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Authors
Biagioli, Mario
Pottage, Alain

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Patenting Personalized Medicine: Molecules, Information, and the Body

by Mario Biagioli* and Alain Pottage§

ABSTRACT

The histories of patent law and medical practice in the United States have intersected in various ways over the past 150 years, beginning with the professional campaign against “patent medicines” in the late nineteenth century, and culminating, for now, in attempts to patent the diagnostic procedures discussed in this article. The patenting of diagnostic procedures provokes a set of fundamental questions about the episteme of patent law. These questions are not new. They emerged at the very origins of patent jurisprudence, centered on the question of what distinguished an invention from a law of nature, and this question of patentability has persistently reemerged over the past century in the contexts of plant breeding, biotechnology, and now diagnostic medicine. So far, the question has been addressed in terms that imagine the invention as a machine, understood in the figurative sense of a transformative organization of forces and elements. But diagnostic procedures, because they address the body informationally, as a system based on the recursive patterning of signals rather than a linear transformation of inputs into outputs, stretch the figure of the machine to the point at which it ceases to be effective. How then should one define and delimit invention?

The role of patents in medicine is intriguing not so much because of their predictable ability to expand and intensify the commodification of medical knowledge and technology, but rather because of the extent to which their uses and functions have qualitatively changed over time across medical and biomedical disciplines. These developments hinge on the increasingly complex relationship between medical objects and the concepts of patent law, the different patent-based business and research models that have shaped the recent culture of biomedical research, and the way patent law itself has changed over time—changes that have generally expanded but also constrained the protection of medical innovations. It is the specificity of the multilevel interaction between patents and medical cultures and businesses that interests us here.

In the last two decades, significant cracks have developed in the stable long-term alignment between the objects of medicine and the concepts of patent law—an
alignment that has enabled the development of today’s globalized medical industry. These tensions do not destabilize traditional medical technologies like pharmaceuticals and devices but affect (and are in fact generated by) the emergence of so-called personalized medicine and the new actors behind it. These are companies (large and small, independent or affiliated with larger pharmaceutical or biotech concerns) that are exclusively dedicated to diagnostics, often with further specializations like cancer diagnostics, prenatal diagnostics, and so forth. After relying on patents for so long, the medical industry may have run into an obstacle precisely as it strives for what is often presented as its “new frontier.” As the cosponsor of a new US patent law bill puts it: “Today, U.S. patent law discourages innovation in some of the most critical areas of technology, including artificial intelligence, medical diagnostics, and personalized medicine.”

For scholars, this predicament provides prime material to study two long-term genealogies—of medical diagnostic methods and of patent law—and the discontinuities that are now being generated by their intersection. This is a very specific context. On one side, medical diagnostics have come to use highly individualized evidence—either genetic information about individual bodies or about those bodies’ responses to specific medications based on their genetic makeup. Over the same period, and on the other side, patent law has been reacting to serious challenges to its fundamental distinction between “invention” and “discovery,” as well as to traditional categories of patentable subject matter like “machine,” “process,” and “composition of matter.” Many of these challenges have come directly from new information-based diagnostic methods, as well as from other information-based technologies like business methods and software, which struggle to fit a legal episteme that is still rooted in the figure of the machine, the technological exemplar of the industrial revolution.

In the following discussion we flesh out the tensions between the traditional historical figure of invention as a “machine,” and a new but still embryonic notion of invention based on the elusive figure of “information.” After mapping out areas of key historical significance concerning the use of patents in medicine, we analyze the way the evolution of medicine has created specific challenges to patent law precisely because of the kind of discipline it is—one that focuses on the healing of unique human bodies rather than the production or optimization of identical machines. This is particularly clear when we consider recent diagnostics based on the body’s metabolic response to a probe, as in the case of methods devised to optimize the dosage of certain drugs. Like other information-based inventions, these tests destabilize the machine-based logic of patent law, but even more so because of the body’s agency in producing that information.

**MONOPOLY**

Today’s policy discussions of medical patenting tend to stress its function as an economic tool for incentivizing increasingly expensive innovation in the pharmaceutical and medical equipment industry, and then agreeing or disagreeing on whether those incentives balance the higher costs patients and taxpayers come to shoulder due to the

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higher pricing that results from patent protection. Joseph Gabriel and others have shown, instead, that the discourse of medical patenting was framed rather differently in the first half of the nineteenth century, and that the way such discourse changed over time indexes historical changes in practitioners’ culture, self-perception, and notions of professional ethics, more than the economics of pharmaceutical innovation.

The first Code of Ethics introduced by the American Medical Association (AMA) at its foundation in 1847 stated that it was “derogatory to professional character . . . for a physician to hold a patent for any surgical instrument, or medicine.” 2 This stern stance was significantly softened by 1912 when the AMA dropped the prohibition for physicians to hold patents, while still maintaining that it was “unprofessional to receive remuneration from patents for surgical instruments or medicines.” 3 By 1955, its Principles of Medical Ethics no longer listed any prohibition against holding patents and financially benefitting from them, “as long as doing so did not retard medical research or restrict the benefits from such research.” 4 This apparent trend toward the acceptance of patents by the medical community hides a series of complex changes: the evolution of the business models of pharmaceutical companies (which came to rely less exclusively on physicians’ endorsements and more on patents); the emergence of synthetic chemistry (followed by the entry into the pharmaceutical field of large chemical firms for which patenting was already second nature); and, especially, the changing cast of competitors against which medical practitioners construed their own professional identity as proper physicians. 5 The oppositions to patents that we find in the United States and Britain around 1850 did not stem from physicians’ concerns about an overpowering pharmaceutical industry and its global pricing strategies but about the fact that the often mischaracterized “patent medicine” was the province of “quacks,” against which physicians and drug manufacturers were casting themselves as orthodox and ethical.

The opposition to patents was part of a more general rejection of pharmaceutical “monopoly”—a term that was then construed more in ethical and cognitive terms than in economic ones. Patents were associated with secrecy, selling products without fully disclosing their ingredients, and thus reducing physicians’ ability to check the therapeutic claims the seller made for them or to use their successful therapies as a step to further medical research. Essentially, patents were turned into an identity issue; the very act of patenting put a physician outside of the community of proper medical practitioners and drug manufacturers (who at that time generally avoided patents). Gabriel makes the intriguing suggestion that the eventual embracing of patents by the medical establishment marked the beginning of bioethics as we know it. Problems associated with “monopoly” framed medical ethics into the twentieth century, and it was only when those concerns—including the opposition to patents—faded away after World War II that we see the “birth of bioethics” concomitant with the refocusing on informed consent as the key ethical question. 6

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3 Ibid., 584.
4 Ibid., 593.
If one could look at the present through the lenses of the medical culture of the 1950s, one would be struck by how sharply the role of patenting has changed yet again. Not only has the pharmaceutical industry reached remarkable levels of capitalization through patents (and, increasingly, through trademarks), but patenting has become essential to its research model as well. As R&D costs for a “blockbuster drug” reach into the billion-dollar range, it is commonly assumed that the industry would not be able to sustain current levels of innovation without patent protection. Surprisingly, that position is shared even by scholars who are skeptical of the need for patent protection in other high-tech industries such as software. The pharmaceutical industry has thus become the paradigmatic (if not the sole) example of a technological field where a positive relation can be argued to exist between patents and inventive activity.

Another trend that would have probably been unimaginable to either a medical practitioner or a biomedical researcher from the 1950s is the role that patents have come to play in the new culture of biomedical entrepreneurship. Expressed in the wave of biotech start-ups that has emerged at the interface between academia and industry since the 1980s, this trend was made possible by the expansion of patent protection to the products of genetic engineering stemming from Diamond v. Chakrabarty (1980)—the first case in which the US Supreme Court found a genetically modified bacterium to be patent eligible. In addition to using the newly available protection of genetically modified organisms, sequences, and then isolated genes to prevent appropriation by competitors, these start-ups also mobilized patents as assets to bring to the table when negotiating venture capital investments, or to signal the “hotness” of the company to potential buyers, partners, and employees.

The critics’ arguments have changed, too. Those objecting to the proliferation of patents in recent and contemporary biomedicine (especially in academic settings) have tended to focus less on the economic and health effects of pharmaceutical monopolies, and more on the negative effects of patenting by universities on knowledge production itself, especially in upstream research. The concern has been with the so-called anticommons effects, the economic burdens that patent licensing may impose on research activities, and the cultural change produced or emblemized by patenting—the erosion of the traditional scholarly ethos and the widespread emergence of academic entrepreneurship.

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13 John Walsh, Ashish Arora, and Wesley Cohen, “Effects of Research Tool Patents and Licensing on Biomedical Innovation,” in Patents in the Knowledge-Based Economy, ed. Cohen and Stephen...
STABILIZING AND DESTABILIZING MEDICAL INVENTION

Underneath these changing ethical, cultural, and political debates, there has been, from 1800 until very recently, a stable match between the objects of medicine and the concepts of patent law. In US patent law parlance, pharmaceutical drugs fall in the “composition of matter” category, while surgical instruments, medical devices, and other technologies like prostheses are “machines.” Both categories of invention (as well as the methods to produce or use them) have been patent eligible in the United States since the 1793 Patent Act, and long before that in Europe and colonial America. Chemical inventions, machines, and methods have long been patentable virtually anywhere in the world. It is safe to assume that the complex political negotiations that have slowly led to the near-global “harmonization” of patent protection through the Paris Convention and the later passage of the World Trade Organization’s (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) would have been impossible without the prior conceptual standardization of basic categories of patentable subject matter that were adopted at least since the early nineteenth century. So, how does the emergence of personalized medicine unsettle the relationship between medical objects and patent concepts?

The US Supreme Court has recently decided a number of cases concerning medical diagnostic methods. One prominently featured in the media was Association for Molecular Pathology v. Myriad Genetics, Inc. (2013), where the court ruled that isolated genes are not patentable because they constitute “products of nature” rather than inventions. This invalidated a number of Myriad Genetics’ very profitable patents relating to breast and ovarian cancer tests based on the BRCA1 and BRCA2 genes. In one sense, Myriad reawakened a set of fundamental questions about the meaning of invention that were first provoked by the landmark Diamond v. Chakrabarty (1980) case, which held that patents could encompass “anything new under the sun,” including living organisms. Chakrabarty was found to have modified the bacterium he was


15 Surgical methods are an interesting exception to this pattern of unproblematic medical patenting. A European patent cannot be issued for “methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body”; see “Guidelines for Examination,” Law and Practice, European Patent Office website, https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_ii_4_2.htm. Close to eighty countries have similar exclusions, which can be traced back to at least the early nineteenth century; see Sally Frampton, “Honour and Subsistence: Invention, Credit, and Surgery in the Nineteenth Century,” Brit. J. Hist. Sci. 49 (2016): 561–76. While the United States allows for such patents, it still poses considerable limitations to their enforcement when these methods are performed by medical practitioners on human bodies, cadavers, or animals as part of medical research for humans; see the statute in the Code of Laws for the United States, 35 U.S.C.A. § 287(c). Notice that the prohibition of patents on these methods (as opposed to the allowance of patents on methods to produce certain drugs or certain medical devices) seems to hinge on the fact that these procedures are ways to intervene on the body, directly and physically.

16 Kevles, “Ananda Chakrabarty Wins” (cit. n. 10).
seeking to patent to such an extent that it was no longer a product of nature (a discovery) but a human artifact (an invention). That modification made it patentable.

That the invention in question was a living organism did not concern the court; living or inanimate, an invention is an invention. For scholars, however, the question of whether a living organism could be patented, and what distinguished patentable invention from unpatentable discovery, prompted analyses of the cultural politics and economic stakes of contemporary patent law, as well as questions about its somewhat mysterious conceptual foundations. A body of law that had been the preserve of patent attorneys and of a relatively small group of economists, economic historians, and historians of technology and medicine was quickly drawn into the purview of anthropology, religion, ethics, science studies, and critical theory. In particular, the importance of the diagnostic tests that were monopolized by Myriad, and the aggressive strategy the company adopted in marketing the tests and pursuing infringers, refocused attention on the practice of granting gene patents, which, at least in the United States, had become relatively unproblematic.

This rethinking was crucially informed by the fact that the Myriad patents claimed medical diagnostic methods of great public utility—technologies that the ACLU (a key early actor in the case) saw as impacting women’s rights.\textsuperscript{17} (Myriad is the first patent case to reach the Supreme Court that started from concerns with health justice rather than infringement claims.) The first human gene patents, which were granted in the 1980s and 1990s, were constructed as claims to molecules. That is, genes were treated like chemical inventions: structurally defined nucleotide sequences that produced useful effects, in the form of proteins. The commercial objective was to identify and clone genes that coded for known and therapeutically valuable proteins, and then to use cloned genes to produce these proteins on a commercial scale. Proprietary gene sequences served as the molecular templates for the production of pharmaceuticals, so judges and patent examiners treated applications for patents relating to DNA sequences as analogous to applications for patents relating to novel chemical compounds of pharmaceutical utility—both were considered “composition of matter.” In the language of European patent law, biotechnology patents were based on “compound \textit{per se}” or “product \textit{per se}” claims: “a patent which claims a physical entity \textit{per se} confers absolute protection upon such physical entity; that is, wherever it exists and whatever its context (and therefore for all uses of such physical entity, whether known or unknown).”\textsuperscript{18}

The question whether patents relating to isolated sequences were consistent with the utilitarian mission of the patent system had been raised since the early days of gene patenting. In the United Kingdom, the Nuffield Council on Bioethics observed in 2002 that “where the discovery is routine and the prospective use speculative, the owner of the patent stands to gain a reward which may not be commensurate with his contribution.”\textsuperscript{19} This question lay behind opposition to Myriad’s gene patents in various jurisdictions. Did the patenting of the genes associated with breast and ovarian cancer grant a monopoly that priced genetic tests out of many women’s reach, while


\textsuperscript{19} Nuffield Council on Bioethics, \textit{The Ethics of Gene Patenting} (2002), paragraph 5.9, on 49.
arguably also delaying research into the genetics of breast cancer? Or did the patent system provide the incentive without which much needed tests for breast and ovarian cancer might have never come into being? Noting that the decision to uphold the patents would have “broad consequences,” the dissenting opinion in the US Court of Appeals for the Federal Circuit took the view that “Myriad’s contribution to the field is not remotely consonant with such effects.”

A closely related question raised by Myriad concerned the changing academic norms of information sharing and the thorny relationship between public research funding and privately-held patents. Most of the research leading to the identification of BRCA1 and BRCA2 was supported by federal grants to universities. The University of California Berkeley’s Mary-Claire King and her team named and disclosed the approximate chromosomal location of BRCA1 in a 1990 *Science* article, starting a race involving twelve teams over three continents that concluded in 1994, when the University of Utah’s Mark Skolnick and his collaborators were able to identify and locate BRCA1 and, shortly after, BRCA2. The University of Utah and other stakeholders affiliated with the university applied for a patent, which was then exclusively assigned to Myriad Genetics—a start-up that Skolnick had established with other entrepreneurial academic biologists. Although Myriad had secured private funding in the last stretch of the project, the bulk of the race was overwhelmingly supported by public federal funds, both in Utah and elsewhere.

The patenting of BRCA1 and BRCA2 and their subsequent exclusive licensing to Myriad was made possible by the Bayh-Dole Act (1980) that strongly encouraged universities to patent results produced from federal grants, and to then license them to private sector actors better equipped to develop and bring them to market. Framed by outdated notions of innovation, however, the Bayh-Dole Act did not differentiate between traditional inventions that require substantial additional development to yield commercial products (development work that the university was ill-suited to perform), and new information-based inventions like diagnostic methods that instead require little or no additional development work because they involve well-known tools and techniques available to any properly trained geneticist. Bayh-Dole aimed at making sure that potentially useful innovations would not be forgotten, half-developed in a drawer in some university lab; however, inventions like Myriad’s never really run that risk. At least in this case, the outcome seemed to run counter to Bayh-Dole’s stated goal. In addition to pricing the test out of many patients’ reach, the patenting and exclusive licenses promoted by Bayh-Dole seemed to create bottlenecks that could ultimately harm the patients by slowing down oncological research. Patents on BRCA1

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and BRCA2 would prevent not only their diagnostic use but virtually all unauthorized research on the genes themselves.

But while the emergence of new diagnostic tests and their patenting is emblematic of the goals of personalized medicine and the business models associated with it, they do not all fit Myriad’s technical and legal typology. Myriad’s patent hinged on the comparison between a genetic sequence of reference and the patient’s specific sequence to detect potentially dangerous mutations, raising the legal question of whether an isolated gene was an inventive human artifact or a product of nature. In recent years, however, the courts have been confronted by various other diagnostic tests that probe the elasticity of patent law from different directions.

A 1990 patent by Metabolite Laboratories (also derived, like Myriad’s, from the work of academic researchers) involved the correlation between a biomarker and a medical condition; that is, if your blood test indicates a high level of homocysteine, most likely you have vitamin B deficiency. No blood-testing technology was claimed in this patent, only the correlation. You can have your blood tested anywhere, using whatever method or equipment, but if your homocysteine level turns out to be high, and you self-diagnose as having vitamin B deficiency, you are infringing Metabolite’s patent because what is being protected is the diagnosis-producing correlation, not the blood-testing technology. In this case, the patent law question was not whether homocysteine or vitamin B were products of nature, but whether their correlation was an invented “process” (that is, a patent-eligible diagnostic method) or a plain, noninventive application of a preexisting and thus unpatentable “law of nature” tying high homocysteine levels to low Vitamin B levels.25

A different scenario is found in Ariosa v. Sequenom (2015); this involved a method to test fetal blood for genetic conditions such as Down syndrome that did not rely on the common but more dangerous amniocentesis process.26 Sequenom used the fact (discovered by the inventors themselves almost twenty years earlier) that very small quantities of fetal DNA find their way through the placenta into the maternal blood and, once identified, could provide genetic material for the test. Sequenom then used the presence of paternal DNA in the fetal DNA as a way to distinguish it from maternal DNA and collect it. Sequenom’s method was a new and powerful improvement over the riskier amniocentesis but was found to be patent ineligible because it did not constitute an invention. According to the Federal Circuit, “the method begins and ends with a natural phenomenon.” It was rooted in the discovery that some fetal DNA floats in maternal blood and can be identified because of its paternal DNA component, and that small quantities of fetal DNA could then be amplified with well-known techniques like PCR (polymerase chain reaction). It was all rather ingenious, but not patent eligible.

Another important case that has left a large legal footprint (and to which we shall return) is Mayo Collaborative Services v. Prometheus Laboratories, Inc. (2010). It involved a patent for a method of adjusting the dosage of thiopurine drugs for the treatment of autoimmune conditions such as Crohn’s disease and ulcerative colitis. It was already known that different patients metabolize thiopurine compounds differently. Therefore, a dose might be either too high (and hence toxic) or too low (and

hence ineffective), depending on the metabolism of the particular patient. (Unlike the other diagnostic cases listed above, Prometheus Laboratories did not test something already existent in the body—fetal DNA or BRCA genes—but the body’s reaction to the administration of the drug in the form of its production of metabolites.) Prometheus’s invention did not involve the thiopurine drugs either, which were well known and already used to treat autoimmune diseases. It centered, instead, on what was admitted to be a law of nature: the relationship “between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.” Prometheus claimed to have developed this law of nature into a patentable diagnostic protocol that included the identification of ranges of metabolites from “too low” to “too high,” thus advising the physician to tweak the dosage accordingly. In sum, it claimed to have patented not a law of nature but a method for perfecting the dosage based on the inventive application of a law of nature. Mayo disagreed. After conducting additional research, it selected different metabolite ranges of reference that, nonetheless, still overlapped with the ranges listed in the Prometheus patent. When Prometheus sued for infringement, Mayo defended by arguing that the patent was invalid: Prometheus had merely patented a law of nature, with the deleterious effect of preventing further research into more accurate dosages. By and large, the Supreme Court concurred with Mayo.

The list of recent cases could be expanded, but this brief sample should suffice to convey the diverse typologies of these new methods. Still, while their objects and goals are different, they all share three features: (1) they exemplify medical innovation in the age of precision medicine; (2) they run afoul of the law’s exclusion of products of nature, laws of nature, and abstract ideas from patent eligibility; and (3) they do not claim a new material innovation—a new drug or new device—but only methods to produce new information based on a novel combination of often previously known facts, discoveries, and innovations. In all these cases, the key legal question is what kind and how large of a transformative step needs to be applied to either a product of nature or a law of nature to make it cross the threshold from unpatentable discovery to patentable invention. And while, taken together, these cases seem to exemplify a trend toward more restrictive views of patentability, they in fact reflect a recent and somewhat haphazard pushback, mostly by the Supreme Court, against the rather liberal construction of patentability that started with Chakrabarty in 1980 and then gained momentum with the patenting of genetic sequences, genetically modified organisms, software, and business methods. More importantly, this recent pushback does not reflect a clear consensus over where to draw the line between patentability and unpatentability in information-based technologies. The Supreme Court itself candidly acknowledges that there may be something epochal about the current predicament, citing the distinction between the inventions of the “Industrial Age” and those of the “Information Age,” and the challenges posed by applying to the latter a patent law designed for the former.

**IN THE BEGINNING WAS THE MACHINE**

The questions of ethics, politics, and economics that were precipitated by the *Myriad* and *Mayo* cases are clearly of prime importance, because they engage both patient

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rights and innovation policy. They are also symptoms of the dissolution of what we call the modern patent episteme that framed thinking about invention from the late eighteenth century until the very beginning of the twenty-first century. (We use the term episteme to stress the fact that we are not talking about national patent laws or policies but about the conceptual conditions of possibility that they share.) Two features characterized the modern patent episteme: (1) its representational logic, and (2) the figure of the machine.29 Around 1790, in France and the United States, invention stopped being thought of as a material device (as had been the case in the early modern period) and became a textual and pictorial representation that identified the idea or “principle” of that device. Such “principle” was usually construed as its “mode of operation”—that is, the way its various connected parts worked together to produce a certain useful effect, like planing wood planks, curing rubber, and so on. Representation construed the invention as intangible (the “principle”), but it also turned it into knowledge—knowledge of the operation of the machine. By moving invention from the domain of specific devices to that of representation, a conceptual space was opened up, making possible the emergence of a discourse that has eventually grown into the doctrines and techniques of modern patent law. Literally, it was when invention became represented that it also became a matter of law. Prior to its representation, an invention was a device—a matter of mechanics. In fact, the early modern view of invention construed it as inherently material and tied to one specific machinic embodiment. What could be protected was the specific tangible and working invention one presented and demonstrated to the authorities.

Another striking difference between the early modern and modern patent epistemes concerns their political economy. Early modern inventions were locally rewarded through privilege based on their local utility (water pumps in the Netherlands, canal dredging devices in Venice, etc.) and were typically contingent on the actual delivery of a working invention or model. Very little disclosure of the invention was required, provided the inventor could show that it worked or could work. By contrast, in the modern patent episteme—operative in virtually all nations of the world—inventors became entitled to property rights, as opposed to privileges that the authorities could grant or withdraw as they saw fit. Furthermore, those property rights concerned the idea of the invention (and thus “intellectual” property), not the material embodiment of that invention. And while this modern inventor no longer needs to demonstrate the actual functioning and utility of the invention, they must make a full disclosure of it available to the government and to the public in a quid pro quo exchange for the temporary rights received. This is the so-called patent bargain, not a gift from the sovereign to the subject, but a contract between the inventor and the public. The modern patent is thus not just the result of a new conceptualization of invention but of an entirely new and historically specific political economy that emerged right after the French and American revolutions and, more gradually, in Britain.30

But if the invention went from being a matter of mechanics to becoming a matter of law, patent law became “mechanical” itself in the sense that it was the figure of the


machine that became the conceptual template for understanding what the principle of that material invention could be. The figure of the machine came to inform the conceptualization and apprehension of “invention” across technological fields, and not just of mechanical machines, but chemical inventions, electrical inventions, software inventions, and even inventions involving living organisms. For instance, chemical inventions are categorized as “compositions of matter,” where that crucial term—composition—was conceptualized through an analogy with the way the parts of a machine are connected to each other, how the configuration of those connections determines what the machine does, and thus what invention it embodies. The chemical substances that were brought together in a new chemical invention (in the specific ways that were both designed by the inventor and constrained by the compound’s natural chemical qualities) were figured as parts of a “machine.” And when inventions concerned processes rather than individual products, machines, or chemical compounds, the assumption was that such processes were machines writ large. In the same way that machines were seen as combinations of connected parts aimed at producing a useful effect, processes were assemblages of machines or means organized to achieve useful goals.

The invention-as-representation was never a Platonic idea that existed separately from the material machine. Yes, the invention was construed as the principle or form of the machine, and the law prioritized this form or principle and placed it “above” the machine by attaching property rights to it rather than to the material machine it informed. At the same time, the invention was always the principle of a machine (or perhaps of a family of machines), rather than an independently existing principle that was then embodied in a machine. That is, the invention as form of a machine could only be a specific kind of form, the kind of form that could emerge from a machine or, rather, from the observation and understanding of what a machine did. The inherently unstable relation between the tangible and intangible halves of invention has been mediated (or rather made graspable or imaginable) by figures that could function as exemplary forms of what invention is in a given technological context or era. In the nineteenth century, the machine itself provided that figure—not the machine as a stationary object of wood or cast iron, but the machine as a material assemblage characterized by a specific mode of operation resulting from the combination and interconnection of its parts so as to produce a certain useful effect. Not only was this machine a concept rather than a material entity, but it was also a kinematic concept: the way the machine moved in time, cyclically and without deviation from its mode of operation, to produce something. For a few decades, the model functioned as the best material tool to convey what that conceptual machine was.31

The machine also functioned as a way to demarcate patentable inventions from unpatentable ones. For instance, laws of nature were categorized as discoveries, and thus unpatentable unless incorporated into a machine, like a telegraphic apparatus based on the principles of electromagnetism; then, they could be patent eligible. The same logic supports the Diamond v. Diehr (1981) decision to make software patent eligible when embedded in an industrial apparatus and, subsequently, in a separate computer. While software does not look like a steam engine, it was deemed patentable by being

construed as functionally equivalent to a machine.\textsuperscript{32} From this perspective, software is “a machine whose medium of construction happens to be text.”\textsuperscript{33} In other words: “Where physical machines are built from physical structures like gears, wires, and screws, programs are built from information structures, such as algorithms and data structures. In software, these components must work together in a very carefully orchestrated way that resembles nothing so much as an intricate mechanical device consisting of thousands of delicate gears and levers.”\textsuperscript{34} The requirement for embodying an invention involving an otherwise abstract process into a machine was then applied—often with substantial difficulty—to the next wave of information-based inventions, such as business methods and diagnostic methods.

**DIAGNOSTICS, INFORMATION, AND THE CRISIS OF THE PATENT EPISODEME**

It is important to appreciate how different the challenges posed by the patenting of diagnostic methods are from those associated with the patenting of genetically modified organisms or other products of recombinant DNA techniques. Since Chakrabarty, inventions that involve genetic modifications are no longer seen as products of nature but as biological machines whose parts have been altered, rendering them patent eligible. Myriad has not changed that. What has been affected, instead, is the type of gene-based innovation involved in diagnostic tests that claim genes not as “modified machines” but as “bioinformation.” Throughout the 1990s and up to Myriad, the US Patent Office has routinely granted patents to inventions involving specific manipulations of genetic sequences, but also to genes and sequences that were only minimally modified by “snipping” them out of a longer sequence (which involved breaking chemical bonds and creating, \textit{sensu stricto}, a nonnaturally occurring molecule) or by “purifying” them of their introns.\textsuperscript{35} In Myriad, however, the Supreme Court did not judge those types of modifications sufficient to make isolated genes patent eligible. Although chemically significant, those changes did not affect the informational dimensions of the genes at the center of Myriad’s diagnostic method, thus leaving them in the “product of nature” category:

Myriad did not create or alter either the genetic information encoded in the BRCA1 and BRCA2 genes or the genetic structure of the DNA. It found an important and useful gene, but groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 [patent eligibility] inquiry. . . . Myriad’s claims are not saved by the fact that isolating DNA from the human genome severs the chemical bonds that bind gene molecules together. The claims are not expressed in terms of chemical composition, nor do they rely on the chemical changes resulting from the isolation of a particular DNA.


\textsuperscript{34} Ibid., 2321.

\textsuperscript{35} Such patents may have been awarded due to an authoritative but flawed opinion about the patent eligibility of purified chemicals; see Jon M. Harkness, “Dicta on Adrenalin(e): Myriad Problems with Learned Hand’s Product-of-Nature Pronouncements in Parke-Davis v. Mulford,” \textit{Journal of the Patent and Trademark Office Society} 93 (2011): 363–99.
section. Instead, they focus on the genetic information encoded in the BRCA1 and BRCA2 genes.36

The Supreme Court’s ruling demonstrates the categorical nature of the challenge faced by those arguing for the patentability of diagnostic methods like Myriad’s. Before and after Myriad, patent law treated genes as patent-eligible “compositions of matter” when manipulated beyond “snipping” and “purifying.” Therefore, had Myriad claimed an invention comprising BRCA genes whose sequence had been modified to achieve some other useful purpose, it might have secured a patent for that. But because the diagnostic method that Myriad had based on the BRCA genes hinged on naturally occurring “wild type” sequences and their natural mutations, modifying those genes would have been self-defeating given the logic and purpose of the test.

From the perspective of the classic patent episteme, Myriad simply failed to satisfy the criteria of invention: it did not modify or transform the BRCA sequences sufficiently to remove them from their state of nature. However, Myriad’s patents should be appreciated not in terms of their failure to meet the classic standard, but as the expressions of a new and different logic of invention, one that construes “nature” not in industrial terms (as an input for the production of pharmaceutical products), but in cybernetic terms (as diagnostic information that is used to fine-tune therapeutic procedures). As exemplified by later cases like Mayo v. Prometheus (which we discuss in a moment), in these modes of diagnosis, bioinformation abstracted from the body is returned to the body as a prompt for the body’s own information-processing circuitry. It is this shift from an industrial or manufacturing paradigm to a bioinformational paradigm that informs the new sense of invention.

If Myriad had modified the BRCA sequences any further, it would have undermined a diagnostic method that required the genes to stay in their natural state, precisely so as to be able to engage the body’s metabolism. As the court put it: “Notwithstanding Myriad’s repeated use of the phrase ‘present invention,’ it is clear from the text of the patent that the various discoveries are the ‘invention.’”37 More precisely, these “discoveries” were mobilized within a process that was “inventive” in a way that was inconsistent with the logic of transformation, which imagines genes as “biological machines,” and that is therefore antithetical to the emergent logic of bioinformational diagnostics. To function as useful innovations, discoveries like Myriad’s must not become what the law calls an invention.

Still, the problem does not end here. There are diagnostic methods whose business model does not hinge on the patenting of “inputs” (genes or genetic sequences, in Myriad’s case), but on controlling the method or algorithm to be followed to achieve the diagnosis. The claim is on a “process,” not a “composition of matter.” As a result, these methods challenge the classic machine-based patent episteme from yet another angle. If Myriad-style diagnostics run against the distinction between invention and product of nature, other methods struggle to negotiate the equally crucial distinction between invention and law of nature, or between invention and abstract idea. For instance, the Metabolite patent discussed above involved a method that utilized a correlation between a biomarker and a medical condition, which the law construes as an unpatentable law of nature. The same applies to Prometheus’s method to calibrate

37 Id. at 592 n.4.
the dosage of a certain class of drugs, which the Supreme Court found to be patent ineligible largely because it merely applied the natural correlation between a drug dosage and the levels of metabolites produced by the body’s response to that drug. (Notice, however, that in both Metabolite’s and Prometheus’s cases the “law of nature” was not deployed to produce material effects—like thermodynamics in James Watt’s separate condenser design—but to yield diagnostic information.)

Finally, some diagnostic methods overlap with yet another legally challenging form of invention of the Information Age: business methods. Recent decisions concerning diagnostic patents have been in fact framed by the Supreme Court’s ruling in *Bilski v. Kappos* (2010), which concerned an algorithm for hedging risk in commodities trading, involving rather general information-gathering and information-processing steps. That invention was eventually deemed patent ineligible because it amounted to an “abstract idea” devoid of specificity and of any technological dimension. In addition to being seen as un inventive applications of a natural law, new medical diagnostics like Prometheus’s are also at risk of resembling Bilski’s hedging method due to the fact that they involve algorithmic steps that are not attached to machines. Because some of those steps may be construed as merely “information gathering” or “mental steps,” they may fall into the unpatentable “abstract ideas” category.

Information has been part of the invention landscape starting with the telegraph in the nineteenth century and continuing with the patenting of software and mathematical algorithms, but these were all scenarios where information still could be attached to a machine (a telegraph, a computer, etc.). This is not the case in modern medical diagnostics. In addition to the remarkable complexification of “invention” that they are engendering, these new methods pose equally remarkable political and policy challenges because, unmoored from the machines that embedded and delimited them, inventions of the Information Age run the risk of expanding like a genie out of the lamp, creating very large monopolies—not just economic monopolies, but monopolies on knowledge that may constrain the development of future inventions. Getting the definition of “invention” right is therefore crucial to achieving a proper description of what innovation has become, but also to balancing the rights of today’s inventors, today’s public, future publics, and future inventors.

While it is impossible to predict what may lay behind the conceptual and legal limbo currently occupied by new medical diagnostics, we continue to see evidence of the endurance, against all odds, of the conceptual form of the invention as machine, demonstrating yet again the depth of classic patent law’s dependence on it. In *Bilski*, the Federal Circuit defined a patent-eligible process by applying a “machine-or-transformation” (MORT) test, which Bilski’s invention failed to pass: “A claimed process is surely patent-eligible under §101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.”38 The Supreme Court, however, rejected the Federal Circuit’s attempt to bring the information genie back into the material bottle, acknowledging that the time of the machine episteme of patent law may be running out:

The machine-or-transformation test may well provide a sufficient basis for evaluating processes similar to those in the Industrial Age—for example, inventions grounded in

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38 In re Bilski, 545 F.3d 943, 954 (Fed. Cir. 2008), aff’d but criticized sub nom. Bilski v. Kappos, 561 U.S. 593 (2010).
a physical or other tangible form. But there are reasons to doubt whether the test should be the sole criterion for determining the patentability of inventions in the Information Age. . . . The machine-or-transformation test would create uncertainty as to the patentability of software [and] advanced diagnostic medicine techniques . . . As a result, in deciding whether previously unforeseen inventions qualify as patentable “process[es],” it may not make sense to require courts to confine themselves to asking the questions posed by the machine-or-transformation test.39

It is important to keep in mind that these patent eligibility questions were never raised by traditional drugs and medical devices. More than an evolution of the role of patenting in medicine, we are witnessing a discontinuity that, while obviously energized by the logic of capital, is substantially triggered by the development of personalized medicine. This specificity is reflected in two trends or responses we want to analyze in lieu of a conclusion. One is political-economic in nature (redrawing “invention” based on policy goals), and the other points to the epistemological specificity of personalized medicine (redrawing “invention” based on the new research and therapeutic practices).

**BEYOND ETHICS AND ONTOLOGIES: A NEW POLITICAL ECONOMY OF INVENTION?**

If the Supreme Court did not grant paradigmatic status to the MORT test, leaving the door open for other patent-eligibility tests to emerge, other players have put forward more radical and, in our view, problematic proposals.40 Already, in *Mayo v. Prometheus*, counsel for the government proposed that most inventions that were caught by the law of nature exception (and, by extension, by the abstract idea exception) would in any case fail to meet the other patentability requirements like novelty, utility, obviousness, or disclosure.41 The not-so-veiled suggestion was that patent law could function well, or even better, if it gave up on threshold tests of what kind of things should or should not fall in the category of “invention,” and simply left it to the other conceptually simpler requirements to decide whether an invention deserves a patent. According to this view, the challenges posed by information-based inventions were in fact artifacts of patent law’s anachronistic desire to categorize “invention” as a conceptual species rather than an essence-free notion associated with a series of discrete attributes—novelty, utility, nonobviousness, and so on. The court was not receptive to this suggestion and, in the course of refuting it, observed that it would not meet “the kind of risk that underlies the law of nature exception, namely, the risk that a patent on the law would significantly impede future innovation.” The court continued:

> There is a danger that the grant of patents that tie up [the use of laws of nature] will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to “apply the natural law,” or


40 The current patent-eligibility test, the “Alice/Mayo” inquiry, was sketched out by the Supreme Court in *Mayo v. Prometheus*; for a discussion of this, see “2106 Patent Subject Matter Eligibility,” US Patent and Trademark Office, Department of Commerce, https://www.uspto.gov/web/offices/pac/mpep/s2106.html. This test has been widely debated and criticized, suggesting that it is not likely to provide a long-lasting standard.

otherwise forecloses more future invention than the underlying discovery could reasonably justify.\textsuperscript{42}

In other words, even if the patent statute is supposed to be interpreted in such a way as to promote innovation (by granting patents), the “risk” is that patents relating to laws of nature as such would restrict the potential for further invention by preventing others from using those broad laws for the duration of the patent. The court observed that the balance here—how much future innovation is foreclosed relative to the contribution of the inventor—is very difficult to judge. So, what the court in \textit{Bilski} called the “public domain” interest has to be secured by articulating a clear rule: “the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying ‘building-block’ concern.”\textsuperscript{43}

In the nineteenth century, and for much of the twentieth, the product of nature doctrine was not construed in terms of this kind of balance. The question of how to represent machines was based on a sense that the intangible form of the invention had to be specified, expressed in text, and distinguished from a mere law or product of nature. In other words, the distinction between discovery and invention was understood as categorical rather than functional. What we see emerge now, instead, is a tendency to stop asking what invention is, or to stop emphasizing the formerly all-important distinction between discovery and invention. If “something” produces useful effects, is new, nonobvious, and can be properly described in a patent application, that “something” should be patentable whether or not it is a discovery or an invention, or whether it involves a product of nature, a natural law, or an abstract idea.\textsuperscript{44} (Such a radical re-definition of invention informs a patent reform bill currently supported by the biotech and diagnostic industry.)\textsuperscript{45} The fact that courts no longer reflect on the ontology of the invention, and no longer understand the product of nature exception accordingly, is an essential symptom of the dissolution of the patent episteme of the nineteenth and twentieth centuries.

\textbf{THERAPEUTIC INVENTIONS, OR A NEW KIND OF DISCOVERY?}

The dispute between Mayo and Prometheus foregrounds some of the slippages between “discovery” and “invention” typical of new diagnostic methods, but it also shows how the agency of the patient’s body adds another layer of complexity to discussions of the inventions of personalized medicine and their patent eligibility. Those who, like the Federal Circuit, have made a case for the patent eligibility of diagnostic methods like Prometheus’s have not put forward a new notion of information-based invention, but have argued, instead, that such inventions are conventional (and thus patentable) because they meet the machine-or-transformation test. The body of the patient is transformed by the diagnostic test, just as rubber is cured by a rubber-curing

\textsuperscript{43} Id. at 89.
\textsuperscript{44} “In other words, if a discovery otherwise meets the requirements of patentability, then the discovery will be properly patentable without need to consider non-statutory subject matter restrictions such as the bars against mathematical algorithms, products of nature, or natural phenomena”; see Risch, “Everything is Patentable” (cit. n. 41), 591.
\textsuperscript{45} “Sens. Tillis and Coons” (cit. n. 1).
apparatus. More precisely, Prometheus’s test is part of and overlaps with the therapeutic treatment—a treatment that eventually modifies the body by healing it. In explaining the transformation requirement, the Federal Circuit returned to its proposition in *Bilski* that “transformation must be central to the purpose of the claimed process,” and then agreed with Prometheus’s characterization of the transformations involved in their patent:

> With respect to the transformation prong, Prometheus points to three “transformations” within its claimed process: (1) the first step of administering a synthetic drug transforms the biochemical makeup of the patient’s body for the purpose of treating disease; (2) the second step requires the transformation of a bodily sample to determine the created metabolites’ concentration levels; and (3) the metabolite levels are transformed into a warning for a doctor to alter the dosage. Regarding the first asserted transformation, Prometheus argues that physical transformations, such as the human body’s metabolic reaction to drugs, initiated by human actions and artificial chemical compounds, such as the administration of a thiopurine drug into the body, cannot be unpatentable under *Bilski* simply because they proceed according to natural laws or occur within the human body. Prometheus contends that *everything proceeds according to natural laws.*

The words italicized by us capture one of Prometheus’s key arguments: namely, the first transformation—one that the Federal Circuit takes to be simultaneously therapeutic and diagnostic—is triggered by the administration of a thiopurine drug by a physician, but was then affected by natural processes within the body. The body is not transformed by the drug the way a press pounds a bar of steel into the shape of a knife. Instead, it both transforms and heals itself by being administered that drug, which means that the body is both healed and self-healed in uniquely specific ways. The object of the invention is to take the product of that first therapeutic self-transformation (the level of metabolites that the body, based on its specific genetic makeup, produces in response to the drug) and use it as an index—that is, as information—to fine-tune the dosage of the medication so that it is neither too low (ineffective) nor too high (toxic). The determination of the final dosage is the result of human intervention, but is based on information specifically produced by that body, and ultimately fine-tuned to its specific metabolism.

We believe that this type of scenario informed an intriguing remark by Gregory Castanias, Myriad’s counsel, in his oral argument before the Supreme Court in 2013:

> Modern medicine, particularly the area of personalized medicine, is trying to get to a point where what we are administering to individual patients is giving them the opportunity to mimic the actions of the body. And—so actually, the goal of medicine is to get closer to nature, rather than farther away. And anything that takes the product of nature doctrine beyond the simple truism that the product of nature is something that is not a human invention, then that’s very dangerous, not just for our case.  

Castanias calls for a rethinking of the product of nature doctrine (into which he folds the law of nature exclusion) that has framed all recent patentable subject matter cases

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from software to diagnostic methods. Throughout his argument, he criticizes that doctrine as being “dangerous,” having “serious analytical problems,” while referring to it as a “so-called doctrine.” He explains: “I don’t believe that as a separate doctrine it really exists. It’s just the flip side of the coin of something that shows a lack of invention.”

Castanias’s argument tries to undermine the bright-line function that the product of nature doctrine had played so far—a goal that was perfectly aligned with his client’s interests. At the same time, it does manage to capture something intriguing about the specific form that innovation has taken in the area of personalized or precision medicine—a form that appears to be diametrically opposed to the canonical notion of invention as a human manipulation of something away from its natural state, carrying it across the threshold from discovery to invention. (We have encountered the same predicament in Myriad, where the genes’ sequence had diagnostic power only if left in its state of nature, as a discovery.)

If we zoom out from the technicalities of patent doctrine, the sense of innovation that is emerging with personalized medicine can be understood in terms of what Hannah Landecker calls postindustrial metabolism: “This new metabolism is a regulatory zone, not a factory system; it is understood to be constituted by a dynamic web of cellular signals, built by and responding to environmental information—food molecules or food’s pollutants. It has a distinctive mode—that of the signal rather than the chemical reaction.” The body of the patient becomes a medium very unlike the instrumentalized nature that was the foil to the machine of the old patent episteme. Instead of being a source of either materials or tools, the body is a self-regulating form that “has a modular architecture, is robust to perturbations, and responds to biological stimuli and environmental conditions”; these include the administration of medications.

So, when Castanias says that the goal of precision medicine is “to get closer to nature, rather than farther away,” what this actually means is that invention is no longer exemplified by a machine (like an artificial heart, which is evidently nonnatural), but has become a mode of running interference with the body’s own way of processing signals. Prometheus’s fine-tuning of the dosage was based on the “discovery” of the body’s response to the drug, but what was discovered was not some general natural law or category of objects but the responsiveness of a body’s specific metabolism to the introduction of a particular “signal.” The administration of a drug involves information processing twice over: the “technology” is essentially a way of processing the information processing of the body, with the former being by far the less complex. This mixing of agencies—the agency of the inventor who introduces the “signal” is mixed with the agency of the body as expressed in the production of metabolites—does indeed suggest a new, if possibly paradoxical, sense of invention.

The diagnostic method claimed by Prometheus’s patent is conceptually and historically distinctive because it involves an intervention on the body that, unlike a surgical operation or an MRI scan, does not modify or engage the body with a direct and external action upon it. (One could see the body not as an object being transformed but as an actant in a transformation). At the same time, the transformation of the body

49 Id. at 54–5.
51 Ibid., 497.
produced by the administration of the drug is also crucially different from the kind of transformation involved in traditional technologies like the curing of rubber at the center of *Diamond v. Diehr* (1981). In Diehr’s invention, the rubber always responds in the same way to the conditions that the apparatus sets up for the rubber to cure, but in Prometheus’s method the body (because of its metabolic specificity) produces different levels of metabolites. It “cures” itself *differently*, thus requiring an additional adjustment of the dosage to fine-tune that difference/specificity—a process that straddles the line between diagnostics and therapeutics.

If the key to patent eligibility for inventions involving a law of nature is to “add” something to that law while applying it, Prometheus’s invention is therapeutically effective precisely because it does *not add anything* to the law correlating thiopurine drugs to metabolites. Unlike the genetic interventions of recombinant DNA techniques, these therapeutic/diagnostic methods are based on eliciting and observing the body’s genetic specificities as they are performed in response to the administration of a drug. But precisely because they work by intervening only as a trigger (rather than through the kind of material transformations produced by a genetic engineer), they are not sufficiently transformative to qualify as invention. Myriad faced a comparable challenge. Its invention hinged on leaving the informational content of the BRCA genes unmodified, and yet had to claim some transformation to try turning its discovery into a patentable invention. Paradoxically, the only transformations they could claim had to be nontransformative. “Snipping” and “purifying” were the right kind of transformations in that they did not affect the gene’s information content but, for the very same reason, were not enough to transform a discovery into a patent.

This suggests a concluding observation. To the extent that the classic distinction between invention and discovery depended upon a division between scientific knowledge and its technological “applications,” then that difference is short-circuited by the mode of “translational” research that is implicated in personalized medicine: “The funding mechanisms and publishing outlets for translational research deliberately fuse ends to means, making the end goal of the research directly and explicitly shape its character from the get-go.”52 In the case of diagnostic medicine, and as the business model of Myriad Genetics shows, the “fusion” of ends and means takes the form of a recursive loop. As we have seen, diagnostic tests do not transform matter or energy in the manner of a process for curing rubber. Rather, they induce the metabolism of the patient to regulate (transform?) itself by reacting to information (signals that make a difference). The art of personalized medicine is to respond to the responsiveness of individual bodies. At the point of treatment, this is a matter of adjusting dosages. At the scale of the business, it is a matter of refining the parameters within which the responsiveness of an individual metabolism can be apprehended. So, the results of personalized diagnostic tests are fed back into a proprietary archive of test results and associated patient information, which then becomes a resource for enhancing the test in question, or for developing new ones. (For instance, because of the superior diagnostic accuracy enabled by a vast repository of mutations collected from previous patients’ screenings, Myriad was able to maintain a demand for their tests despite being defeated in court. In time, value and capital migrated from the patents to the archive).

The science of diagnostics is therefore not technoscientific knowledge of the kind imagined by twentieth-century patent law, nor is it a resource for producing knowledge

52 Ibid., 498.
of this kind. It does not accrue a body of knowledge about arrangements of matter, application of forces, or flows of energy. Rather, it evolves a “know-how” whose meaning and value is conditioned by the metabolic responses that it seeks to anticipate, and that takes the form of so-called information or data. At this point, the figure of nature, which was both a foil for the patent law conception of the machine and the domain that the product of nature doctrine sought to delimit, has indeed been almost entirely eclipsed.