Epigenetic Patents: A Stressful Environment for an Emerging Science*

By WILLIAM NOONAN, MD,[†] ADRIA DECKER DISMUKE, PhD,[‡]
and MITCHELL S. TURKER, PhD[§]

GENETIC SCIENCE has been a cornerstone of medical research for more than half a century. Since the discovery of the structure of DNA by Watson and Crick in 1953, the central dogma of molecular biology has been that there is a “residue-by-residue transfer of sequential information” from DNA to proteins,¹ and this sequential information was understood to code for the expression of proteins that affected most aspects of health. The detection of DNA mutations associated with disease was regularly reported throughout the last decades of the 20th Century. Genetic research reached a critical point in 2003, when the Human Genome Project was completed and the sequence of the 3 billion nucleotides in the complete human genome was published. It had been expected that this information would solve many of the mysteries of medical science and suggest therapies for previously untreatable diseases. However, before the Project was complete, it became evident that the genomic sequence information would provide only a partial explanation of the causes and cures of disease. A more extensive understanding of genetic medicine would require an inquiry into the “epigenome” and the effect of the history of the cellular environment on gene expression. The biologically deterministic paradigm of the central dogma has now yielded to a more subtle understanding that gene function can be affected by environmental factors. Such factors can

modify genes in somatic cells and lead to disease, or potentially modify genes in germ cells to pass harmful modifications to subsequent generations.²

Epigenetic research has suggested that environmental conditions can cause chemical modifications (such as the addition or removal of methyl groups) to DNA or histones to alter the health of humans and their offspring—even in a transgenerational manner—apart from changing the nucleic acid sequences of their genes. An early published example of this phenomenon was a Swedish study that showed an abundant food supply for a grandfather before his pre-pubertal growth spurt increased the likelihood that his *grandson* would die of a diabetes-related disorder.³ A father’s poor food supply and a mother’s ample food supply were associated with a lower risk of cardiovascular death in their subsequently born children.⁴ Differences in early post-natal life have also been found to result in lasting, transgenerational changes in behavior, mediated in part by changes in epigenetic histone

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[†]Klarquist Sparkman, LLP, 1600 One World Trade Center, 121 SW Salmon Street, Portland, OR 97204.

[‡]Lewis and Clark Law School, 10015 S.W. Terwilliger Boulevard, Portland, OR 97219.

[§]Center for Research on Occupational and Environmental Toxicology (CROET) and Department of Molecular and Medical Genetics, Oregon Health & Science University, Portland, OR 97239.

¹Crick F. Central dogma of molecular biology. *Nature* 1970;227:561–3.

²Indeed, subtle yet heritable changes in gene expression not associated with DNA mutations, termed “epigenetic modifications,” have recently been implicated as a novel mechanism in speciation. Natt D et al. Heritable genome-wide variation of gene expression and promoter methylation between wild and domesticated chickens. *BMC Genomics* 2012;13:59, 2–9 (2012); Gupta S. Epigenetics posited as important for evolutionary success. *Nature* 2013; available at www.nature.com/news/epigenetics-posited-as-important-for-evolutionary-success-1.12179

³Lalande M. Parental imprinting and human disease. *Annu Rev Genet* 1996;30:173–95.

⁴*Id.* A similar study of the children of women who were pregnant during the Dutch Hunger Winter of 1944 showed that the children were more likely to develop obesity, cardiovascular risk factors, and other health problems. Roseboom TJ et al. Effects of prenatal exposure to the Dutch famine on adult disease in later life: An overview. *Molec Cell Endocrinol* 2001;185:93, 96–97. See also John Cloud, “Why DNA Isn’t Your Destiny,” *Time*, January 6, 2010.

marks and DNA methylation states.⁵ For example, early parental care-giving in rodents causes epigenetic changes that can alter an offspring's life-long response to stress, an effect that can be passed from one generation to the next, perhaps by affecting the parental care behavior of subsequent generations.⁶ One of the best-documented examples in humans of a transmissible epigenetic effect was the use of the estrogenic agent diethylstilbestrol (DES) to prevent miscarriages in pregnant women, which led to the development of a rare form of vaginal cancer in their prenatally exposed daughters.⁷

The growing knowledge of epigenetic science and the relation between this science and human health has led to an increasing number of patents that could aid in the discovery and treatment of the root causes of many common diseases. As these patents proliferate, however, a shifting legal landscape could reduce intellectual property rights in various aspects of epigenetic science, thus reducing commercialization of this new technology. This article examines epigenetic science and resultant patents, how these patents are changing over time as basic scientific discoveries lead to new treatments, and how future epigenetic patents might fare in the light of recent court decisions limiting the patent eligibility of biomedical technologies. A stressful prenatal and perinatal environment can alter the lifetime health of a human, and a harsh legal environment can have similar effects on the commercial development of new technologies.

THE ORIGIN AND CURRENT STATE OF EPIGENETIC SCIENCE

Epigenetics is a relatively new science that studies differences in gene expression in the absence of changes in DNA sequences. The "epigenome" is the aggregate of the heritable cellular markers (such as histone modification and DNA methylation) that control the differential expression of genes. Charles Waddington coined the term "epigenetics" in a 1942 article to describe the study of causal mechanisms during development. He was attempting to explain the creation of many different cell types from a single fertilized egg. In the same article, he coined the term "epigenotype" to describe the "complex of developmental processes" that connect phenotype with genotype, and then introduced the concept that disturbances of the epigenotype could cause abnormalities in organs and tissues.⁸ Today, the epigenotype is called the epigenome because specific epigenetic modifications have been found that connect phenotype to genotype.⁹ These modifications are cell-type specific and can also be disease specific, thus providing a link between an understanding of the epigenome and Waddington's prediction that perturbations in the epigenome could lead to disease processes.¹⁰ At present, the commonly accepted definition of epigenetics is "the study of changes in gene function that are mitot-

ically and/or meiotically heritable and that do not entail a change in DNA sequence."¹¹

The first epigenetic modification proposed to play a causal role in gene expression was methylation of cytosine bases, which in mammals is limited to cytosines that are followed by guanines (CpGs).¹² Increased DNA methylation is linked to loss of gene expression and vice versa.¹³ In mammalian cells, the DNA methylation modification is added by three enzymes that recognize different regions or conformations of the genome.¹⁴

Epigenetic modifications are not limited to DNA methylation, but can also occur on histone proteins that the DNA molecule is wrapped around.¹⁵

⁵McEwen *et al.* Stress and anxiety: Structural plasticity and epigenetic regulation as a consequence of stress. *Neuropharmacology* 2012;62:3, 7.

⁶Weaver *et al.* Epigenetic programming by maternal behavior. *Nat Neurosci* 2004;7:847–54.

⁷Mitchell S. Turker. Banning bisphenol A in the United States and Canada: Epigenetic science, the precautionary principle, and a missed opportunity to protect the fetus. 8 *JOURNAL OF HEALTH AND BIOMEDICAL LAW* 173, 187–190 (2012).

⁸Waddington. The epigenotype: 1942. *Int J Epidemiol* 2012;41: 10. Waddington specifically referred to "the processes involved in the mechanisms by which the genes of the genotype bring about phenotypic effects." In doing so, he was taking the science of genetic inheritance out of the discussion and instead asking the more basic question of how genes are expressed differentially in different cell types as development of an embryo progresses.

⁹Esteller. The necessity of a human epigenome project. *Carcinogenesis* 2006;27:1121.

¹⁰*Id.* at 1121–3.

¹¹Dupont *et al.* Epigenetics: definition, mechanisms and clinical perspectives. *Semin Reprod Med* 2009;27:351. Broadly interpreted, Waddington's version of epigenetics during development refers to all molecular pathways that transform genotype into phenotype. This definition is somewhat limited because it would not appear to include stable epigenetic changes in post-mitotic neurons, although most researchers would agree that DNA methylation changes in these cells would indeed constitute an epigenetic change.

¹²Holliday, Pugh. DNA modification mechanisms and gene activity during development. *Science* 1975;187:226, 228–30.

¹³Vaissiere *et al.* Epigenetic interplay between histone modifications and DNA methylation in gene silencing. *Mut Res* 2008;659:40, 42–3.

¹⁴Goll, Bestor. Eukaryotic cytosine methyltransferases. *Annu Rev Biochem* 2005;74:481, 487–93, 495–7 (2005). All three of the DNA methylated enzymes, termed "DNA methyltransferases," are required for development. In mouse models, loss of any of these genes leads to death of the developing fetus or death shortly after birth.

¹⁵See histone definition, *Webster's New World Medical Dictionary* 199 (3d ed. 2008). A histone is "[a] protein around which DNA coils to form chromatin. Without histones, DNA could not organize into chromosomes." *Id.*; see also Nestler. Hidden switches in the mind. *Sci Am* Dec. 2011, at 77, 79. "[DNA] is wrapped around clusters of proteins called histones—like thread on a spool—and then further bundled into structures we call chromosomes. The combination of protein and DNA in chromosomes is known as chromatin."

Modifications to histones create a second set of epigenetic modifications. The most common of these are acetylation and methylation,¹⁶ which—like DNA methylation—can influence gene expression.¹⁷ The combination of DNA methylation and histone modifications at a given gene are heritable in somatic cells to ensure that gene expression does not change each time a cell divides.¹⁸ Although this heritability is important to preserve normal gene expression over time, it can also preserve disease-causing epigenetic modifications that, like mutations, sometimes arise as a consequence of normal cellular processes or of environmental exposures.¹⁹ Just as genomics revolutionized medical genetics by describing and quantifying DNA sequence variations, the emerging science of epigenomics is pushing the field further by describing and quantifying epigenetic modifications.²⁰ In total, elucidation of the molecular underpinnings of epigenetics has transformed this field in 70 years from one that was both speculative and descriptive to one that explains both developmental processes and how these processes cause disease when they go awry.

EPIGENETIC DISEASE DETECTION, DIAGNOSIS, AND POTENTIAL TREATMENTS

Waddington's prediction in 1942 that alterations of the epigenome could cause diseases in organs and tissues was prescient. Beginning with reports in the late 1980s of altered DNA methylation in cancer, the field of cancer epigenetics emerged.²¹ By the mid-1990s, DNA methylation took its place alongside mutations as a major factor in the development of cancer.²² Genes with high levels of DNA methylation ("hypermethylation") have been described in essentially every major cancer type, with the affected genes and regions often corresponding to the type of cancer.²³ Epigenetic changes are also implicated in other diseases, including autoimmune disease, asthma, type 2 diabetes, metabolic disorders, autism, and neurodegenerative and psychiatric disorders.²⁴ Moreover, the developmental origins-of-disease theory predicts that the genesis of many epigenetic diseases occurs during gestation, which is the time when the epigenome is primarily established.²⁵

To better detect and diagnose epigenetic diseases, a variety of methods have been developed to identify epigenetic modifications in biological specimens. DNA methylation detection is currently the best surrogate marker for epigenetic change in disease because methylation alterations track with disease state, particularly for cancer. DNA methylation markers can also indicate success or failure of drug treatment, are stable in isolated DNA and can be measured by a variety of quantitative and qualitative methods.²⁶ Moreover, disease-specific DNA methylation patterns can be

detected in preparations isolated from non-invasively obtained samples, such as stool, serum, or urine to detect methylation alterations consistent with colon²⁷ and bladder²⁸ cancer. In contrast, histone modifications are meaningful only in the context of the DNA sequence to which they are bonded, which requires isolation of whole cells from a tumor specimen and of intact histone/DNA complexes from the cells.²⁹

Most methods to detect DNA methylation in clinical specimens are based on polymerase chain reaction (PCR) amplification of segment of bisulfite-treated DNA.³⁰ This technique can distinguish a methylated from an unmethylated cytosine in a given DNA sequence.³¹ The bisulfite approach has led to a number of patent applications because it can be used to detect DNA methylation for target loci associated with a specific disease.³² To better understand epigenetics

¹⁶Sawan, Herceg. Histone modifications and cancer. *Adv Genet* 2008;70:57, 61–65. Histone acetylation is associated with gene expression, with loss of histone acetylation accompanying loss of gene expression. The rules for histone methylation are more complicated because some forms are associated with gene expression and others with gene repression.

¹⁷Dawson, Kouzarides. Cancer epigenetics: from mechanism to therapy. *Cell* 2012;150:12–21.

¹⁸Sarkies, Sale. Cellular epigenetic stability and cancer. *Trends Genet* 2012;28:118–22.

¹⁹Weidman Dolinoy, Murphey, Jirtle. Cancer susceptibility: epigenetic manifestation of environmental exposures. *Cancer J* 2007;13:9–14.

²⁰Callinan, Feinberg. The emerging science of epigenomics. *Human Genetics* 2006;25:R95–R100.

²¹Feinberg, Tycko. The history of cancer epigenetics. *Nat Rev Cancer* 2004;4:143, 145–146.

²²*Id.* at 145–146.

²³Esteller. Epigenetics in cancer. *N Engl J Med* 2008;358:1148–1152; Kulis, Esteller. DNA methylation and cancer. *Adv Cancer* 2012;70:27–38.

²⁴Szyf. Epigenetic, DNA methylation, and chromatin-modifying drugs. *Annu Rev Pharmacol Toxicol* 2008;49:243; Best, Carey. Epigenetic therapies for non-oncology indications. *Drug Discov Today* 2010;15: 1008, 1010–1011.

²⁵Thornburg, Shannon, Thuillier, Turker. In utero life and epigenetic predisposition for disease. *Adv Cancer* 2010;71:57, 61–66.

²⁶Heyn, Esteller. DNA methylation profiling in the clinic: applications and challenges. *Nat Rev Genet* 2012;13:679–680.

²⁷Kim, Lee, Sidransky. DNA methylation markers in colorectal cancer. *Cancer Metast Rev* 2010;29:181–189.

²⁸Kim, Kim. Epigenetic markers as promising prognostic indicators for bladder cancer. *Int J Urol* 2009;16:17–20.

²⁹Esteller. Epigenetics in cancer. *N Engl J Med* 2008;358:1148–1154.

³⁰Chaudhry. *Strategies for Detecting DNA Methylation: A Survey of US Patents*, 4 RECENT PATENTS ON DNA & GENE SEQUENCES, 79, 79–81.

³¹*Id.*

³²*Id.*

and disease, bisulfite treatment also can be used with next-generation sequencing to view global DNA methylation changes that occur in the context of disease.³³ Standard DNA sequencing could also be useful for understanding epigenetic changes in cancer, because epigenetic modifier genes are frequently mutated in cancers, and these mutations may explain some observed perturbations to the epigenome.³⁴

Epigenetic modifications and the enzymes that create them are seen as attractive drug targets to treat disease because the modifications are reversible.³⁵ In theory, reversal of a modification that is causally involved in a disease should lead to amelioration of symptoms, and perhaps even provide a cure. At the present time, the FDA has approved four epigenetic drugs for disease management: two with inhibitory activity for DNA methylation and two that inhibit histone deacetylation.³⁶ A significant caveat for epigenetics drugs is that they are relatively nonspecific in targeting genes and thus could have severe side effects.³⁷ Nonetheless, patent applications are being submitted for the use of epigenetic enzymes such as histone deacetyltransferase inhibitors, alone or in combination with other drugs, although drugs with greater target specificity are being developed.³⁸

PATENTABILITY REQUIREMENTS IN THE UNITED STATES

A patentable invention in the U.S. is defined by the claims.³⁹ The claimed invention must be directed to (1) patent-eligible subject matter that is (2) new; (3) non-obvious to a person of ordinary skill in the art; (4) useful in a specific, substantial, and credible way; and (5) described in a way that demonstrates the inventor was in possession of the invention at the time the patent application was filed.⁴⁰ Each of these requirements has, in recent years, been the subject of judicial scrutiny—particularly as they apply to the relatively new fields of biotechnology and software. However, in the last few years, particular judicial attention has been given to whether certain types of biological inventions qualify as “patent-eligible” subject matter. This question is of fundamental significance because patent-ineligible inventions are disqualified from patent protection, and thus are not even scrutinized to determine whether they satisfy the other requirements for patentability such as novelty and non-obviousness. Supreme Court decisions have recently demonstrated hostility toward some types of patent protection for biological inventions that may create a much-different set of incentives for the commercial development of epigenetic inventions than were available for genetic inventions.

EPIGENETIC PATENTS INITIALLY Arose in a FAVORABLE LEGAL ENVIRONMENT

In 1980, the PTO issued the first major biotechnology DNA patent, one of three that came to be known as the “Cohen–Boyer recombinant DNA cloning patents” after inventors Stanley N. Cohen of Stanford and Herbert W. Boyer of the University of California, San Francisco (UCSF).⁴¹ The first patent of this group is based on the 1973–1974 development of a fundamental molecular biology process known as recombinant DNA technology.⁴² The use of this technology became ubiquitous in laboratories all over the world, and the Cohen–Boyer patents ultimately netted Stanford and UCSF more than \$200 million in licensing fees thanks in part to the Bayh–Dole Act.⁴³ The success of these patents and the Supreme Court decision in *Diamond v. Chakrabarty*⁴⁴ signaled administrative and judicial approval for an expansive interpretation of patent-eligible subject matter that opened the flood-

³³Lee et al. Analyzing the cancer methylome through targeted bisulfite sequencing. *Cancer Lett*; Epub November 28, 2012. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2320067/>

³⁴Esteller. Cancer epigenetics for the 21st Century: what's next? *Genes Cancer* 2011;2:604, 605. Mutated epigenetic modifiers found in human cancers include histone methyltransferases, histone demethylases, histone deacetylases, and chromatin-remodeling proteins.

³⁵Sharma, Kelly T, Jones PA. Epigenetics in cancer. *Carcinogenesis* 2010;31:27–33.

³⁶Boumber, Issa. Epigenetics in cancer: what's the future. *Oncology* 2011;25:220–226. The DNA methylation inhibitors are used to treat myelodysplastic syndrome; see Leone et al. Targeting DNA methylation for epigenetic therapy. *Clin Immunol* 2003;109:89–97.

³⁷Szyf. Epigenetic, DNA methylation, and chromatin modifying drugs. *Annu Rev Pharmacol Toxicol* 2008;49:243–254.

³⁸Carafa, Nebbioso, Altucci. *Histone Deacetylase Inhibitors: Recent Insights from Basic to Clinical Knowledge & Patenting of Anti-Cancer Actions*, 6 RECENT PATENTS ON ANTI-CANCER DRUG DISCOVERY 131, 139–140 (2011).

³⁹Holman. Debunking the myth that whole-genome sequencing infringes thousands of gene patents. *Nature Biotechnol* 2012;17:240.

⁴⁰These requirements for patentability are set forth in Title 35 of the United States Code (USC), particularly in §§101, 102, 103, and 112.

⁴¹Cohen, Boyer. Process for producing biologically functional molecular chimeras. U.S. Patent No. 4,237,224 (Dec. 1980).

⁴²Hughes. Making dollars out of DNA: the first major patent in biotechnology and the commercialization of molecular biology, 1974–1980, 92 *Isis*, 541, 541–2 (2001).

⁴³Rauber. “\$200M patent runs out: UCSF and Stanford scramble to replenish looming loss of income,” *San Francisco Business Times* (November 23, 1997). Available at www.bizjournals.com/sanfrancisco/stories/1997/11/24/story2.html

⁴⁴447 U.S. 303 (1980). This decision upheld the patentability of a genetically modified microorganism and broadly extended the scope of patent-eligible subject matter under 35 USC §101 to “anything under the sun that is made by the hand of man.”

gates for the issuance of DNA patents. The subsequently patented technologies evolved through time from basic analysis and cloning methods, such as those found in the Cohen–Boyer patents, to claims for isolated DNA sequences and their use in recombinant protein expression⁴⁵ or disease diagnosis,⁴⁶ methods and constructs for use in gene therapy,⁴⁷ and eventually, bioinformatics tools that combined data from large-scale gene projects (such as the Human Genome Project), DNA microarrays, and software programs for data mining and analysis.⁴⁸ These categories are classified herein as techniques, diagnostics, therapeutics, and bioinformatics. “Techniques” are basic laboratory methods used to study and manipulate the epigenome; “diagnostics” rely on observation or biological correlations for diagnostic, prognostic, or theranostic purposes;⁴⁹ “therapeutics” are clinical interventions to treat disease; and “bioinformatics” inventions apply software techniques and database mining to organize and analyze data.

As demonstrated below, epigenetic patents are in the midst of a similar evolution from basic laboratory techniques for detecting and modifying epigenetic changes, to methods of using those techniques to observe biological correlations, make therapeutic interventions, and store epigenetic data for subsequent retrieval and analysis. Unlike DNA sequence patents that claim isolated DNA molecules, most epigenetic patents are method patents. No epigenetic patents have been noted that claim an isolated, epigenetically altered DNA sequence, because no clear epigenetic analog exists to an isolated or purified nucleic acid. The first epigenetic patents to be granted were filed in the 1990s, and were primarily *technique* patents. These patents claimed laboratory methods that lay the foundation for future epigenetic advances by describing how to detect and manipulate DNA methylation. For example, U.S. Patent No. 5,871,917 claims methods of detecting hypomethylation (decreased DNA methylation) or hypermethylation in a CpG sequence. Only nine epigenetic patents were granted prior to 2000. Although most claimed techniques, the first *diagnostic* epigenetic patent application was filed in 1998 and subsequently issued in 2001 as U.S. Patent No. 6,180,344. It claimed a method of sequencing the methylation pattern upstream of *MyoD1* and utilizing the information to indicate the presence of rhabdomyosarcoma.⁵⁰ This is a classic example of using a biological correlation to diagnose a disease. An early epigenetic *therapeutic* patent was U.S. No. 6,613,753 (filed in 2001 and issued in 2003), which claimed a method of treating cancer using a methylation inhibitor to reverse epigenetic methylation changes that had been observed in certain cancers.⁵¹

Epigenetic patenting expanded rapidly in recent years. The 5-year period from 2000 to 2004 saw a sharp increase in the number of successful epigenetic patent applications filed (Table 1), subsequently pro-

TABLE 1. TYPES OF GRANTED EPIGENETIC PATENTS CATEGORIZED BY FILING DATE

	1995–1999	2000–2004	2005–2012	Totals
Techniques	8	18	19	45
Diagnostics	1	23	18	42
Therapeutics	0	5	4	9
Bioinformatics	0	1	4	5
Total	9	47	45	101

ducing 47 granted patents, nearly half of which were diagnostic patents that relied on biological correlations.⁵² There were also five patents issued for therapies based on epigenetic technologies. In 2006, the first epigenetic bioinformatics patent issued (based on a 2003 application), with claims to a method of identifying members of a biological pathway in a species by clustering quantitative trait data that utilized epigenetic information, such as DNA methylation.⁵³

⁴⁵An example is U.S. Patent No. 4,652,525, which claimed a recombinant plasmid or microorganism modified to contain a nucleotide sequence that is the reverse transcript of an mRNA that encodes insulin. Another example is U.S. Patent No. 4,703,008, which claimed a purified and isolated DNA sequence encoding human erythropoietin.

⁴⁶For example, the patents included in *Association for Molecular Pathology et al. vs. United States Patent and Trademark Office and Myriad Genetics*, such as U.S. Patent No. 5,709,999, which claimed a method of detecting specified germline alterations in the *BRCA1* gene, and U.S. Patent No. 5,710,001, which claimed a method of screening a tumor sample from a human subject for a somatic alteration in a *BRCA1* gene by comparing the tumor *BRCA1* sequence with a non-tumor *BRCA1* sequence.

⁴⁷For example, U.S. Patent No. 7,265,153, Compositions and methods for the treatment of cystic fibrosis (issued Sept. 4, 2007).

⁴⁸M. Scott McBride, Bioinformatics and intellectual property protection, 17 BERKELEY TECH. L.J. 1331 (2002).

⁴⁹Theranostic processes link bio-markers with safe and effective drug use by guiding treatment decisions in personalized medicine. See Kesselheim, Karlawish. Biomarkers unbound. N Engl J Med 2012;366:2338, 2340. An example of such a process is found in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S.Ct 1289 (2012), discussed in greater length below.

⁵⁰This patent was also a gene patent because it claimed an isolated DNA molecule that encoded a specified upstream sequence from the human *MyoD1* gene.

⁵¹Many epigenetic patents have claims to more than one category of invention, such as U.S. Patent No. 6,410,273, which claims methods of producing methylated DNA in the form of a plasmid to be used in gene therapy. Although such a method ultimately has therapeutic purposes, the present practical utility is limited to laboratory uses, and the patent is therefore categorized herein as a laboratory technique instead of a therapy.

⁵²We have categorized epigenetic patent activity by the filing date of the patent applications instead of the issue date to correct for delays in patent issuance that would otherwise confound the data.

⁵³U.S. Patent No. 7,035,739 “Computer systems and methods for identifying genes and determining pathways associated with traits.”

Epigenetic patent activity has continued, with at least 45 epigenetic patent applications granted between the years of 2005–2012 (Table 1). These more recently issued patents include four for bioinformatic inventions that focus on personalized medicine, utilizing epigenetic data as one of many diagnostic parameters. The changes in numbers and types of issued epigenetic patents from 1995 to 2012 are shown in Table 1.

TRENDS IN RECENT EPIGENETIC PATENTS

To determine the direction in which epigenetic patenting is moving, a survey of 100 recently published, pending epigenetic patent applications was completed. This survey showed a shift in the types of epigenetic patent applications being filed from the patents granted previously ($p < 0.001$) because the percentages of patent applications claiming therapeutic methods and bioinformatics inventions have increased (Table 2). This observation suggests that these types of patent applications are increasing as epigenetic technology evolves. The possibility also exists that some types of epigenetic patent applications, particularly the diagnostic method patents, are being issued (or even filed) less frequently as they face greater scrutiny under court decisions such as *Association for Molecular Pathology v. Myriad Genetics*⁵⁴ and *Mayo Collaborative Services v. Prometheus Laboratories*.⁵⁵ These decisions have expressed judicial skepticism about the patent eligibility of diagnostic methods that rely on biological correlations (see below). The judicial limitation of patent protection for epigenetic diagnostic methods may have a chilling effect on patenting and commercializing these methods. Private investment may be more difficult to obtain without the security afforded by patent protection, potentially affecting the availability of epigenetic technologies for clinical use.

RECENT LEGAL DEVELOPMENTS MAY PRECLUDE PATENTING SOME EPIGENETIC INVENTIONS, ESPECIALLY MANY DIAGNOSTIC METHODS

The biotechnology industry developed during the last few decades with the encouragement of strong pat-

ent protection for inventions in molecular biology and genetics. Two recent U.S. court decisions about patent-eligible subject matter have made it less likely that meaningful patent protection will be available for some types of epigenetic inventions in the United States. The first of these decisions concerns the long-running controversy about the patentability of isolated *BRCA* DNA molecules and methods of using *BRCA* polymorphisms to predict the development of breast and ovarian cancers. In *Myriad Genetics*, the U.S. Court of Appeals for the Federal Circuit decided that an “isolated” DNA molecule corresponding in sequence to a naturally occurring gene is patent-eligible subject matter. The claimed isolated genomic DNA sequence was said to be physically transformed from its naturally occurring state because it lacked covalent bonds that would normally be found at the terminal ends of the phosphodiester DNA backbone. Isolated eukaryotic cDNA molecules were also considered to be non-naturally occurring compositions of matter because they lacked introns. These physical differences distinguished the claimed compositions from patent-ineligible products of nature.

Although the Federal Circuit found that isolated molecules derived from nature were patent-eligible subject matter, this outcome was not significant for epigenetic inventions because no epigenetic correlates exist to an isolated DNA molecule.⁵⁶ Method claims are the primary type of protection for epigenetic inventions. It is therefore significant that the Federal Circuit in *Myriad Genetics* also decided that methods of detecting germline or somatic *BRCA1* alterations in a subject or tumor were ineligible for patent protection because such methods were only a series of mental steps that did not qualify for patent protection. Hence, the Federal Circuit decided that composition claims (that would be of little importance to epigenetic

⁵⁴ *Association for Molecular Pathology et al. v. United States Patent and Trademark Office and Myriad Genetics, et al.* 653 F.3d 1329 (Fed. Cir. 2011), reversed in part 569 U.S. __ (2013).

⁵⁵ *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 SCt 1289 (2012).

⁵⁶ The Federal Circuit’s decision in *Myriad Genetics* that isolated DNA molecules are patentable was recently overturned by the Supreme Court. The outcome of that decision is expected to have minimal direct effect on epigenetic patents because the Supreme Court considered only the patentability of the DNA composition itself, not methods of using it for diagnostic or prognostic purposes. Because there are no clear epigenetic correlates to “isolated DNA” compositions, the outcome of that decision should have minimal direct impact on epigenetic patents. An indirect impact could be felt, however, if the Supreme Court continues to demonstrate a reflexive legal hostility to biotechnology patents, as they did in *Myriad Genetics*. As noted later in this article, the Supreme Court requested that the parties in *Myriad Genetics* brief only a question that is not at issue in the case (“Are human genes patentable?”), which suggested the decision itself would be conceptually distorted.

TABLE 2. TYPES OF PENDING EPIGENETIC PATENT APPLICATIONS

Techniques	Diagnostics	Therapeutics	Bioinformatics	Total
26%	34%	20%	20%	100%

inventions) were patent eligible whereas method claims (that are of vital significance to epigenetic inventions) had limited patent eligibility.

The *Myriad Genetics* decision did not address some important questions about the patent eligibility of methods of diagnosing or predicting disease. The patent claims at issue in *Myriad Genetics*, which were very broad, only required comparing a *BRCA1* DNA sequence to a reference sequence to identify differences. The claims did not require obtaining a sample from a patient, determining a *BRCA1* DNA sequence in the sample, or making a clinical prediction based on the identification of polymorphisms in the sequence. The *Myriad* case did not address whether such additional steps would make a method of genetic diagnosis patent eligible. However, the Supreme Court in *Prometheus*⁵⁷ suggested that even the addition of such specific mental and non-mental steps to the method would not usually render a method patent eligible if the method primarily concerned the observation of a biological correlation.

The *Prometheus* patent claimed a method of adjusting the dosage of a thiopurine drug by administering the drug to a subject having an immune-mediated gastrointestinal disorder, determining the concentration of 6-thioguanine in the blood, and modifying the dosage of the drug based on concentration of 6-thioguanine that was measured. The Supreme Court unanimously decided that the claimed method was a patent-ineligible law of nature because it relied on the recognition of a correlation between thiopurine metabolite concentrations and the toxicity and efficacy of the drug. Although this patent did not concern the identification of genetic or epigenetic markers of disease, the Supreme Court decision appeared to broadly preempt patent eligibility for any medical methods that rely on the mere observation of biological correlations. Such biological correlations would include methods of predicting or treating disease by detecting a genetic or epigenetic variation that is associated with that disease or that predicts a response to therapy. According to the Supreme Court in *Prometheus*, methods of using biological correlations are not patentable subject matter even if the method requires obtaining a sample from the patient, subjecting it to analysis, and changing treatment decisions in response to the information obtained. Such steps were said to add nothing of significance to the natural law; a method does not become eligible for patent protection by applying the natural law in a series of conventional steps. The Court expressed particular caution about interfering with a physician's treatment decisions based on inferences drawn from biological correlations.⁵⁸

Following the *Prometheus* decision, the Federal Circuit decided *PerkinElmer, Inc. v. Intema Limited*⁵⁹ invalidating a patent claim to a method of calculating prenatally the risk of an infant having Down's syndrome by assaying for and measuring screening

markers in the first and second trimesters of pregnancy. The screening markers could be serum markers or ultrasound results. The method was patent ineligible because it merely claimed mental steps and was directed to a law of nature. The "measuring" steps did not add enough to the patent-ineligible subject matter to direct the claims to patent-eligible aspects of the concept. The mere observation of a biological correlation to make diagnostic or therapeutic conclusions could not be validly patented, even if combined with non-mental steps. The use of conventional assays to determine the concentration of the fetal markers was insufficient to transform the patent-ineligible biological correlation into a patent-eligible application of the law. Although *PerkinElmer* is a non-precedential opinion, it suggests that future Federal Circuit case law will interpret *Prometheus* to deny the patent eligibility of epigenetic inventions that rely on the observation of epigenetic markers in fetuses or other test subjects to establish a biological correlation with health or disease.

The PTO has complained that the Supreme Court has provided inadequate guidance about patent-eligible subject matter.⁶⁰ However, the PTO recently issued Interim Procedures in view of the *Prometheus* decision to instruct its more than 7,000 patent examiners about how to determine subject matter eligibility of claims that involve "laws of nature."⁶¹ According to these guidelines, a claim to a newly discovered natural correlation is not patent eligible.⁶² The method must include an additional element or step that amounts to significantly more than the natural principle itself. The PTO Interim Procedures cite several examples of medical methods that would be considered patent eligible or ineligible under the guidelines, but none of these examples specifically addresses the patent eligibility of genetic or epigenetic diagnostic tests.

⁵⁷*Mayo Collaborative Services v. Prometheus Laboratories*, 132 S Ct 1289 (2012).

⁵⁸The method claimed in the *Prometheus* patent did not require that the dose of the thiopurine drug actually be adjusted in response to the measured metabolite concentration. The patent claim only stated that the metabolite concentration "indicates a need" to adjust the dosage, which implicates the physician's treatment decisions and not his or her actions in administering a different dose of the drug.

⁵⁹Case No. 2011-1577 (Fed. Cir. November 20, 2012), which has been designated as a non-precedential opinion.

⁶⁰www.law360.com/ip/articles/393360/uspto-vexed-by-high-court-s-limited-ip-guidance-gc-says (accessed November 13, 2012).

⁶¹www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf (accessed November 18, 2012).

⁶²As stated by the guidelines at page 3: "A bare statement of a naturally occurring correlation, albeit a newly discovered natural correlation or a very narrowly confined correlation, would fail this [patent eligibility] inquiry."

However, the Interim Procedures indicate that methods of observing biological correlations can be patent eligible if they use new reagents or a combination of assays that were not previously used together.⁶³ The Interim Procedures also suggest that methods of treating patients based on the observation of natural correlations are patent ineligible unless the treatment method incorporates specific steps that avoid broadly precluding others from using the natural law.⁶⁴

PATENT ELIGIBILITY OF EPIGENETIC INVENTIONS UNDER THE *PTO* GUIDELINES

The recent decisions in the *Myriad Genetics* and *Prometheus* cases have potentially limited the scope of patent protection in the United States in a way that could have a disproportionate impact on epigenetic inventions. As noted in our review of U.S. epigenetic patents, these inventions generally fall into four major categories: (1) techniques (laboratory methods and reagents for epigenetic analysis); (2) diagnostics (methods and reagents for predicting risk, modifying therapy, or confirming a diagnosis in personalized medicine, often by relying on observation of a biological correlation); (3) therapeutics (methods and reagents for treatment of a specific condition); and (4) bioinformatics (methods of analyzing and storing epigenetic information). A notable difference between genetic and epigenetic inventions is the absence of patents on epigenetic compositions that are analogous to isolated DNA sequences. Although in the *Myriad Genetics* case, the Supreme Court concluded that isolated DNA sequences are not patent eligible, there is no clear epigenetic analog to a DNA sequence that can be meaningfully patented.⁶⁵ For this reason, a significant proportion of epigenetic patents protect only methods of diagnosis or treatment that rely on the observation of biological correlations, such as the presence of epigenetic modifications associated with disease. The *Myriad* and *Prometheus* cases, and the *PTO Guidelines*, cast doubt on the patent eligibility of any such method that relies on an observation of a biological correlation. Even if the patent claims a method that includes assay or treatment steps,⁶⁶ the method may be patent ineligible as claiming a “law of nature” unless the patent claim also contains detailed steps that avoid broadly precluding application of the natural law.

For example, the *PTO Guidelines* suggest that a combination of assays may be patent eligible if the assays were not previously used together.⁶⁷ Hence, a diagnostic method that analyzes multiple epigenetic markers (for example, at different genetic loci) could be patent eligible even if a method of using only one of the markers is not. A patent claim that requires analysis of a *combination* of markers is narrower in scope

than a claim to a single marker, and infringement can be avoided by not using one of the markers. However, to the extent that combined epigenetic markers increase the specificity or sensitivity of the assay, such a claim may have commercial value. Even more complex methods of epigenetic diagnosis that require computer-implemented analysis of multiple markers are more likely to be patent eligible, at which point, diagnostic assays merge with bioinformatic inventions.

The *PTO Guidelines* also suggest that a diagnostic method could be patent eligible if it relies on a new reagent that was not known in the field to detect a newly identified target, such as a monoclonal antibody that had not previously been used for that purpose. Claiming a method of using a particular monoclonal antibody would protect a specific implementation of a method, instead of precluding use of the underlying observation that a particular antigen is associated with a disease. Similarly, identification of a new epigenetic modification would not be patentable, but claiming a method to detect this modification with a specific reagent could be. In sum, in the absence of commercially valuable novel reagents that specifically or unexpectedly identify a target epigenetic modification, the diagnosis of disease by detection of a newly identified epigenetic change may be impractical to patent

⁶³The pertinent example provided in the Interim Guidelines is a method of determining an increased likelihood of developing rheumatoid arthritis by obtaining serum from a patient and detecting binding of an anti-IgM antibody to IgM rheumatoid factor in the serum. Although this method would be considered a patent-ineligible natural correlation, the method could become patent eligible if it used a monoclonal antibody that was not known in the field, or if the method was carried out using assays that were not routinely used together.

⁶⁴The Interim Guidelines cite the example of treating a psychiatric disorder by exposing the patient to sunlight or a source of white light. Such a treatment method would be considered a patent-ineligible application of a natural law. However, positioning the patient a designated distance from a light source of a particular wavelength could be considered patent eligible because it sufficiently narrows the method to steps more specific than a mere application of the natural law.

⁶⁵One possible epigenetic analog to a DNA sequence is an isolated DNA amplificate having a specified methylation status at a designated region of a gene, similar to that claimed in European Patent 1339873. Although the amplificate may be patent-eligible subject matter, we did not note any issued U.S. patents on such amplificates. The value of such patent claims would be diminished by the availability of detection methods that did not require production of an isolated amplificate.

⁶⁶The *PTO Interim Procedure Guidelines* have instructed patent examiners to bar claims to “laws of nature” if the claims only add conventional assaying or treatment steps to the method.

⁶⁷Combinations of known assays from the first and second trimesters of pregnancy were insufficient to render the method of screening for Down’s syndrome patent-eligible in *PerkinElmer, Inc. v. Intema Limited*, Case No. 2011-1577 (Fed. Cir. November 20, 2012).

under the current *PTO Guidelines*. Also, claims that require using a particular reagent to detect an epigenetic change will often fail to protect the actual invention (the biological correlation); potential infringers often can appropriate the invention while changing an incidental detail (e.g., substituting another reagent to detect the change). Although patent protection would be available, the commercial value of the invention could be impaired by such limitations in the claim that are present only to satisfy the seemingly empty formalisms required by *Prometheus*.

Related problems arise with patent claims to methods of medical treatment. Epigenetic treatment methods may rely, for example, on the detection and reversal of an aberrant methylation of target DNA. If the reasoning of the Supreme Court in *Prometheus* and the *PTO Guidelines* were followed, the detection of the aberrant DNA methylation would constitute the recognition of a “law of nature” and its correction by conventional means would probably be an ineligible application of a natural law. The ability to patent methods of treating disease by reversing epigenetic abnormalities would seem to require that the invention use a new reagent or a novel combination of existing reagents, or include detailed treatment steps such as treatment with a particular drug, to avoid broadly preempting the “law of nature” that a specific epigenetic abnormality is correlated with a particular disease. Using a drug to treat a disease would include use of a prior art drug that was not previously known to be effective in treating the disease. An invention that combines multiple conventional treatments for improved epigenetic abnormalities may also be patent eligible. However, infringement of claims that include this degree of specificity is often readily avoided by competitors who can appropriate the substance of an invention while evading the formalistic requirements of a patent claim.⁶⁸

Patents directed to laboratory techniques for detecting DNA methylation or histone modifications will probably continue to be patent eligible as long as their claims recite a series of specific steps that physically transform the DNA or histones for the purpose of analyzing them. New drugs that are useful to modify the epigenome, or the use of old drugs that are newly discovered to have that effect, continue to be patent eligible, as they involve more than a series of mental steps related to the observation of a biological correlation.⁶⁹ Bioinformatic methods for analyzing and storing epigenetic data, or determining a treatment regimen in view of detected epigenetic changes, also will continue to be patent-eligible subject matter if they contain sufficiently detailed steps that do not broadly preclude the application of a natural law.⁷⁰ Computer operations must play a significant part in the performance of the invention for it to be patent eligible.⁷¹ However, Supreme Court and Federal Circuit precedent about the patent eligibility of software inventions has been evolving rapidly and is likely to continue to do so.

A STRESSFUL LEGAL ENVIRONMENT FOR AN EMERGING SCIENCE

Although legal rules about the patent eligibility of biological correlations are still developing, it seems apparent at this point that less-robust patent protection will be available for epigenetic inventions than was available for the nascent biotechnology industry during the 1980s and 1990s. The era of broad patents on biological correlations may have come to an end in the U.S. Absent a statutory change that overrules recent court decisions, or an unlikely recognition by the Supreme Court of the far-reaching—and perhaps unintended—consequences of its recent case law, it will not be possible to patent or enforce broad claims to methods of diagnosing or predicting disease, or selecting a treatment based on the detection of a genetic or epigenetic abnormality in a patient. These limits on patent eligibility of biological correlations in the U.S. are more restrictive than those imposed by most other developed nations, such as those of Europe, Canada, Australia, and Asia. The relatively restrictive nature of this patent protection could create a nation-specific difference in the value of biotechnology inventions (including epigenetic patents)

⁶⁸Patent eligibility requirements imposed by *Prometheus* are less likely to change the scope of epigenetic patent claims for methods of treating epigenetic disorders because the 35 USC §112 description requirement, as interpreted by decisions such as *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004), already requires that method-of-treatment inventions have progressed beyond the mere recognition of a biological mechanism before they can be patented. In the *Rochester* decision, a claim to reducing inflammation by selectively inhibiting the COX-2 enzyme was found invalid under §112 because the inventors had not identified specific agents that would selectively inhibit COX-2. The mere recognition of a mechanism to reduce inflammation was insufficient evidence that the inventors were in possession of the claimed method of treatment. Similarly, the recognition that epigenetic demethylation at a genetic locus could treat a disease may be insufficient to satisfy the requirements of §112 in the absence of the identification of an agent that would specifically demethylate the target. Hence, identifying and often claiming a particular treatment reagent is already necessary for the description requirement, and the additional burdens imposed by *Prometheus* under §101 may prove to be only a redundant burden.

⁶⁹In *Prometheus*, the U.S. Supreme Court noted that a “patent on a new drug or a new way of using an existing drug” confined its reach to particular applications of natural laws and therefore were patent-eligible inventions.

⁷⁰Compare *Parker v. Flook*, 437 U.S. 584 (1978)(a method of using a mathematical algorithm for updating an alarm limit in a manufacturing process is not patent eligible) and *Diamond v. Diehr*, 450 U.S. 175 (1981)(a method of curing synthetic rubber using a mathematical equation to determine when to open the rubber mold was patentable where the mathematical equation was used to open the mold when the rubber had finished curing).

⁷¹*Bancorp Services, L.L.C. v. Sun Life Assur. Co. of Canada* (U.S.), 687 F.3d 1266 (Fed. Cir. 2012).

that would make it more desirable to develop and market such inventions outside the U.S. Alternatively the restrictive U.S. patent law could remove a “patent thicket” that has been alleged to impede scientific progress in the U.S.⁷² and promote the development of an industry less impeded by intellectual property rights. The significant gap that has opened between the patent eligibility of biological correlations in the U.S. and other countries may finally provide the evidence to support or rebut the long-hypothesized (but unproved) assertion that a “patent thicket” impeded the commercialization of new biotechnologies in the U.S. The development and commercialization of relatively new epigenetic technologies in countries with such different degrees of patent protection may provide clues to the importance of intellectual property to the progress of science.

The enduring judicial controversy about the proper scope of patent-eligible subject matter suggests a drawback of current 35 USC §101, which defines patent-eligible subject matter in the U.S. This statute broadly encompasses any “new and useful process, machine, manufacture, or composition of matter, or any new or useful improvement thereof.” It is a technology-neutral statute that originated in the 1793 Patent Act⁷³ and still provides an 18th Century paradigm to solve 21st Century problems. The statute then (and now) does not require that the claimed subject matter relate to “technology” or the *practical application of science to industrial or commercial objectives*. The technology-neutral definition of patent-eligible subject matter has required courts to limit the language of the statute by carving out unwritten exceptions to patent-eligible subject matter for “laws of nature” and “abstract ideas” that are not practical applications of theoretical ideas.⁷⁴

This judicial departure from the language of the statute, in the absence of any guidance about protecting technological innovation, has led the Supreme Court to speculate about natural laws and degrees of abstraction that would disqualify inventions from patent protection. Under these speculations, patent-eligible subject matter has ranged erratically from “anything under the sun made by the hand of man”⁷⁵ to the clearly inconsistent requirement that patent-eligible methods of diagnosis and treatment must be confined to particular technical applications and sometimes—but not always—satisfy multiple sections of the patent statute, such as the novelty requirement of 35 USC §102.⁷⁶ If §101 were interpreted to require a technological advance in which science was applied in a tangible way to an industrial or commercial objective then at least §101 could be applied with some consistency. Such an interpretation would exclude patent eligibility of mere intangible mental steps such as reviewing a subject’s epigenetic data to identify a theranostic mutation while preserving the patent eligibility of laboratory methods to detect them.

An even more fundamental problem with the Supreme Court’s interpretation of §101 in *Prometheus* is that the Court combines different statutory provi-

sions of 35 USC to find patent-ineligible subject matter. Giles Rich, one of the authors of the 1952 Patent Act that established the requirements for patentability in §§101, 102, 103, and 112, later served for many years as a judge on the Court of Customs and Patent Appeals, the predecessor court of the Federal Circuit. This co-author of the Patent Act helpfully wrote an “Anatomy of the Patent Statute” in the landmark case *Application of Bergy*⁷⁷ in which he clarified that the requirements of §§101, 102, 103, and 112 should not be combined: each section is a separate “door” to patentability that must be separately entered.⁷⁸ Judge Rich, as an architect of the statutory scheme he was interpreting, characterized the combination of the separate statutory requirements as “subversive nonsense”⁷⁹ that

⁷²Carl Shapiro, “Navigating the patent thicket: cross licenses, patent pools, and standard-setting.” In Jaffe, Adam B. *et al. Innovation Policy and the Economy* I. Cambridge: MIT Press. pp 119–150 (2001).

⁷³The 1793 Patent Act defined the four classes of statutory subject matter as “art, machine, manufacture, or composition.” The 1952 Patent Act replaced the term “art” with “process” to arrive at the current language.

⁷⁴*Ibid.* n. 70.

⁷⁵*Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

⁷⁶In *Prometheus v. Mayo* the Supreme Court proposed that “the §101 patent-eligibility inquiry and, say, the §102 novelty requirement might sometimes overlap.” A more suitable approach to defining patent-eligible subject matter is found in the European Patent Convention (EPC) Article 52(1), which defines patent-eligible subject matter as being “susceptible of industrial application.” The implementing regulations of the EPC specify that the invention must have a technical feature (Rule 43(1)) which is related to a technical field (Rule 42(1)(a)) and concerned with a technical problem (Rule 42(1)(c)). A key precondition for patent-eligible subject matter in Europe is the “technicality” of the claimed invention.

⁷⁷596 F.2d 952 (C.C.P.A. 1979). This appeal from the PTO addressed the patentability of a microorganism that had been isolated from nature and produced an antibiotic. The Supreme Court originally granted *certiorari* to consider the patentability of claims to the isolated microorganism, but the appeal was eventually abandoned, and the Supreme Court instead considered the appeal only of *Chakrabarty* about the allowability of claims to a microorganism that had been modified by the introduction into a bacterium of a plasmid that encoded enzymes that degraded hydrocarbons.

⁷⁸“Section 101 states three requirements: novelty, utility, and statutory subject matter. The understanding that these three requirements are separate and distinct is long-standing and has been universally accepted....Thus, the questions of whether a particular invention is novel or useful are questions wholly apart from whether the invention falls into a category of statutory subject matter.”

⁷⁹“It is transparently clear that the above argument makes the opening words of §101, ‘Whoever invents or discovers,’ into a requirement for compliance with §103, the 1952 replacement for the old requirement for ‘invention’; one must get through the third door in order to get past the first one! That is not the statutory scheme. The statement that respondent Flook was asking for a rule under which ‘anyone who [applies for a patent on] any...’ of the §101 named categories should have a patent ‘issue’ to him is subversive nonsense.”

would undermine the carefully crafted structure of the Patent Act. According to Judge Rich, when considering patent-eligible subject matter under §101, the only question is whether the claimed subject matter falls into one of the named §101 categories (“process, machine, manufacture, composition of matter, or improvement thereof”). This was the disciplined approach that the Supreme Court adopted in *Chakrabarty* when it broadly interpreted §101 to include “anything under the sun made by the hand of man.” The other requirements for patentability, such as novelty and non-obviousness, were to be considered separately. The Supreme Court in *Prometheus* abandoned this disciplined scheme adopted by the architects of the Patent Act in favor of piecing together different patentability requirements of (at least) §§102 and 103 into §101⁸⁰ that together will do something very different from what the separate statutes were intended to do apart.⁸¹ In so doing, the Court has introduced a “subversive” conceptual confusion into the complex field of patent law that will create an atmosphere of uncertainty and stress that may adversely affect the commercial development and applications of epigenetic science.

The Supreme Court granted review of the Federal Circuit’s decision in *Myriad* to uphold the patent eligibility of *isolated DNA molecules* having sequences of various lengths found in *BRCA* genes. The petition for *certiorari* was granted to consider only one question: “Are human genes patentable?” When answering this question, it seemed unlikely that the Supreme Court in *Myriad* would return to a disciplined approach, because the question imprecisely asked by the Supreme Court is not even at issue in the case. Human genes are not patentable in the United States and never have been because they exist in nature as part of a complex biological matrix. *Myriad* did not patent a human gene; it patented an isolated DNA molecule having a particular sequence found in *BRCA* genes. An isolated DNA sequence that is found in a laboratory is not “a human gene” and is not found in nature. The actual question the Supreme Court could have asked is whether an isolated DNA molecule is patentable if the isolated molecule uses information found in nature. However, the Court seems to have answered its own question in the negative by posing a question that misstates the issue in a manner that suggested the answer to its question would be “no,” as indeed it was. Since the Court answered the wrong question to find the *Myriad* patent claims ineligible, and did not narrowly limit the reasons for its decision to the patentability of DNA, the Court continued to create confusion about the patent eligibility of emerging technologies, such as those in epigenetics.

CONCLUSION

The science of epigenetics is changing rapidly, as scientists move from performing basic research to

using their findings to improve human health. Epigenetics has been compared to the “dark matter of the universe”⁸² and a “revolution in biology that is forever going to transform the way we understand genetics, environment, the way the two interact, [and] what causes disease.”⁸³ Although this transformative biological theory should open up a large number of patent opportunities, recent court decisions could have a chilling effect on some types of epigenetic patents. *Prometheus* in particular has erected barriers to the patentability of diagnostic and predictive assays that could reduce private investment in this technology, at least in the United States. A selective weakening of patent protection for biological inventions in the United States (compared with the rest of the world) will provide an opportunity to better understand the effect of weak patent protection on national technology development. The Supreme Court’s adoption of a §101 analysis that an architect of the Patent Law called “subversive nonsense” has created further uncertainty about the patentability of many types of epigenetic inventions. Whether the *Prometheus* and *Myriad* decisions will have an adverse effect, or whether they will free American science from commercial concerns that inhibit it, will soon be better understood. The stressful legal environment epigenetic patents have encountered in the U.S. will likely have a transgenerational effect on the health of this new technology.

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⁸⁰The Supreme Court in *Prometheus* rejected arguments that §§101, 102, 103, and 112 should be considered separately. “We recognize that, in evaluating the significance of additional steps, the §101 patent-eligibility inquiry and, say, the §102 novelty inquiry might sometimes overlap. But that need not always be so. And to shift the patent-eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do.... These considerations lead us to decline the Government’s invitation to substitute §§102, 103, and 112 inquiries for the better established inquiry under §101.”

⁸¹Mary Shelly’s novel about a similar composite creature was coincidentally entitled *Frankenstein: or, The Modern Prometheus*. The Supreme Court’s decision might more appropriately be called *Prometheus: or, the Modern Frankenstein* in recognition of its piecing together the different parts of 35 USC into §101 to create a legal framework that will behave unpredictably.

⁸²Andrew Feinberg of Johns Hopkins University on Nova’s “Ghost in Your Genes,” broadcast on PBS October 16, 2007. Transcript available at www.pbs.org/wgbh/nova/transcripts/3413_genes.html (accessed February 6, 2013).

⁸³Mark Mehler of Albert Einstein College of Medicine University on Nova’s “Ghost in Your Genes,” broadcast on PBS October 16, 2007. Transcript available www.pbs.org/wgbh/nova/transcripts/3413_genes.html (accessed February 6, 2013).