in AMP v. USPTO on appeal.

III. METHOD CLAIMS AT ISSUE IN AMP V. USPTO

The dispute in the AMP v. USPTO litigation arose when the plaintiffs, a collection of doctors, researchers and patients led by the American Civil Liberties Union, filed a complaint seeking a declaratory judgment of invalidity with respect to 15 claims in seven patents owned by defendant Myriad Genetics, Inc. ("Myriad") (US Patent Nos. 5,693,473; 5,709,999; 5,710,001; 5,747,282; 5,753,441; 5,837,492; and 6,033,857). Plaintiffs' motion for summary judgment of invalidity for all of the contested claims was granted by the U.S. District Court for the Southern District of New York on the ground that the claims are not drawn to statutory subject matter under 35 U.S.C. § 101. Myriad has appealed the decision on all counts, and the case is currently pending before the Federal Circuit.

The Myriad patents are based on Myriad's isolation of DNA molecules encoding BRCA1 and BRCA2. The Myriad patents also describe the correlation between mutations in the BRCA1 and BRCA2 genes and a subject's predisposition to breast and ovarian cancer. The claims at issue broadly fall into two categories: claims drawn to isolated DNA molecules encoding BRCA1 and/or BRCA2, and claims drawn to methods relating to the identification of mutations in the BRCA1/BRCA2 genes. The composition of matter claims present the interesting issue of whether or not isolated DNA molecules are patent-eligible under 35 U.S.C. § 101, or whether they are instead "products of nature" that fall outside the scope of statutory subject matter. This issue has been debated extensively elsewhere, and will not be considered further here.

The method claims at issue will give the Federal Circuit the opportunity to consider the patent-eligibility of diagnostic method claims of varying scope. A decision regarding the patent-eligibility of the method claims of the Myriad patents will hopefully

clarify for the patent community the metes and bounds of 35 U.S.C. § 101 as applied to diagnostic methods.

Six of the 15 claims at issue are drawn to methods. These claims are presented in Table 2. The active steps of each claimed method have been highlighted for emphasis.

Table 2: Disputed method claims in AMP v. USPTO.

Patent No.	Claim Language	Claim Type
5,747,282	20. 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**.	Screening method (growing, determining, and comparing steps)
5,709,999	1. 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 said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.	Detection method (analyzing step)
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 ***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**.	Screening method (comparing step)
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**.	Screening method (comparing step)
6,033,857	1. A **method for identifying a mutant BRCA2 nucleotide sequence** in a suspected mutant BRCA2 allele which comprises ***comparing the nucleotide sequence*** of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence, **wherein a difference between the suspected mutant and the wild-type sequences identifies a mutant BRCA2 nucleotide sequence**. 2. A **method for diagnosing a predisposition for breast cancer** in a human	Identification method (comparing step) Diagnostic method

	subject which comprises ***comparing the germline sequence*** of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, **wherein an alteration in the germline sequence** of the BRCA2 gene or the sequence of its mRNA of the subject **indicates a predisposition to said cancer**.	(comparing step)

As illustrated in Table 2, the method of claim 20 of the '282 patent contains the steps of growing cells, determining the rate of growth, and comparing the rate of growth. The method of claim 1 of the '999 patent contains the step of analyzing a gene sequence. The methods set forth in the remaining four claims all contain the step of "comparing" one nucleic acid sequence to another.

IV. LEGAL STANDARD FOR DETERMINING THE SCOPE OF STATUTORY SUBJECT MATTER UNDER 35 U.S.C. § 101

The United States Constitution gave Congress the power "to promote the progress of Science and useful Arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." U.S. Const. art. 1, § 8, cl.8. Accordingly, Congress enacted 35 U.S.C. § 101, which sets forth the statutory scope of patentable subject matter. In particular, 35 U.S.C. § 101 provides that "[w]hoever 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." Congress thus established four categories of subject matter that are eligible for patent protection: processes, machines, manufactures, and compositions of matter. With respect to processes, 35 U.S.C. § 100(b) defines this term to mean a "process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material." By using such expansive terminology, Congress clearly intended that the scope of patent protection provided by § 101 would be broad. Diamond v. Chakrabarty, 447 U.S. 303, 308-309 (1980). Broad general language was employed when drafting §101 in order to ensure that inventions relating to technologies that were unforeseeable to the drafters would nonetheless enjoy the protections of the patent law. Id. at 316. In enacting such protections, Congress intended to foster inventive efforts that ultimately have a positive effect on society "through the introduction of new products and processes…into the

economy, and the emanations by way of increased employment and better lives for our citizens." Id. at 307.

The broad scope of §101 does not, however, mean that patent protection is available for every discovery. While not specifically enumerated by statute, the Supreme Court has recognized three exceptions to § 101's patentability criteria: "laws of nature, physical phenomena, and abstract ideas." Id. at 309. It is now widely accepted that these abstract concepts should remain in the public domain. Notwithstanding, the Court has struggled to define the critical distinction between claims drawn to abstract ideas *per se*, and claims instead drawn to the *application* of abstract ideas in a manner that confers patent eligibility. The Court has repeatedly used two questions to focus the analysis with respect to process claims: firstly, "does the claimed process require a particular machine or apparatus, or does it transform an article to a different state or thing?"; and secondly, "does the claimed process preempt use of the underlying scientific principle upon which the process is based?"

For example, in Gottschalk v. Benson, 409 U.S. 63 (1972), applicants attempted to claim a method for converting binary coded decimal numbers into pure binary form. The Court noted that all of the steps of the claimed method could be performed mentally, and thus the claim was, in effect, an attempt to patent a mathematical formula. Id. at 67, 71. In holding the claim unpatentable under § 101, the Court stated that patents may not be granted to abstract ideas, and this would essentially be the result if they allowed a patent claiming a mathematical formula. The Court stressed that the claimed method could be performed without the use of any apparatus. Id. at 64, 68. The Court noted, however, that this was not dispositive, as a process can be patentable irrespective of the particular instrumentation used to perform it. For example, in pointing out the patent-eligibility of a method of manufacturing fat acids and glycerine in Tilghman v. Proctor, 102 U.S. 707 (1881), the Court commented that the clue to the patentability of a process claim that does not include particular machines is whether the process transforms or reduces an article to a different state or thing. Benson, 409 U.S. at 70. The Court then noted that the claim in Benson was not limited to any particular technological application or end use, and concluded that the claim in question cannot be patentable because

allowing the claim would wholly preempt all uses of the recited mathematical formula. Id. at 72.

In Parker v. Flook, 437 U.S. 584 (1978), applicants attempted to patent a method of updating an "alarm limit" (a number that signals the occurrence of an abnormal condition, *e.g.*, an abnormality in operating conditions such as temperature, pressure, etc.) during a catalytic conversion process. The method recited essentially the following three steps: (1) measuring the value of a process variable, (2) using an algorithm to calculate an updated alarm-limit value, and (3) adjusting the alarm limit to the updated value. Id. at 585. The point of novelty of the claimed method was the mathematical algorithm used to calculate the updated alarm limit. The method was not physically tied to any particular apparatus, and was not directly involved in the transformation of any physical object. The claims did, however, recite that the method was limited to a process for the catalytic conversion of hydrocarbons. Id. at 586. This limitation confined the scope of infringing activity to persons practicing the method in this specific field. As a consequence of this limitation, the claims did not "wholly preempt" the use of the recited mathematical formula. Flook thus presented the question of whether limiting the use of a mathematical formula to a particular application was sufficient to make the formula in this limited context patent-eligible. Id. at 585. The Court held that it did not, reasoning that a mathematical formula itself is an abstract idea, and a claim drawn solely to a abstract idea should not become statutory subject matter merely because a claim limitation confines the use of the idea to a specific context. See Id. at 595.

Diamond v. Diehr, 450 U.S. 175 (1981) presented the question of whether inclusion of an abstract idea (*i.e.*, calculation of a mathematical formula) as one step in an otherwise patentable process removes the process as a whole from the scope of patent eligible subject matter. Applicants claimed a method of operating a rubber-molding press using a digital computer which calculates the optimal curing time for rubber articles by inputting the temperature inside the press at different time points into the Arrhenius equation. Id. at 181. The Court distinguished the claims at issue in Diehr from those in Benson and Flook by noting that Diehr did not seek to patent a mathematical formula *per se*. Rather, the claims in Diehr were drawn to a process for curing rubber that happened to employ a mathematical formula at one step. Diehr, 450 U.S. at 187. As in Benson and

Flook, the claims in Diehr were not tied to any particular apparatus; however, the claims in Diehr did recite a process that results in the physical transformation of an article (uncured rubber) into a different state or thing (cured rubber). Diehr, 450 U.S. at 185. By claiming a process for curing rubber, the claims in Diehr did not generally preempt all uses of the recited equation, but rather only foreclosed others from using the equation in combination with all of the additional steps in the claimed rubber-curing process. Id. The Court acknowledged that the claimed method in Flook was also limited to a particular field, but distinguished Flook on the ground that the Flook application was directed to a formula itself, rather than to an application of the formula, evidenced by the fact that Flook did not explain how the variables in the claimed formula were to be selected, or what chemical processes were at work. Diehr, 450 U.S. at 191, 192. Accordingly, the limitation to a particular technological environment in Flook was viewed merely as a pretext added to the claim in an attempt to circumvent the principle that a mathematical formula in the abstract is not accorded patent protection under § 101.

Following Diehr, the Federal Circuit formulated a new test to clarify the distinction between claims drawn to an unpatentable abstract idea and a patentable practical application in State Street Bank & Trust v. Signature Financial Group, 149 F.3d 1368 (1998). The State Street test asks simply whether or not a claimed invention "produces a useful, concrete and tangible result." Id. at 1373. If so, the invention satisfies the threshold test of § 101 for patent eligibility. The court applied this new test to claims drawn to a data processing "system" for configuring financial services termed the "Hub and Spoke" model, and found the claims to be patent-eligible. Id. at 1375. Under the State Street test, any claimed method that produces a useful, concrete and tangible result would be patentable, provided that the other conditions of Title 35 are satisfied. Accordingly, the low threshold established by the State Street test would permit the patenting of claims drawn to, for example, business methods, computer software programs, and diagnostic methods, provided that the claimed methods are capable of producing a useful, concrete and tangible result.

The State Street test was revoked by the Federal Circuit in its decision in In re Bilski, 545 F.3d 943 (2008), and was replaced by the far more stringent "machine or transformation" test. Under the "machine or transformation" test, a claimed process is

patent-eligible only if it (1) is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing. Id. at 954. The Federal Circuit applied the "machine or transformation" test to deny Bilski's patent claims, drawn to methods for hedging risk in commodities trading, under § 101. The Supreme Court subsequently affirmed the conclusion that the Bilski claims are not patent-eligible, but rejected the Federal Circuit's adoption of the "machine or transformation" test as the exclusive test for identifying patent-eligible subject matter. In re Bilski, 130 S. Ct. 3218 (2010). The Court acknowledged that the "machine or transformation" test is a useful clue for determining whether some inventions are patent-eligible, but stressed that this test is too narrow for determining the patent-eligibility of inventions in the current "Information Age," including inventions relating to "advanced diagnostic medicine techniques." Id. at 3227. The Court instead evaluated the Bilski claims by asking whether the claims are drawn to an abstract idea, consistent with the Court's precedent in Benson, Flook, and Diehr. Id. at 3229, 3230. The Court held that the Bilski claims were drawn to an unpatentable abstract idea, characterized as the concept of risk hedging, and reasoned that allowing a patent to the Bilski claims would preempt the use of hedging in all fields, effectively granting Bilski a monopoly over this abstract idea. Because the Court was able to resolve the question presented by Bilski by relying narrowly on Benson, Flook, and Diehr, the Court did not set forth a new test for determining patent-eligibility, but noted that "Section 101's terms suggest that new technologies may call for new inquiries." Id. at 3228.

The Federal Circuit has addressed the issue of patent-eligible subject matter in two cases that have been decided following Bilski. These decisions offer a glimpse into the framework the Federal Circuit may adopt to determine patent-eligibility in the post-State Street era. In the first of these cases, the Federal Circuit was presented with the question of whether claims drawn to methods for the halftoning of digital images are patent-eligible. Research Corp. Technologies, Inc. v. Microsoft Corp., 627 F.3d 859. The method claims at issue recite a single active step: "*utilizing a pixel-by-pixel comparison* of the image against a blue noise mask." See U.S. Patent No. 5,111,310 claim 1 (filed December 4, 1990).

In determining patent-eligibility, the court first determined whether the claims are directed to one of the categorically patentable subject areas recited in § 101: a process, machine, manufacture, or composition of matter. Research Corp., 627 F.3d at 868. As the claims recite a method, the court found that the subject matter qualifies as a process under § 101. Id. The next step in the court's analysis was to determine whether any of the Supreme Court's three exceptions (laws of nature, physical phenomena, abstract ideas) will nonetheless bar patent-eligibility. Id. In order to determine whether a claimed process is abstract, the court noted that "this disqualifying characteristic should exhibit itself so manifestly as to override the broad statutory categories of eligible subject matter and the statutory context that directs primary attention on the patentability criteria of the rest of the Patent Act." Id. Holding that the claimed methods employing the step of "comparing" are not so abstract as to remove them from patent-eligibility, the court stated that "inventions with specific applications or improvements to technologies in the marketplace are not likely to be so abstract that they override the statutory language and framework of the Patent Act." Id. at 869. This "manifestly abstract" standard appears to have substantially greater breadth than the "machine or transformation" test.

In a second post-Bilski decision, the Federal Circuit confronted the issue of patent-eligible subject matter in the biomarker space when it addressed whether claims drawn to methods for optimizing therapeutic efficacy using 6-thioguanine drugs satisfy § 101. Prometheus Laboratories, Inc. v. Mayo Collaborative Services, 628 F.3d 1347 (2010). Claims 1 and 46 of U.S. Patent No. 6,355,623 are representative of the claims at issue:

> 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 in 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.
>
> 46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:
> (a) ***determining the level of 6-thioguanine or 6-methyl-mercaptopurine in a subject*** administered a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptoriboside, 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 or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Claim 1 requires two active steps, "administering" a drug, and subsequently "determining" the level of the drug in a subject. In contrast, claim 46 requires only one active step, "determining" the level of a drug in a subject to whom it had been previously administered. In both claims, the information gained from the "determining" step "indicates a need" to adjust the dosage of the drug, but does not require that any adjustment is made.

The issue before the court in Prometheus was whether the claims are drawn to an abstract idea – the natural phenomenon that drug metabolite levels correlate with efficacy and toxicity – or whether the claims are instead drawn to a particular application of that idea. Id. at 1354. To decide this issue, the court articulated an analysis whereby the claims were evaluated for satisfaction of both the "preemption test" and the "machine or transformation test." Id. at 1359.

Regarding the "machine or transformation test," the court found that both the "administering" and "determining" steps were transformative. Id. at 1356, 1357. With respect to the administering step, the transformation results from the physical change that occurs within a subject (*e.g.,* being treated) as a consequence of receiving a drug. Regarding the determining step, the transformation results from the manipulation and modification of a physical sample that is required to make the measurement recited by the claims. Id.

Notably, this does not end the "machine or transformation" analysis. The transformative steps must subsequently be examined to ensure that they are "central to the claims" and are not merely "insignificant extra-solution activity" or "data-gathering steps." Id. at 1357. The court found that both the administering and determining steps are central to the claims because they are "not 'merely' for the purpose of gathering data…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." Id. The court distinguished

this situation from that presented in In re Grams, 888 F.2d 835 (1989), which the court characterized as claiming an unpatentable fundamental principle together with a data-gathering step. Prometheus, 628 F.3d at 1358. The claim at issue in Grams was drawn to a method of diagnosing an "abnormal condition" by performing a laboratory test on an individual to measure a set of parameters, comparing the quantities obtained from the test to a predetermined value, performing additional comparisons on different combinations of the parameters, and identifying a subset of parameters that correspond to an abnormal condition. Although the Grams claim contained the active step of "performing a laboratory test," the claim was not limited to any particular condition or set of conditions, and the specification stated that the invention may be applied to any complex system, be it electrical, mechanical, chemical, etc. Thus, the court found that the claim was in fact directed to the algorithm for performing the comparison, rather than to the application of the algorithm for the diagnosis of any condition in particular. Id. See also K. Noonan, Patent Eligibility and In re Grams, http://www.patentdocs.org/2010/12/patent-eligibility-and-in-re-grams.html.

In addition to the "machine or transformation" analysis, the Prometheus court also examined whether the claims at issue pass the "preemption test" by asking whether they "wholly preempt all uses" of the naturally occurring correlation between metabolite levels and drug efficacy or toxicity. Prometheus, 628 F.3d at 1355. The court found that the claims did not preempt all uses of the natural correlations, but rather that they apply the correlations to a series of specific steps comprising particular methods of treatment, and note that other drugs may be administered to the subject to optimize therapeutic efficacy outside of the scope of the claims. Id. Because the claims satisfy both the "preemption test" and the "machine or transformation test," the court held that the method claims at issue are drawn to patent-eligible subject matter. Id. at 1359.

V. APPLICATION OF 35 U.S.C. § 101 TO THE METHOD CLAIMS AT ISSUE IN AMP V. USPTO

As noted above, there are six method claims currently under consideration by the Federal Circuit in AMP v. USPTO (see Table 2). Claim 20 of the '282 patent is directed to a method for screening potential cancer therapeutics in host cells, and requires the

steps of "growing" a host cell containing an altered BRCA1 gene in the presence and absence of a compound suspected of being a cancer therapeutic, "determining" the rate of growth of the host cell, and "comparing" the growth rate (see Table 2, '282 patent). AMP argues that this claim attempts to patent the abstract idea of comparing the growth rates of two cells, and that the physical step of "growing" is merely a data-gathering step for making this comparison (Appellee Br. 59). They further contend that limitation of the claimed method to the BRCA1 context is analogous to limiting the algorithm in Flook to the field of catalytic conversion, and thus does not convert a patent-ineligible claim to an abstract idea into patent-eligible subject matter merely by limiting the practice of this idea to a specific end use (Appellee Br. 59).

Based on prior precedent, it is likely that claim 20 will be found to satisfy § 101. Applying the reasoning the Federal Circuit used in Prometheus, the step of "growing" a host cell in the presence of a potential therapeutic is transformative in the sense that the therapeutic alters the physical makeup of the cell (*e.g.*, by altering proteins involved in growth and survival pathways). This transformative step is central to the claimed method of screening potential cancer therapeutics, and is not merely a "data-gathering" step. The foregoing conclusion is evidenced by the fact that the growing step provides the therapeutics to host cells containing BRCA1, enabling a transformation to occur within the host cells, such that compounds effecting this transformation may be identified.[2]

Moreover, the recitation of BRCA1 in claim 20 is not a mere pretext to avoid preempting the scientific principle that therapeutic compounds can affect the growth rate of cells. In order to be selected as a cancer therapeutic, the screened compounds must be capable of exerting a transformative effect on cells containing a BRCA1 mutation. This fact inextricably ties the BRCA1 mutation to the claimed method. Thus, claim 20 is properly characterized as an application of the scientific principle to a specific problem (*i.e.,* identification of therapeutic compounds that are effective against cells having an altered BRCA1 gene) analogous to Diehr. The claimed method as a whole does not preempt the use of the underlying scientific principle, as researchers are free to apply this

[2] The "determining" [the rate of growth of a host cell] step in claim 20 of the '282 patent is likely not "transformative" in the same sense as the step of "determining the level of [a drug]" in a subject as recited in the Prometheus claims, because determining the rate of growth of cells can be achieved by inspection, and does not require transformation of the cells in order to make the measurement being "determined."

principle to screen for therapeutics that are effective on any other type of host cells (*i.e.*, host cells not having an altered BRCA1 gene) without risk of infringement. They are likewise not preempted from identifying cancer therapeutics which are effective against BRCA1 containing cells using any other method (*e.g.*, comparing the longevity of animals to whom the compounds are or are not administered, etc.). As claim 20 satisfies both the machine and transformation test and the preemption test, the claim is drawn to patent-eligible subject matter, as established by Prometheus.

Claim 1 of the '001 patent and claim 1 of the '441 patent are drawn to methods of screening samples for alterations in the BRCA1 gene (see Table 2). Claims 1 and 2 of the '857 patent are drawn to a method of identifying a mutant BRCA2 nucleotide sequence, and a method of diagnosing a predisposition to breast cancer, respectively. In all four of these claims, the only active step recited is "comparing" the sequence of a gene with a reference sequence (*e.g.*, a sequence obtained from a non-tumor sample, a sequence of a wild-type BRCA gene, etc.). AMP argues that the claims are drawn to an abstract idea – the mental process of comparing two sequences – and notes that the claims do not require the separate step of determining the sequences of the material being compared (Appellee Br. 56). In contrast, Myriad argues that the term "comparing [a nucleotide sequence]" should properly be construed to require analysis of the DNA molecules being compared, rather than merely comparing the sequences as "letters on a page" (Appellant Br. 56-58).

The construction of the term "comparing a sequence" ultimately adopted by the court will likely be outcome-determinative with respect to the question of patent-eligibility for these claims. A person of ordinary skill in the biological sciences is likely to understand that the sequences of nucleic acid molecules are compared by inspecting an alphabetical representation of the molecules (*i.e.*, as letters on a page) and identifying any differences between the letters representing one sequence and the letters representing the sequence with which it is compared. The comparison may be performed mentally, or it may be performed with the assistance of a computer which aligns the letters representing both sequences with one another. The specification does not expressly define the steps required to "compare a sequence," and the usage of "sequence" in the specification is inconsistent with respect to whether this term is synonymous with "DNA molecule" or if

instead it refers to an alphabetical representation. Given the ambiguity of the specification and the art-recognized meaning of "comparing a sequence," the court is likely to construe the claim to require that an infringer only compare the alphabetical representation of two sequences, rather than requiring them to experimentally derive the sequence of the molecules being compared. Under this construction, the claims at issue are broad enough to capture a person who performs the mental step of comparing one sequence to another, regardless of how the sequence information they are comparing was obtained.

Applying the reasoning articulated in Prometheus, the claims at issue in the '001, '441 and '857 patents will likely fail the machine-or-transformation test. The process of comparing two sequences is not tied to any particular machine or apparatus, and, similar to the process in Benson, can be performed without the use of any apparatus. Performance of the claimed methods also fails to transform any article into another state or thing.

Failure of the machine-or-transformation test is no longer determinative following the Bilski court's rejection of this test as the sole means for resolving questions of patent eligibility. The Prometheus court additionally questioned whether the claims satisfy the "preemption test." The court framed this question by asking whether the claims "wholly preempt all uses" of the subject matter exempted from patent-eligibility. In Prometheus, the naturally occurring correlation between metabolite levels and drug efficacy was the subject matter that should not be preempted. In the instant case, the appropriate question is whether the claims wholly preempt all uses of the abstract idea that the sequence of a given gene can vary from one source to another. Unlike Prometheus, the claims at issue in the '001, '441 and '857 patents do not contain additional (non-mental) steps that use the information gained from the comparison step in any tangible application. Thus, the claims prohibit the act of comparing two BRCA1 or BRCA2 sequences for any purpose. The claims do limit the comparison to the context of BRCA1 and BRCA2 genes, and consequently do not preempt comparing the sequences of other genes to each other. However, based on the reasoning in Flook that a mathematical formula doesn't become patentable merely because a claim limits the field of its application, the claims at issue

here are likely unpatentable despite the fact that the scope of preemption is limited to the genes recited in the claims, because the only active step can be performed mentally.

Notably, the Prometheus court remarked that the claims at issue in that case were not drawn "merely to correlations between metabolite levels and toxicity or efficacy," implying that claims drawn to correlations are not patent-eligible. Prometheus, 628 F.3d at 1358. Moreover, the Prometheus court expressly noted that no claim in the Prometheus patents comprised only mental steps. Id. This dicta indicates a sentiment that claims reciting mental steps as the only active steps in a method will be considered unpatentable. Notwithstanding, the claims in Research Corp. were held patent-eligible despite reciting a single active step consisting of *utilizing a pixel-by-pixel comparison* of an image against a blue noise mask. Thus, at least in this context, a comparison step was sufficient to make a method patent-eligible. When analyzing this claim, the Research Corp. court asked the question of whether the abstractness of the claimed invention exhibited itself "so manifestly as to override the broad statutory categories of eligible subject matter." Research Corp., 627 F.3d at 868. In articulating this "manifestly abstract" standard, the Research Corp. court appeared to appreciate that a distinction should be drawn between claims that are so abstract that they do not pass muster under a § 101 analysis, and claims that pass through this coarse filter but yet may not be described with sufficient particularity to satisfy § 112. The court did not attempt to articulate any criteria to help the public identify where this line is to be drawn, beyond the vague statement that "inventions with specific applications or improvements to technologies in the marketplace" are unlikely to be so abstract that they fail to satisfy § 101. With respect to the Myriad claims, a strong argument can be made that the claimed methods of comparing BRCA nucleic acid sequences have specific application to the problem of determining one's predisposition to developing cancer, and represent a dramatic improvement over preexisting methods of for solving this problem, which were largely nonexistant. Notwithstanding, the claims at issue do not apply the comparison of BRCA sequences to the problem of diagnosing a predisposition to developing cancer (with the exception of claim 2 of the '857 patent), but rather are broadly drawn to detecting an alteration in the BRCA genes in any context. It is possible that such a

distinction may persuade the court to hold that the Myriad claims are "manifestly abstract" on this ground.[3]

The remaining method claim at issue in AMP v. USPTO is Claim 1 of the '999 patent, which is drawn to a method for detecting one of the specific alterations in the BRCA1 gene sequence set forth in Tables 12A, 14, 18 or 19 of the specification. These tables describe roughly 100 particular sites in the BRCA1 gene (which contains over 24,000 base pairs) where the applicants identified alterations in persons susceptible to BRCA1-mediated cancer. The method contains the single active step of "analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample." AMC argues that the step of "analyzing a sequence" is equivalent to the step of "comparing" one sequence to another, and is likewise nothing more than a mental step (Appellee Br. 55). Myriad argues that "analyzing a sequence" requires the transformative steps involved in obtaining the sequence, such as isolating the nucleic acid to be sequenced and hybridizing this to a probe (Appellant Br. 56). Again, the claim construction adopted for the term "analyzing a sequence" is likely to determine whether or not the claim is drawn to patent-eligible subject matter. The resolution of patent-eligibility of claim 1 of the '999 patent will be significant as the step of "analyzing" more closely tracks the language commonly used in diagnostic method claims, which typically recite a step of "assaying" a sample for the presence of a biomarker of interest (see Table 1, '658 patent; see also Metabolite Labs, Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354 (2004)).

VI. A PATH FORWARD FOR THE PROTECTION OF INVENTIONS RELATING TO DIAGNOSTIC METHODS?

The importance of diagnostic methods based on correlations between biomarkers and disease states to the field of medicine cannot be disputed. Such methods represent a practical advance in the science of diagnostic medicine, and the performance of such

[3] The Federal Circuit found a claim drawn to "a method of determining whether an immunization schedule affects the incidence or severity of a disorder" to be outside the scope of statutory subject matter in Classen Immunotherapies, Inc. v. Biogen Idec, 304 Fed. Appx. 866 (2008). The claim contained two active steps: (1) ***immunizing*** mammals; and (2) ***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. The decision was based solely on the court's determination that the method did not satisfy the machine-or-transformation test. The Supreme Court vacated this decision and remanded the case to the Federal Circuit for reconsideration in view of the Court's decision in Bilski.

methods produces a tangible end result – an improved diagnosis of a disease state in a subject. Such inventions are surely of a type that merits protection under the broad reach of the patent laws. The question for the patent community is how to draft claims that provide meaningful protection for such inventions without traversing the judicially created law of nature, physical phenomenon, and abstract idea exceptions to 35 U.S.C. § 101.

As described above, claims drawn to a biomarker as a composition of matter were traditionally thought to provide thick protection for the use of the biomarker in diagnostic assays. However, the validity of composition of matter claims drawn to isolated nucleic acid molecules has recently been called into question. Moreover, it is often the case that a diagnostic test is developed based on a newly discovered correlation between a known gene or protein and a particular disease state. In this scenario, composition of matter claims would not be patentable because the biomarker lacks novelty. Patenting the biomarker per se is therefore insufficient to provide a valuable measure of protection to inventions in this field.

A starting point for determining the appropriate claim drafting strategy is to consider the activity that the patentee seeks to prevent in a potential infringer. The hypothetical infringer should not be the medical doctor using the information from a diagnostic test to diagnose a patient. In addition to the public relations disaster that would result from enforcement of a patent against medical doctors whose infringing activity took place in the context of treating a patient, medical doctors are essentially exempted from infringement liability for practicing any patented "medical activity" under 35 U.S.C. § 287(c). As a practical matter, it is more important to capture the infringer who is (1) performing the diagnostic test on biological samples (typically this is a laboratory services provider who takes a patient sample and determines whether the sample contains a biomarker of interest), or (2) manufacturing and selling a test that may be used to evaluate whether a sample contains a biomarker of interest.

The activity of an infringer who is performing a diagnostic method may be prevented by a claim that contains the step of analyzing a sample for the presence of a biomarker. The precise language used in such a claim may depend on the type of biomarker and its relationship to a given disease state. By way of example, such a claim

can contain an active step of "determining whether a sample contains (exhibits, displays, etc.) Biomarker X." The claim may also contain a wherein clause linking the determining step with the disease state in question, *e.g.*, "wherein the presence of Biomarker X indicates that the subject has colon cancer (or is amenable to treatment with Y drug, or has a predisposition to developing Z disorder, etc.)." Under the reasoning articulated in Prometheus, the "determining" step should be transformative, in the sense that in order to make the determination required by the claim, it is necessary to transform the sample upon which the test is performed. The transformation can involve lysing cells, isolating nucleic acids, etc – as long as the "determining" step inherently requires performing any activity that transforms the sample (or a component thereof) to another state or thing it is likely sufficient. And linking the "determining" step to a particular disorder should satisfy the preemption test, by placing the method in a finite context. This link also supports a contention that the claim is not "manifestly abstract" because practicing the method produces a tangible result – diagnosis of a disease, determining suitability for treatment with a particular therapy, etc. For additional examples of claims that will likely satisfy the machine-or-transformation test and the preemption test, see Table 1, '531 patent ("detecting a higher level of ASCT2 protein…wherein the higher level of ASCT2 protein indicates that said individual has pancreatic cancer"), '395 patent ("assaying a blood sample…for an increase in the mRNA level of [x] genes…wherein the increase in the mRNA level…indicates that the…individual has systemic lupus erythematosus (SLE)), and '658 patent ("assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine…with a deficiency of cobalmin or folate"). Provided that the active steps of the claims satisfy the transformation prong of the machine-or-transformation test, there is no need to draft claims such that they satisfy the machine prong as well. In fact, tying the claim to a given machine or apparatus is unduly limiting, as the determining step may be performed using any number of different apparatus known in the art. Reciting a particular apparatus in the claims invites a potential infringer to use an alternate means for achieving the straightforward goal of determining the presence, activity, etc. of a biomarker in a sample.

Drafting a claim to cover the infringer manufacturing a test for determining whether or not a sample contains a biomarker is not so straightforward. This party will not be directly infringing a claim drawn to determining whether a sample contains Biomarker X, although they may be liable on a theory of indirect/induced infringement. Notwithstanding, it is desirable to obtain a claim that would cover this activity directly. One possibility is to claim a kit comprising reagents that may be used to detect the presence of a biomarker in a sample, together with instructions for using the kit to determine if an individual has a particular disorder. Alternatively, a kit could be claimed which recites a "means for" detecting the biomarker in a sample, together with suitable instructions for using the kit to identify a subject having the disorder in question. Means-plus-function limitations are rarely used in relation to biotechnology inventions, and have fallen out of favor with the patent community generally because of the narrow manner in which the means-plus-function language is construed. In order to interpret a means-plus-function limitation, it is necessary to identify the structure in the specification that is described as performing the recited function, and then to identify the corresponding structure in an accused infringing product. Literal infringement requires that the structure in the accused infringing device perform the identical function recited in the claim and be identical or equivalent to the corresponding structure in the specification. Applied Med. Res. Corp. v. U.S. Surgical Corp., 448 F.3d 1324 (2006). While in many contexts means-plus-function language is viewed as being unduly narrowing, in the instant case it would allow a patentee to extensively describe the means that could be used to perform the "determining" step of the method in the specification without having to recite each such means in a separate claim, where the means themselves are not the point of novelty of the kit.

Some patentees have included a treatment step in their diagnostic method claims, *e.g.*, a method of treating Y Disorder comprising (a) detecting Biomarker X, and (b) if Biomarker X is detected, administering an effective amount of Drug Z (see Table 1, '914 patent). While the administering step is surely transformative under Prometheus, and thus places this claim squarely in the realm of patent-eligible subject matter, it is rare that the same party performing the detecting step is the party administering the prescribed

treatment to the subject. While such claims are patent-eligible, their relative value is low, as enforcement will likely depend on proving contributory infringement.

The Federal Circuit's treatment of the method claims at issue in AMP v. USPTO will be studied in detail, as this decision will likely provide some much-needed clarity to the patent community with respect to the intellectual property protections available for diagnostic medicine. In the meantime, it is to the benefit of patent applicants to draft claims of varying scope which arguably pass muster under the various judicial tests for determining patent-eligibility. Depending on the scope of protection that the court ultimately decides is warranted under 35 U.S.C. § 101, it may fall to Congress to create protections specifically designed to encourage innovation in the diagnostic medicine industry.