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**Author**
Burk, DL

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# Edifying Thoughts of a Patent Watcher: The Nature of DNA

Dan L. Burk

## ABSTRACT

In the pending case *Myriad Genetics v. Association for Molecular Pathology*, the U.S. Supreme Court will consider the patentability of human genes under the "product of nature" doctrine. Patentable subject matter is generally held to encompass materials and artifacts created by humans, and not that which exists independently in nature. However, it is not clear that this is a meaningful or helpful distinction. Given on one hand that the concept of a gene is a human construct, and on the other hand that all human creations are drawn from the material environment, the question of gene patenting is better addressed as a matter of innovation policy than of imponderable labeling.

## AUTHOR

Dan L. Burk is Chancellor's Professor of Law at University of California, Irvine.

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> Like me, this pipe so fragrant burning
> Is made of naught but earth and clay;
> To earth I too shall be returning.
> It falls and, ere I'd think to say,
> It breaks in two before my eyes;
> In store for me a like fate lies.[1]

## INTRODUCTION

On November 30, 2012, the U.S. Supreme Court granted certiorari in *Association for Molecular Pathology (AMP) v. Myriad Genetics, Inc.*,[2] agreeing to hear arguments on the single question, "Are human genes patentable?"[3] The case concerns patent claims to DNA molecules, some isolated from human cells (gDNA) and some constructed in the laboratory (cDNA), which have been challenged as constituting unpatentable subject matter. A trial court ruling initially found both types of molecules to be unpatentable "products of nature."[4] A panel of the U.S. Court of Appeals for the Federal Circuit reversed this holding, both on initial appeal and after the case was remanded from the Supreme Court for reconsideration in light of other recent Supreme Court holdings.[5]

In this Essay I consider a particular strain of argument that has grown up during the progress of the case, involving unproductive formulations of patent law's product of nature doctrine. The Supreme Court has held that U.S. patent law encompasses "anything under the sun that is made by man";[6] the inverse proposition would imply that patent law does *not* cover anything under the sun *not* made by man. This leaves the problem, of which the Supreme Court's question is a particular version, as to how we might recognize which entities constitute products of nature rather than products of inventive human activity. I hope here to refocus the discussion away from the misleading and unhelpful "product of nature" label, which is otherwise bound to obfuscate the discussion before the Supreme Court, as it has done in the lower courts.

1. J.S. Bach, *Edifying Thoughts of a Tobacco Smoker*, *in* THE BACH READER 97 (Hans T. David & Arthur Mendel eds., 1966).
2. 133 S. Ct. 694 (2012).
3. Petition for Writ of Certiorari at i, Ass'n for Molecular Pathology v. Myriad Genetics, Inc., (U.S. Sept. 25, 2012) (No. 12-398), 2012 WL 4502947.
4. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*AMP I*), 702 F. Supp. 2d 181, 227–28 (S.D.N.Y. 2010), *aff'd in part, rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011).
5. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office (*AMP II*), 689 F.3d 1303, 1308 (Fed. Cir. 2012).
6. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (quoting S. REP. NO. 1979, at 5 (1952)).

## I. PRODUCTS OF NATURE

We should begin by recognizing the simple and obvious proposition that genes don't exist in nature. There is no entity in nature that comes with a label declaring "This is a gene," or even with some type of pointer declaring "Gene starts here" or "Gene ends there." What exist in nature, in the physical environment, are diverse globs of material interacting in highly complex networks of energy transfer.[7] Dividing those networks into conceptual bits such as genes is a practice that is useful to humans, but not one that is somehow mandated by the structure of the universe. The divisions are determined by humans as part of our penchant for "sorting things out."[8]

So it is no sense acting as if the category of genes, or for that matter any given gene, is in a fundamental sense ever *anything* but the product of human invention. The concept of a gene is entirely a human construct, and there is considerable room for debate as to what ought to be included in the concept of the gene, or, by the same token, what ought to be excluded from the concept of the gene.[9] Some such constructs are more useful to humans than others, but the constructs themselves change over time, resulting in what we term scientific progress—we add or revise or amend the criteria for our constructs, subject to an array of social choices that yield amended or revised or additional outcomes. This is not to say that the decision to lay down a marker is arbitrary—or at least that it is typically not, and never is entirely, arbitrary; but inclusion or exclusion of the features considered relevant changes depending on the question being asked and the purpose being pursued.

Thus science informs—but cannot answer—the legal question as to whether a gene is a product of nature. The concept of the gene itself has long been the subject of ongoing and lively technical debate which may seem obscured by technical terminology. Does a gene include only the series of nucleotide bases that code for a gene product—for a protein or for RNA? Or does the gene include the base sequences that control transcription of the coding portion? Do certain technical designations, such as *operon* or *cistron* define the gene?[10] Does the gene include the noncoding portions—the intervening sequences—that in eukaryotes are ex-

7. *See* Dan L. Burk, *The Problem of Process in Biotechnology*, 43 HOUS. L. REV. 561, 587 (2006).
8. *See generally* GEOFFREY C. BOWKER & SUSAN LEIGH STAR, SORTING THINGS OUT: CLASSIFICATION AND ITS CONSEQUENCES (2000) (discussing the social structure of classification systems).
9. *See, e.g.*, JOCELYN E. KREBS ET AL., LEWIN'S GENES X 4, 27–28 (2011) (describing historical variations on the definition of the gene).
10. A cistron is a genetic sequence characterized by its potential for mutation. *Id.* at 29–30. An operon is a series of coding sequences under the control of a single regulatory sequence. *Id.* at 737.

cised out of the RNA transcript? Does the gene include associated macromolecules, such as the proteins that transcribe the DNA, or unwind it, or hold it stable while it is being replicated or transcribed? Does it include the DNA sequences that code for and control the transcription and translation of *those* proteins? Does it include the molecules—some macromolecules, some small molecules—that switch the coding regions on and off in response to cell stimuli, or the array of cellular machinery that produces such signaling molecules?

This series of questions should demonstrate that the concept of *gene* is not monolithic. Each of these technical queries asks us to look a little beyond the frame previously chosen for our viewpoint, and in each case the picture entirely changes. This has essentially nothing to do with the character of the universe—only with the character of human inquiry. To take only one example, early investigators of the gene were surprised to discover that certain genetic sequences—dubbed "enhancers"—seemed to increase transcription of coding regions, even though these enhancer sequences were very far removed from the coding region—often millions of base pairs away, along the DNA strand of the chromosome.[11] It had been thought that sequences belonging to a given gene must be contiguous, or at least near to one another. It was unclear how enhancers could be part of the gene when they were located away from what was thought of as the gene.

As it turns out, the enhancers were in fact physically near to the coding region because of the intricate folded structure of the chromosome—in three-dimensional space, pieces of the gene may be near to one another without being contiguous along the linear DNA strand.[12] In other words, the puzzle of the enhancer's effects was a conceptual artifact created by a fixation on the nucleotide sequence of the strand—on what we term the molecule's "primary" structure. But when science moved past that fixation, to consider the other characteristics of what might be included in the gene, the apparent separation between enhancers and coding regions was no longer a puzzle. Enhancer sequences interact with coding sequences whether or not they fit our notions of how DNA ought to act; the only question for us is whether or not *we* take account of them in defining what we call the gene.

As Jacob Bronowski was fond of saying, in science there are no facts, only judgments.[13] Every scientific fact is fundamentally a scientific judgment as to what matters in a given instance and what doesn't. This is unquestionably true of the entities we label genes. Someone in any given instance has judged that the nu-

11. JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE 601 (6th ed. 2008).
12. *Id.* at 602.
13. *See* JACOB BRONOWSKI, *The Abacus and the Rose: A New Dialogue on Two World Systems*, *in* SCIENCE AND HUMAN VALUES 77, 88–91 (rev. ed. 1965).

cleic acid residues up to this certain point should be included, and those beyond that point should be excluded; or has judged that this set of molecules is important, and the remaining molecules are unimportant—at least to the question under consideration. And of course when someone decides to include additional residues beyond the old cut-off point, or to consider a group of molecules formerly considered unimportant, then our picture of the universe, and our picture of nature, changes.

## II. THE NATURE OF PRODUCTS

Viewing the same issue through the other end of the telescope, it should be clear that all human artifacts are in some sense products of nature. As the epigraph from Bach quoted at the beginning of this Essay reminds us, everything we produce—pipes, computers, recombinant plasmids, breakfast cereals, nectarines, Saran Wrap,[14] Velcro[15]—is a product drawn from elements of the material world; all embody and conform to the same fundamental physical laws of motion, gravitation, conservation, symmetry, relativity, thermodynamics, and electromagnetism. Human artifacts (and humans) are drawn from nature and return to nature in one form or another. Indeed, I am not entirely certain what it means to say that the products of human activity are ever *not* a part of nature; beavers build dams, bees build hives, and humans build semiconductor chips. It's all quite natural.

The perverse corollary to this truth is that the product of nature doctrine invites its devotees to indulge in a mad search for some aspect of an invention that might be considered *un*natural. It should come as no surprise that the primary focus of the arguments presented in *AMP* have centered upon finding some aspect of the DNA molecules that might be considered man made. For example, both parties disputed the significance of the differences between genomic coding regions and the sequence as found in the complementary DNA (cDNA), which is derived from RNA transcripts.[16] Eukaryotic coding sequences typically have long

14. *See* CARL REINER & MEL BROOKS, *2000 Year Old Man*, *in* THE COMPLETE 2000 YEAR OLD MAN (Rhino Records 1994) (declaring Saran Wrap "the greatest thing mankind ever devised").

15. *See* David Kronke, *2,034—And Still Ticking: Comedy: Rhino Releases a Boxed-Set of Albums With the 2,000 Year Old Man. 'I Listened to the Last Record Yesterday, and It's Still Funny,' Carl Reiner Says of the Routines He Did With Mel Brooks*, L.A. TIMES, May 27, 1994, http://articles.latimes.com/1994-05-27/entertainment/ca-62989_1_carl-reiner (quoting Mel Brooks: "Velcro is state-of-the-art, Velcro can kick Saran Wrap's ass . . . . [I]t's the only thing in the last 30 years I like as much.").

16. cDNAs are DNA sequences artificially derived from reverse transcription of messenger RNAs (mRNAs), which are the gene product of most coding gene sequences. *See* WATSON ET AL., *supra* note 11, at 749. Because cDNAs are derived from mRNA, they correspond to the sequence of the RNA, rather than to the sequence of the genomic DNA from which the RNA is derived. KREBS ET AL., *supra* note 9, at 82–83. The transcription is termed "reverse" because transcription

intervening sequences, or introns, that are not included in the production of RNA transcripts, and so appear in the native coding sequence, but are not in reverse transcribed into the cDNA that is generally used in the laboratory.[17]

Myriad, defending its cDNA patents, therefore argued at trial and before the Federal Circuit that its cDNA sequences, lacking introns, could not possibly be products of nature, but rather were the product of human-designed reverse transcription. The trial judge attempted to gloss over this rather stark difference by holding that the informational content of the native genomic and complementary molecules is the same, making the cDNAs equivalent to naturally occurring DNA.[18] The Federal Circuit unanimously rejected this distinction by focusing instead on the structural differences between the cDNA Myriad claimed and DNA found in the wild. All the Federal Circuit judges agreed that the cDNAs were structurally different from native molecules; the disagreement was over the sufficiency of structural difference in the genomic or gDNA molecules.

Judge Alan D. Lourie, a classically trained chemist, writing for the majority noted and relied upon the covalent bonds that are missing in the laboratory version of the gDNA molecule. In its native state, the nucleotide sequence is bonded to the remainder of the chromosome. In its isolated laboratory state, the unattached DNA is left with free electron pairs that thermodynamically must attach to something, and that typically adopt stray hydrogen atoms for bonding.[19] This unquestionably alters the structure of the molecule from that in the wild, not simply because there are vast stretches of nucleotides on each side that are missing, but because the atoms that assume those positions create a different physical shape.

In dissent, Judge William C. Bryson accused Judge Lourie of focusing on structural differences too inconsequential to make the molecules unnatural—that is, to make them the product of human intervention.[20] But if Judge Lourie's distinctions seem trivial, it is only because of a naïve focus on the similarities of nucleotide sequence that he shared with the rest of the panel, and indeed with the trial court—the same kind of preoccupation with primary structure that led to the

of DNA from RNA is contrary to the usual paradigm of transcription in living cells. *Id.* at 15; WATSON ET AL., *supra* note 11, at 340. The enzymes used for the process are derived from certain viruses that have RNA genomes, and so they routinely follow a "reverse" transcription model. KREBS ET AL., *supra* note 9, at 440–41.

17. WATSON ET AL., *supra* note 11, at 415.

18. Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181, 228–30 (S.D.N.Y. 2010).

19. *See AMP II*, 689 F.3d 1303, 1329–30 (Fed. Cir. 2012); *see also* KREBS ET AL., *supra* note 9, at 8 (describing the free 5' ("5-prime") and 3' ("3-prime") termini of nucleotide chains); WATSON ET AL., *supra* note 11, at 104.

20. *AMP II*, 689 F.3d at 1351 (Bryson, J., concurring in part and dissenting in part).

supposed puzzle of enhancer sequences.[21] Nucleotide sequence is only important to the extent that it contributes the physical configuration of the molecule, and if one is looking for differences, the differences between the native and laboratory molecules are even more numerous and significant than Judge Lourie imagined.

In its native environment, the constrained helical DNA molecule quite literally ties itself into knots.[22] This same effect can easily be seen in the handset cords of desktop telephone sets; the cords are generally helical, and inevitably coil themselves into tangles when the handset is replaced into the cradle after a few calls. The only feasible way to unwind the cord is to release the constraints on the cord by dangling the handset and allowing it to spin freely. DNA winds itself into coils in exactly the same fashion. This coiled structure of the helix, whether seen in telephone cords or in macromolecules, can be mathematically described as two variables termed the *twist* and *writhe* of the strand.[23]

In the molecule's natural state, this molecular tangling is constrained by a lattice of scaffolding proteins, as well as by ambient globular proteins that hold the strands open, closed, or stable depending on the state of a given molecular function, such as transcription or replication.[24] These associated structures do not accompany the nucleotide strand into artificial settings such as the laboratory; the structural constraints are removed during the extraction process, and are of course never present for molecules generated by artificially initiated reverse transcription. Judge Lourie is correct that snipping a piece out of the chromosome makes a difference, but it is not simply in the bonds at the ends of the strand; the twist and writhe found in the wild are eliminated.

A DNA molecule outside the cellular environment is in fact characterized by a large number of other differences—the pitch (or "wind") of the helix, the ionic shell surrounding the molecule, the charge of the phosphate backbone of the molecule, the manner in which the molecule folds or "sticks" to itself and other molecules—depending on the medium in which it is immersed. Indeed, laboratory conditions such as pH—acidity—and buffer composition are generally chosen precisely in order to avoid the natural configuration of the molecules; the strands are nearly impossible to work with when wrapped up in knots around themselves.

Such molecular configurations matter. They define the physical characteristics, and hence the biological function, of the molecules. The primary sequence is important because it is a key factor in defining the molecule's secondary and tertiary configurations; it is necessary to molecular function, but not sufficient. Mov-

21. *See supra* notes 10–11 and accompanying text.
22. *See* KREBS ET AL., *supra* note 9, at 8–9.
23. *Id.* at 9.
24. *Id.* at 197–98; WATSON ET AL., *supra* note 11, at 170–74.

ing the substance out of the cell inevitably alters it in ways not reflected by the primary sequence.

The Solicitor General's office, arguing against the patentability of gDNA in oral argument to the Federal Circuit, suggested a "magic microscope" analogy: that if one could use a magic microscope to examine native DNA, one would find naturally occurring in cells the identical sequence to the Myriad gDNA.[25] Judge Lourie's analysis, which relied on the covalent bonds missing in the gDNA molecule, is in effect an answer to the government's "magic microscope" argument, recognizing that it is clearly wrong. But the differences are not limited to the sequence's connection to the rest of the chromosomal strand. If one could in fact microscopically—actually nanoscopically—scrutinize the native DNA molecule and compare it to either the cDNA or the excised gDNA sequence in a test tube, one would not see the same thing at all. The molecule found suspended in buffer in a test tube simply is not the molecule coiled, knotted, and intertwined within the cell.

For small molecules, essentially this same insight regarding the three dimensional aspect of molecules was the basis of the *In re Papesch* revolution in patent law's nonobviousness criterion more than fifty years ago.[26] Prior to the *Papesch* decision, courts had routinely held that it was obvious to add standard moieties to known families of molecules, for example adding an additional hydroxyl or carbonyl group to known molecules.[27] The obviousness rationale was based on the routine extension of known two-dimensional molecular formulae. Alkanes, alkenes, alcohols, esters, and other more complex families of organic molecules are constructed as a regular array of sequential molecular extensions that are typically represented on paper as predictable chemical structures. Adding an additional known moiety to a known molecular structure in a routine family sequence was considered to be an obvious extension of the art.

But this presumption ignored the reality that molecules in fact exist in three dimensions, not merely in a two-dimensional depiction. The configuration defined by a predictable addition to the known formula often resulted not in the expected two-dimensional extension of the formula, but rather in an unpredictable three-dimensional physical structure with unpredictable new characteristics. The *Papesch* decision recognized the three-dimensional reality of small molecule struc-

25. *AMP II*, 689 F.3d at 1326.
26. *In re* Papesch, 315 F.2d 381 (C.C.P.A. 1963).
27. *See* Bruce M. Collins, *The Forgotten Chemistry of the Hass-Henze Doctrine*, 44 J. PAT. OFF. SOC'Y 284 (1962).

ture, and held that such unexpected characteristics rendered the "predictable" extension of the known molecule nonobvious.[28]

Recognizing the structural character of DNA sequences requires much the same conceptual reorientation. Even were we to credit the *AMP* trial judge's view of informational equivalence between the sequences of cellular and laboratory DNA, this accounts for only the information seen in a two-dimensional depiction—the base pairs represented by combinations of the letters "ATCG" in a textbook, or in a patent. But the information carried by the three-dimensional secondary and tertiary configurations of the molecules in a human cell as opposed to in the laboratory was certainly quite different. Putting the most charitable reading on the judge's view, one would need to say that the informational content of the molecules is *effectively* the same, or that the *pertinent* informational content is the same.

Of course, we might wish to say that as a matter of patent law we only care about the sequence of nucleic acid residues and, that we consider differences in configuration, context, and definition for isolated DNA to be for some reason inconsequential. There are perhaps arguments for doing so, but that is a choice of policy; not an outcome dictated by the state of nature. There is nothing in the natural order of the universe that demands such a focus, or that somehow declares that the nucleotide sequence of the molecule is a natural consideration while its other structural characteristics are inconsiderable or unnatural.

## CONCLUSION

Unfortunately, many of the briefs filed in the *AMP* case tend to go on as if our view of the universe—and of the patent system—is predestined, rather than a creative human endeavor. Even more unfortunately, some of the worst offenses in this regard are advanced by scientists or scientific societies. But as I have shown here the definition of *gene* is a human, not a natural, construct, and that the physical properties of DNA molecules are necessarily altered to some degree from their native state anytime they are the subject of human investigation.

Indeed, having here taken a hard look at the characteristics of the contested molecules in the *AMP* case, one wonders whether the most sensible course is to simply abandon the product of nature exercise altogether. At its endpoints, the doctrine either proves everything or proves nothing. Either everything is a product of nature—drawn from and existing in the world—or nothing is a product of nature—having been intellectually and socially constructed by human cognition.

28. Harold C. Wegner, *Foreword*, 6 APLA Q.J. 253, 253 (1978).

This is not to say that the product of nature doctrine is utterly without content or, at least, that a proper formulation of it need not be. If the universe will not tell us outright what we ought to consider natural or inventive, how do we decide what items fit these categories? We look to the policy work that the doctrine is intended to do. The proper criterion has been articulated by the Supreme Court in the related context of laws or principles of nature: "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work."[29]

Such tools are essential to any technical progress; granting exclusive rights in such fundamental and necessary concepts would likely impede rather than promote innovation. Similarly, if the product of nature doctrine stands for anything, it is surely a shorthand for the parallel concept that there may be some materials so fundamental to further inventive activity that restricting them through grants of exclusive rights would prove detrimental to innovation. At the same time, there is nearly universal agreement that patents are intended to reward inventive activity by means of exclusive rights.[30] Failure to provide such rights could deter investment in the development or acquisition of fundamental materials.

Thus, the product of nature question is not a question of ontology, but a question of epistemology: What do we know or hope to know about a certain material to promote the progress of science and the useful arts? There will be a fine line between enabling access to required tools and undersupplying them. Drawing the line is purely a matter of public policy informed by economic reality and technical practice. The label "product of nature" does not tell us where that line lies, nor does the fact that a given tool was extracted at some level from material substance. In the end, the label product of nature is a conclusion rather than a criterion, and no substitute for the hard policy choice entailed in the Supreme Court's question in *AMP v. Myriad*.

29. Gottschalk v. Benson, 409 U.S. 63, 67 (1972).

30. *See* DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 66 (2009) (summarizing the dominant policy justifications for patent law).