tal Health, put it, "The unfortunate reality is that current medications help too few people to get better and very few people to get well."[3] Although the medications given to children with a diagnosis of bipolar disorder have been effective at managing the symptoms of adult bipolar disorder, a 2007 "practice parameter" from the American Academy of Child and Adolescent Psychiatry described evidence for their efficacy in children as "sparse at best." Even with the addition of treatment trials published in the intervening 3 years, our knowledge base is still very small and seldom extends to children younger than 10 years of age.

The same 2007 practice parameter strongly recommends that psychotherapeutic treatments should accompany medications for almost all children diagnosed with bipolar disorder. Some physicians go further, arguing that psychosocial, educational, or behavioral therapy should be the first-line treatment, especially for young children with mental health problems.[4] It is widely agreed that treatment with medications alone is seldom sufficient. Yet a recent study of large databases of privately insured individuals showed that most young children who were prescribed antipsychotic medications did not receive adjunctive psychosocial treatment.[5] The exact reasons for this failure to provide children with recommended comprehensive mental health care are complicated; causes include a paucity of well-trained therapists, insurers' reluctance to cover nonpharmacologic treatments, and the time-intensive nature of the treatments. The mere addition of diagnostic categories such as TDD does not address the pressing need to transform our systems of delivering mental health care to children.

The good news is that the addition of TDD to the psychiatric manual may lend some clarity to the debate about the most appropriate diagnostic home for some deeply troubled children. The bad news is that our understanding of the nature of these children's heterogeneous disturbances is in its infancy. The risk–benefit ratios of the medications used to treat severe outbursts have not been established. And though effective nonpharmacologic treatments are being developed, it's probable that too few children will receive these interventions. Troubled children, regardless of their diagnostic label, deserve better.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Hastings Center, Garrison, NY (E.P., J.J.); and the Division of Child and Adolescent Psychiatry, Stony Brook University School of Medicine, Stony Brook, NY (G.A.C.).

1. Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry 2007; 64:1032-9.

2. Carlson GA, Potegal M, Margulies D, Gutkovich Z, Basile J. Rages — what are they and who has them? J Child Adolesc Psychopharmacol 2009;19:281-8.

3. Insel TR. Disruptive insights in psychiatry: transforming a clinical discipline. J Clin Invest 2009;119:700-5.

4. Barbaresi WJ. Use of psychotropic medications in young, preschool children: primum non nocere. Arch Pediatr Adolesc Med 2003; 157:121-3.

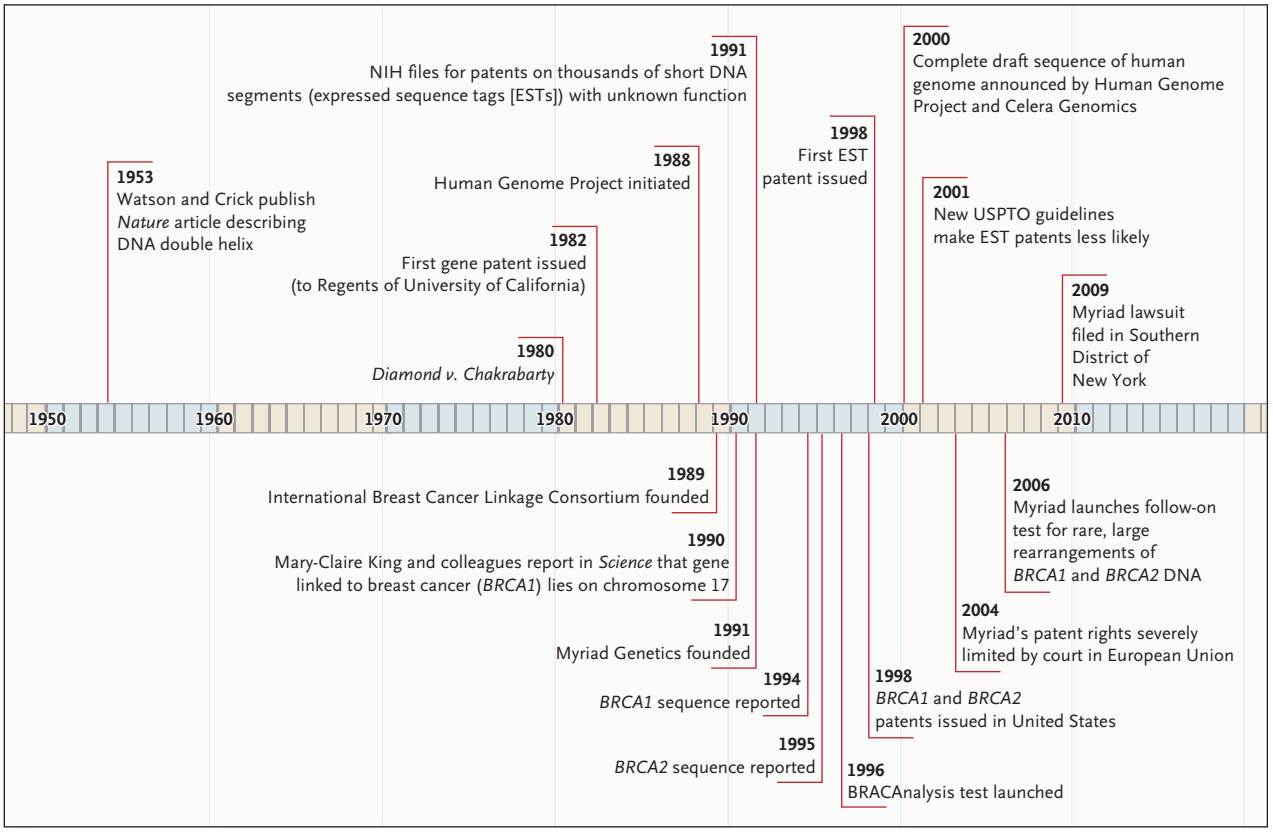
5. Olfson M, Crystal S, Huang C, Gerhard T. Trends in antipsychotic drug use by very young, privately insured children. J Am Acad Child Adolesc Psychiatry 2010;49:13-23.

Gene Patenting — Is the Pendulum Swinging Back?

Aaron S. Kesselheim, M.D., J.D., and Michelle M. Mello, J.D., Ph.D.

Are human genes and the process of comparing DNA sequences patentable? These questions were raised by a group of researchers, pathologists, patients with cancer, and medical professional organizations challenging some of Myriad Genetics' patents covering the *BRCA1* and *BRCA2* genes and their use in screening for elevated risks of breast and ovarian cancer. On March 29, in a startling decision, a federal district court judge invalidated many of Myriad's patent claims,[1] reigniting a long-simmering debate about the patentability of genes.

The Patent Act permits exclusive control for a limited time (currently 20 years) of any "process, machine, manufacture, or composition of matter," and since its inception, the U.S. Patent and Trademark Office (USPTO) has granted patents on new pharmaceuticals and medical devices. However, as recently as the 1970s, the view among many medical researchers and legal scholars, as well as members of the USPTO, was that DNA sequences were not patentable, primarily because DNA is a naturally occurring substance



Timeline of Important Events in DNA Patenting (Top) and the Discovery and Use of Genes Conferring Susceptibility to Breast and Ovarian Cancer (Bottom).

NIH denotes National Institutes of Health, and USPTO U.S. Patent and Trademark Office.

rather than a human invention. This perception changed in 1980 with the Supreme Court's landmark ruling in *Diamond v. Chakrabarty*,[2] which involved a dispute over the patentability of a microbe that dissolves oil and that had been specially constructed to include a DNA plasmid. The Court held that although the Patent Act did not authorize ownership of laws of nature, "products of nature," or physical phenomena, "anything under the sun made by man" was patentable, including the human-made bacterium at issue in the case.

After the decision, gene patents — specifically, patents on "isolated DNA" — soon became commonplace. USPTO examiners justified this extension of patent protection on the grounds that the patented genes and DNA sequences had been purified (and therefore transformed) from their natural form through the application of artificial tools. By the 1990s, technological advances in DNA-sequencing strategies began enabling scientists to discover and isolate new genes at a rapid rate. Ultimately, thousands of patents were awarded on different parts of the human genome sequence; reportedly, about 20% of human gene DNA sequences are currently patented.

Myriad was founded in 1991 by Walter Gilbert, who won a Nobel Prize for his work in nucleic acid sequencing, and Mark Skolnick, a geneticist who had spent his career working on the familial characteristics of cancer. In 1994, building on publicly funded research on the hereditary predisposition to breast cancer that had been conducted in several countries throughout the 1980s and using about $22 million in private venture capital, Myriad's team won a race with several other groups to identify the nucleotide sequences composing the *BRCA1* gene (see timeline). Myriad's team included collaborators from the University of Utah, the National Institute of Environmental Health Sciences, McGill

University, and Eli Lilly and was also supported by grants from the National Institutes of Health and the National Cancer Institute of Canada. A year later, Myriad filed for a patent on the *BRCA2* gene, although it may not have been the first to identify its sequence. Myriad's patents, the earliest of which expire in 2014 and 2015, cover isolated gene sequences, as well as methods of "analyzing" and "comparing" the gene sequences to determine whether the mutations conferring an increased risk of breast or ovarian cancer are present. Myriad launched its combined genetic test, BRACAnalysis, in November 1996. In 2009, the test accounted for most of the company's $326 million in annual revenue from molecular diagnostics.[3]

Though the *BRCA* tests are of undeniable public health importance, questions arose about the appropriateness of the underlying patents. In 2004, the European Patent Office rejected some of Myriad's patent claims and limited others because they did not meet its legal standard of inventiveness. In the United States, legal scholars argued that the Patent Act does not apply to naturally occurring gene sequences, even in their "isolated" form, contending that Congress's constitutional power to grant patents was intended for inventions in the limited sense of human, physical creations.[4] Similarly, Supreme Court precedent suggested that natural products and naturally occurring properties of living things are legally distinguishable from goods manufactured using substantial ingenuity. From this perspective, DNA sequences are discovered, not invented, and are therefore quite different from genetically engineered products such as those in the *Chakrabarty* case.

Physician groups have voiced concern about the impact that Myriad's patents have on the use of the genetic test in patient care. The BRACAnalysis test, which was initially priced at approximately $1,600, had nearly doubled in cost, to $3,150, by 2009, which may be prohibitively expensive for some patients. Though Myriad reports that insurance covers more than 90% of the cost of 90% of the tests it performs, the number of tests that are forgone because of cost or lack of coverage is unknown. The DNA patents prohibit other entrepreneurs from selling less expensive tests based on the same genes, even if the test technologies are different. Physicians also noted that the patents prevented other genetic tests with greater sensitivity or specificity from being commercialized. Physician-researchers objected that although Myriad allowed free use of its test in research, it barred investigators from telling women the results, compromising their ethical obligations to their patient-subjects. Myriad and its supporters responded that gene patents are crucial to attracting private capital investment and stimulating research and development in fields such as personalized medicine.

In invalidating Myriad's patents on the DNA sequences, U.S. District Court Judge Robert Sweet cited the Supreme Court's prior rulings that patentable products must have "markedly different characteristics" from what is found in nature.[1] Purification alone, he held, does not change the essential characteristic of DNA — its nucleotide sequence. Indeed, the ability to reliably detect mutations depends on this essential characteristic's remaining unchanged.

Judge Sweet also rejected Myriad's patent claims relating to the use of these DNA sequences in evaluating a patient's susceptibility to cancer. Building on the principles outlined in a 2008 federal appeals court decision, *In re Bilski*,[5] he found these claims to be inappropriate subject matter for a process patent because they related to "abstract mental processes" of "analyzing" or "comparing" and did not involve a transformative step in which matter was turned into a different state or thing. That is, the patented method consisted only of comparing the nucleotide sequence in a test sample to the reference sequence.

The *Bilski* case has been argued before the Supreme Court and is currently under consideration; a decision that a transformation is not required for patentability could undermine Judge Sweet's holding on Myriad's process patents. Even murkier, however, is the fate of his decision about patents on the DNA sequences themselves. Although well-grounded in legislative history and Supreme Court precedent, his decision flies in the face of years of decision making by the USPTO and is headed next to the Court of Appeals for the Federal Circuit, which is known for its friendliness to patent seekers.

How will the decision against Myriad Genetics, if upheld, affect biotechnology research and development? Judge Sweet was careful to limit his holding to the patentability of isolated DNA sequences, as distinct from other compounds, writing that they are

unique as "a physical embodiment of information." The decision thus will affect only a narrow segment of the biotechnology industry — but it may do so deeply. Genes themselves will be off-limits for patents, and in conjunction with *Bilski*, it is difficult to see how any tests that consist of comparing gene sequences will be patentable either, because they do not involve a transformative step. Therefore, companies whose focus is the discovery of new genes and the development of tests that compare DNA sequences would enter a new commercial landscape. Such tests could still be marketed but could face competition much sooner than they have in the past.

At the same time, research into aspects of our genome will remain an important avenue for public research funds, as it was in the discovery of the *BRCA* genes, and having fewer competing intellectual property claims at the basic-science level may enhance the prospects for parties interested in building therapeutics based on this information. How any changes may affect innovation is unclear at this point, but potential competitors for *BRCA* testing will almost certainly wait for the outcome of the appeal. If the Myriad decision is upheld, we will have seen the pendulum on the legal status of DNA patents swing back from the lack of restraint that has characterized the past two decades.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School (A.S.K.); and the Department of Health Care Policy and Management, Harvard School of Public Health (M.M.M.) — both in Boston.

This article (10.1056/NEJMp1004026) was published on April 7, 2010, at NEJM.org.

1. Association for Molecular Pathology v. United States Patent and Trademark Office, No. 09 Civ. 4515 (S.D.N.Y., Mar. 29, 2010).
2. Diamond v. Chakrabarty, 447 U.S. 303 (1980).
3. Myriad Genetics. An apple can't do it all: preventing disease. 2009 Shareholders annual report. (Accessed April 6, 2010, at http://files.shareholder.com/downloads/MYGN/882107750x0x321196/42ECFDDF-2D7D-48DC-AAFE-3471F4CF6B91/Annual_Report_2009.pdf.)
4. Andrews LB, Sarnoff JD, Katz AL. Amici curiae brief of American Medical Association et al. to the District Court of the Southern District of New York (No. 09 Civ. 4515) (Aug. 27, 2009).
5. *In re Bilski,* 545 F.3d 943 (Fed. Cir. 2008).

Haiti Earthquake Relief, Phase Two — Long-Term Needs and Local Resources

Dominique Bayard, M.D.

A month and a half after January's devastating earthquake in Haiti, the National Organization for the Advancement of Haitians, a U.S.-based nonprofit organization with a division dedicated to improving health care in Haiti, sent in teams of U.S. physicians and other health care professionals, primarily of Haitian descent, as the acute phase of disaster response was ending. As part of this group, I worked in a makeshift hospital in Tabarre, a section of northeast Port-au-Prince.

As a first-generation Haitian-American and an internist, I expected to be prepared for the situation I was walking into. Haiti was a country I knew, I spoke the language, I understood the people, and by this point I had been watching the disaster on television daily for over a month. I knew that with the threat to life no longer minute to minute but week to week, the long-term recovery phase was beginning. According to my relatives in Haiti, the initial shock was passing. Dead victims had been cleared from the streets, families were either reunited or mourning their losses, the roads were somewhat drivable, and food and water were slowly making their way to survivors. Yet when I came face to face with the disaster, I realized that the media hadn't even begun to capture the extent of the devastation. Seeing Haiti through a framed television screen had given me only a snapshot of destroyed buildings, misplaced families, and stories of loss and survival.

When you're on site, there is no television to turn off, no place to avert your gaze, no way to avoid hearing endless conversations about loss and devastation — and fears about worse to come. Nor could I turn off the unrelenting heat, or the airborne dust from the rubble of destroyed buildings, or the smoke rising